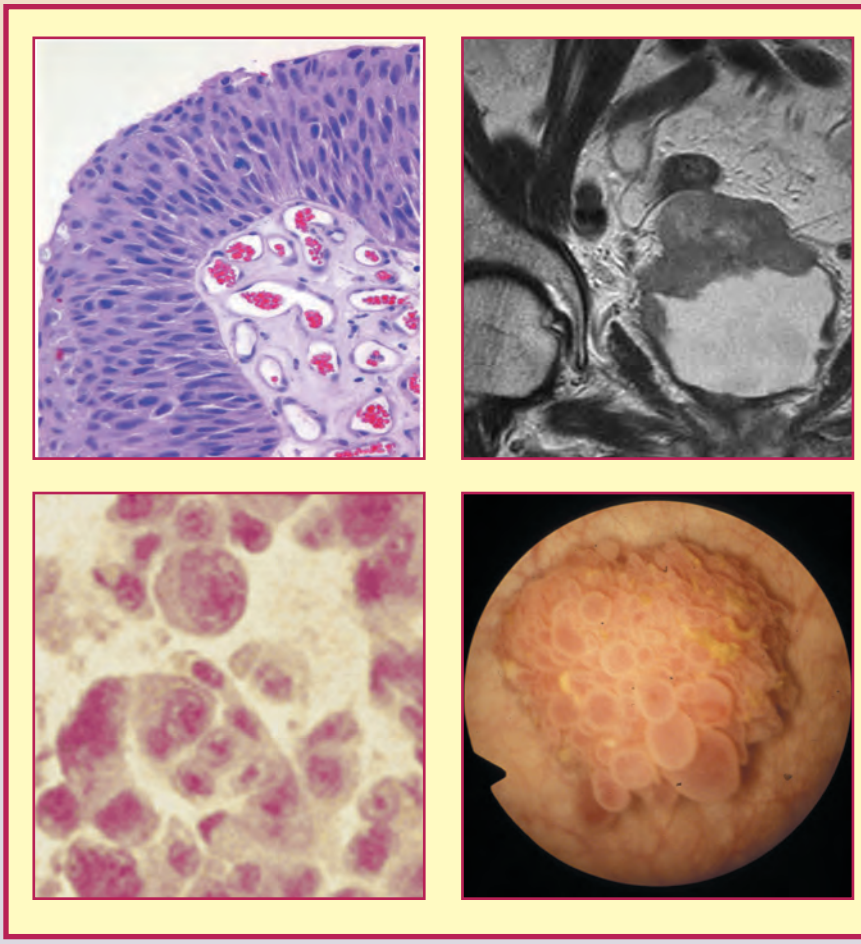
Bladder Tumors

EDITORS

Mark Soloway,
Adrienne Carmack, Saad Khoury



1st International Consultation on Bladder Tumors - Hawaii October 3-7, 2004

Co-Sponsored by

SIU (International Society of Urology),
ICUD (International Consultation on Urological Diseases),
EORTC Urology (European Organisation for Research and Treatment of Cancer)

Distributor : EDITIONS 21
76, rue de la Pompe - 75016 Paris - FRANCE
Fax: +33 1 45 04 72 89 E-mail : editions21@wanadoo.fr

ISBN 0-9546956-4-X

LAY-OUT: S.Taieb

INTRODUCTION: INTERNATIONAL CONSULTATION ON BLADDER TUMORS

The title of this text makes a statement. All bladder tumors are not malignant and thus, the title is bladder tumors and not bladder cancer. This is appropriate. Tumors of the urinary bladder are heterogeneous. Not all neoplastic growths in the bladder are a threat to the host. Papilloma, papillary urothelial neoplasms of low malignant potential and even most low-grade, non-invasive papillary tumors sometimes termed low grade transitional cell carcinoma do not behave as a malignancy with the potential for invasion or metastasis. Yet, almost 50% of our patients with bladder tumors have one of these benign neoplasms and much of our attention is directed at treating them.

Bladder tumors are indeed a major health problem. The prevalence of bladder tumors is high due in part to their propensity to "recur" once resected and the many etiologic factors related to their development. Some of the causative agents are known such as cigarette smoking and hair dyes while others have yet to be determined. It is likely that many of the chemicals in our environment are concentrated in the urine and capable of causing mutations in the bladder urothelium thus leading to a bladder neoplasm. It has been stated that the cost of taking care of patients with bladder tumors is among the highest of all neoplasms.

This text details the final report of the consultation on bladder tumors and provides an extensive resource for all those interested in this disease. It has been an honor and privilege to chair this International Consultation on Bladder Tumors. I was confident that the many experts throughout the world would agree to share their expertise and participate in this major effort. I subdivided the subject of bladder tumors into eleven areas. Each committee had the task of collecting information on their subject area and, after an extensive review, arrive at a consensus or guidelines. Although there are relatively few randomized trials dealing with bladder tumors, we have produced many guidelines whose foundation largely rests on the experience of those who have studied this disease for many years. Guidelines may change as new techniques, knowledge and treatments evolve. Most of these, however, are based on an understanding of the biology of bladder tumors and will likely remain for many years.

I particularly want to express my deep appreciation to all of the chairs, vice-chairs and committee members who unselfishly provided us with their time and energy to accomplish this goal. This was a labor of love. Each of the chairs had the task of synthesizing the often diverse opinions of their committee members and reaching a consensus when possible.

I am particularly grateful to two individuals that guided the project from its inception to completion. Saad Khoury formulated the concept of an international consultation. I believe this is a worthy goal and although some may challenge individual guidelines, most would agree that a periodic review of the literature with the discussion on appropriate management is a productive endeavor. Working with Mustafa Elhillali and the SIU, Saad provided the challenge and the mechanism to carry out the task. The second individual is Adrienne Carmack. While only a mid-level urology trainee, Adrienne is an accomplished editor, skilled communicator and most importantly, has superb time management skills. She was able to attend three international meetings, communicate regularly with the committees, and helped me edit the manuscripts while still taking part in a demanding residency program. Without email even Adrienne could not have accomplished this task.

Many of you will not have the opportunity to read the entire text but will use this volume as a resource and select topics of interest. I will take the chairman's prerogative of highlighting some of the guidelines and recommendations from the 11 committees.

Epidemiology and Diagnosis

Bladder tumors are common. It is the most common malignancy in some countries (Egypt) and ranks very high in many others e.g. Turkey, China, United States. Since we know some of the risk factors, e.g. age, cigarette smoking, hair dyes, there is an opportunity for early detection. Unfortunately many of our patients are diagnosed at a stage when even our optimal treatments are only

palliative. Since we have effective treatments for Ta – T1 urothelial tumors, it only seems reasonable to devote some resources to identifying bladder cancer at an early stage. This strategy has made an impact on some other tumors, e.g. breast, prostate, cervix. Importantly, the majority of bladder tumors left untreated will eventually require therapy so the problem of overdetection does not seem pertinent.

The committee urges pathologists and urologists to adopt the 2004 WHO/ISUP classification which divides grades into low or high eliminating the ambiguous Grade 2 category.

Markers

The development of urine based tumor markers provides an opportunity for early detection as well as non-invasive surveillance following the initial diagnosis of a bladder tumor. Of course, urologists will not abandon the cystoscope which is the foundation of the diagnosis and initial treatment. It is, however, invasive. Some of the monitoring can be supplemented or substituted by a tumor marker. This is applicable particularly for those with low risk tumors. This chapter provides an extensive review of cytology and the various markers.

Low grade, non-invasive tumors

There is sufficient evidence from prospective randomized trials to recommend the instillation of intravesical chemotherapy within hours of resection of low grade, Ta tumors provided that the bladder wall remains intact. Upper tract monitoring is not necessary in these patients as the risk of an upper tract urothelial tumor is very low. Office fulguration is felt to be an acceptable mode of therapy for small, low grade “recurrences”.

High grade Ta, carcinoma in situ, and T1 (2 committees)

The term bladder cancer is appropriate for these grades and stages. Not only is the likelihood of a subsequent tumor following initial resection high but there is a risk of progression to a higher stage. The clinician must assure removal of all of the tumor, accurate staging, and make an effort to minimize the likelihood of a subsequent tumor. Depending on certain prognostic factors such as multifocality and stage, one might even consider proceeding with a radical cystectomy in a subset of these patients, e.g. multifocal high grade T1 with CIS. The concept of a reTUR is a strong recommendation in this group of patients given the critical role of staging in the decision making process. In general, this should be performed within a few weeks of the initial endoscopic resection of a high grade Ta or T1 bladder cancer. One must exclude muscle invasion since this would change the treatment algorithm. Muscle must be present in the resection specimen.

BCG is the treatment of choice following resection of a high-grade Ta, CIS or T1 urothelial carcinoma. It is yet to be established that maintenance BCG is necessary, although the majority of the committee members felt that a minimum of one-year maintenance has been shown to reduce the recurrence rate if not the progression rate. The three and six month evaluation is critical. If a high grade tumor recurs or persists within this time frame, one should consider proceeding without undue delay to radical cystectomy.

The committee felt that following the initial resection of a high grade Ta or T1 tumor, a single dose of post-operative intravesical chemotherapy is appropriate to decrease the chance of tumor implantation. This does not alter the recommendation to use BCG.

Muscle invasive urothelial cancer

Radical cystectomy remains the optimal treatment for tumors which invade the muscularis propria of the bladder. There are occasional patients who meet the criteria for bladder preservation, which includes a “complete transurethral resection” followed by combination chemotherapy and radiation therapy. Careful and persistent monitoring is necessary. This approach requires the expertise of three disciplines (urology, radiation and medical oncology). The presence of hydronephrosis is generally felt to exclude the role of bladder preservation.

The committee commented on two of the problems related to this group of patients. A delay from diagnosis to cystectomy greater than 12 weeks is an adverse prognostic factor. Many patients who would ordinarily be candidates for cystectomy, are not having an opportunity to have this therapy. This needs to be explored further.

Urinary diversion

Twenty years ago virtually all patients had an external appliance upon removal of the urinary bladder. With the introduction of a continent cutaneous diversion and subsequently the development of an orthotopic neobladder. Fifty percent of patients now avoid an external appliance. Ileum is the bowel segment of choice for construction of an orthotopic neobladder. Patients must be motivated and understand the possibility of nocturnal incontinence and the need for clean intermittent catheterization. The orthotopic neobladder as currently performed in many major medical centers has the same morbidity as other forms of urinary diversion and patient acceptance has been excellent.

Radiation therapy

External beam radiation therapy remains a common form of treatment for muscle-invasive bladder cancer in many geographic areas and in particular in patients older than 75. There are groups of patients in which the success rate is low and this includes patients with ureteral obstruction and clinical stages T3-T4. Concurrent cisplatin should be administered along with external beam radiation therapy unless there is a contraindication such as impaired renal function. For the advanced clinical stages, multiagent systemic chemotherapy should precede external beam radiation therapy.

Systemic chemotherapy

Cisplatin-based multiagent systemic chemotherapy for urothelial cancer rarely provides a cure in those who have metastasis; however, many patients have significant palliation. The current most active combinations consist of either MVAC or gemcitabine plus cisplatin. Other combinations have been explored and many are active.

Adverse risk factors for patients with clinically localized muscle invasive bladder cancer include lymphovascular invasion, hydronephrosis, stage T3-T4 and prostatic stromal invasion. Such patients can be considered for neoadjuvant chemotherapy although prospective randomized trials show only a modest benefit with this approach. There is insufficient evidence to recommend routine adjuvant chemotherapy for patients with pT2 and pT3 bladder cancer.

Urothelial carcinoma of the prostate

It is important for the urologist to monitor the prostatic urethra, particularly in the presence of a high grade urothelial carcinoma of the bladder. Treatment for urothelial carcinoma of the prostate depends on the stage: confined to the urothelium, involvement of the prostatic ducts or stromal invasion. The treatment for carcinoma confined to the urothelium is transurethral resection followed by BCG if the cancer is high grade. Once the tumor involves the stroma radical cystectomy is necessary, assuming that the patient is a candidate for major surgery. When the tumor involves only the prostatic ducts, some would proceed with transurethral resection plus BCG while others think this warrants proceeding to cystectomy.

Non-urothelial carcinoma of the bladder

Squamous cell carcinoma, adenocarcinoma and small cell carcinoma are uncommon but important neoplasms of the urinary bladder. Radical cystectomy is the treatment of choice for squamous cell and adenocarcinoma. Systemic chemotherapy is a critical component of the treatment for small cell carcinoma of the bladder.

This has been only a few highlights from the extensive amount of material that follows in this book. Whenever possible, the authors have attempted to provide guidelines and indicate the grades of recommendation as identified in the Oxford Center for Evidence-Based Medicine. On behalf of all of those who worked so diligently in this project, we sincerely hope that the information provided will be used to help all of us optimize the care of our patients with bladder tumors.

Mark S. Soloway, M.D.

Professor and Chairman

Department of Urology

University of Miami – Miller School of Medicine

Miami, Florida

MEMBERS OF THE COMMITTEES *(by Committee)*

Committee 1 Bladder Cancer: Epidemiology, Staging and Grading, and Diagnosis

Z. KIRKALI (TURKEY),
T. CHAN (USA),
M. MANOHARAN (USA),
F. ALGABA (SPAIN),
C. BUSCH (SWEDEN),
L. CHENG (USA),
L. KIEMENEY (NETHERLANDS),
M. KRIEGMAIR (GERMANY),
R. MONTIRONI (ITALY),
W. MURPHY (USA),
I. SESTERHENN (USA),
M. TACHIBANA (JAPAN),
J. WEIDER (USA)

Committee 2 Cytology And Tumor Markers:Tumor Markers Beyond Cytology

V.B LOKESHWAR (USA),
T. HABUCHI (JAPAN),
H.B. GROSSMAN (USA),
W.M. MURPHY (USA),
G.P. HEMSTREET, III (USA),
S.H. HAUTMANN (GERMANY),
A.V. BONO (ITALY),
R.H. GETZENBERG (USA),
P. GOEBELL (GERMANY),
B.J. SCHMITZ-DRÄGER (GERMANY),
M. MARBERGER (AUSTRIA),
J. A. SCHALKEN (NETHERLANDS),
E. MESSING (USA),
Y. FRADET (CANADA),
M.J. DROLLER (USA)

Committee 3 Low Grade, Ta (Noninvasive) Urothelial Carcinoma of the Bladder

W. OOSTERLINCK (BELGIUM),
E. SOLSONA (SPAIN),
H. AKAZA (JAPAN),
C. BUSCH (SWEDEN),
P.J. GOEBELL (GERMANY),
P.-U. MALMSTRÖM (SWEDEN),
H. ÖZEN (TURKEY),
P. SVED (USA)

Committee 4 High Grade Ta Urothelial Carcinoma and Carcinoma in Situ of the Bladder

R. SYLVESTER (BELGIUM),
A.V.D MEIJDEN (NETHERLANDS),
J.A. WITJES (NETHERLANDS),
G. JAKSE (GERMANY),
N. NONOMURA (JAPAN),
C. CHENG (SINGAPORE),
A. TORRES (MEXICO),
R. WATSON (AUSTRALIA),
K.H. KURTH (NETHERLANDS)

Committee 5 T1 Urothelial Carcinoma of the Bladder

M.A.S JEWETT (CANADA),
A.M. NIEDER (USA),
M. BRAUSI (ITALY),
D. LAMM (USA),
M. O'DONNELL (USA),
K. TOMITA (JAPAN),
H. WOO (AUSTRALIA)

Committee 6 Muscle-Invasive Urothelial Carcinoma of the Bladder

S. B. MALKOWICZ (USA),
H. VAN POPPEL (BELGIUM),
G. MICKISCH (GERMANY),
V. PANSADORO (ITALY),
J. THÜROFF (GERMANY),
M. SOLOWAY (USA),
S. CHANG (USA),
M. BENSON (USA),
I. FUKUI (JAPAN)

Committee 7 Urinary Diversion

R. E. HAUTMANN (GERMANY),
H. ABOL-ENEIN (EGYPT),
K. HAFEZ (USA),
I. HARA (JAPAN),
W. MANSSON (SWEDEN),
R. D. MILLS (UK),
J. D. MONTIE (USA),
A. I. SAGALOWSKY (USA),
J. P. STEIN (USA),
A. STENZL (GERMANY),
U.E. STUDER (SWITZERLAND),
B.G. VOLKMER (GERMANY)

Committee 8 Urothelial Carcinoma of the Prostate

J. Palou (Spain),
J. Baniel (Israel),
L. Klotz (Canada),
D. Wood (USA),
M. Cookson (USA),
S. Lerner (USA),
S. Horie (Japan),
M. Schoenberg (USA),
J. Angulo (Spain),
P. Bassi (Italy)

Committee 9 Chemotherapy for Bladder Cancer: Treatment Guidelines for Neoadjuvant Chemotherapy, Bladder Preservation, Adjuvant Chemotherapy, and Metastatic Cancer

C. Sternberg (Italy),
S.M. Donat (USA),
J. Bellmunt (Spain),
R.E. Millikan (USA),
W. Stadler (USA),
P. De Mulder (Netherlands),
A. Sherif (Sweden),
H. von der Maase (Denmark),
T. Tsukamoto (Japan),
M. Soloway (USA)

Committee 10 Radiotherapy for Bladder Cancer

M. Milosevic (Canada),
M. Gospodarowicz (Canada),
A. Zietman (USA),
F. Abbas (Pakistan),
K. Haustermans (Belgium),
L. Moonen (Netherlands),
C. Rödel (Germany),
M. Schoenberg (USA),
W. Shipley (USA)

Committee 11 Non-urothelial Cancer of the Bladder

H. Abol-Enein (Egypt),
B.R. Kava (USA),
A.J.K. Carmack (USA)

CONTENTS

Summary of the International Consultation on Urologic Disease Modified Oxford System for Levels of Evidence and Grades of Recommendations

Levels of Evidence

Level 1 Metanalysis of RCTs or a good quality RCT

Level 2 Low quality RCT or metanalysis of good quality prospective cohort studies

Level 3 Good quality retrospective case control studies or case series

Level 4 Expert opinion based on "first principles" or bench research, not on evidence

Grades of Recommendation

Grade A Usually consistent level 1 evidence

Grade B Consistent level 2 or 3 evidence or "majority evidence" from RCTs

Grade C Level 4 evidence, "majority evidence" from level 2/3 studies, expert opinion

Grade D No recommendation possible because of inadequate or conflicting evidence

*Adapted from Evidence-based medicine: Overview of the main steps for developing and grading guideline recommendations, by P Abrams, A Grant, and S Khoury, January 2004

Bladder Tumors

EDITORS

MARK SOLOWAY,

ADRIENNE CARMACK, SAAD KHOURY

Committee 1

Bladder Cancer: Epidemiology, Staging and Grading, and Diagnosis

Chair

Z. Kirkali (Turkey)

Vice Chairs

T. Chan (USA)

M. Manoharan (USA)

Members

F. Algaba (Spain)

C. Busch (Sweden)

L. Cheng (USA)

L. Kiemeney (Netherlands)

M. Kriegmair (Germany)

R. Montironi (Italy)

W. Murphy (USA)

I. Sesterhenn (USA)

M. Tachibana (Japan)

J. Weider (USA)

CONTENTS

Bladder Cancer: Epidemiology, Staging and Grading, and Diagnosis

Z. KIRKALI

T. CHAN, M. MANOHARAN

F. ALGABA, C. BUSCH, L. CHENG, L. KIEMENEY, M. KRIEGMAIR, R. MONTIRONI, W. MURPHY, I. SESTERHENN, M. TACHIBANA, J. WEIDER

Bladder cancer is a heterogeneous disease with a variable natural history. At one end of the spectrum, low grade Ta tumors have a low progression rate and require initial endoscopic treatment and surveillance, but rarely present a threat to the patient. At the other extreme, high grade tumors have a high malignant potential associated with significant progression and cancer death rates.

The true natural history of untreated noninvasive disease is not fully known. Seventy percent of bladder tumors present as superficial disease and the rest as muscle-invasive disease. Among the superficial cancer group, approximately 70% present as Ta lesions, 20% as T1, and 10% as carcinoma in situ (CIS, Tis).

Many characteristics of urothelial (transitional cell) carcinoma have been studied in an attempt to predict the variable tumor behavior. These include pathologic features, cytologic analysis, and molecular markers. Accurate staging and grading of the disease is important to decide the optimal treatment. An understanding of the epidemiology and bladder screening strategies helps in the prevention and early detection of the disease.

I. EPIDEMIOLOGY OF BLADDER CANCER

1. INCIDENCE AND MORTALITY

Bladder cancer is the fourth most common ma-lignancy among Western men, following prostate, lung, and colon cancer. In Europe and the United States, bladder cancer accounts for 5% to 10% of all malignancies among males (**Figure 1**). The risk of developing bladder cancer before the age of 75 years is 2% to 4% for males and 0.5% to 1% for females, compared to, for example, 8% and 2% for lung cancer, respectively (**Figure 2**) [1]. The median age at diagnosis is 65 to 70 years.

Some of the differences between countries are caused by differences in registration or reporting of (low grade) pTa tumors. Unfortunately, this makes the comparison between countries very difficult. Age-standardized (world) mortality rates vary from 2 to 10 per 100,000 per year for males and 0.5 to 4 per 100,000 per year for females (**Figure 3**) [2].

Bladder cancer is 3 to 4 times more common among males than females. On the other hand, it has been suggested that the stage-adjusted survival of bladder cancer among women is worse than among men [3]. The excess of bladder cancer in males is not fully explained by gender differences in smoking habits and occupation (the 2 most well-known risk factors for bladder cancer). Surveys of cancer incidence and mortality suggest that parous women have a lower risk of bladder cancer than nulliparous women, probably due to hormonal changes related to pregnancy, and that the risk may decrease with increasing parity [4-7]. Furthermore, in animal experiments, rats treated with androgenic hormones developed more bladder tumors than animals treated with estrogenic hormones [8]. It is therefore suggested that at least some androgenic hormones stimulate (or do not inhibit) oncogenesis while estrogenic hormones do the opposite.

For yet undetermined reasons, blacks experience only half the risk of whites (**Figure 4**), but the overall survival among blacks seem to be worse. The higher incidence among whites compared to blacks is limited to superficial tumors, with blacks and whites having a similar risk of more invasive tumors [9,10] . This suggests that some low stage, low grade tumors among blacks remain undetected. The higher risk in whites may also be due to different risk fac-

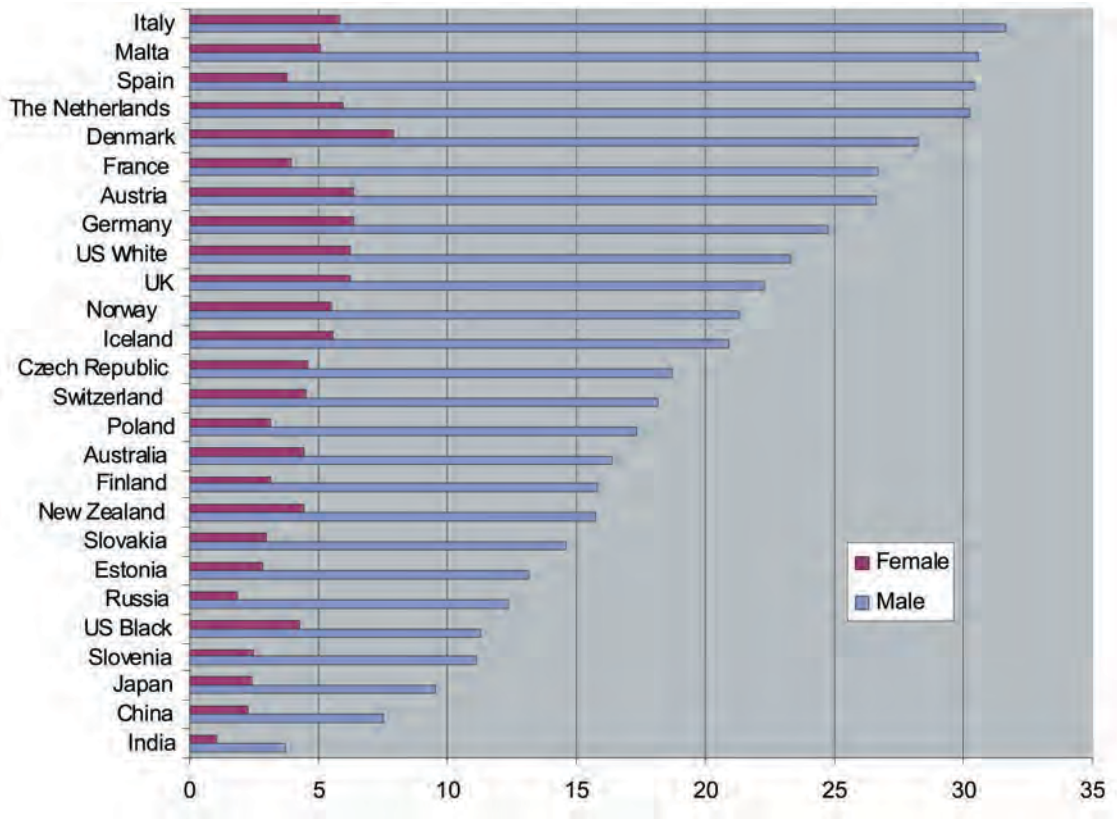


Figure 1. Age-standardized (World) Incidence Rates (per 100,000) of Bladder Cancer [1]

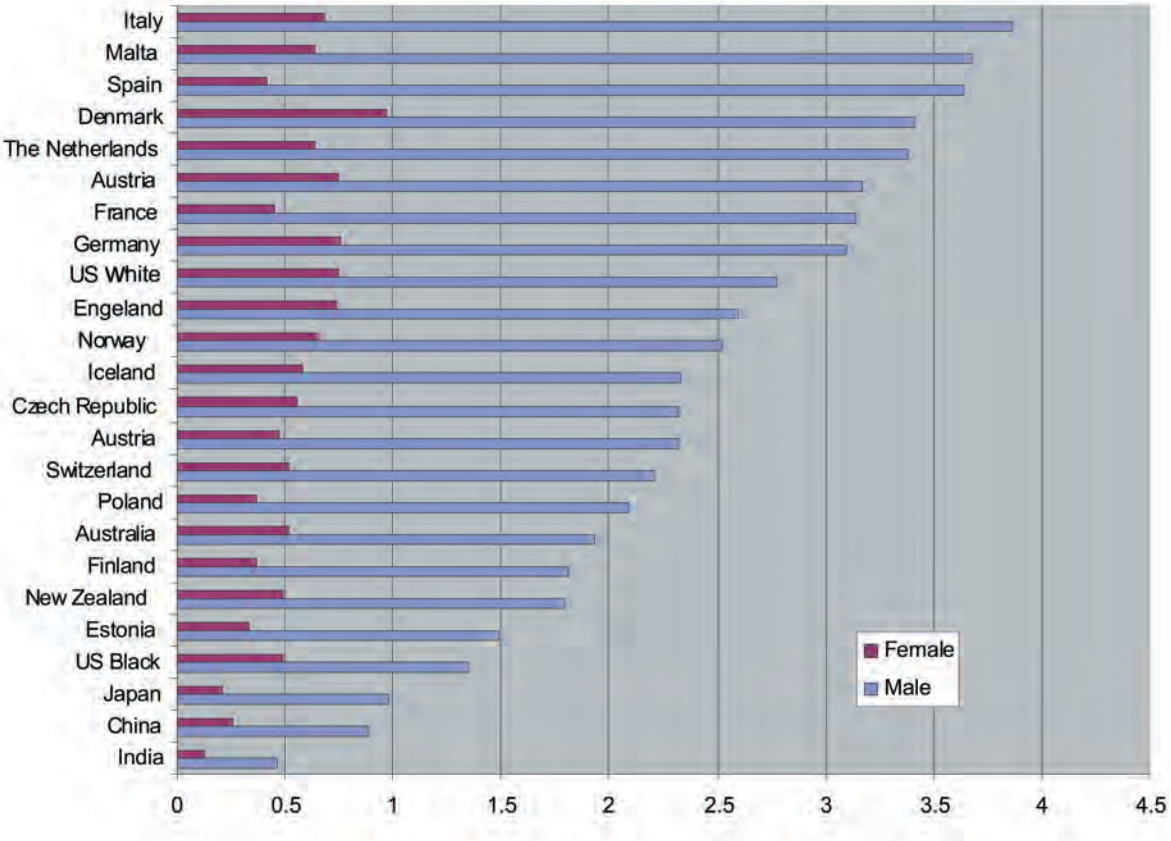


Figure 2. Cumulative Risk (%) of Bladder Cancer Before the Age of 75 Years [1]

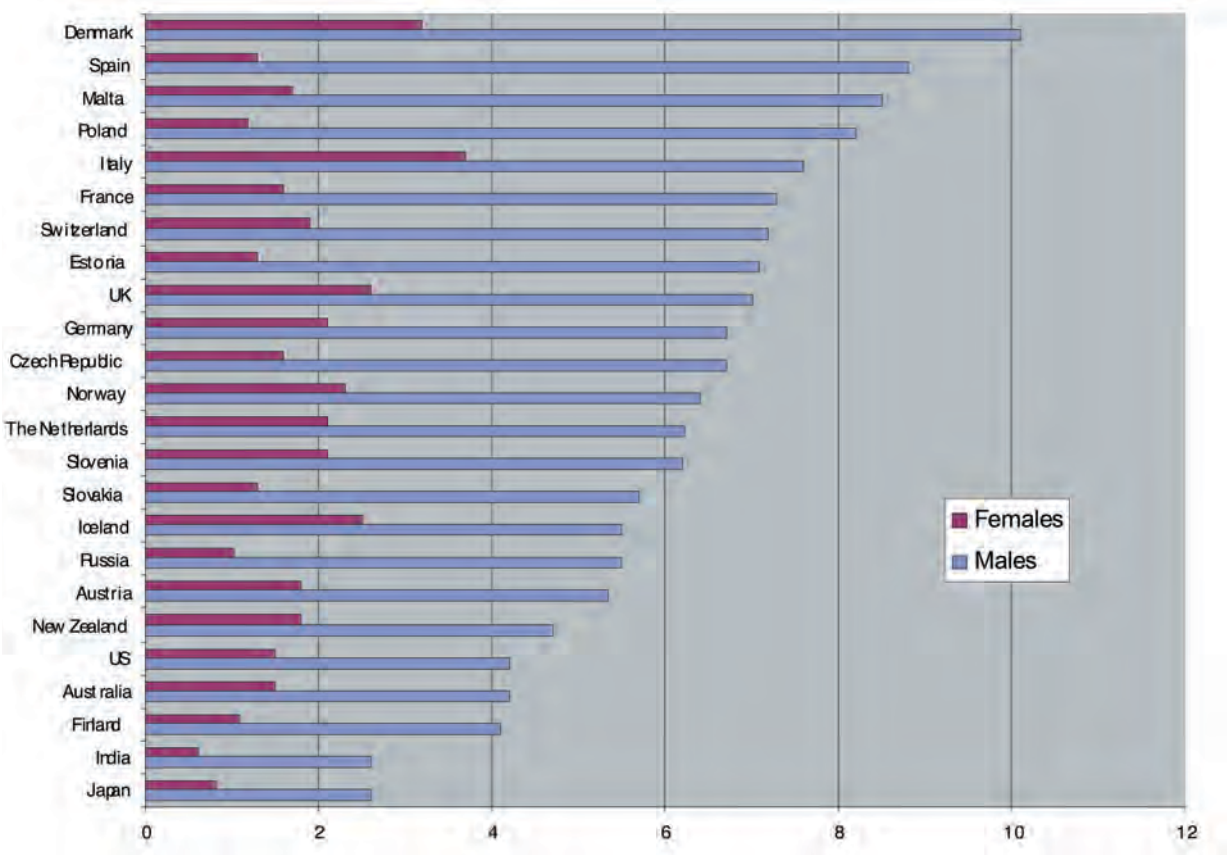


Figure 3. Age-standardized (World) Mortality Rates (per 100,000/year) of Bladder Cancer [2]

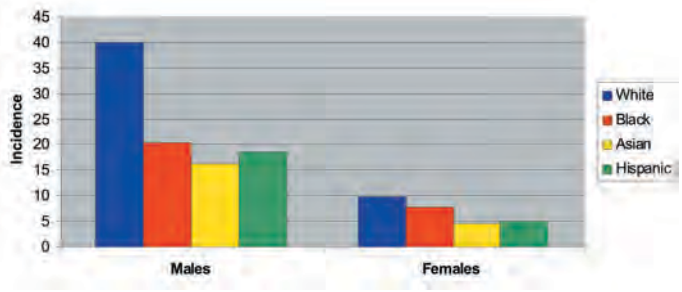


Figure 4. Bladder Cancer Incidence in the US / 10^5 Person-years by Race [11]

tors operating in the black and white populations. Also, racial biologic variations and within-race individual differences may modify various phases of carcinogenesis such as the capacity to convert procarcinogens to carcinogens, to detoxify carcinogens, and to repair DNA.

2. Environmental Risk Factors

a) Smoking

The most well-established risk factor for bladder cancer is cigarette smoking (**Table 1**), although the association is not as strong as that observed for smoking and respiratory tract cancers.

Although it is well-recognized that cigarette smoking is the most important risk factor for bladder cancer on a population basis, additional factors have to play a role in modifying the risk of smoking-related bladder cancer. Populations exist with high smoking rates but low bladder cancer rates (for example, Polynesian men including native Hawaiians and New Zealand Maoris) [12]. This suggests differences in the metabolism of smoking-related carcinogens. For example, N-acetyltransferase 2 slow acetylators are known to have a higher risk of bladder cancer from smoking than rapid acetylators [13]. Exogenous agents (such as vitamin intake) may modify the susceptibility to smoking-induced bladder cancer as well.

All over the world, time trends in bladder cancer follow trends in smoking behavior, comparable to time trends in lung cancer but with a longer delay. In most Western communities, bladder cancer incidence and mortality in men has decreased in the last decade.

b) Occupation

Occupation is the first known and, on a population

Table 1. Smoking and Bladder Cancer

- Cigarette smoking increases bladder cancer risk two- to fourfold
- 30% to 50% of all bladder cancer is caused by cigarette smoking
- Latency period is approximately 20 to 30 years
- Increasing intensity and/or increasing duration → increasing risk
- Quitting smoking → immediate decreasing risk approaching baseline after 20 to 30 years
- Black tobacco threefold increased risk vs. blond tobacco
- Unfiltered cigarettes 35% to50% higher risk than filtered cigarettes
- Deep inhalation 30% to 40% higher risk than no inhalation
- Pipe/cigar smoking → higher risk? (inhalation pattern)
- Snuff or chewing tobacco → no elevated risk

level, second most important risk factor for bladder cancer. It has been estimated that occupational exposures may account for as much as 20% of all bladder cancer [14]. Exposure to beta-naphthylamine, 4-aminobiphenyl (ABP), and benzidine, principally among workers in the textile dye and rubber tire industries, are the only specific agents that have been associated with bladder cancer unequivocally. Due to strict regulations, these specific chemicals are now banned from the workplace and contribute minimally to the current incidence of bladder cancer in Western countries. However, many other strong candidates for bladder carcinogens still exist such as ortho-tolui-dine, which is used now in the manufacture of dyes, rubber chemicals, pharmaceuticals, and pesticides [15]. In fact, many occupations have been marked as potentially high-risk occupations. As already pointed out, a strongly increased risk of bladder cancer may still exist for (ex-)workers in the dye, rubber, and chemical industries, as a result of (historical) exposure to aromatic amines (arylamines) like benzidine, 2-naphthylamine, 4-ABP, 4,4'-methylene-dianiline, 4,4'-methylene-bis (2-chloroaniline), o-toluidine, 4,4'-methylene-bis (2-methylaniline), and 4-chloro-o-toluidine [16,17]. The risk of bladder cancer among workers in such industries should therefore be monitored continuously. If specific plants are suspected, the identification of the causative agent should be started immediately, preventive measures should be taken, and exposed workers may have to be screened for bladder cancer for at least 2 decades.

Excess risks have been frequently observed among painters, which is thought to be due to exposure to possible carcinogenic constituents of paints like benzidine, polychlorinated biphenyls, formaldehyde, and asbestos and solvents like benzene, dioxane, and methylene chloride [18]. A moderately increased risk is also found among leather workers and shoe makers, although the responsible agent is still un-known [19]. The workers are exposed to leather dust, dyes, and solvents. Therefore, it is imaginable that the earlier mentioned aromatic amines play an important role.

An excess risk of bladder cancer is also observed in aluminum, iron, and steelworkers, which may be the result of exposure to aromatic amines and polycyclic aromatic hydrocarbons (PAHs) in coal-tar pitch volatiles [20-22].

Furthermore, many studies have assessed the relation between bladder cancer and diesel exhaust exposure, and evidence is accumulating that diesel exhaust moderately increases the risk of bladder cancer [23]. Garage mechanics; drivers of trucks, buses, and cabs; and other maintenance workers in transport companies appear to have an increased risk of bladder cancer. A positive trend in risk with increasing duration of employment seems to be present (**Table 2**).

Table 2. Motor Exhaust and Bladder Cancer [24]

Duration of Employment (years)	**Cases**	**Controls**	**Odds Ratio**
Never any motor exhaust-related occupation	1353	2724	1.0
< 5	74	129	1.2
5-9	32	45	1.4
10-24	33	31	2.1
25+	22	19	2.2

Number adjusted for age and smoking

Exhaust emissions contain PAHs and nitro-PAHs. The PAHs are formed mainly as a result of pyrolytic processes, in particular the incomplete combustion of organic materials. Diesel engines emit at least 10 times more nitro-PAHs than gasoline engines.

Although an increased risk of bladder cancer has been reported for many other occupations, findings for most of these occupations are not consistent [25,26].

c) Drinking Water Quality

1. Chlorinated Drinking Water

In the United States and many other countries, drinking water is disinfected with chlorine. The chlorination is important for the microbiologic safety of drinking water. During the chlorination process, chlorine reacts with organics in water resulting in halogenated organic compounds (mainly trihalomethanes such as chloroform and bromoform). Bio-assays and in vitro studies suggest that some of these halogenated compounds are mutagenic or carcinogenic. On the other hand, a recent study from Australia found that the trihalomethane concentration in chlorinated drinking water was not related to DNA damage in bladder cells [27].

Several studies have been performed on chlorinated drinking water and bladder cancer, and all of these reported increased risks [28-35]. The (smoking-adjusted) risks varied from 1.4 to 2.2 for both sexes combined (exposure time varied from 20 to over 60 years). In most studies, the risks tend to increase with duration of exposure. Despite these studies, a report of the International Agency for Research on Cancer (IARC) from 1999 concluded that there was inadequate evidence that individual chlorination by-products such as chloroform and other trihalomethanes were carcinogenic [36]. Although some studies showed an association of chlorinated drinking water intake with cancer, it was argued that single compounds could not be evaluated because these compounds occur in mixtures. A report of the World Health Organization, published in 2000, concluded that the evidence was insufficient to determine whether observed associations were causal or to determine which specific byproduct or contaminant plays a role.

In 2004, Villanueva and colleagues reported a pooled analysis in which primary data from 6 case-control studies with individual-based exposure assessments were pooled [37]. These studies were conducted in 5 countries (Italy [unpublished data 2003], Canada, Finland, USA, and France) using trihalomethanes as a marker for the total mixture of chlorination byproducts [29,31,32,38,39]. Exposure information and covariates were extracted from the original databases including age, sex, smoking, occupation, coffee, fluid consumption, and socioeconomic status. The final pooled dataset comprised 3419 cases and 6077 controls. All cases were histologically confirmed. All studies followed similar approaches to estimate the trihalomethane levels in the water source. The exposure-related variables were the amount of daily tap water consumption and yearly average trihalomethane concentration. The average trihalomethane levels between the studies varied from 10 to 30 µg/L. An exposure window of 40 years was defined, extending from 45 to 5 years before the interview. Exposure to trihalomethanes was associated with an excess risk among ever-exposed men (odds ratio [OR] 1.32, 95% confidence interval [CI] 1.10 to 1.59). The risk increased with increasing exposure. Among women, no increased risk was found. This discrepancy between men and women is still unclear [40]. It may be due to several mechanisms, for example, the role of sex hormones in the metabolization of chlorination byproducts [41,42] or the activity of CYP2E1, which is important in the metabolism of chloroform to active metabolites, and appears to be higher in men compared to women [43-46].

In conclusion, exposure to chlorinated drinking water probably increases the risk of bladder cancer. Although the observed risks are relatively small, the attributable risk may be considerable, given the size of the exposed population.

2. Arsenic in Drinking Water

Several large studies have evaluated the association between ingestion of arsenic in drinking water and the risk of bladder cancer. Most studies have been performed in Asia and Latin America.

Several studies have been performed in the endemic area of Taiwan. Between 1930 and the mid-1960s, the population in this region was exposed to highly contaminated well water (arsenic levels of 170 to 800 µg/L; current regulation is maximum 10 µg/L). These studies have shown a clear dose-response relation with bladder cancer. The age- and sex-adjusted odds ratios of developing bladder, lung, and liver cancers for those who had used well water for 40 or more years were 3.9, 3.4, and 2.7, respectively, as compared with those who never used well water [47]. In contrast to Taiwan, Bangladesh and West Bengal experience an ongoing problem with very high concentrations of arsenic in drinking water that exceed in some sources 2000 to 4000 µg/L [48]. Arsenic levels in drinking water in the United States and Europe are much lower than reported in Taiwan. A recent case-control study by Steinmaus et al. included 7 counties in the Western United States in which the levels of arsenic in drinking water vary from 10 to 100 µg/L [49]. All odds ratios were near 1.0 when an exposure window of 5 to 20 years was

defined. When an exposure window of 40 years or more was used, increased odds ratios were found for arsenic intakes greater than 80 µg/day, although none were statistically significant. Overall, no clear association is found between low to intermediate exposure to arsenic in drinking water and the risk of bladder cancer.

d) Medical History

1. Chronic Urinary Tract Infection

Chronic urinary tract infection is associated with the development of bladder cancer, especially invasive squamous cell carcinoma [50]. This type of cancer may occur in patients with spinal cord injury in whom chronic cystitis is inevitable. This may be the result of formation of nitrites and nitrosamines by bacterial flora and/or the inflammatory process, which leads to an increased cell proliferation, providing more opportunities for spontaneous genetic mistakes.

2. Phenacetin

Heavy consumption of phenacetin-containing analgesics (not sold anymore) increases the risk of upper urinary tract cancer, but has only a marginal effect on bladder cancer risk [51,52].

3. Cyclophosphamide

Cyclophosphamide, an alkylating agent used in the treatment of malignant neoplasms, particularly lymphoproliferative and myeloproliferative diseases, increases the risk of bladder cancer (mainly urothelial carcinoma) with a clear dose-response relationship (**Figure 5**).

Cyclophosphamide is acutely toxic to the bladder mucosa and produces cellular abnormalities in the epithelium. Most cyclophosphamide-induced tumors present themselves as muscle-infiltrating lesions at the time of diagnosis with a relatively short latency period (6-13 years). It is unclear whether cyclophosphamide-induced urothelial malignancies are due to its immunosuppressive or inherent carcinogenic properties, but it is likely that the 2 factors work together. Of 4 known metabolites of cyclophosphamide, acrolein and phosphamide mustard have been demonstrated to bind to DNA, and acrolein is known to be responsible for its bladder toxicity.

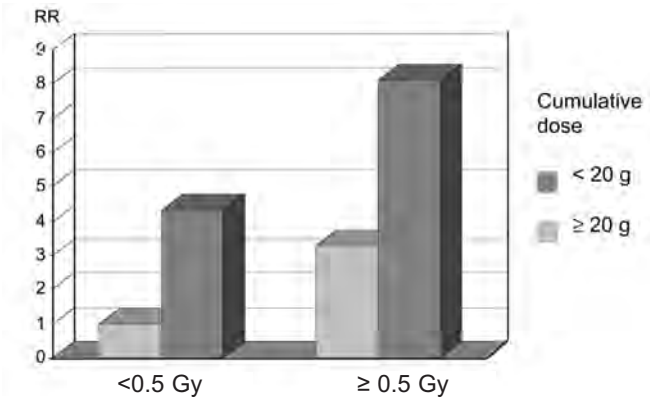


Figure 5. Risk of Bladder Cancer According to Cumulative Dose of Cyclophosphamide and Administration of Radiotherapy **[53]**

4. Radiotherapy

Radiotherapy is also a known risk factor for bladder cancer. Kaldor et al. carried out a case-control study of tumors of the bladder in women who had previously been treated for ovarian cancer [54]. The risk of bladder tumors was increased for patients who had been treated with radiotherapy or chemotherapy (thiotepa and melphalan) compared to patients treated with surgery. Moreover, the risk seemed to be much higher in patients who received both.

e) Schistosomiasis

Squamous cell carcinoma of the urinary bladder has been known to be associated with *Schistosoma haematobium* infection for many years. The epidemio-logic association is based both on case-control studies and on the close correlation of bladder cancer incidence with the prevalence of *S. haematobium* infection within different geographic areas [55-58]. *S. haematobium* is found throughout much of Africa and the Middle East. The life cycle of *S. haematobium* requires waterborne transmission of infection between man and snail. Water becomes contami-nated by *Schistosoma* eggs when people urinate in the water. The eggs release larval forms (miracidia) that have to penetrate appropriate snail hosts within 16 to 32 hours. Inside the snail, the larvae will grow and develop into cercariae over 6 weeks. After this period, the cercariae leave the snail and are able to survive in water for 2 to 3 days. In this period, the parasites have to find a human host and penetrate the skin by mechanical action and enzymatic secretions of the cephalic glands. The parasites migrate by the blood vessels where they mature to male and female worms. These mate and travel to the vesical veins to deposit eggs in the bladder wall. Finally, the eggs are extruded into the urine (**Figure 6**).

It is not the worms but the eggs that cause the disease in humans; the egg deposit causes a response that results in cystitis and hematuria. Over time, the

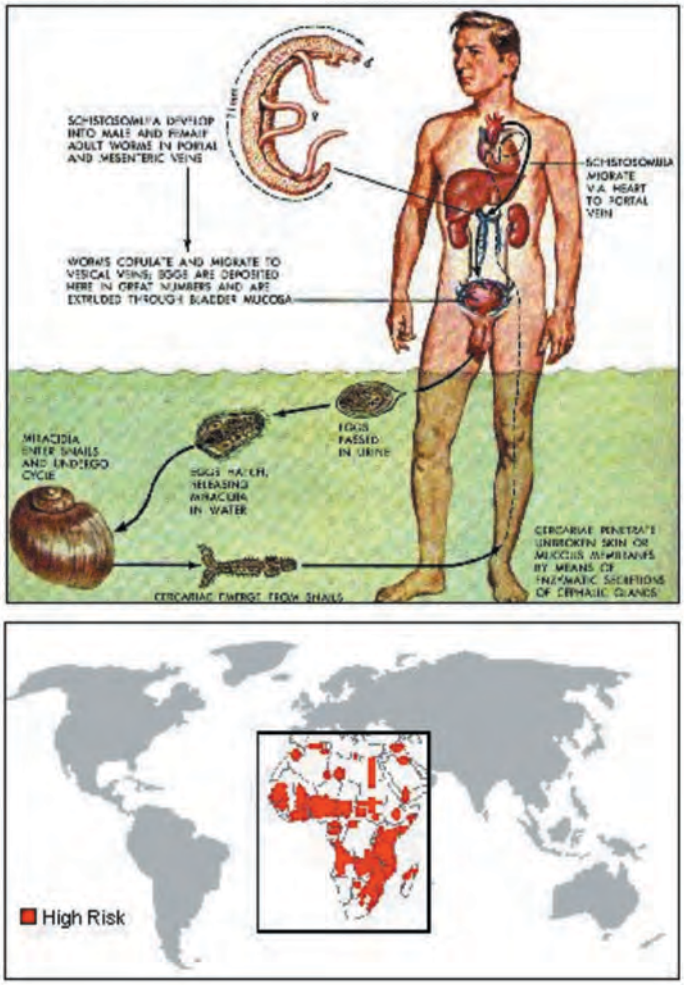


***Figure 6. Life Cycle and Geographic Distribution of* Schistosoma haematobium [61]**

chronic inflammatory response from schistosomiasis leads to changes in the urothelium resulting in squamous metaplasia of the epithelium. Individuals with chronic schistosomiasis may eventually develop squamous cell carcinoma, probably as a result of a higher amount of carcinogenic nitroso compounds in the urine and/or a depressed immunocompetence of infected patients [59,60].

f) Diet

In observational studies, high vegetable and fruit consumption has been associated with a decrease in the risk of almost all cancers including bladder, although several large cohort studies report no protective effect [62,63]. A role of diet and nutrition in bladder carcinogenesis is plausible since most substances and metabolites (including precarcinogens) are excreted by the urinary tract. A possible biologic mechanism is that several antioxidants (vitamins A, C, and E; retinol; selenium; and folate) detoxify free radicals and thereby decrease cancer risk. Surprisingly, large intervention trials did not find clear protective effects of antioxidants. The Physicians' Health Study (PHS), involving 22 000 male physicians in the United States, and the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC cohort study), involving 29 000 Finnish male smokers, investigated supplements of antioxidant nutrients in different doses and combinations and produced surprising results [64,65]. One arm of the ATBC cohort study involved daily supplementation with beta-carotene and, after 5 to 8 years of supplementation, an unexpected 18% higher incidence of lung cancer and an 8% higher overall mortality was found. In the PHS, no effect of beta-carotene on disease and death was observed. Concerning alpha-tocopherol, a 34% lower incidence of prostate cancer, but no effect on lung cancer, was found in the ATBC cohort study.

During the follow-up period of the ATBC cohort study, 344 men developed bladder cancer. Consumption of fruits and vegetables was not associated with the risk of bladder cancer [66]. Similarly, no associations were observed for specific groups of fruits or vegetables. Dietary intake of alpha-carotene; beta-carotene; lycopene; lutein/zeaxanthin; beta-cryptoxanthin; vitamins A, E, and C; and folate were not related to the risk of bladder cancer. This study suggests that fruit and vegetable intakes are not likely to be associated with bladder cancer risk. However, in a meta-analysis by Steinmaus et al., a risk of 1.4 (95% CI 1.08 to 1.83) was found for a diet low in fruit intake [67].

Evidence for an increase in bladder cancer risk because of a high total fat intake is insufficient. The same holds for the relation with diets high in cholesterol or saturated (animal) fat. People with a high intake of fried food were found to have 2 to 3 times the risk of bladder cancer than people who did not consume fried foods. Although this association was found in several studies, evidence remains insufficient.

Fairly convincing evidence exists with regard to a risk-increasing effect of food pyrolysis products (mutagenic and carcinogenic heterocyclic amines), which are formed during cooking, broiling, grilling, or barbecuing of meat and fish.

1. Alcohol

Although consumption of low levels of alcohol (1 or 2 drinks a day) is believed to reduce cardiovascular disease, positive associations have been reported with the risk of several types of cancer (such as oral

cavity and pharynx, larynx, liver, esophagus, colon, and breast). Alcohol consumption has often been studied as a possible risk factor for bladder cancer. The results are not consistent but point in the direction of no association. For example, in a large study among Danish brewery workers with a very high average beer intake of 2 to 2.5 liters/day, no elevated risk was found [68]. The positive findings in some studies may be the result of residual confounding by smoking (several case control studies did not adjust for smoking habits) or chance.

2. Coffee

Similar to the above mentioned association, coffee and the risk of bladder cancer has often been studied but the results are very inconsistent, although pointing in the direction of a weak positive association. In the United States bladder cancer study with 2982 cases and 5782 controls, the largest population-based case-control study on bladder cancer, the risk for ever versus never coffee drinkers (adjusted for age, race, geographical area, and tobacco consumption) was found to be 1.6 (95% CI 1.2 to 2.2) for males and 1.3 (95% CI 0.8 to 1.7) for females [69]. However, in a Danish study no elevated risk was found for coffee drinking and bladder cancer, though in Scandinavian countries coffee consumption is about 2.5 times as high as in the United States [70]. In a recent pooled analysis of several case-control studies in Europe, 564 cases and 2929 controls were included who had never smoked [71]. No excess risk was found in ever versus never coffee drinkers. For coffee drinkers with more than 10 cups per day, an increased risk was found in both men and women (OR 1.0; 95% CI 1.0 to 3.3).

Most inconsistencies in the reported data are probably due to the effect of residual confounding by smoking or by other correlates of coffee drinking. Because coffee drinking and smoking are strongly correlated, an incomplete controlling of smoking (because of misclassification of smoking habits) can result in an apparent relation of coffee drinking and bladder cancer. Another, more theoretical, possibility is that people with a relatively high bladder cancer risk (slow acetylators) drink more coffee [72].

3. Artificial Sweeteners

No consistent positive association between bladder cancer risk and the use of artificial sweeteners (like saccharine and cyclamate) has been found, although animal models (rats) suggested a strong relation. This may be due to the fact that the specific biologic mechanism in some animal models does not exist in man. In studies among diabetics in the United States and United Kingdom who have substantial use of artificial sweeteners, no elevated bladder cancer mortality rates were found [73]. In a study by Takayama et al., 20 monkeys were treated with sodium saccharine (5-10 times the daily intake for humans) for 5 days a week from 24 hours after birth until the age of 24 years [74]. Sixteen monkeys served as controls. No evidence was found of formation of solid material (crystals) in the urine, providing additional evidence that sodium saccharine has no carcinogenic effect on the primate urinary tract. The most recent study among humans on this subject was conducted by Sturgeon et al [75]. Bladder cancer patients (1860) and controls (3934) were grouped into low (<1.68 mg/day) and high (>1.68 mg/day) sweetener consumption. High consumption of sweeteners was correlated with a modest increased risk of developing bladder cancer (OR 1.3, 95% CI 0.9 to 2.1).

4. Total Fluid Consumption

Several observational studies have assessed the relationship between total fluid intake and the risk of bladder cancer, but the results of these studies are very inconsistent. Positive, negative, and no association have been reported [28,76-78].

g) Hair Dyes

The risk of bladder cancer through the use of hair coloring products has been studied since the late 1970s but received more interest in the last few years. Hair dyes are widely used in Western communities. It is estimated that more than one-third of women above the age of 18 and more than 10% of men above the age of 40 use some type of hair dye. Some hair dyes contain aromatic amines such as 4-aminobiphenyl, of which small amounts may be absorbed percutaneously [79]. The levels of suspected carcinogens differ between the different types of dyes (permanent, semi-permanent, and temporary rinse dyes) and between the different colors. Occupational exposure to hair dyes by hairdressers is believed to moderately increase the risk of bladder cancer (combined analysis of studies yielded OR 1.4) [80]. Since the publication of a study in 2001, the personal use of hair dyes has received much attention. After 2 cohort studies from the United States (the Nurses Health Study and the American Cancer Society CSP-II study) did not find an association between personal use of permanent dyes and bladder cancer, Gago-Dominguez and colleagues reported a case-control study from Los Angeles that involved almost 900 incident cases of bladder cancer

and an equal number of age-, sex-, neighborhood-, and ethnicity-matched controls [81-83]. Overall, regular use of hair dyes did not increase the risk of bladder cancer. However, women who used permanent hair dyes at least once a month experienced a cigarette-smoking adjusted 2.1-fold risk of bladder cancer relative to non-users. The use of this type of hair dye among men was too rare (about 2% among controls) for meaningful analyses. Semi-permanent and temporary dyes did not increase the risk of bladder cancer. In further analyses, women who used these types of dyes were combined with the non-users. The relative risk of permanent dyes among women showed dose-response relationships with duration of use, frequency of use, and cumulative number of times used over lifetime [83]. In response to this study, 1 of the 2 earlier studies with negative results, the American Cancer Society CSP-II study, published an update. After 16 years of follow-up of a cohort of more than 500 000 women, the death rate of bladder cancer among women (N=336) was not related to the use of permanent hair dyes. Even among women who used these dyes for more than 20 years, the relative risk for bladder cancer mortality was not increased [84].

In a case-control study from New Hampshire, including 98 women with bladder cancer and 238 controls, the use of permanent hair dyes was associated with a 1.5-fold increased risk of bladder cancer. However, the use of rinse dyes was associated with an increased risk as well (OR 1.7). Both associations were not statistically significant and clear dose-response effects were not observed [85]. The different results between these studies are difficult to explain. At the end of 2001, Gago-Dominguez et al. reported an additional analysis of their data. They phenotyped 61% of the female cases and 60% of the controls for N-acetyltransferase, an important enzyme in the detoxification of aromatic amines.

They found that the increased risk of the use of permanent hair dyes was restricted to N-acetyltransferase 2 slow acetylators [86]. Recently, this study was extended with the genotyping of GSTM1, GSTT1, GSTP1, and NAT1, and the phenotyping of NAT2 and CYP1A2. Again, it was demonstrated that differences in arylamine activation and detoxification pathways (especially NAT2, NAT1, and CYP1A2) modify the relationship between permanent hair dyes and bladder cancer in women [87]. These findings support a causal role of permanent hair dyes but leave the discrepancy with earlier studies unanswered.

3. Genetic Susceptibility

a) Gene-Environment Interactions

The Los Angeles County bladder cancer study on hair dyes and bladder cancer is a good example of the possible modifying role of constitution on the effect of environmental or lifestyle factors [87]. Although many environmental risk factors have been implicated in the etiology of bladder cancer, only occupation and smoking are responsible for a considerable part of all new cases. Without any doubt, genetic susceptibility will prove to be responsible for another considerable part, most importantly by gene-environment interactions. Most environmental carcinogens are activated inside the body into reactive oxygenated intermediates (which may interact with DNA) by phase I enzymes. Subsequently, these reactive intermediates are detoxified into conjugated water-soluble products by phase II enzymes. For example, oxidation of arylamines in the liver by cytochrome P450 1A2 leads to N-hydroxylated metabolites. These may enter the circulation and react covalently with hemoglobin in erythrocytes. After filtration into the bladder lumen the metabolites may react with urothelial nucleic acids (**Figure 7**). Detoxification of the reactive metabolites into non-carcinogenic N-acetylated arylamides may take

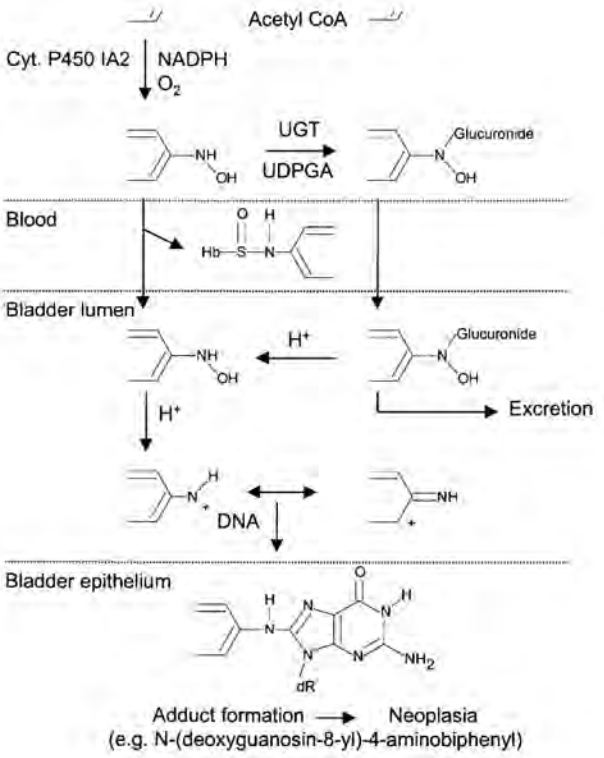


Figure 7. Biochemical Pathway for Urinary Bladder Cancer Induction by Aromatic Amines **[88]**

place by N-acetylation, which is catalyzed by the N-acetyltransferases, preferentially by NAT2 in the liver and by NAT1 in skin cells.

The genes that code for these enzymes show interindividual variability leading to differences in catalytic activity. Most of this variability comes from single nucleotide polymorphisms (SNPs) and tandem repeats, but small homozygous deletions in specific genes may even lead to a total absence of enzyme activity. Numerous studies have examined the role of metabolic gene polymorphisms in the development of bladder cancer. Genes that have been studied include NAT1, NAT2, GSTM1, GSTT1, GSTP1, CYP1A1, CYP1A2, CYP1B1, CYP2D6, CYP2E1, CYP3E4, ADH3, NQO1, SULT1A1, MPO, COMT, and MnSOD. The role of NAT2 slow acetylation phenotype or genotype and bladder cancer is most frequently studied. In a meta-analysis of 22 studies, it appeared that slow acetylators have a 40% (95% CI 1.2 to 1.6) increased risk of bladder cancer. This increased risk, however, may be different in different populations (higher in Asians and lower or even absent in United States Caucasians) [13].

The phase II glutathione-S-transferases are classified into at least 4 genetically distinct classes of enzymes (alpha, theta, mu, and pi), which conjugate reactive entities with glutathione. In humans, mu and theta class of *GST* isoenzymes, *GSTM*1 and *GSTT*1 display different phenotypes due to deletions of the genes. *GSTM*1 is highly efficient in conjugating aryl epoxides, which are formed by phase I cytochrome P450 enzymes after exposure to certain PAHs. *GSTM*1 may also detoxify aromatic amines. Enzyme activity is found in several organ systems such as the liver and bowel, in lymphocytes, and also in the bladder endothelium. *GSTM*1 activity is absent in approximately 40% of the Western population because of a homozygous deletion of the *GSTM*1 locus on chromosome 1p13 [89]. In a meta-analysis of 17 studies, a lack of *GSTM*1 activity was associated with bladder cancer with an odds ratio of 1.44 (95% CI 1.23 to 1.68) [90]. For specific variants in most other metabolic genes that were studied until now, the results are fairly inconsistent or were reported in 1 study only.

Recently, attention has also been paid to polymorphisms in genes with other functions, such as DNA repair, cell cycle control, immune response, folate metabolism, and cell adhesion (for example XRCC1, XPD, XRCC3, CDH1, TP53, TNF, HER-2, HRAS1, CCND1, MTHFR, and MS). Many positive findings have been reported. It is too early, however, to assess the relevance of these findings. Again, inconsistent results, potential (or perhaps even probable) publication bias, and the absence of validation studies suggest that false positive findings are a real problem. This research area would benefit greatly from international collaborations where large-scale projects study the role of many polymorphisms simultaneously using high-throughput array technology, while validating the findings in collaborative projects. The present non-standardized study-by-study and gene-by-gene approach will only lead to a lot of confusion. Furthermore, perhaps the most important aim of studies on gene polymorphisms should be to identify subgroups in which environmental risk factors can be evaluated with increased power. It is therefore advised to give as much emphasis with data collection on hypothesized environmental risk factors as on genetic polymorphisms.

b) Familial Bladder Cancer

Urothelial carcinoma of the ureter and renal pelvis is known to be part of the Hereditary Non-polyposis Colon Cancer (HNPCC) syndrome, which is caused by mutations in DNA mismatch repair genes. For yet unknown reasons, urothelial carcinoma of the bladder is not part of this syndrome [91]. In fact, familial bladder cancer is a fairly rare phenomenon compared to the familial occurrence of many other tumor sites. Nevertheless, numerous case reports describe fa-milial clustering of urothelial carcinoma. Several demonstrate an extremely early age at onset, suggesting a genetic component [92]. Only a few epidemiological studies specifically addressed familial bladder cancer. Goldgar and colleagues studied the risk of cancer in first-degree relatives of cancer probands, yielding an increased risk for bladder cancer among first-degree relatives of 1.5 (95% CI 1.0 to 2.2) [93]. When only young probands (age < 60 years) were considered, the familial risk was 5.1 (95% CI 1.0 to 12.5). In a study from New York, demographic data and cigarette smoking status on all the first degree relatives of 319 male bladder cancer cases and 319 neighborhood controls were collected. The cohorts were linked to the cancer registry, yielding an almost twofold risk (hazard ratio [HR] 1.9, 90% CI 0.9 to 4.1) of bladder cancer for first-degree relatives [94]. By contrast, a comparable study among the population of Iceland reported only a slightly elevated risk of urothelial carcinoma among relatives of 190 bladder cancer patients with an observed-to-expected ratio of only 1.2 (95% CI 0.9 to 1.7) [95]. The largest study on familial bladder

cancer was conducted by the same group but in the Netherlands. Using a family case-control design, 1193 patients newly diagnosed with urothelial carcinoma of the bladder, ureter, renal pelvis, or urethra were contacted. Information on the patients' first-degree relatives was collected by postal questionnaire and subsequent telephone calls. The patients' partners filled out a similar questionnaire on their relatives. All reported occurrences of urothelial carcinoma among the 8014 first-degree case-relatives and 5673 control-relatives were verified using medical records. Disease occurrence among case-relatives and control-relatives was compared with random effect proportional hazards regression analyses while adjusting for age, sex, and smoking behavior. Among the case-relatives, 101 individuals were diagnosed with cancer of the bladder (97), ureter (3), and renal pelvis (1), compared to 38 individuals among the control-relatives (bladder 36, ureter 1, and urethra 1). In 6 case-families and 2 control-families, 2 affected first-degree relatives were found. Overall, 8% of the patients had a positive family history of urothelial carcinoma compared to 4% of the controls. The mean age at diagnosis of patients with a positive family history was similar to that of patients with a negative family history (62 years). The mean age at diagnosis of urothelial carcinoma among affected case-relatives was only slightly lower than that of affected control-relatives (64 vs. 66 years). The cumulative risk of urothelial carcinoma among case-relatives was 3.8% compared to 2.1% among control-relatives. The age- sex-, and smoking-adjusted hazard ratio of urothelial carcinoma for case-relatives compared to control-relatives was 1.8 (95% CI 1.3 to 2.7). This risk appeared to be higher among women (HR 3.2) and among nonsmokers (HR 3.9). When only parents were included in the analyses, the hazard ratio increased to 2.2, while it decreased to 1.5 when only siblings were included. After stratification by tumor site in the probands (upper vs. lower urinary tract), the adjusted HR was 1.8 among relatives of probands with upper urinary tract urothelial carcinoma and 1.9 among relatives of probands with bladder urothelial carcinoma. When all the relatives of probands with a pTa tumor were excluded from the analyses, the HR increased only slightly to 2.0. The same was found when the relatives of probands older than 60 years were excluded from the analyses (HR 2.4). A striking clustering of tumors at other sites among the case-relatives was not found although an increased risk was observed for tumors of the hematolymphopoietic system (HR 1.9, 95% CI 1.2 to 3.0). Familial clustering with other tumors was also evaluated among the relatives of probands with a positive family history of urothelial carcinoma. There was some suggestion (nonsignificant) of a clustering of tumors of the female genital organs, non-urothelial urinary tract tumors, and cancer of the hematolymphopoietic system [96].

From these epidemiological studies, it can be concluded that the risk of bladder cancer is increased approximately twofold with a positive family history of bladder cancer. The next question is whether this is caused by genetic susceptibility or shared environment. In a twin study from Scandinavia (Denmark, Sweden, and Finland), Lichtenstein et al. reported 5 concordant and 146 discordant pairs of bladder cancers among 7231 monozygotic male twin pairs. Among 13 769 dizygotic male twin pairs, 2 concordant pairs and 253 discordant pairs were found. The relative risk of bladder cancer among monozygotic twins was 6.6 (95% CI 2.6 to 16.9). The relative risk among dizygotic twins was 1.7 (95% CI 0.4 to 6.9). The concordance rate was 3 times higher among monozygotic twins (6%) than among dizygotic twins (2%). Assuming that the correlation in environmental risk factors is similar among monozygotic and dizygotic twins, this finding suggests the existence of a genetic etiology of bladder cancer [97]. In a study on the Swedish Family-Cancer Database, it was estimated that 7% of the occurrence of bladder cancer is due to genetic effects, 12% to shared environmental effects, 4% to childhood environmental effects, and 77% to nonshared environmental effects [98].

The group from the Netherlands evaluated whether mutagen sensitivity plays a role in developing urothelial carcinoma and whether this sensitivity is different in familial and nonfamilial cases. Intrinsic susceptibility was quantified by a mutagen sensitivity assay (mean number of chromatid breaks per cell (PBLs) after damage induction with bleomycin in the late S-G2 phase of the cell cycle). Twenty-five sporadic patients, 23 familial patients (2 patients in 1 nuclear family), and 13 hereditary patients (2 patients < 60 years or 3 patients in 1 nuclear family) were selected and compared with control subjects without a history of cancer. Patients with urothelial carcinoma showed a higher mutagen sensitivity score compared to control subjects (mean number of chromatid breaks per cell 0.91, 95% CI 0.84 to 0.97, and 0.74, 95% CI 0.69 to 0.79, respectively; P = 0.001), suggesting a genetic origin [99].

Recently, a new bladder cancer gene was discovered by the collaborative group of Schoenberg and

Sidransky at Johns Hopkins in Baltimore [100]. In 1996, this group identified a family in which a male was diagnosed with grade 2 superficial urothelial carcinoma of the bladder at the age of 29 years. He subsequently developed renal pelvis carcinoma. His mother died of metastatic urothelial carcinoma of the bladder at the age of 65. Because both the proband's wife and his mother had a history of miscarriages, a karyogram was made which showed a balanced germline translocation t(5;20)(p15;q11) [101]. Dr. Sidransky's lab zoomed in at the breakpoints of this translocation, which finally resulted in the discovery of a new bladder cancer gene at 20q11 [100]. This gene, *CDC91L1*, encoding CDC91L1, which is also called phosphatidylinositol glycan class U (PIG-U), has a role in the glycosylphosphatidylinositol (GPI) anchoring pathway. Further research suggested that the gene is amplified and overexpressed in as many as one-third of bladder cancers and primary tumors. *CDC91L1* should therefore be regarded as an oncogene. The translocation led to overexpression of the gene and, probably, to both bladder cancers in this pedigree. Carriers of the translocation in this family were therefore genetically susceptible for bladder cancer. Because the exact translocation site should be regarded as an extremely rare phenomenon, this gene should not be considered as a candidate for the genetic cause of many patients with hereditary bladder cancer. For that, tumor suppressor or DNA mismatch repair genes have yet to be discovered. Recently, it was shown that inherited mutations in the retinoblastoma tumor suppressor gene may cause bladder cancer. In a long-term follow-up study from the UK, 5 bladder cancer cases were found among 144 hereditary retinoblastoma cases, an observed to expected ratio of 26.3 (95% CI 8.5 to 61.4) [102]. This study shows that bladder cancer should be put on the list of tumors for which hereditary retinoblastoma patients should be checked during lifetime follow-up.

4. Lifestyle and Prognosis

Although much research has been done and is still ongoing on prognostic factors in invasive and superficial bladder cancer (such as angiogenesis, cell cycle control proteins, and cell adhesion molecules) the management of patients is usually based on clinical characteristics only (such as tumor stage, grade, and lymph node involvement). Based on these characteristics, it appears to be very difficult to predict prognosis on an individual level. This applies both to the risks of recurrence and progression in superficial disease and to the risk of metastases and death in invasive disease. Surprisingly, little attention has been paid to the role of lifestyle and constitution on prognosis. With the current knowledge, it is impossible for clinicians to advise patients about the prognostic benefit of lifestyle changes. Bladder cancer prognosis is related to age (younger patients having a better prognosis), gender (males having a better prognosis), and race (whites having a better prognosis), but all of these differences can be largely explained by a different stage at diagnosis.

In a systematic review by Aveyard et al., 15 studies were identified in which the prognostic role of smoking and stopping smoking was reported [103]. Overall, the results suggested that continued smoking or a lifetime of smoking constitutes a moderate risk f actor for recurrence and death. Also, stopping smoking probably results in a clinically relevant prognostic improvement. Unfortunately, most of the studies had major methodological shortcomings. Firm evidence-based conclusions can therefore not be drawn. In a study from Japan of 258 patients, drinking of alcoholic beverages was significantly associated with a better survival (HR 0.46, 95% CI 0.3 to 0.8), but a clear dose-response relationship was not observed. No prognostic significance was found for the use of artificial sweeteners, coffee, powdered green tea, and cola consumption [104]. Without any doubt, a large body of data still exists from studies on the etiology of bladder cancer. These data may be supplemented quite easily with follow-up data in order to learn more about the prognostic value of lifestyle. Also, future epidemiological studies should consider the collection of follow-up data for this purpose.

II. STAGING AND GRADING OF BLADDER CANCER

1. Classification of Urothelial Neoplasms

In December 1998, members of the World Health Organization (WHO) and the International Society of Urologic Pathologists (ISUP) published the WHO/ISUP consensus classification of urothelial (transitional cell) neoplasms of the urinary bladder *(Level 4,* [105]*)*. This new classification system arose out of the need to develop a universally acceptable classification system for bladder neoplasia that could be used effectively by pathologists, urologists, and

oncologists. Prior to this classification system, numerous diverse grading schemes for bladder cancer existed whereby the same lesion seen by different pathologists would result in very different diagnoses solely based on definitional differences of lesions. Another strength of the consensus classification system is that it provides detailed histological criteria for papillary urothelial lesions. In contrast, prior grading systems for bladder tumors were vague and subjective. This classification system not only covered neoplastic conditions, but also the nomenclature of preneoplastic lesions .

a) Normal and Hyperplastic Urothelium

Many pathologists overuse the diagnosis of "mild dysplasia" to describe flat lesions with minimally disordered growth pattern or cellular hyperchromasia due to variation in tissue fixation, staining, or specimen orientation. The consensus classification states that the term "mild dysplasia" should not be used and that flat lesions with minimal cytologic atypia and architectural disorder should be diagnosed as "normal."

Flat urothelial hyperplasia consists of a markedly thickened mucosa without cytologic atypia, and may be seen adjacent to low grade papillary urothelial neoplasms, but there is no data as to its premalignant potential when seen by itself.

Papillary urothelial hyperplasia is characterized by urothelium of variable thickness with undulating growth. In contrast to papillary urothelial tumors, these lesions lack distinct fibrovascular cores. Papillary urothelial hyperplasia without cytologic atypia, because of its frequent association with either a prior or concurrent history of a low grade papillary bladder neoplasm, is thought to be a precursor lesion of these neoplasms (*Level 3,* [106]*).* Papillary urothelial hyperplasia may also be lined by cytologically atypical urothelium ranging from dysplasia to flat CIS, which are often associated with and thought to be a precursor of high grade papillary urothelial carcinomas *(Level 3,* [107]*).*

b) Flat Lesions With Atypia

Prior to the consensus classification, different pathologists variably used the terms "atypia" and "dysplasia" to denote either inflammatory atypia or a preneoplastic condition. The WHO/ISUP system described the histological findings associated with inflammatory atypia and designated these lesions as "reactive atypia," which should not be considered neoplastic.

Dysplasia (intraurothelial neoplasia) was defined as a lesion with appreciable cytologic and architectural abnormalities felt to be neoplastic, yet falling short of the diagnostic threshold for carcinoma in situ. There is evidence along several lines of investigation that dysplasia may be a precursor of invasive carcinoma (108-111, *Level 3*; 112, *Level 2*; 113, *Level 3*).

CIS is a flat lesion of the urothelium, and documented precursor of invasive cancer in many cases (**Figure 8A**). Prior to the consensus classification, CIS was frequently underdiagnosed and described as moderate dysplasia or atypia. The WHO/ISUP system described the key histologic features of CIS, including its more subtle variations that were often underrecognized. Under the WHO/ISUP system, all CIS are by definition high grade lesions.

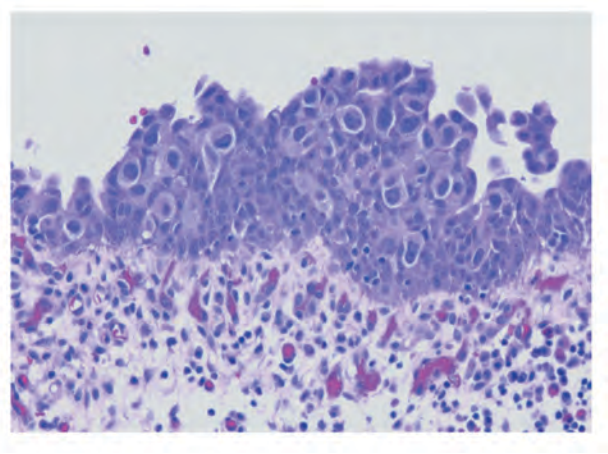


Figure 8A. Flat Urothelial Carcinoma in Situ

c) Papillary Urothelial Neoplasms: Classification

The classification of papillary urothelial neoplasms has been a long-standing source of controversy *(Level 4,* [114]*).* One source of controversy lies in the grading of papillary urothelial carcinomas. There are numerous grading systems, all of which have poor interobserver reproducibility, with most cases falling into the intermediate category (115, *Level 4*; 116, *Level 2*; 117, *Level 4*; 118,119, *Level 3*; 120, *Level 2*; 121, *Level 3*; 122, *Level 2*). The WHO/ISUP system is a modified version of the scheme proposed by Malmström et al. [120]. A major limitation of the WHO 1973 grading system is the vague definition and lack of specific histological criteria of the various grades. The following statement is the sole description of the difference between WHO grades 1, 2, and 3, as written in the original WHO 1973 book: "Grade 1 tumors have the least

degree of anaplasia compatible with the diagnosis of malignancy. Grade 3 applies to tumors with the most severe degrees of cellular anaplasia, and Grade 2 lies in between" [117]. Detailed histological description of the various grades, employing specific cytologic and architectural criteria is one of the major contributions of the WHO/ISUP system. These criteria are based on the architectural features of the papillae and the overall organization of the cells. Cytologic features encompassed in the WHO/ISUP system include nuclear size, nuclear shape, chromatin content, nucleoli, mitoses, and umbrella cells. The terminology used in the WHO/ISUP system parallels that used in urine cytology. Having a consensus classification between cytology and histopathology is also advantageous. A website (www. pathology. jhu. edu/bladder) illustrating examples of the various grades was developed to further improved accuracy in using the WHO/ISUP system.

1. Relation of WHO 1973 to WHO/ISUP

A major misconception is that there is a one-to-one translation between the WHO/ISUP and the WHO 1973 classification systems. Only at the extremes of grades in the WHO 1973 classification, does this correlation hold true. Lesions called papilloma in the WHO classification system would also be called papilloma in the WHO/ISUP system. At the other end of the grading extreme, lesions called WHO grade 3 are by definition high grade carcinoma in the WHO/ISUP system. However, for WHO grades 1 and 2, there is no direct translation to the WHO/ISUP system. Some lesions classified as WHO grade 1 in the 1973 system that upon review show no cytologic atypia, some nuclear enlargement, and merely thickened urothelium are papillary urothelial neoplasms of low malignant potential (PUNLMP) in the WHO/ISUP system. However, other WHO grade 1 lesions showing slight cytologic atypia and mitoses are diagnosed in the WHO/ISUP system as low grade papillary urothelial carcinomas. WHO grade 2 is a very broad category. It includes lesions that are relatively bland, which in some places are diagnosed as WHO grade 1 to 2; these lesions in the WHO/ISUP system would be called low grade papillary urothelial carcinoma. In other cases, WHO grade 2 lesions border on higher grade lesions, which in many institutions are called WHO grade 2 to 3; these lesions in the WHO/ISUP classification system would be called high grade papillary urothelial carcinoma.

2. Papilloma

Using the WHO 1973 system, some experts applied very restrictive criteria for the diagnosis of urothelial papilloma, in part based on the number of cell layers, and regarded all other papillary neoplasms as carcinomas. Others applied a broader definition of "urothelial papilloma" so as not to label all patients with papillary lesions with minimal cytologic and architectural atypia as having carcinoma. The WHO/ISUP system has very restrictive histologic features for the diagnosis of papilloma, where normal appearing urothelium lines papillary fronds. Defined as such, it is a rare benign condition typically occurring as a small, isolated growth seen primarily in younger patients. The majority of these lesions once excised will not recur *(Level 3,* [123]*).*

3. Papillary Urothelial Neoplasms of Low Malignant Potential (PUNLMP)

The category of PUNLMP was derived to describe lesions that do not have cytologic features of ma-lignancy, yet have thickened urothelium as compared to papilloma (**Figure 8B**). There is no or very little

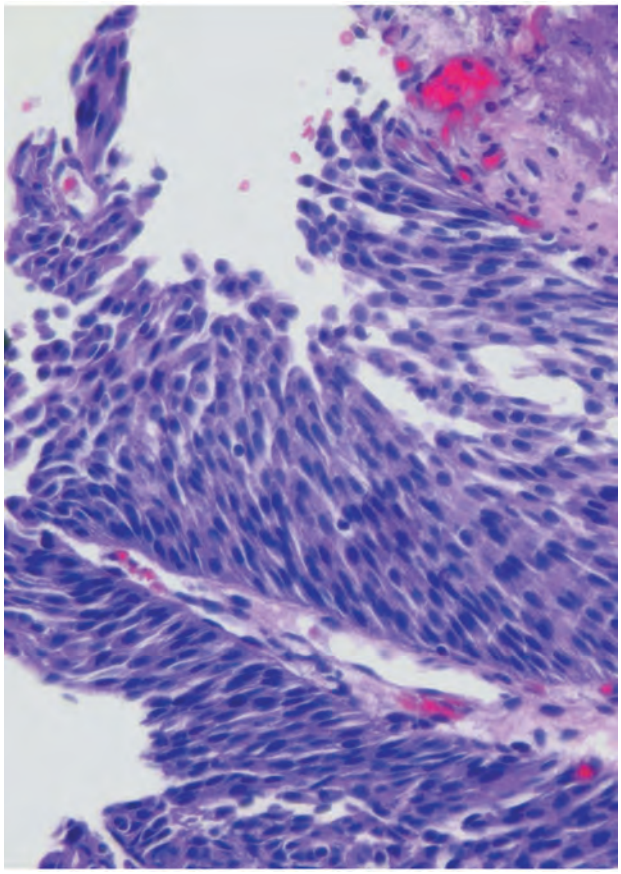


Figure 8B. Papillary Urothelial Neoplasm of Low Malignant Potential (PUNLMP)

variation of nuclear features or the pattern of organization. Having a category of PUNLMP avoids labeling a patient as having cancer with its psychosocial and financial (i.e., insurance) implications, although they are not diagnosed as having a benign lesion (i.e., papilloma), whereby they might not be followed as closely. The prognosis of these lesions and other papillary tumors in the WHO/ISUP system will be discussed later in this work. The current classification system allows for designation of a lesion (papillary urothelial neoplasm of low malignant potential), that biologically has a very low risk of progression, yet is not entirely benign. In the past, these lesions were a source of controversy, as some experts would label such lesions as malignant, while others, not wanting to label a patient with such a low grade papillary lesion as having carcinoma, would diagnose these lesions as papilloma. This inter-mediate category allows both schools of thought to diagnose a lesion as not fully malignant, yet still documents need for additional follow-up.

4. Low and High Grade Papillary Carcinoma

In an attempt to simplify the WHO 1973 system and avoid an intermediate cancer grade group (WHO grade 2), which is often the default diagnosis for many pathologists, the WHO/ISUP system classifies papillary urothelial carcinoma into only 2 grades. Low grade papillary urothelial carcinoma exhibits an overall orderly appearance but has minimal variability in architecture and/or cytologic features, which are easily recognizable at scanning magnification (**Figure 8C 1&2**). High grade papillary urothelial carcinomas are characterized by a disorderly appearance due to marked architectural and cytologic abnormalities, recognizable at low magnification (**Figure 8D**). It is important to remember that a single papillary urothelial neoplasm may contain a spectrum of cytologic and architectural abnormalities. In tumors with variable histology, the tumor should be graded according to the highest grade, although current practice is to ignore minuscule

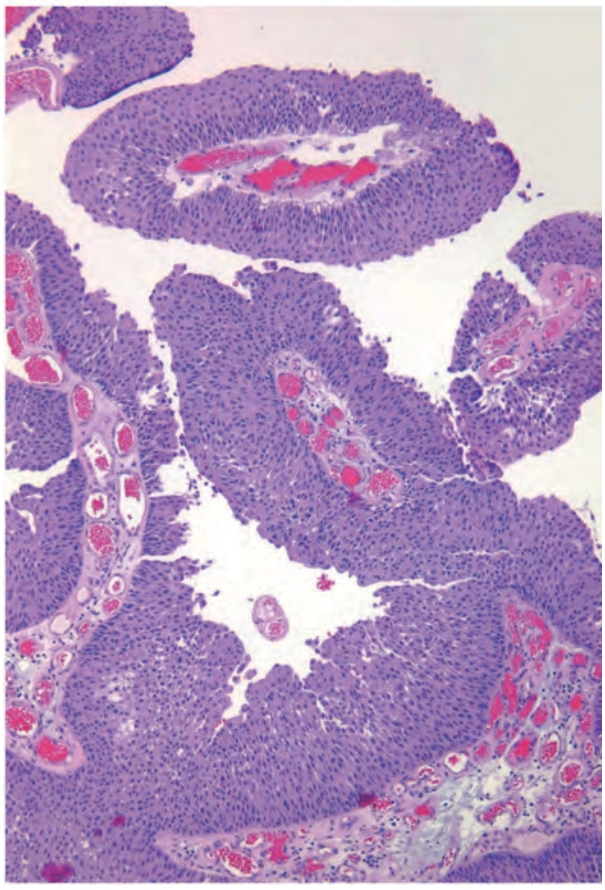


Figure 8C1. Papillary Carcinoma, Low Grade

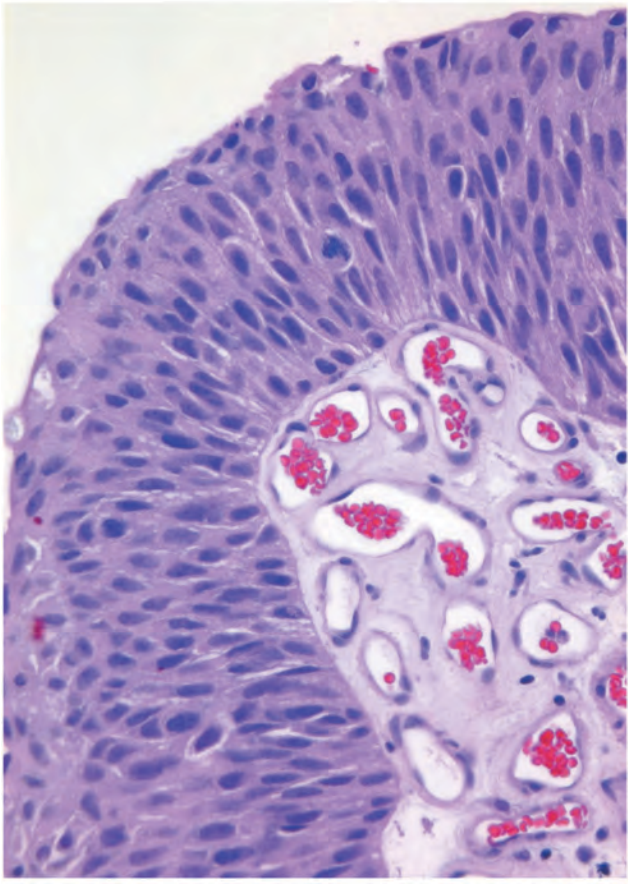


Figure 8C2. Papillary Carcinoma, Low Grade

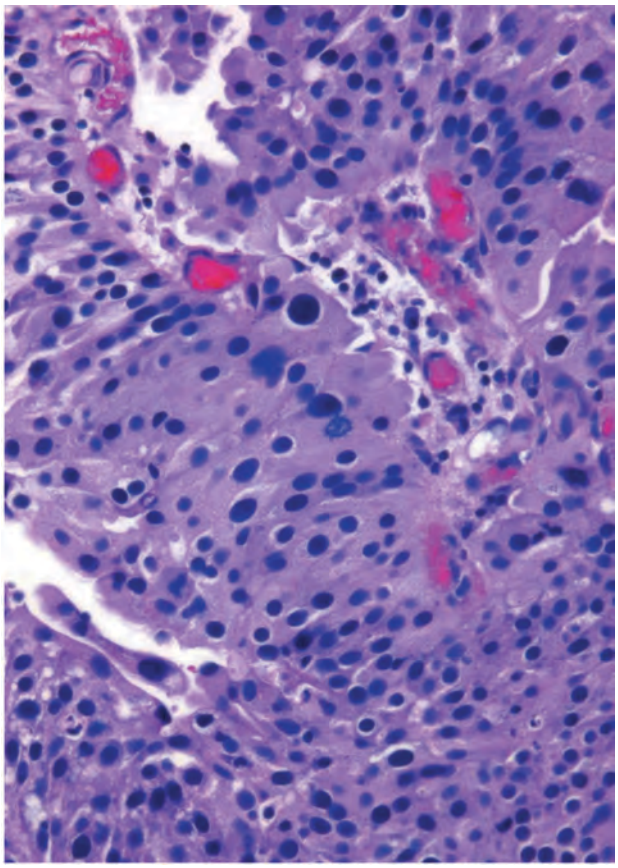


Figure 8D. Papillary Carcinoma, High Grade

areas of higher grade tumor. Studies are needed to determine how significant a minor component must be in order to have an impact on prognosis.

d) Papillary Urothelial Neoplasms: Prognosis

One of the earliest papers reported to have used the WHO/ISUP system has led to misconceptions regarding the classification system. In October 1998, a manuscript was submitted for publication and eventually published in *Cancer* entitled "Papillary Urothelial Neoplasms of Low Malignant Potential" *(Level 3,* [124]*)*. This article was submitted before the WHO/ISUP classification system was even published and before there were detailed illustrations or descriptions on how to classify tumors using the new system. The authors took lesions that were formerly called WHO grade 1 and designated them as PUNLMP. As described above, there is not a one-to-one translation between the WHO/ISUP and WHO 1973 classification systems. If these lesions were analyzed correctly using the WHO/ISUP classification system, many of these lesions would not be classified as PUNLMP, but would be diagnosed as low grade urothelial carcinomas. It is no surprise that the cases they classified as PUNLMP had an increased risk of recurrence, progression, and death from bladder cancer. This article has been cited as an argument against the use of the WHO/ISUP system. However, given that WHO grade 1 cancers were simply renamed as PUNLMP in that study, it should not even be considered as having used the WHO/ISUP system.

Before discussing the prognosis of tumors using the WHO/ISUP system, it is worthwhile to briefly highlight differences among studies in terms of their inclusion criteria and definition of progression. Some reports restrict their study to only cases without invasion (pTa). Although stage pT1 disease is still considered to be "superficial bladder cancer," once lamina propria invasion is identified, these patients are at an increased risk of subsequently developing detrusor muscle (muscularis propria) invasion (stage pT2). Consequently, including pTa (noninvasive) and pT1 (superficially invasive) tumors leads to a heterogeneous group of patients. Another difference in inclusion criteria is that some studies include patients with CIS, while others do not. CIS is one of the more aggressive lesions in the bladder despite its flat morphology. Including patients with CIS in a study of noninvasive or minimally invasive papillary carcinomas adds an additional variable, which must be taken into account when analyzing prognosis. The definition of progression also varies among studies. Some include progression from pTa to pT1, while others require evolution to pT2. In some but not other studies, a change in grade or the development of CIS is considered progression.

The first article to use the WHO/ISUP system as it was meant to be used and to correlate its lesions with prognosis was published by Desai et al. in 2000 (*Level 2,* [125]). The authors examined 120 pTa and pT1 tumors, including patients even if they had CIS. They showed significant differences in prognosis among the various categories. While papillomas did not recur or progress, and PUNLMP tumors recurred but did not progress, low grade and, to a greater extent, high grade carcinomas experienced progression and, in some cases, death (**Table 3**).

In 2001, Alsheikh et al. examined 49 patients with pTa tumors who did not receive any additional treatment after an initial transurethral resection *(Level 2,* [126]*)*. The authors focused on the differences between the 20 PUNLMPs and 29 low grade carcinomas. Twenty-five percent of the PUNLMPs recurred, in contrast to 48% of the low grade carcinomas. Of the 2 patients who progressed to high grade muscle-

Table 3. Relation of WHO/ISUP Grades to Progression [125]

	Papilloma (n=8)	PUNLMP (n=8)	Low Grade (n=42)	High Grade (n=62)
Recurrence	0%	33.3%	64.1%	56.4%
Any Stage Progression	0%	0%	10.5%	27.1%
Lamina Propria Invasion	0%	0%	2.6%	8.3%
Detrusor Muscle Invasion	0%	0%	5.3%	6.3%
Metastases/Death	0%	0%	10.6%	25.0%

invasive carcinoma, both were initially low grade carcinomas. There was also one patient who progressed to CIS who also initially had low grade carcinoma.

The largest study to date looking at the WHO/ISUP classification system is that by Holmang et al. *(Level 2,* [127]*)*. Of the 363 pTa tumors evaluated, 83% of the patients received no additional treatment until later. Progression was defined as tumors that developed lamina propria invasion beyond the muscularis mucosa or metastatic disease. Most patients with PUNLMP had no evidence of disease, and only a small percentage of patients had tumor at last follow-up, but no one was dying of disease. In contrast, patients with low grade carcinoma had an increased risk of tumor being present at last follow-up, in addition to a small percentage of patients dying of disease. Patients with high grade carcinoma had a larger risk (16%) of dying of disease (**Table 4**). Low and high grade carcinomas had similar risks of recurrence, in contrast to a lower risk with PUNLMPs. In terms of progression, PUNLMPs and low grade carcinomas had similar risks compared to an increased risk with high grade carcinomas. When the authors compared the risk of progression between WHO grade 2 and grade 3 lesions, there was a greater difference in terms of the risk of progression compared to the difference between low grade and high grade carcinomas using the WHO/ISUP classification system. Since most WHO grade 3 cases are aggressive tumors and already have coexisting invasive cancer, very few patients with WHO grade 3 tumors initially satisfied the criteria of having noninvasive papillary carcinoma; of the 363 noninvasive papillary carcinomas, only 3.6% were classified as WHO grade 3. Furthermore, some of the WHO grade 3 noninvasive papillary cancers had coexistent CIS. With the WHO/ISUP system, Holmang et al. classified 28% of the cases as high grade carcinoma, with an increased risk of progression.

Pich et al. also focused their investigations on differences between PUNLMPs and low grade carcinomas *(Level 2,* [128]*)*. In addition to recurrence and progression, p53 expression and proliferation markers were analyzed. Sixty-two pTa tumors were studied. No patients received adjuvant therapy until recurrence. Progression was defined as any invasion or metastases. Differences in recurrence were noted between PUNLMPs and low grade cancers with recurrence rates of 47.4% and 76.7%, respectively. While none of the PUNLMPs progressed, 11.6% of the low grade carcinomas progressed. There was also a difference in the recurrence-free interval between PUNLMPs and low grade carcinomas, with 76- and 15-month recurrence-free intervals, respectively. Differences were also noted between the 2

Table 4. Relation of WHO/ISUP Grades to Progression [127]

	PUNLMP (n=95)	Low Grade (n=160)	High Grade (n=108)
No Evidence of Disease	94%	76%	67%
Alive With Disease	3%	10%	9%
Dead With Disease	1%	6%	7%
Dead of Disease	0%	4%	16%
No Follow-up	2%	4%	1%

WHO/ISUP grades in their p53 expression, mitoses, and MIB1 (a proliferation marker) activity.

Cina et al. have also analyzed tumors using the WHO/ISUP classification system for p53 expression and proliferation as measured by KI67 *(Level 3,* [129]*)*. Increases in p53 expression of 0.4%, 2.9%, and 25.7% were documented in cases of PUNLMP, low grade carcinoma, and high grade carcinoma, respectively. Proliferation also increased among the 3 grades: 2.5%, 7.3%, and 15.7%, respectively. In a separate study, 134 patients with pTa tumors without prior or concurrent CIS or invasion were analyzed *(Level 2,* [130]*)*. Progression was defined as tumor recurrence with any invasion (pT1 or pT2) or CIS. The 90-month actuarial risks of progression for WHO papilloma and carcinomas grade 1, grade 2, and grade 3 were 0%, 11%, 24%, and 60%, respectively. The corresponding progression rates for WHO/ISUP papilloma, PUNLMP, low grade and high grade carcinomas were 0%, 8%, 13%, and 51%, respectively. WHO grade ($P = 0.003$) and tumor size ($P = 0.03$) and WHO/ISUP ($P = 0.002$) and tumor size ($P = 0.04$) independently predicted progression. Although WHO grade 3 cancers had a more rapid progression rate and a slightly worse long-term progression rate compared to WHO/ISUP high grade cancer, only 4.5% of tumors were WHO grade 3 as compared to 21.6% classified as WHO/ISUP high grade. These findings are similar to Holmang's study, where only 3.6% of tumors were classified as WHO (1973) grade 3, as compared to 28% classified as WHO/ISUP high grade carcinoma *(Level 2,* [127]*)*. As patients with high grade noninvasive papillary carcinoma are not treated with definitive therapy (such as cystectomy), the goal should not be to restrict this high risk group to a very small population, but to expand it to include all patients at significant risk of progression for close monitoring.

e) Invasive Urothelial Carcinoma

Confusion in terminology is not limited to the diagnostic entities in the various classification schemes, as it also exists for the descriptive terminology applied to invasive urothelial lesions. Various terms include "superficial muscle invasion," "deep muscle invasion," "muscle invasion (not otherwise specified)," and "superficial bladder cancer." The latter term is particularly confusing as it could be applied to CIS, noninvasive papillary neoplasms, or truly invasive urothelial carcinoma. Due to variations in treatment and prognostic significance related to the depth of invasion of bladder tumors, the consensus group developed several recommendations to provide clinicians with this essential information in an unambiguous manner.

Invasion of the lamina propria is characterized by nests, clusters, or single urothelial cells, which have breached the epithelial basement membrane. A useful feature in identifying invasion is the presence of marked retraction artifact around the infiltrating cellular clusters, which may closely mimic lymphovascular invasion. Since vascular invasion is uncommon in urothelial carcinomas limited to the lamina propria, care should be taken not to overinterpret this artifact. As invasion extends into the mid-level of the lamina propria, carcinoma will eventually infiltrate into wispy smooth muscle bundles, the muscularis mucosae. Although several studies have shown that the depth of lamina propria invasion with respect to the muscularis mucosae has prognostic significance, the consensus committee chose to make substaging of lamina propria invasion optional. Pathologists are encouraged, however, to assess the extent of invasion (focal vs. extensive) to help guide urologists to an appropriate treatment plan.

The distinction between invasion of the muscularis mucosae and muscularis propria (detrusor muscle) is critical but may be difficult. The presence of nu-merous blood vessels admixed with small bundles of smooth muscles favors muscularis mucosae whereas dense bundles of smooth muscle characterize the muscularis propria (detrusor muscle). It is recognized that the depth of invasion will not be able to be accurately determined in all instances. In these equivocal biopsies, the pathologist should convey his/her uncertainty to the urologist, which will likely initiate a restaging procedure.

Three final comments on depth of invasion are warranted. First, the pathologist has done his job if he can discriminate between invasion of the muscularis mucosae and muscularis propria on a bladder biopsy specimen. Attempts at substaging the depth of invasion of the muscularis propria on a biopsy specimen are neither required nor expected. Definitive assessment of the depth of invasion should be reserved for the final resection specimen. Second, the presence of adipose tissue admixed with tumor on a biopsy specimen is not necessarily indicative of extravesical spread of tumor. In fact, fat may be present at any level of the bladder including both the lamina propria and muscularis propria. Lastly, the consensus committee recommends mentioning the presence or absence of muscularis propria in all bladder biopsy specimens as this provides useful feedback to the urologist regarding biopsy technique and adequacy.

Summary

The potential advantages of the WHO/ISUP system are: 1) acceptance across a broad spectrum of uro-logical pathologists allowing for uniform terminology and common definitions; 2) detailed definitions of various preneoplastic conditions and various grades of tumor, hopefully leading to greater interobserver reproducibility; 3) more or less consistent terminology used in the WHO/ISUP system and urine cytology, creating a consensus classification between cytology and histopathology; 4) creation of category of tumor that identifies a tumor (PUNLMP) with a negligible risk of progression, whereby patients avoid the label of having cancer with its psychosocial and financial (i.e., insurance) implications. These patients are also not diagnosed as having a benign lesion (papilloma), whereby they might not be followed as closely. Whether this classification system also helps to stratify patients for further treatment remains to be studied; 5) identification of a larger group of patients at high risk for progression for urologists to more closely follow; and 6) recommendations for reporting extent of invasive carcinoma in an unambiguous manner, essential for proper treatment and management.

In 2004, the WHO made its recommendations on the classification of noninvasive urothelial lesions *(Level 4,* [131]*)*. The recommendations are essentially the same as the 1998 WHO/ISUP system, and thus there is now only 1 unified nomenclature system.

2. Staging of Bladder Cancer

Pathologic stage is one of the most important prognostic factors in bladder cancer. Accurate staging is critical for patient management. The 2002 TNM (tumor, lymph nodes, and metastasis) staging system defines pT1 tumors as those invading the lamina propria, but not the muscularis propria; pT2 tumors as those invading into the muscularis propria; pT3 tumors as those invading perivesical tissue; and pT4 tumors as those invading into other organ structures (prostate, uterus, vagina, pelvic wall, or abdominal wall).

a) pT1 Tumor

The diagnosis of pT1 tumor is often difficult, with substantial interobserver and intraobserver variability [132]. In one study, 7 experienced pathologists could agree on lamina propria invasion in only 61% of cases after 3 separate evaluations [133]. In another study, 35% of tumors initially diagnosed as stage pT1 were downstaged to pTa, and 3% were upstaged as pT2 to pT4 tumors [134]. In a recent study, there was complete interobserver agreement on pT1 stage among reviewers in 80% of cases, which rose to 88% after a second review [135]. In this study, of the 63 tumors originally diagnosed as stage pT1, the consensus diagnosis by experienced genitourinary pathologists resulted in downstaging of 35 (56%) to pTa and upstaging of 8 (13%) to pT2 to pT3 tumors [135]. Progression was more common in the 20 consensus-confirmed stage pT1 cases (25%) when compared to the 55 original pT1 cases (20%) [135]. Tumors that were downstaged to pTa showed less frequent progression than the stage pT1 tumors (17% vs. 25%) confirmed when reviewed. It was concluded that prognostic variation resulting from observer variability in staging and grading is considerable with significant implications for patient management [135].

The prognosis of patients with pT1 tumors is highly variable. There is a need for an accurate, easy-to-use, reproducible substaging system to stratify patients into different prognostic groups. Several studies have explored the utility of muscularis mucosae for subclassification of pT1 tumor [136-142]. Muscularis mucosa consists of thin and wavy fascicles of smooth muscle, which are frequently associated with large caliber blood vessels. Muscularis mucosa can be identified in only 15% to 83% of biopsy specimens, and 6% of radical specimens do not have muscularis mucosa [143-145]. Thus, the “large” vessels have been used as a surrogate marker of muscularis mucosa in all published studies that have proposed T1 substaging based on muscularis mucosa invasion. For example, Angulo et al. were able to identify muscularis mucosa in 39% of their cases and utilized the blood vessel landmark in a remaining 26% [139]. Thus, in 35% of their cases, substaging could not be performed. Platz et al. identified muscularis mucosa in only 33% of their cases [140]. Furthermore, when they used the vascular surrogate anatomic landmark in the remainder of the cases, they did not find any prognostic significance in substaging pT1 disease [140]. These practical problems have prompted recent questioning as to whether substaging pT1 disease based on the muscularis mucosa is the best system, and, as a consequence, substaging of pT1 tumors based on muscularis mucosa invasion is not universally advocated [105].

In 1999, Cheng et al. proposed a novel system of

substaging pT1 tumors based on the micrometric measurement of the depth of invasion of tumor into the subepithelial connective tissue [143,145]. They studied a series of 55 patients with stage pT1 urothelial carcinomas diagnosed on TURBT specimens and eventually treated by cystectomy [143]. By using an ocular micrometer to measure the depth of invasion from the mucosal basement membrane, they found a significant correlation between depth of invasion in the TURBT specimen and final pathologic stage at cystectomy. A 1.5 mm of depth of invasion predicted advanced stage of disease at cystectomy with a sensitivity of 81%, a specificity of 83%, and positive and negative predictive values of 95% and 56%, respectively [143]. They further applied the same criteria to a group of 83 consecutive patients diagnosed with pT1 bladder cancer and found a 5-year progression free survival of 67% in patients with a depth of tumor invasion greater than 1.5 mm, compared to 93% for those tumors with a depth of invasion less than 1.5 mm [145].

b) pT2 Tumor

The clinical utility of substaging of pT2 tumors has been questioned [146]. The 2002 TNM staging system subclassifies pT2 tumor into 2 categories: cancer invading less than one-half of the depth of muscular propria (pT2a) and cancer invading greater than one-half of the depth of muscularis propria. A number of studies have compared clinical outcomes between pT2a and pT2b tumors and have failed to find a prognostic difference between these 2 groups. Among 145 bladder cancer patients, 5-year survival was 65% for patients with pT2a tumor, compared to 61% for patients with pT2b tumors [147]. Pollack et al. studied 49 patients and found no difference in 5-year survival between patients with pT2a tumor (78%) and pT2b tumors (77%). In a multivariate analysis, Cheng et al. found that tumor size, rather than the depth of invasion, was predictive of distant metastasis-free and cancer-specific survival in patients with muscularis propria invasion [146].

c) pT3 Tumor

The subdivision of pT3 tumors into pT3a (tumors with microscopic extravesical tumor extension) and pT3b (tumors with gross extravesical extension) is also controversial. Quek et al. examined 236 patients with pT3 tumor [148]. With a median follow-up of 8.9 years, no recurrence or survival difference was found between patients with pT3a and pT3b tumors. Lymph node and surgical margin status were the only factors associated with patient prognosis.

d) pT4 Tumor

The classification of bladder carcinoma involving the prostate as pT4 tumors has been debated. Esrig et al. studied 143 bladder cancers with prostatic involvement and divided them into 2 groups; group I were those tumors that have penetrated the full thickness of the bladder wall to involve the prostate and group II were those tumors that involved the prostate through the prostatic urethra [149]. Five-year overall survivals were 21% and 55% for group I and group II patients, respectively. Among group II patients, the presence of stromal invasion was associated with worse prognosis compared to those involving urethral mucosa only [149]. Similarly, Pagano et al. found that 5-year survival was only 7% among group I patients, compared to 46% among group II patients [150]. In group II patients, all patients with urethral mucosal involvement were alive and free of disease, compared to a 40% to 50% survival among patients with stromal invasion.

III. DIAGNOSIS

1. Bladder Cancer Screening

The goal of screening is to improve survival by detecting bladder cancer at an earlier stage. The optimal method to determine whether screening accomplishes this goal is a prospective randomized controlled trial that compares the mortality of screened and unscreened patients. Unfortunately, such a trial has not been completed. Nonetheless, a review of the literature may provide insight into bladder cancer screening.

a) Background

In 1968, the World Health Organization outlined principles for early disease detection *(Level 4,* [151]*):*

1. The condition sought should be an important health problem.
2. There should be a suitable test or examination which is valid, reliable, inexpensive, easy and quick to perform, and acceptable to the population undergoing testing. The efficacy of the test must be satisfactory as determined by sensitivity, specificity, and positive predictive value.
3. The natural history of the condition should be adequately understood.

In 1977, a state-of-the-art conference on bladder cancer screening addressed these principles and concluded *(Level 4,* [152]*)*:

1. Bladder cancer is suitable for screening because it is a disease with serious consequences.

2. Urine cytology has the characteristics of a good screening test (for high grade cancers only), including high sensitivity, high specificity, low cost, and little inconvenience. Cytology has a high positive predictive value when used in populations with a high prevalence of bladder cancer.

3. Data on the natural history of bladder cancer (with regard to screening) were lacking.

This state-of-the-art conference reconvened in 1989 *(Level 4,* [152]*)*. Although the natural history of bladder cancer was better understood, definitive screening recommendations were hindered by the lack of clinical trials. Subsequently, computer models suggested that screening may be cost-effective and may reduce mortality from bladder cancer (*Level 3,* [153,154]*)*. However, there still is insufficient clinical data to confirm these models.

Although the current data is inconclusive, it serves as a foundation for developing screening protocols. When designing a screening program, two crucial questions must be considered: "Who should be screened?" and "What tests should be used for screening?"

b) Who Should Be Screened?

The performance of a screening test improves as the prevalence of the disease increases. In the general population, the low prevalence of bladder cancer limits the utility of screening. However, patients at high risk for bladder cancer have a high prevalence of the disease, leading to a more favorable performance by a screening test. ***Thus, screening should probably be confined to patients at higher risk for bladder cancer.***

Screening studies have been conducted in high-risk populations exposed to occupational carcinogens including beta-naphthylamine *(Level 4,* [155-157]*)*, 4,4'-methylene-bis-2-chloroaniline, (*Level 4,* [155]*; Level 3,* [158]), benzidine [155], and coal-tar-pitch volatiles [159]. The screening protocols usually included medical history (including voiding symptoms and other risk factors for bladder cancer), hematuria testing, and voided urine cytology. Although these studies may help serve as models for the development of screening protocols, they have not proven that screening improves outcome in high-risk patients.

c) What Tests Should Be Used for Screening?

The ideal screening test is noninvasive, inexpensive, and exhibits high sensitivity, specificity, and accuracy. Tests that may be utilized for bladder cancer screening include hematuria testing, cystoscopy, bladder imaging, urine cytology, and bladder tumor markers (nuclear matrix protein, telomerase, hyaluronic acid, etc.). Bladder imaging with intravenous urogram or ultrasound often fails to detect bladder tumors *(Level 3,* [160]*)*. Cystoscopy and bladder wash cytology are too invasive for routine use. While no tests have been adequately evaluated for bladder cancer screening, voided urine cytology and chemical dipstick for hematuria are the only tests in which screening trials have been conducted with a large sample size or with long-term follow-up.

1. Dipstick for Hematuria

The rationale for utilizing hematuria as a screening test is that nearly 85% of patients with bladder cancer have painless hematuria (microscopic or gross). Although screening should be performed in high risk patients, most screening studies have evaluated hematuria testing in the general population (asymptomatic patients).

• **Studies examining a single screening test:** In a retrospective study of 20 571 asymptomatic patients undergoing a single chemical dipstick test for hematuria (men $\geq$ 35 and women $\geq$ 55), the urologic cancer rate was the same in patients with and without microscopic hematuria *(Level 3,* [161]*)*. The authors concluded that these findings are consistent with the "lack of recommendation for screening for microhematuria among asymptomatic adults." This conclusion was based on screening with a *single* hematuria test. However, hematuria from bladder cancer may be intermittent and its detection may require repetitive screening *(Level 3,* [162,163]*)*. Studies that utilize repetitive screening may be more applicable to clinical practice.

• **Studies examining repetitive screening:** A total of 2356 asymptomatic men aged 60 years and above underwent repetitive screening for hematuria with a chemical strip *(Level 3,* [164-166]*)*. Bladder cancer was found in 17 men. At the time of initial diagnosis, none of the patients had muscle-invasive cancer, but 9 patients had tumors with a high risk of progression (CIS or stage T1). After 7 years of follow-up, 2 of 9 patients (22%) progressed to muscle-invasive disease and 3 of 9 (33%) died from bladder cancer. Thus, the screening test detected life-threatening cancer and detected these cancers at an early stage

when cure may have been achieved. The authors concluded "…as their disease was identified at a superficial stage it may have been amenable to aggressive early management…" [166].

Outcome from bladder cancer in 1575 asymptomatic men aged 50 years and above undergoing repetitive hematuria screening with a chemical strip (screened cases) was compared to men with newly diagnosed bladder cancer from the Wisconsin cancer registry in 1988 (unscreened cases) *(Level 3,* [167]*)*. At the time of diagnosis, screen-detected cancers were less likely to be muscle-invasive than unscreened cancers (4.8% vs. 23.9%, respectively). In cases of grade 3 cancer, 0% of the screen-detected tumors were muscle-invasive, whereas 51.9% of unscreened tumors were. Furthermore, death from bladder cancer (within 2 years of diagnosis) was significantly less in the screened group compared to the unscreened group (0% vs. 16.4%, respectively). The authors concluded that "hematuria...screening detects high grade cancers before they become muscle invading and significantly reduces bladder cancer mortality." ***These studies suggest that hematuria screening in the general population may help detect bladder cancer at an earlier stage and may reduce cancer -related deaths.***

2. Urine Cytology

The state-of-the-art conference on bladder cancer screening in 1977 determined that urine cytology has the characteristics of a good screening test (for high grade cancers only) because of its high sensitivity, high specificity, low cost, and minimal inconvenience *(Level 4,* [152]*)*. ***Unfortunately, studies evaluating urine cytology as a screening test are sparse***. One study utilized an annual voided urine cytology to screen aluminum production workers exposed to coal-tar-pitch volatiles *(Level 3,* [159]*)*. Cancers detected during screening were more likely to be noninvasive than cancers detected before screening was initiated (63% vs. 39%, respectively). Survival was improved in patients whose cancer was detected by screening; however, the improvement had not achieved statistical significance at the time of the report.

d) Screening Interval

Current evidence suggests that screening should probably be performed annually *(Level 3,* [159,163]*)*.

Summary

The optimal screening test and testing interval are unclear. The population that would benefit most from bladder cancer screening is unknown; however, patients at high risk for bladder cancer are thought to be the best candidates for screening. Screening has been conducted mainly by hematuria testing and urine cytology. The role of other tumor markers is unclear. Screening may detect bladder cancers at an earlier stage and may reduce cancer-related deaths. However, there is still no conclusive data that proves that screening reduces mortality from bladder cancer.

2. Signs and Symptoms

The most common presenting symptom of bladder cancer is painless hematuria, which occurs in about 85% of patients. In reality, nearly all patients with cystoscopically detectable bladder cancer have at least microhematuria if enough urine samples are tested [168].

a) Gross Hematuria

The vast majority of bladder cancers are diagnosed as a result of evaluating patients for hematuria. Total gross hematuria (blood in the urine throughout micturition) without pain is the typical sign suspicious for bladder cancer. Kretschmer studied 860 patients with hematuria and found that 28% of the patients had bladder cancer [169]. Varkarakis et al. studied 95 patients with gross painless hematuria and found 12 patients (13%) with bladder cancers [170]. In a similar study of 1000 patients with gross painless hematuria by Lee et al., 15% of the patients had bladder cancers [171]. Careful characterization of hematuria as initial, terminal, and total hematuria is important to identify the location of bleeding. Therefore, with these high incidences of bladder cancer in patients with gross hematuria, the modern examination by flexible cystoscopy seems to be necessary. However, hematuria is quite often intermittent so that a negative result on 1 or 2 specimens has little meaning in ruling out the presence of bladder cancer.

b) Microscopic Hematuria

Mohr et al. reported that asymptomatic microhematuria occured in 13% of the general population and of those patients only 0.4% had urothelial neoplasia [172]. On the other hand, Golin et al. found that 16 patients (6.5%) had bladder cancer among 246 patients with asymptomatic microscopic hematuria who were referred to a urology clinic [173]. Mohr

also showed the poor correlation between the number of red blood cells per high power field and the probability of significant disease [172].

The policy regarding microscopic hematuria is still unclear, except in patients over 50 years of age, who should be examined in the same way as for macroscopic hematuria, since the incidence of underlying malignancy in patients over 50 years with asymptomatic hematuria is 5%, while an incidence of 10.5% is found with symptomatic microscopic hematuria [174].

Moreover, screening with dipstick for asymptomatic hematuria is not recommended by the American Cancer Society or the Canadian Taskforce [175].

Mayo Clinic investigators reviewed the charts of 2312 patients with asymptomatic microscopic hematuria [176]. The positive predictive value for bladder cancer was too low (0.5%) to warrant mass screening, as reported by Mohr et al. [172].

Therefore, routine screening for microscopic hematuria may be indicated only for high-risk populations such as those exposed to bladder carcinogens and/or heavy smokers.

c) Other Symptoms

The symptom complex of bladder irritability and urinary frequency, urgency, and dysuria is the second most common presentation of bladder cancer, and is usually associated with diffuse CIS or invasive bladder cancer.

Hematuria associated with irritative symptoms such as frequency, dysuria, and urgency should be carefully examined after infection and neurogenic bladder have been ruled out since it may indicate relatively advanced tumors or CIS that extends to the bladder neck or the prostatic urethra. Jewett suggested that urinary frequency was an important symptom that was complained of in about one-third of the cases [177].

CIS of the bladder may be asymptomatic or may produce severe symptoms of urinary frequency, urgency, and dysuria [178].

Other symptoms and signs of bladder cancer include flank pain due to ureteral obstruction, lower extremity edema, and a palpable pelvic mass. Very rarely, patients present with symptoms of advanced disease, such as weight loss and abdominal or bone pain from distant metastases.

However, these symptoms almost never occur without microscopic or macroscopic hematuria.

3. URINARY CYTOPATHOLOGY

a) Definitions

1. BLADDER CANCER

Bladder cancer is an ill-defined term ordinarily used to connote malignant neoplasms occurring in the urinary bladder. Most of these neoplasms are urothelial (transitional cell) but bladder cancers can be squamous, glandular, small cell, and even non-epithelial. If the term is confined to urothelial neoplasms, it actually refers to a group of tumors that range from phenotypically and biologically benign to phenotypically and biologically malignant. Anyone attempting to understand the role of any detection method must be aware that the term “bladder cancer” does not define a homogeneous group of neoplasms with aggressive behavior but includes neoplasms that are histologically and biologically benign.

2. UROTHELIAL NEOPLASM

A urothelial neoplasm is a misregulated proliferation of urothelial cells differentiating toward urothelium. Nearly all such neoplasms occur in organs lined by urothelium and most of these arise in the urinary bladder. When processed and viewed using a light microscope, urothelial neoplasms comprise a morphologic spectrum from normal epithelium on a delicate fibrovascular stalk to anaplastic cancers with or without homologous or heterologous elements. As defined and illustrated in the 1998 WHO/ISUP Consensus classification, these neoplasms have been named as follows [105]:

- papilloma;
- papillary urothelial neoplasm of low malignant potential (PUNLMP);
- urothelial carcinoma, low grade;
- urothelial carcinoma, high grade (+/- variants); and
- carcinoma in situ (CIS).

The nature of urothelial dysplasia remains in dispute. Some experts include it among the neoplasms, whereas others consider it a precursor, and still others think of it as a reactive process with the potential to transform. In the WHO/ISUP scheme, dysplasia is defined as a flat urothelial lesion that “falls short” of CIS.

The 1998 WHO/ISUP scheme is *not* simply a renaming of the categories G1, G2, and G3 of the 1973 system. The major gain is the removal of the term “carcinoma” from the lowest grade tumors (essen-

tially all G1). The classification recognizes the difference between the *potential* of the patient to develop a malignant neoplasm and the *presence* of such a tumor. Other advantages include:

- recognition that most true carcinomas are high grade (many G2 and all G3) and that further subclassification of this group has no practical meaning,
- limitation of the intermediate group (G2) by a more explicit histologic definition,
- recognition that CIS should not be graded, and
- recognition that urinary cytopathology is an important aspect of evaluation.

The 1998 WHO/ISUP scheme has been adopted by the 2004 WHO committee and the 4th Series AFIP Fascicle and is becoming widely accepted among practicing pathologists [131,179].

It is important to note that whereas urothelial neoplasms seem to comprise a *morphologic* spectrum of increasing degrees of anaplasia, this spectrum does not translate into a biologic spectrum of concomitant degrees of aggressive behavior. Urothelial papillomas and PUNLMPs, for example, lack the ability to invade or metastasize [119,180-182]. *Patients* presenting with these tumors are at increased risk for an adverse outcome but the neoplasms themselves do not progress. Thus, any adverse outcome requires the development of a *new*, high grade carcinoma. Similarly, patients who present with urothelial CIS (defined as a flat, noninvasive neoplasm of high cytologic grade) develop invasive lesions during clinical observation in less than one-third of cases, even though the cells comprising CIS have nearly every component of malignancy identified to date [183,184].

1. Urinary Cytopathology

Urinary cytopathology (aka cytology) is a *medical consultation* based upon a cytopathologist's *interpretation* of changes in disaggregated cells as they appear in specimens processed for light microscopy. The literature often seems to promote the misconception that this consultation is merely an observation and that cytopathologists are "observers" (see section on Interobserver Variation). Cytopathologists are often asked to "read" slides, as if the information therein required fluency in a language foreign to the requestor and one merely needed to have acquired fluency in it to comply. This conceit of the language is known to the sophisticated, but it tends to create an erroneous concept, nonetheless.

In fact, medical consultations from the limited information available on glass slides processed for light microscopy require a good deal of induction and some intuition. In addition to knowledge of the cellular features (which essentially represent descriptions of the interpretations of individuals with a special interest in the subject), other components enter into an interpretation. These include the

- adequacy of the specimen,
- accuracy of the clinical information,
- confidence of the cytopathologist,
- perceived consequences to the patient of a positive interpretation,
- perceived consequences to the pathologist of a misinterpretation,
- reason for the request (screening normal, or screening symptomatic, monitoring), and
- terminology used for reporting the interpretation.

As with any judgment made by a human, temporary distractions and lack of education may play a role in any particular case, but there is very little evidence that these factors are important in the general application of urinary cytopathology to patient care.

b) Application of Urinary Cytopathology to Clinical Practice

Among the many applications of urinary cytopathology (UC) to patient care, the most important is for the detection of bladder neoplasms. Using UC, cytopathologists can detect squamous, glandular, small cell, and even sarcomatous lesions, but the method is primarily used to detect urothelial neoplasms. UC is not particularly suited to screening. The yield for primary urothelial tumors reflects the low incidence of these lesions in the population. Even among symptomatic individuals, the most thoroughly conducted study found only 106 cases among 35 000 "tested" (0.3%) [185].

UC is most efficacious for monitoring patients for the appearance of *high grade* neoplasms (including CIS) [186]. It is especially useful for patients treated with topical agents, where the effects of therapy tend to confound cystoscopic examination, and for recognizing the presence of persistent or recurrent carcinomas that may be confined to the prostatic ducts, urethra, or distal ureters. UC interpretations can assist the urologist in timing a cystoscopy during patient monitoring. Patients being followed after the diagnosis of a PUNLMP or noninvasive low grade

carcinoma who have no recognizable tumor cells in their urinary specimens can undergo cystoscopy at longer intervals than patients with tumor cells in their UC [187]. Urinary cytopathology interpretations can be of prognostic value. Patients treated with topical therapy who have high grade cells in their urinary samples are very likely to come to cystectomy [188]. A negative interpretation can be reassuring in many circumstances and should not be discounted.

UC is less useful for the detection of low grade neoplasms. There are several reasons. The cells of low grade urothelial tumors lack many features associated with malignancy, such as nuclear pleomorphism, coarsely clumped chromatin, and large nucleoli. In contrast to high grade neoplasms, the expression of phenotypic features considered important in the recognition of low grade neoplastic cells tends not to occur in every cell. In tissue specimens, low grade urothelial neoplasms are recognized as neoplastic primarily because their cells are arranged on delicate fibrovascular stalks. Similar cells in flat urothelium cannot be recognized as neoplastic in histologic sections and are often termed "dysplasia." In other words, ***it is not the cells but the stalk that allows the histopathologist to diagnose low grade urothelial neoplasms.***

Other factors affect the interpretation of any individual specimen. One of the most important and least discussed of these factors is the adequacy of sampling. In a study from the University of Florida, for example, 23% of bladder washings from patients having histologically documented high grade urothelial carcinomas at the time of the washing lacked tumor cells [189]. A "negative" cytopathologic interpretation in such a situation can hardly be construed as a diagnostic error or a failure of the method itself. Properly performed, a bladder washing should include the residual urine collected when the instrument is introduced plus a vigorous lavage done immediately after a full cystoscopy is performed but prior to any other manipulation. If the residual urine is discarded or the operator performs an initial cystoscopy prior to the washing, diagnostic elements can easily be lost [190].

Fortunately for patients, nearly all aggressive urothelial neoplasms are of high cytologic grade, the type that is readily detectable using UC. ***The primary purpose of monitoring patients with UC is to detect high grade neoplasms, as persistent or recurrent lesions if the initial neoplasm was high grade (including CIS), or as new tumors if the initial lesion was low grade (PUNLMP, low grade carcinoma, [G1, many G2 in 1973 WHO]).*** UC has the further advantage that it is the neoplastic cells themselves that are being identified.

c) Terminology

Communication of the interpretation of a urinary specimen is an important aspect of the consultation. As with histologic lesions, each practice setting may recognize the patient care implications of their particular vocabulary. Uncritical data collection from the charts of multiple institutions for collaborative reports may be misleading. The term "atypia," for example, has been rejected by many groups but considered an important indicator of risk by a few [191]. When modified by the word "severe," many would consider it a synonym for CIS. "Positive" and "transitional cell carcinoma" may indicate either high or low grade tumors, the latter being associated with a far higher false positive rate than the former. "Suspicious" calls for the question, "Suspicious for what?" Some authors have included suspicious among the positives for assessing results whereas other authors have included suspicious among the negatives for the same purpose. In at least one study, the diagnostic yield has been configured both ways [192].

Since the features used to classify urothelial neoplasms histologically may not be present in the cytologic sample (to wit, the stalk), Murphy has recommended the following terminology to communicate the cytopathologic interpretation:

- positive, consistent with high grade neoplasm;
- positive, consistent with low grade neoplasm;
- suspicious for high grade neoplasm;
- dysplastic cells, rule out low grade neoplasm;
- negative, neoplastic cells not identified; and
- unsatisfactory, insufficient cells for interpretation [186].

In this lexicon, suspicious should be construed to mean that the cells have features of a high grade neoplasm, but there are too few for an unequivocal interpretation. As those who have studied asymptomatic, high-risk individuals have discovered, factors other than a developing neoplasm can cause a few cells in a urinary specimen to appear neoplastic [183,193]. We are also cautious with the interpretation of a few malignant-looking cells in specimens from symptomatic, untreated individuals, because high grade urothelial neoplasms in such cases should shed nu-

merous cells into a urinary sample. Similarly, the only difference between some reactive lesions, flat dysplasias, and many low grade papillary neoplasms is the stalk. Thus, dysplastic cells warrant attention but in many cases can not be considered diagnostic. ***Depending on the circumstances, cells with essentially the same phenotypic features can be interpreted using differing terminology in daily practice.***

The expectation that an interpretation will result in a specific action is important to cytopathologic consultation. It focuses the mind on the evaluation and reminds us that patients will be affected. In one practice setting, the cytopathologists expect that interpretations will lead to the following actions:

positive, consistent with high grade neoplasm	cystoscopy with biopsies, even if no lesions are identified
positive, consistent with low grade neoplasm	cystoscopy with biopsy of lesions only
suspicious for high grade neoplasm	cystoscopy with biopsy of lesions only
dysplastic cells, rule out low grade neoplasm	cystoscopy with biopsy of lesions only
negative, neoplasm not identified	no action

These recommendations are the result of a study that indicated that for the entire group of four cytopathologists, high grade cells were essentially always associated with a neoplasm in the bladder at the time of specimen collection and that dysplastic cells were associated with a neoplasm in 60% of cases [189]. Other practice settings may achieve different results and should perform their own studies. It is probably inappropriate to assume that data from one setting can be extrapolated to all others.

d) The Diagnostic Yield of Urinary Cytopathology

This subject is far from simple. The value of UC in the detection of urothelial neoplasms depends upon a variety of factors. These include

- the type of specimen upon which the interpretations are made - whether voided urine or bladder washings;
- the design of the study from which the data are taken - whether to test the method itself, compare to other methods, assess the added yield of other methods, or to assess UC diagnoses in daily clinical practice;
- the definition of a cytohistologic correlation – whether an immediate or a delayed histologic correlation;
- the grade of tumor being correlated;
- whether or not the correlation is cystoscopic only;
- the number of cytopathologists involved and their interaction with each other as well as their involvement in the data analysis;
- the types of cases (primary neoplasms, persistent or recurrent neoplasms);
- the case mix (the percentage of neoplasms versus negatives will affect the specificity and the predictive value);
- the presence or absence of topical therapy;
- the histopathologic classification used for correlation; and
- the (nearly inevitable) biases contained within the work.

One can select almost any figures from the literature. This section is concerned primarily with discussing the issues.

Specimen selection is important to diagnostic yield. Random voided urines are well known to contain fewer and more degenerated neoplastic cells than bladder washings [190]. The cytopathologist must be on heightened alert for an accurate interpretation of voided urine, especially during follow-up. Knowledge that the patient is being followed for “bladder cancer” is usually essential and the further information that the “bladder cancer” is high grade would be even better. The problems associated with few abnormal cells in a specimen are usually functional here, especially when patients have been exposed to topical agents. Topical agents are designed to reduce the number of tumor cells in a urinary sample and the combination of only a few cells and the degeneration common to voided urine can be diagnostically daunting. If the purpose of the study is to find a way to reduce patient instrumentation during follow-up, then urinary cytopathology is at a disadvantage. Still, voided UC has detected tumor cells under such circumstances and may even be positive when the bladder washings are not [190,192,194-197].

Bladder washings are associated with a higher yield than voided urines, primarily because of better cell preservation and more numerous neoplastic elements in the sample. Patients must be instrumented but cystoscopy is not an adequate substitute for UC since persistent and recurrent neoplasms are not always

evident cystoscopically, especially after topical therapy.

In the literature, the diagnostic yield of UC seems to vary with the purpose of the study. If the study is designed to assess the efficacy of the method, then patient care implications are specifically excluded. The cytopathologist (usually only one) is most often "blinded" to all clinical circumstances. Cases are grouped and examined in a concentrated fashion that facilitates the reproduction of fine distinctions in a visual analysis. Specimens are very often bladder washings. It is assumed that they are representative of the actual state of the bladder. Cytohistologic correlations with bladder biopsies are almost always the measure of success but the correlation need not be immediate. A cytohistologic correlation may be considered positive if the patient has a documented neoplasm many months after the positive cytopathologic interpretation. Since urothelial neoplasms are unusual in the population and periodic biopsies of otherwise normal people are not ordinarily possible, the study is usually weighted with patients being followed for urothelial neoplasms and this factor is ordinarily known to the cytopathologist.

If the purpose of the study is to assess the yield of UC in a clinical setting, then relevant information is not concealed from the cytopathologist, although neither is it always provided. Many of the same factors - case selection weighted toward "cancer" cases, assumption of specimen adequacy, type of histopathologic classification used, endpoint of cytohistopathologic correlation, etc. - apply but the studies are different in important ways. In a clinical practice study, it is the immediate (usually histologic but sometimes cystoscopic only) correlation that is paramount. The correlation may include all grades of urothelial neoplasms or separate results according to grade. More than one cytopathologist is ordinarily involved. The study is very often retrospective, the cytopathologists not being aware that their interpretations will be used for publication. Cases have come sporadically, among other types of specimens, requiring the cytopathologists to switch mental gears rather than to concentrate their thoughts on reproducing the subtleties of urothelial tumor assessment. In a clinical setting, there may be consequences to an interpretation. Pathologists have been schooled to be cautious, since a false positive interpretation is ordinarily more harmful to patients than a false negative one. This no doubt accounts for the high specificity of most results. Many studies have been multi-institutional reviews. In most of the recent literature, the study compares a laboratory test performed on voided urine with the cytopathologic consultation, sometimes, but not always, on the same sample.

When the study is designed to evaluate the method itself, the diagnostic yield is most often good, even when all grades are combined in the results, and are especially favorable for the interpretation of high grade neoplastic cells [194-203]. Sensitivities in the range of 60% to 90%, specificities of 90% to 100%, and positive predictive values (PPVs) of greater than 85% are often recorded. The higher numbers are ordinarily achieved for bladder washings, but success has been claimed for voided urines. The numbers tend to decline when individual specimens are compared to cases, voided urine is compared to bladder washings, and low grade neoplasms are compared to high grade cancers. Sensitivities for voided urine specimens and low grade urothelial neoplasms are usually reported in the range of 30% to 60%. Specificities have remained greater than 85%, however.

When the study is designed to assess the diagnostic yield in clinical settings, especially when the intent is to compare UC with ancillary laboratory tests, the numbers for sensitivity and specificity tend to fall into the voided urine range [204-211]. Diagnostic yields of less than 40% for high grade neoplasms are not unusual. In 2 reviews of the literature, sensitivities in the range of 35% to 80% and specificities of 80% to 100% were most often cited [212,213]. The reasons for this lower yield, especially in marker comparison studies (when cytopathologists are "on the line" compared to when they are "in the dark") have not been rigorously addressed. The lower yield of the voided urines (compared to bladder washings) upon which many of the comparison studies are based has been well-documented. The cytopathologist is detecting actual neoplastic cells rather than a byproduct of the neoplastic state, and this probably accounts for maintenance of relatively high specificities and PPV.

The diagnostic yield of UC tends to vary considerably among individual reports, a situation that has led to a plea for more thorough education for practicing cytopathologists. The assumption that cytopathologic interpretations could be made more uniform by a more standard approach seems reasonable but probably does not adequately address the issue (see section on Interobserver Variation). Confidence and aversion to the perceived consequences of a misdiagnosis may play a more important role in clinical practice than one might expect. In a study

comparing the daily practice results in 3 different settings, the diagnostic yield varied in unexpected ways [204]. At the cancer referral center, where every specimen could be assumed to have come from a patient with cancer and only 11% of histologically documented cases were very low grade (G1), the sensitivity was only 66% (specificity 98%, PPV 88%). Similar figures for specificity and PPV were recorded for the academic practice. At the private practice, where most specimens could be expected to be from patients with no bladder neoplasm and 33% of histologically documented cases were very low grade (G1), the sensitivity of 85% was associated with a specificity of 74% and a PPV of only 56%. Could it be that the perceived consequences of a positive interpretation at the cancer center and academic practice differed from those at the private practice (for example more treatment versus additional evaluation)? Or could it be concern with the consequences of missing a cancer patient (fewer at the cancer center and academic practice where many cases are referrals versus increased medicolegal exposure at the private prac-tice)?

The diagnostic yield can be affected by the definition of a cytohistopathologic correlation. Is a positive interpretation of high grade neoplasm a false positive if the patient is lost to follow-up? What if the patient had had a high grade carcinoma histologically documented previously? Should PUNLMPs have positive cytology interpretations and, if so, positive for what? Isn't "dysplastic cells" a closer correlation, even though the 1973 WHO designates these tumors as "carcinomas"? In a study conducted on our material, the PPV could vary as much as 15%, depending on the definition of a correlation [189]. The histologic documentation of a neoplasm after a positive cytopathologic interpretation has sometimes required months and even years. If the endoscopist can't find the lesion, is the interpretation false? On the other hand, tumor cells can apparently continue to be shed from a resected tumor for several weeks, even though the treatment will eventually prove effective [214]. Should a positive interpretation during those weeks be considered erroneous?

In summary, ***urinary cytopathology is best applied in follow-up of patients with urothelial neoplasms.*** Given adequate sampling and at least 3 specimens, up to 90% of recurrent high grade urothelial carcinomas can be detected in cytologic samples and the positive predictive value is greater than 90%. Urinary cytopathology is less valuable for the detection of low grade urothelial neoplasms but should be utilized for monitoring patients having low grade, non-invasive urothelial neoplasms to detect any high grade tumors that might develop. Given adequate samples, especially bladder washings from patients monitored for "bladder cancer," the PPV for an interpretation of high grade neoplasm in a UC is so high that it can almost never be considered falsely positive. In contrast, the PPV for interpretations of low grade neoplasm and "dysplastic cells, rule out low grade neoplasm" is in the range of 60%, high enough to warrant a cystoscopy but not selected site biopsies.

The diagnostic yield of UC varies among practice settings and a wide range of numbers for sensitivity, specificity, and positive predictive value have been recorded. In general, the method itself holds more promise than has been realized in daily practice. Increasing the efficacy in any particular practice setting may not be simply a matter of education but may involve addressing risk aversion.

e) The Cellular Features of Urothelial Neoplasms

The cellular features of urothelial neoplasms have been described and illustrated in numerous publications [186,189,198,201,203,204,211]. Since the features used for histologic distinctions may not be present in the disaggregated cells of cytologic samples and, since it is not always possible to distinguish glandular neoplasms from urothelial tumors, the most accurate approach to classification in this area would seem to be separation on the basis of degree of cytologic anaplasia (**Table 5**).

High grade neoplastic cells may be numerous or sparse, depending on the type of specimen, the approach to collection, and the prior application of topical therapy. The key diagnostic changes are nuclear pleomorphism and coarsely granular, irregularly dispersed chromatin. Large nucleoli may appear in high grade neoplastic cells but are rarely numerous and not essential for interpretation. Occasionally, cells may be small with degenerated nuclei lacking chromatin detail but the increased nuclear-cytoplasmic ratios and peculiar nuclear shape of these cells tend to reveal their nature. Importantly, ***nearly all high grade neoplastic cells contain all of the diagnostic features listed in Table 5.***

Low grade urothelial neoplasms are composed of cells lacking many features of malignancy; they can be construed as lesions composed of dysplastic cells on delicate fibrovascular stalks. It is the stalk rather than the cells that allows histologic classification of these tumors as neoplasms. When disaggregated into urinary samples, there is very little difference be-

Table 5. Features of Urothelial Neoplasms

Features of Urothelial Neoplasms: WHO/ISUP 1998

	Carcinoma			
	High Grade	**Low Grade**	**PUNLMP**	**Papilloma**
Configuration				
Papillary	+	+++	+++	+++
Nodular	+++	±	0	0
Architecture				
Normal	0	+	++	+++
Abnormal	+++	±	0	0
Cell Distribution				
Even	0	+	+++	+++
Clustered	+++	±	0	0
Superficial Cell Layer	±	+	+++	+++
Nuclear Features				
Pleomorphism	+++	+	±	+++
Fine chromatin	0	+++	+++	0
Coarse chromatin	+++	±	0	0
Even chromatin	±	++	+++	+++
Irregular chromatin	+++	0	0	0
Large nucleoli	+	±	0	0
Mitoses	++	+	±	0

WHO/ISUP = World Health Organization/International Society of Urological Pathology; PUNLMP = papillary urothelial neoplasm of low malignant potential; 0 = absent/rare; ± = may occur sporadically, + = occurs in some tumors but not constant; ++ = occurs in most tumors; +++ = characteristic feature, occurring in most or all cases.
From: Murphy WM, Urinary Pathology. Chicago; ASCP Press:15.

tween the cells on stalks and similar cells that might occupy flat areas of urothelium. Therefore, low grade and dysplastic cells will be described together.

Low grade/dysplastic cells are often numerous in urinary specimens, perhaps because patients have not been exposed to topical therapy. The abnormally high number of cells is often the most important clue to the presence of a low grade carcinoma or PUNLMP and should be reported as "numerous cells, a very low grade neoplasm cannot be excluded," even if the cells themselves look relatively normal. Neoplastic cells tend to be loosely clustered. They have markedly eccentric nuclei and increased nuclear-cytoplasmic ratios. The nuclei are irregular, a feature usually manifested by a single notch, crease, or shallow depression. The nuclear chromatin is more granular than normal but evenly dispersed. Large nucleoli are not a feature of these cells but are typical of the reactive or regenerative elements from which they must sometimes be distinguished. Importantly, ***all of the features listed in Table 5 are usually not present in every cell.***

The cytohistologic correlation is not always exact, even when the diagnostic approach recommended here is utilized. Given the cytopathologic interpretations listed on the left, the histologic correlates on the right can be expected [186].

high grade neoplasm	urothelial carcinoma, high grade carcinoma in situ
low grade neoplasm	urothelial carcinoma, low grade urothelial carcinoma, high grade
dysplastic cells,	PUNLMP
rule out low grade neoplasm	urothelial carcinoma, low grade

The cells of squamous cell carcinomas, small cell carcinomas, and some adenocarcinomas can be distinguished in urinary specimens but the subject is beyond the scope of this monograph.

f) Limitations in the Use and Interpretation of Urinary Specimens

Consultations based on urinary specimens have been

extremely beneficial in certain clinical situations, primarily to identify high grade neoplastic cells in the bladders of patients being monitored for persistent or recurrent disease. The use of urinary cytopathology has limitations in the following areas:

- screening the asymptomatic population;
- detection in the upper collecting system;
- detection of renal parenchymal carcinomas;
- detection of prostatic carcinomas;
- localization of neoplasms;
- detection of nonaggressive neoplasms;
- detection of some adenocarcinomas and some squamous cell carcinomas of the urinary bladder;
- detection of nonurothelial neoplasms;
- detection of neoplasms with little or no surface components, even though they may be deeply invasive;
- detection in single specimens versus multiple specimens from the same patient; and
- detection in random voided urine, especially versus bladder washings.

The interpretation of urinary specimens can be confounded by nuclear changes caused by polyoma viruses, most commonly BK. Polyoma viruses are ubiquitous in the population but pathogenic to the kidney only in patients with disorders associated with immunosuppression. In such cases, numerous cells with increased nuclear-cytoplasmic ratios and irregular nuclei can appear in urinary samples. Ordinarily, these cells have the smudged nuclear chromatin typical of viral infection. The fact that many patients have been treated with cyclophosphamide may further confound the interpretation of any particular case.

Electrocautery, applied prior to specimen collection, can alter the shape and cytoplasmic orientation of neoplastic cells, thus destroying features important to accurate interpretation.

Exposure of urothelium to alkylating agents such as mitomycin C often results in enlargement and increased chromatin in the nuclei of superficial cells. In fact, nearly every feature described for high grade malignancy can be seen in superficial cell nuclei. Fortunately, superficial cells retain their very low nuclear-cytoplasmic ratios and polygonal shape even after exposure to alkylating agents, thus allowing accurate assessment by knowledgeable cytopathologists.

Patients in the age group most likely to develop bladder neoplasms are also prone to prostatism, bladder outlet obstruction, and trabeculated bladders. Urinary specimens from such individuals often contain balls of cells that can be mistaken for neoplastic papillary aggregates. The cells in these balls lack features of a neoplasm and should not be interpreted as emanating from a low grade papillary neoplasm.

Urinary specimens from the ureters and renal pelves are collected with instrumentation and are ordinarily very cellular. The cells of the upper collecting system tend to be larger than cells from the bladder and tend to have higher nuclear-cytoplasmic ratios, 2 features important to the assessment of low grade neoplasms. The absence of other features of a low grade neoplasm (eccentric nuclei, increased chromatin, and nuclear irregularities) facilitates the correct interpretation in most instances. Nevertheless, we recommend that a cytopathologic interpretation of low grade neoplasm be made and accepted with caution when specimens represent the upper collecting system.

Urinary calculi have traditionally been listed among the confounding factors in the interpretation of urinary specimens but this should not be the case. Stones may cause regenerative changes in urothelial cells but these changes should be readily distinguishable from those of a neoplasm, especially when so-called “papillary” aggregation is discounted as an important diagnostic feature.

g) Urinary Cytopathology and Ancillary Tests

A good deal of the recent interest in the early detection of “bladder cancer” centers on finding ways to augment rather than replace urinary cytopathology. Many of these methods are designed to recognize substances in urine that can be measured with laboratory tests alone but some require prior identification of the abnormal (tumor?) cells themselves. Perhaps the best studied of these latter methods is image cytometry [192,205,207,211,215]. Total DNA, expressed as DNA ploidy, can be quantified on selected cells and the results recorded in histograms. In certain cases, this approach can add sufficient confidence to allow an interpretation of “positive” rather than “suspicious” or “atypical.” If enough abnormal cells are present, it may not be necessary to assess them by standard light microscopy but to simply create a histogram from Feulgen-stained material instead. DNA aneuploidy is primarily a feature of high grade urothelial neoplasms, those that are most readily recognized in urinary samples using light microscopy alone.

Abnormal cells in urinary specimens can be assessed for chromosomal aberrations using in situ hybridization or fluorescence in situ hybridization (FISH) [215-217]. If a positive result is defined in terms of only a few cells, this approach can detect recurrent disease long before sufficient cells have accumulated to form a lesion that can be identified by other methods. Of course, the definition of "positive" on the basis of very few cells (1-5 in various publications on the subject) creates its own problems. How many cells are required to achieve the critical mass necessary for a functional recurrence?

Abnormal cells in urinary specimens can be reacted with various antibodies considered to be indicative of neoplastic differentiation [206,207,218,219]. Utilization of these aids can increase sensitivity, oftentimes too much. Perhaps just as importantly, they can allow the cytopathologist to make an unequivocal interpretation in selected cases.

Abnormal cells identified by the cytopathologist can be further analyzed morphometrically [220]. Precision is facilitated by a limited number of measurements augmented by certain calculations.

Many of these approaches are not new. They have not been widely adopted primarily because the increased diagnostic yield does not justify the expense in time, training, and physical resources. Like other methodologies, the benefits are mostly in the detection of low grade, nonaggressive lesions - circumstances in which early detection is not favorably balanced by the level of false positive and negative results.

The important need in early detection of urothelial neoplasms is for a method to identify *high grade* cancers and the research community should be urged, if not required, to focus on this aspect of the issue rather than being rewarded for a generalized approach that detects nonaggressive lesions.

h) Interobserver Variation

The subject of urinary cytopathology cannot be addressed without discussing interobserver variation. As a medical consultation rather than an observation of unequivocal facts, a certain level of legitimate difference of opinion is inevitable. Differences of opinion among cytopathologists affect diagnostic yield and must be factored into any assessment of the clinical value of this approach to detection. An irreducible level of interobserver variation is probably 15% but the issue has rarely been addressed. Instead, the focus has usually been on the adoption of a single nomenclature and, when disagreement on the interpretation occurs within the same nomenclature system, additional cytopathologist education in the cellular features of urothelial neoplasms. The notion that a uniform nomenclature applied by a diagnostic clone of cytopathologists would significantly improve patient care cannot be accepted at face value any more than the proposition that serum PSA (uniformly assessed and reported in standard units) has resulted in a uniform approach to diagnosis and treatment. As long as pathologic diagnoses represent consultations based on the interpretations of human beings, a certain level of interobserver variation will exist and must be accepted.

If interobserver variation in pathology is to be reduced, it is important to understand the nature of pathologic interpretations. Central to this discussion is the fact that there is no phenotypic feature or group of features that all neoplastic cells have all of the time. Accurate assessment of whatever phenotypic changes are present at any particular time requires intuition as well as knowledge. If human carcinogenesis is the result of misregulation of an individual's "normal" physiology, then the early detection of a neoplasm using light microscopy requires recognition of phenotypic clues to dynamic processes *and* assumes that there is a direct and timely correlation between them.

Pathologists cannot accurately define the mental processes through which an interpretation is reached. The exercise has been tried by computer experts over many years. In the end, success in instructing a computer to interpret cellular changes was achieved by showing the instrument the image and asking it to "remember" that image and all future similar examples (neural net).

Pathologists do not "read" slides, as if all of the information were clearly written in some arcane text that only required fluency to decipher. Rather, they function more as critics, who are given a single snapshot of a game in progress and expected to divine the game and its likely outcome. Oftentimes, the snapshot contains the scoresheet but sometimes it contains only a single play and only a few of the players.

Improvement in interobserver variation is not likely to depend on better education or more consensus, at least so long as classification schemes remain complicated. A recent study may be revealing in this regard [221]. The 1998 WHO/ISUP classification scheme represents a broad consensus of experts in urologic pathology, as evidenced by their names list-

ed in the original publication [105]. The scheme is well-illustrated and has been presented in many forums. When a group of practicing pathologists attempted to use the system, a very high degree of agreement (91%) was achieved only when the goal was to distinguish low grade neoplasms (PUNLMP, low grade carcinoma) from high grade carcinomas (high grade carcinoma, CIS). In contrast, when the goal was to distinguish PUNLMP from low grade carcinoma, interobserver disagreement was 50%. And this level of interobserver variation occurred *after* the three collaborators had spent hours together educating themselves on the diagnostic features, viewing slides of the lesions, and creating a diagnostic paradigm. Neither lack of education, sloth, inexperience, nor absence of well-described and well-illustrated "criteria" are likely to account for the results. If anything, the problem lies in attempting to achieve more refinement in classification than the "methodology" can support. The more decision points a system requires and the closer the distinguishing features between one class and another, the more likely that disagreements will occur. In the case of urinary cytopathology, substantial interobserver agreement can be achieved for high grade neoplasms because nearly all of the tumor cells manifest nearly all of the features described and illustrated in the literature. This is not the case for dysplastic or low grade cells, where many of the cells in any sample will lack some or most of the features.

The cytopathologic assessment of urinary specimens is a valuable means to detect tumor cells in patients suspected of harboring a "bladder cancer." Despite its limitations this approach is currently the single most efficacious way to monitor patients for clinically important disease.

4. Imaging of Bladder Cancer at Initial Diagnosis

a) Evaluation of the Upper Urothelial Tract

Most patients with bladder cancer present with hematuria; therefore, they often undergo intravenous urogram (IVU) before the bladder tumor is discovered. Nevertheless, several authors suggest that routine IVU is unnecessary at the initial diagnosis of bladder tumor because synchronous upper tract urothelial cancer is rare, occurring in only 0.3% to 2.3% of cases *(Level 3,* [160,222,223]*)*. The stage, grade, and volume of the primary bladder cancer do not correlate with the risk of upper tract cancer; therefore, these characteristics cannot be used to predict which patients need an IVU *(Level 3,* [222]*)*. In fact, there are no reliable criteria for selecting patients at high risk for upper tract cancers. Routine IVU is unnecessary at the initial diagnosis of bladder cancer, but many patients undergo IVU as part of a hematuria evaluation.

b) Staging of the Primary Bladder Tumor

IVU is not useful for staging bladder cancer; however, bladder tumors causing ureteral obstruction are often muscle-invasive *(Level 3,* [160,224]*)*. Ultrasound is not utilized for staging because of its limited ability to evaluate the perivesical tissue *(Level 3,* [225,226]*)*. Computerized tomography (CT) scan and magnetic resonance (MR) imaging delineate the perivesical tissue, but staging accuracy is quite variable, ranging from 40% to 98% *(Level 3,* [227-229]*)*. MR is slightly more accurate for staging than CT *(Level 3,* [226]*)*.

When pelvic imaging is performed after TURBT, staging accuracy drops to 32% to 55% because postoperative inflammation mimics the appearance of tumor infiltration *(Level 3,* [225,227-229]*)*. Ultra-fast dynamic MR sequences may be a more reliable method for distinguishing residual tumor from postoperative inflammation *(Level 3,* [230]*)*. Currently, MR and CT are not accurate enough for staging of the primary tumor (especially after TURBT), but they are utilized for assessing the presence of metastases *(Level 3,* [228]*)*.

c) Metastatic Evaluation

The accuracy of MR and CT for staging of the lymph nodes ranges from 70% to 98% *(Level 3,* [225,226], with a false negative rate of 20% to 40% *(Level 3,* [225,228]*)*. The main limitation of abdominal and pelvic imaging is that it cannot detect local or distant microscopic cancer invasion, which leads to significant understaging *(Level 3,* [227-229]*)*. Furthermore, routine abdominal and pelvic imaging rarely alters the management of patients with invasive bladder cancer *(Level 3,* [228,231]*)*.

The usual metastatic evaluation for invasive bladder cancer includes chest radiograph, liver function tests, and alkaline phosphatase *(Level 4,* [232]*)*. Abdominal and pelvic imaging (CT or MR) is often reserved for patients with abnormal liver function tests, advanced local cancer based on TURBT and bimanual examination, or high clinical suspicion of metastasis [231, *Level 3*; 232, *Level 4*]. Bone scan is unnecessary in most cases; however, it should be considered when alkaline phosphatase is elevated or bone pain is present *(Level 3,* [233-235]*)*.

5. CYSTOSCOPY

a) Appearance of the Tumor

Appearance of bladder tumors by cystoscopy is important for diagnosis and treatment. Information such as number, size, shape, and location of tumors is easily obtained. Experienced urologists can determine the degree of difficulty of TUR and decide the necessity of obturator nerve block immediately after the first look by cystocope. Utz et al. reported the features of tumors determined by cystocopy in 1973; 20% of the tumors were on the right lateral wall, 15% on the left lateral wall, 17% on the posterior wall, and 10% on the trigone [236]. In 31 patients, the lesions were multiple, but in only 7 patients was more than 1 wall involved. Twelve cancers (6%) were discovered in diverticula.

Cystoscopically, the appearance of the bladder tumor can be classified according to characteristics of the surface and the base of the tumor. Approximately 70% of urothelial tumors are papillary, 10% are nodular, and 20% are mixed.

Similarly, according to the cystoscopic appearance of the base of tumor, bladder neoplasms may be pedunculated or sessile tumors. A majority of low grade urothelial carcinomas are well-pedunculated tumors.

CIS is a flat lesion in the bladder mucosa and may appear as a velvety patch of erythematous mucosa, although quite often it is endoscopically invasive.

Inverted papilloma is a benign proliferative lesion associated with chronic inflammation or bladder outlet obstruction. The appearance of an inverted papilloma is usually a papillary tumor covered by a normal urothelium and may contain an area of cystitis cystica or squamous metaplasia.

Relatively rare tumors in the bladder, urachal carcinomas have a sharp demarcation between the tumor and adjacent bladder epithelium, with the tumor being located in the bladder wall beneath the normal epithelium. Bladder pheochromocytoma appears as a submucosal nodule covered by intact urothelium.

In contrast to the importance of pathological staging of tumor by TUR specimens, whether additional prognostic information can be obtained from cystoscopy remains controversial. Mulders et al. and Jakse et al. reported that patients with multiple tumors were more likely to recur than patients with single tumors [237,238]. Jakse et al. also reported that wide-based tumors were more likely to be poorly differentiated and grade 3 [238].

Regarding the number of tumors (or sites), Pagano et al. reported that 72.5% of 200 patients with superficial bladder tumors had solitary lesions, 11.5% had between 3 and 5 sites, and 16% had more than 5 sites [136]. They found that patients with multifocal tumors were more likely to recur and infiltrate. Abel et al. studied 107 patients with superficial tumors. Of 107 patients, 65 (61%) had single tumors and 42 (39%) had multiple tumors. Of 65 patients with single tumors, 49 (75%) had pTa tumors compared to 64% of patients with multiple tumors [239]. Lutzeyer et al. reported the progression rates in solitary pTa and pT1 tumors of 18% and 33% and 43% and 46%, respectively, for multiple tumors [240].

Pagano et al. divided the patients into 3 groups based on the size of the tumors - diameter less than 1 cm, 1 to 3 cm, and greater than 3 cm *(Level 3,* [165]*)*. They found no correlation between the size and the grade, and the progression of the tumor was not influenced by the size of the tumors.

Dalesio et al. conducted a randomized clinical trial of 308 patients with stage T1 cancer to compare the efficacy of TUR alone or TUR followed by intravesical chemotherapy [241]. Of the 296 patients, 201 (68%) had a largest tumor greater than 2 cm in diameter and the remaining 95 had tumors greater than 3 cm. Those patients with tumors less than 2 cm in diameter had a marginally lower recurrence rate than those with tumors greater than 3 cm ($P = 0.096$).

b) Fluorescence Endoscopy

White light endoscopy of the lower urinary tract is limited in detection of bladder cancer. Flat neoplastic urothelial lesions such as dysplasia and CIS can be concealed in normal-appearing mucosa or nonspecific inflammatory-appearing mucosa. The value of random biopsies, which were initially recommended when flat lesions are suspected, was challenged by Witjes et al., who showed in a cooperative study of 1026 unselected patients that biopsies of normal-appearing mucosa were of little value in determining a patient's prognosis *(Level 3,* [242]*)*.

The risk of overlooking even papillary tumors is significant. Grimm et al. reported that after transurethral resection of superficial bladder cancer, residual tumor has been identified in 33% of cases at repeat resection *(Level 3,* [243]*)*. In 28% of the patients with fractional resection of T1 urothelial carcinoma, residual tumor was found at the margins of the resected area *(Level 3,* [244]).

Patients with newly-diagnosed, superficial, well- or moderately-differentiated tumors had significantly

less recurrence when the bladder was free of tumor 3 months after the initial resection (*Level 3,* [245]).

For years, methods of labeling urothelial neoplasmas have been sought [246,247]. Fluorescent photodetection of neoplastic urothelial lesions using 5-aminolevulinic acid was first described in 1994 (*Level 2,* [248]). 5-ALA is a precursor of heme biosynthesis. Following intravesical instillation, 5-ALA induces selective enhancement of protoporphyrin IX with a strongly fluorescent dye in the mucosa of neoplastic lesions. The fluorescence is excited with blue light (375–440 nm) and becomes visible using an observation filter in the eyepiece of the endoscope for color contrast enhancement (*Level 2,* [249]).

Photodetection using 5-ALA has proved to have high sensitivity for detecting early stage bladder cancer, ranging from 87% to 96%. Specificity is less due to inflammatory lesions (*Levels 2 and 3,* [250-255]). These lesions are found especially after intravesical chemotherapy, BCG treatment, and endoscopic resection (*Level 2,* [256]). Photodetection is recommended primarily for evaluation of the untreated urothelium or if the mucosa has healed after the treatment. Quantification of 5-ALA-induced fluorescence improves the specifity by 30% without affecting the sensitivity (*Level 3,* [257]*).*

Detection of flat neoplastic lesions that can easily be missed during white light endoscopy was significantly enhanced by using 5-ALA photodetection. In comparison to white light cystoscopy, up to 53% more patients with CIS were found (*Level 3,* [258]). Sixty-three patients with cytology positive or suspicious for disease and a negative standard cystoscopy underwent photodetection. In 51 of these cases (80.9%), the cytological findings were verified by fluorescence endoscopy detecting the precise site of malignancy within the bladder. The 12 remaining patients from this group did not show positive fluorescence and no positive histology was found in the random biopsies taken. In all of these cases, neoplastic disease of the upper urinary tract was excluded by a retrograde pyelography (*Level 3,* [259]). In order to improve the diagnostic quality of the procedure, an ester of aminolevulinic acid, hexaminolevulinate (HAL), was investigated in a multicentric study. It was found that photodetection with HAL indentified 28% more patients with CIS than standard cystoscopy (*Level 3,* [260]).

Photodetection of neoplasias that were missed under white light cystoscopy resulted in a change in treatment strategy in 9% (*Level 3,* [261]). Three prospective randomized studies have clearly shown that the risk of residual tumor after transurethral resection of urothelial carcinoma is significantly decreased by 5-ALA fluorescence endoscopy (*Level 3,* [262-264]).

One prospective single center randomized Phase III trial is published, which focuses on the risk of recurrent tumor after transurethral resection with 5-ALA photodection compared with conventional white light endoscopy. Recurrence-free survival in the fluorescence group was 91% after 24 months compared with 70% in the white light group ($P = 0.0005$). The adjusted hazard ratio of photodiagnostic versus white light transurethral resection was 0.29 (95% Cl 0.15 to 0.56) and photodetection proved an independent prognostic factor (*Level 3,* [265]).

Fluorescence cystocopy clearly is superior to the conventional white light endoscopy. It seems to be well verified that the risk of residual tumor is reduced by fluorescence-guided resection. This may lead to lower recurrence rates, as has been shown in the first Phase III trial, but this has to be proven in further studies.

6. Transurethral Resection of Bladder Tumors (TURBT)

Transurethral resection of bladder tumors (TURBT) provides diagnostic information and often achieves therapeutic benefit. The goals of TURBT are to determine the stage and grade of the tumor (diagnostic) and to resect or fulgurate all grossly visible tumor when indicated (therapeutic). The technique for TURBT is based mainly on surgeon experience. The technique described below is based on a review by Shelfo and colleagues *(Level 4,* [266]*).*

General, spinal, or epidural anesthesia may be used. When resecting tumor on the lateral wall, general anesthesia with neuromuscular blockade may help prevent obturator nerve stimulation. Place the patient in the dorsal lithotomy position with the buttocks at the edge of the table. Pad all pressure points, especially the lateral proximal fibula. Prolonged pressure on this area can cause neurapraxia of the common peroneal nerve, resulting in foot drop. Perform a bimanual examination (preferably with the bladder empty), by placing one hand in the suprapubic region and one or two fingers of the other hand in the rectum (for males) or in the vagina (for females). The bladder and other pelvic organs are palpated between the two hands. Identify palpable masses and determine whether they are fixed to adjacent structures. Bimanual examination should also be performed after TURBT.

Insert the cystoscope and inspect the entire urethra. Examine the bladder with the 30 degree and 70 degree lenses. Visualization of the dome and anterior bladder may be enhanced by applying gentle suprapubic pressure, which moves the bladder wall closer to the endoscope. Adequate bladder distension unfurls the folds in the bladder and permits complete inspection of the urothelial surface. Overdistention of the bladder should be avoided because this can induce mucosal hemorrhage. Inspect the interior of any diverticula and cellules. Note the location and size of abnormal areas and their relation to the ureteral orifices.

A bladder wash cytology may be obtained before TURBT by irrigating normal saline through a catheter, cystoscope sheath, or resectoscope sheath (barbotage). Bladder wash cytology detects carcinoma in situ in almost all cases *(Level 3,* [198]), even when the urothelium appears grossly normal, and this obviates the need for routine random bladder biopsies *(Level 4,* [187]*).* During barbotage, the bladder wall can be drawn against the sheath, causing urothelial trauma that may mimic the appearance of CIS. Therefore, it is best to perform the bladder wash cytology after complete inspection of the bladder, though the urine collected immediately upon scope introduction should also be sent for pathologic review.

Insert the resectoscope sheath in an atraumatic fashion and begin resection. Continuous irrigation may improve visualization and prevent overdistention of the bladder. Utilizing a camera and video monitor can improve visualization by magnifying the image and reducing eye strain. With a video system, the surgeon may also experience less cervical stress and less risk of direct exposure to biohaz-ardous fluids. There are 2 basic techniques for performing TURBT: staged and en bloc.

a) Staged Resection

Staged TURBT may consist of several phases *(Level 3,* [267,268]*).* The first phase is resection of tumor that protrudes into the bladder lumen. Begin resecting superficially, starting at one side of the tumor and gradually progressing to the other side. Resect the next layer of tumor in the same fashion. This process is continued until the base of the tumor is reached. The second phase is resection of the base of the tumor and of a portion of the underlying bladder. Tissue removed during the second phase determines the depth of invasion and the status of the deep margins of resection. The third phase is resection of tissue surrounding the tumor base. Tissue removed during the third phase determines the status of the lateral margins of resection. The resected tissue may be combined and sent to the pathologist as a single specimen so that the tissue fragments are analyzed together (collective analysis) or the tissue from each phase may be isolated and sent as a distinct specimen so that each phase is analyzed separately (differential analysis). Some believe that differential analysis achieves more accurate characterization of the cancer *(Level 3,* [267,268]*),* while others believe that differential analysis is unnecessary *(Level 4,* [269]*).* A trial comparing the accuracy of differential and collective analysis has not been conducted.

b) En bloc Resection

The resection loop is approximately 1 centimeter in diameter. Therefore, tumors less than 1 centimeter may be resected in one whole specimen (en bloc resection) using the standard loop. Techniques for en bloc resection of tumors that are up to 3 centimeters in greatest dimension have also been described *(Level 3,* [270-272]*).* Proponents of en bloc resection believe that it may permit more accurate pathological assessment by preventing tumor fragmentation, by preserving the orientation of the tumor relative to the bladder wall, and by decreasing cautery artifact at the tumor base. However, data to support this concept is lacking. A trial comparing staged TURBT and en bloc TURBT has not been conducted.

After resection, obtain hemostasis. Then, inspect the bladder and the ureteral orifices and ensure that all tumor chips have been removed. The operative report should include a detailed description of the procedure including:

1) The appearance (flat, papillary, sessile), number, approximate size, and location of tumors. The size of a tumor can be estimated by using the 1 centimeter width of the resection loop as a reference.
2) The location and approximate depth of resection (superficial, into muscle, into perivesical fat).
3) Whether all gross tumor was removed or whether residual gross tumor remained.
4) Whether bladder perforation occurred.
5) Whether the ureteral orifice was resected or intact at the end of the procedure.
6) The results of the bimanual examination.

c) Tumor Resection in Specific Circumstances

1. DIFFUSE CIS

Because CIS is treated with intravesical therapy, it is probably best to biopsy areas suspicious for CIS and cauterize the affected surface. However, cauterization should be limited in cases when diffuse CIS is suspected because resection or fulguration of large areas may cause bladder contracture. If CIS is confirmed on the biopsies, treatment alternatives are then discussed.

2. MUSCLE-INVASIVE TUMORS

When muscle-invasion is suspected, resect as much tumor as feasible and enough tissue to verify the presence of tumor in the muscularis propria. Intraoperative pathology assessment can ensure that sufficient tissue is available to confirm muscle invasion. If the muscular layer is not evident because of tumor infiltration, the depth of the muscle may be more easily identified at the periphery of the tumor *(Level 3,* [267]*)*. When transurethral resection (alone or in combination with other bladder-sparing therapies) is used as a definitive treatment for muscle-invasive cancer, a deep re-resection can be performed *(Level 3,* [273]*)*. In this case, resection into the perivesical fat may be tolerated in order to remove the cancer.

3. TUMORS AT THE URETERAL ORIFICE

Extensive cauterization of tumors at the ureteral orifice can cause distal ureteral stenosis **(Level 3,** [274,275]**).** ***However, ureteral stenosis is uncommon when cutting current is used*** **(Level 3,** [276-278]). To prevent stenosis of the ureteral orifice, the following techniques have been proposed: employ exclusively cutting current *(Level 3,* [275-278]*)*, perform the resection at maximum controlled speed *(Level 3,* [275-278]*)*, and control bleeding with focal "pinpoint" light touch coagulation using low intensity current *(Level 3,* [275,276,278]*)*. A temporary ureteral stent may maintain a patent distal ureter during healing; however, it is unclear whether it reduces the risk of stenosis. Stent placement may be prudent in patients with a solitary kidney or poor renal function *(Level 4,* [266]*)*. ***To check for postoperative obstruction, a functional study (for example, an intravenous urogram or nuclear renal scan) is recommended 3 to 6 weeks after resection of the ureteral orifice (****Level 4,* [266]; *Level 3,* [279])**.**

Resection of the ureteral orifice can lead to vesicoureteral reflux *(Level 3,* [277,278,280]*)*. In adults, complications from reflux are uncommon, but may include flank pain *(Level 3,* [280]*)*, urinary tract infection *(Level 3,* [277,278]*)*, and deterioration of renal function *(Level 3,* [278,281]*)*. Bladder outlet obstruction may increase the likelihood that reflux becomes clinically significant *(Level 3,* [280]*)*. Reflux increases the occurrence of upper tract tumors by 15- to 22-fold *(Level 3,* [281-284]*)*. Therefore, surveillance of the upper tracts should be conducted more frequently in patients with reflux an d a history of bladder cancer *(Level 3,* [283,284]*)*. It is unclear whether patients with reflux after TURBT require treatment; however, they should probably be treated if they develop pain, recurrent urinary infections, or renal deterioration *(Level 3,* [285]*)*. Vesicoureteral reflux after TURBT has been successfully treated with endoscopic injection of a bulking agent below the intramural ureter *(Level 3,* [286]*)*.

4. TUMORS ON THE ANTERIOR SURFACE

Tumor on the anterior wall may be more easily engaged by counter pressure on the suprapubic region with the nondominant hand *(Level 4,* [266]*, Level 3,* [274]). This maneuver moves the bladder wall closer to the resectoscope.

5. TUMORS ON THE LATERAL WALL/OBTURATOR NERVE STIMULATION

Resection of tumors on the lateral wall can stimulate the obturator nerve, resulting in sudden adduction of the leg. This abrupt movement can force the resectoscope into the bladder wall and lead to bladder perforation. Methods to reduce obturator nerve stimulation include using general anesthesia with neuromuscular blockade, *(Level 4,* [266]*, Level 3,* [287,288]) performing obturator nerve block with a local anesthetic *(Level 4,* [266]*, Level 3,* [288,289]), avoiding overdistending the bladder [266], lowering the resection current [266], and using intermittent instead of continuous cautery [266].

6. TUMORS IN BLADDER DIVERTICULA

Tumors in diverticula present several diagnostic and therapeutic dilemmas. First, ***the diverticular wall is thinner than the normal bladder because it lacks a muscular layer (absent muscularis propria). A thinner wall may increase the risk of perforation when attempting to completely resect the tumor***. Second, a thinner wall may permit the tumor to invade into the extravesical tissue more rapidly. Third, the absence of muscularis propria may make accurate staging difficult. Some authors suggest that stage pT2 should be omitted for diverticular tumors, and that staging should progress from pT1 directly to pT3 *(Level 3,* [290]).

Golijanin and colleagues recently presented a systematic approach to the evaluation and treatment of diverticular tumors *(Level 3,* [291]*)*. Based on bimanual examination under anesthesia, transurethral resection or biopsy of the tumor, and pelvic imaging (computerized tomography or magnetic resonance imaging), the diverticular tumors were classified as noninvasive (Ta or Tis), invasive but confined to the diverticulum (T1), or invasive into extradiverticular tissue *(Level 3,* [291]*)*. The best treatment options for large, high grade, or extravesical tumors is probably diverticulectomy, partial cystectomy, or radical cystectomy (*Level 4,* [266], *Level 3,* [291,292]*)*. For small, low grade, and noninvasive tumors, transurethral resection or fulguration may be appropriate (*Level 4,* [266], *Level 3,* [291,292]*)*. Intravesical therapy may also be utilized *(Level 3,* [291,292]*)*. and may be particularly useful when CIS is present or when resection of the tumor is incomplete. Stage pT1 tumors may be treated with either open surgical excision or transurethral surgery and intravesical therapy *(Level 3,* [291]*)*.

d) Other Important Considerations

1. Avoiding Bladder Perforation

Bladder perforation may increase the risk of postoperative hemorrhage, urinary tract infection, and sepsis *(Level 3,* [293]*)*. The cancer death rate appears to be higher in patients whose bladder is perforated during TURBT, presumably because tumor cells implant in the extravesical tissue *(Level 3,* [293]*)*. Therefore, ***avoiding bladder perforation optimizes oncologic control and minimizes surgical complications***. Methods to prevent bladder perforation include:

- **Use caution when resecting a tumor in a diverticulum.** The diverticular wall is thinner than the normal bladder wall.
- **Avoid the obturator reflex.** An obturator reflex generates an abrupt leg movement that can contribute to perforation.
- **Avoid bladder overdistention** [266]. Overdistention can increase the risk of perforation by reducing the bladder wall thickness and by increasing the intravesical pressure. A continuous flow resectoscope may help prevent overdistention.
- **Administer adequate anesthesia.** Adequate anesthesia reduces patient movement during the procedure and may help relax the bladder.
- **Avoid deep resection at the base of low grade, stage Ta tumors.** Deep resection of tumors that appear superficial is probably unnecessary and may increase the risk of bladder perforation [266].

2. Reducing Cautery Artifact

Data on preventing cautery artifact is lacking. To reduce cautery artifact during resection, the surgeon should use pure cutting current at the lowest possible setting. Coagulating current should be reserved for hemostasis after the tissue has been removed. Cold cup biopsies may be performed prior to resection when the surgeon prefers to avoid cautery artifact.

e) Role of Repeat TURBT

The management of bladder cancer is dependent upon an adequate transurethral resection of the bladder tumor (TURBT) and accurate staging and grading of the disease. Most significantly for high grade Ta and T1 lesions, it is incumbent for the urologist to assure that the tumor is actually not muscle-invasive, since this typically changes the treatment options.

Herr retrospectively evaluated the concordance of the pathological diagnoses between an initial resection and a second TURBT in 150 patients *(Level 3,* [294]*)*. The results of the second resection changed the treatment in 33% of the patients. He importantly noted the inability to accurately diagnose T1 tumors without muscle in the specimen. Of 23 patients with T1 lesions without muscle in the primary resection, 11 (49%) were upstaged to T2 lesions after review of the second TURBT specimen. A caveat of this study is that not only did different urologists perform the first and second TURBTs, but different pathologists read the first and second bladder tumor specimens. Dutta et al. similarly reported a 64% risk of understaging T1 lesions when muscle was absent compared to only 30% when muscle was present in the TURBT specimens *(Level 3,* [295]*)*.

Other authors have found that primary resection of a T1 bladder tumor may be inadequate to remove all tumors. Zurkirchen et al. retrospectively reviewed those patients who underwent follow-up TURBTs within 6 weeks of their initial resections *(Level 3,* [296]*)*. Thirty-seven percent of patients with initially diagnosed T1 bladder tumors had persistent tumors on second resection. Grimm et al. similarly retrospectively reviewed 83 patients who underwent repeat TURBT a mean of 7 weeks after initial TURBT *(Level 3,* [243]*)*. Residual tumor was found in 33% of cases, including 53% of those with bladder tumors initially diagnosed as T1. On univariate analysis, both tumor stage and grade were identified as predictive for residual tumor on restaging TURBT. Furthermore, after 5 years there was a significant decrease in disease-free survival between those who underwent a second TURBT and those

who did not (63% and 40%, respectively). Brauers et al. evaluated 42 patients with moderate or high grade T1 bladder tumors and reported that 24% of patients were upstaged to T2 or Tis on restaging TURBT *(Level 3,* [297]*)*. Schips et al. prospectively evaluated the findings at first and second TURBT for patients with high grade T1 bladder tumors and found residual disease in over 50% of patients *(Level 3,* [298]*)*. Both multifocality and tumor grade increased the risk of finding residual tumor on second TURBT. While 76% of patients with a solitary T1 lesion at first TURBT had a negative second TURBT, only 53% of those with multifocal T1 lesions had a negative repeat TURBT. Moreover, 73% of those with papillary-appearing T1 lesions at first resection had a negative repeat TURBT, compared to only 47% of those with solid-appearing T1 lesions. Klan et al. retrospectively evaluated 69 patients with stage T1 lesions on TURBT, of whom 46 agreed to a repeat TURBT within 2 weeks of initial resection *(Level 3,* [244]*)*. In 20 patients (43.5%), tumor was found at repeat TURBT. The authors noted that those who initially underwent a fractionated TURBT—all visible tumor is resected first, and the tumor margin and base are taken as separate samples—had a lower incidence of residual tumor on repeat TURBT than in those who underwent a standard TURBT.

There are no specific studies available at present regarding the optimal timing of second resection. However, the consensus opinion is that this should be performed within 1 to 4 weeks following the initial resection. May et al. and Sanchez-Ortiz et al. reported that delay of more than 12 weeks in muscle-invasive bladder cancer leads to significant upstaging of the disease *(Level 3,* [299,300]*)*. Hence, undue delay in second resection should be avoided.

In summary, these case control studies show that the risk of upstaging on second TURBT is at least 30% if muscle is present in the specimen and even higher if muscle is not present *(Level 3,* [294,295]*)*. Further, the risk of residual tumor on second TURBT is also significant. Even for solitary, papillary-appearing tumors the risk is 24% to 27%, and it is higher for multifocal, nonpapillary lesions *(Level 3,* [243,244, 294,296,298]*)*. Because of these significant rates, it is recommended that a second TURBT be performed in all patients with high grade Ta or any T1 urothelial carcinoma. Separate tumor base and margin biopsies decrease the chances of under staging *(Level 3,* [244]*)*. Although no evidence regarding the timing of a second TURBT is available, the consensus opinion is that this should be performed within 1 to 4 weeks following the initial resection.

f) Role of Random Bladder Biopsies

Bladder cancer is frequently multifocal and CIS or dysplasia can be found in bladder mucosa that is distant from the tumor in apparently normal-looking areas. It is well-known that the presence of CIS is a significant risk factor for tumor recurrence and progression and that therapeutic options need to be modified accordingly [301,302].

During TURBT, any abnormal appearing urothelium should be biopsied. However, the role of routine random bladder biopsies is still controversial [302-304].

In a European Organization for Research and Treatment of Cancer (EORTC) study, 393 patients with solitary Ta and T1 tumors underwent biopsy of normal appearing mucosa, and CIS was detected only in 6 patients (1.5%). In another EORTC study, 602 patients with multiple or recurrent Ta and T1 tumors (high-risk group) underwent multiple random bladder biopsies. Only 3.5% showed CIS in the random biopsies. Only 1 patient was found to have T2 disease unexpectedly and underwent cystectomy. The study showed that finding additional Ta tumor or CIS in the high-risk group did not change the clinical treatment in most cases and hence the authors concluded that routine random bladder biopsies are not necessary [305].

Taguchi et al. reported that CIS was detected in 14.5% of 83 patients [306]. Fujimato et al. performed random bladder biopsies in 100 consecutive patients [304]. In 8 of 100 patients, bladder cancers were detected in the biopsy specimens. Three cases were Ta and 5 were Tis. All of the 5 patients (17.9% [5/28]) with CIS in their biopsy specimens had multiple papillary broad-based tumors and positive urinary cytology. None of the 72 patients who had a solitary tumor, pedunculated tumor, or negative urinary cytology had concomitant CIS. They conclude that random bladder biopsies are necessary only for patients with multiple papillary broad-based tumors and positive urinary cytology. May et al., in a large series of 1033 patients, reported finding urothelial tumor on random bladder biopsies in 12.4% [302]. This included 7% with Ta, 4% with CIS, 1% with T1, and 0.1% with T2. More importantly, the treatment was altered in 6.8% of patients because of the random biopsy findings.

The potential risk of tumor implantation and tumor recurrence due to random bladder biopsy is contro-

versial. Levi et al. reported that cold cup bladder biopsy increased the risk of tumor recurrence in the presence of CIS [307]. On the contrary, Mufti et al. did not find tumor implantation as a risk factor for subsequent new tumor development [303]. Biopsy by wire loop electrocautery may not contribute to subsequent CIS but random bladder biopsy with cold cup biopsy forceps poses a possible risk for CIS, and hence the biopsy site should be thoroughly cauterized [307].

In summary, the role of random bladder biopsies is still controversial. Though there is no strong evidence to support either way, the consensus opinion is that the random bladder biopsy does not change the clinical treatment in most cases and hence is not recommended on a routine basis. It is recommended in cases with positive urine cytology and normal-appearing mucosa. In cases where random biopsies are indicated, there is no evidence to support the location and the number of biopsies that should be performed. However, it is common practice to perform 4 quadrant biopsies involving the anterior wall, dome, and posterior and lateral walls. In patients who elect to undergo partial cystectomy, random bladder biopsy is advisable.

Fluorescence endoscopy using 5-alpha aminolevulinic acid increases the chances of detection of CIS. Zaak et al. found that 52.8% of specimens with CIS had been missed under conventional white light cystoscopy [258]. Fluorescence endoscopy may become a useful tool for detecting CIS and may alter the practice of random bladder biopsy. The role of fluorescence endoscopy is discussed in detail later in this chapter.

g) Role of Prostatic Urethral Biopsy

Urothelial carcinoma (TCC) of the prostatic urethra in patients with bladder cancer significantly influences the prognosis and affects the choice of therapeutic modality. The reported incidence of primary prostatic urothelial carcinoma is low at 1% to 4% [308,309]. However, the incidence of concomitant urothelial carcinoma of the prostate and bladder is high but variable, ranging from 7% to 43% [310-312].

Nixon et al. reported prostatic urethral involvement in 30 of 192 patients (15.6%) who underwent cystectomy for bladder cancer [313]. Of 80 patients with CIS in the bladder, 31% had concomitant prostatic urethral involvement, whereas only 4.5% of the 112 with no evidence of CIS had prostatic urethral involvement. Likewise, 35% of the 72 patients with multifocal tumors had concomitant prostatic urethral involvement with carcinoma, whereas only 4.2% of the 120 with solitary tumor had prostatic urethral involvement. In the multivariate logistic regression model, the odds of prostatic urethral involvement were 12- and 15-fold greater when CIS and tumor multifocality were present, respectively.

Cystoscopy is a valuable tool in identifying prostatic involvement. Solsona et al. reported that in more than 75% of patients with prostatic urothelial carcinoma, the tumor was macroscopically visible on cystoscopy [314]. Nixon et al. reported that 97% of patients with prostatic urothelial carcinoma showed abnormalities of the prostatic urothelium on cystoscopy [313].

Sakamoto et al. reported that in 29 of 31 patients (93.5%) with urothelial carcinoma of the prostate, the disease was located at the 5 and 7 o'clock positions of the verumontanum [315]. Furthermore, at this location deep stromal invasion was high at 57.7% compared to other locations. Hence, they emphasized that a transurethral electrocautery loop biopsy of the prostate at the 5 and 7 o'clock positions of the verumontanum substantially improved the detection of prostatic involvement. Yield from the cold cup biopsy is inferior to resection biopsy.

In patients with high grade urothelial carcinoma of the bladder requiring intravesical treatment, it is imperative that the status of prostatic urothelium is assessed accurately. Those patients with urothelial carcinoma of the prostate will require formal bladder neck resection to facilitate effective contact between the intravesical medication and prostatic urethra.

Studies have shown that presence of prostatic urothelial carcinoma alone is not a contraindication for neobladder reconstruction and not an indication for synchronous urethrectomy [316,317]. However, preoperative knowledge of prostatic involvement helps the surgeon to counsel the patient and modify surgical procedures accordingly.

RECOMMENDATIONS

I. EPIDEMIOLOGY

1. For the geographical and temporal comparison of bladder cancer incidence rates, it is crucial to separate low grade Ta tumors from high grade CIS and pT1 or higher tumors *(Grade C).*
2. In epidemiological studies on risk factors for bladder cancer, it is advised to distinguish low grade Ta tumors from high grade CIS and pT1 or higher tumors *(Grade C).*
3. The risk of bladder cancer among workers in high-risk industries should be monitored continuously. If specific plants are suspected, the identification of the causative agent should be started immediately, preventive measures should be taken, and exposed workers may have to be screened for bladder cancer for at least 2 decades *(Grade D).*
4. Both epidemiology and toxicology studies should evaluate the role of hair dyes for the development of bladder cancer. Epidemiologists should agree on (and validate) a standard questionnaire for exposure to hair dyes *(Grade D).*
5. Through international collaboration, families with at least 3 first degree relatives with bladder cancer should be collected for the mapping and identification of bladder cancer susceptibility genes *(Grade D).*
6. Consensus should be reached over a screening protocol for unaffected members of such bladder cancer families. Until then, it is suggested to start screening at the age of 40 or 5 years earlier than the age of the youngest patient in the family *(Grade D).*
7. Little is known about lifestyle and constitutional factors in relation to prognosis. Therefore, future epidemiological studies should include follow-up data in order to learn more about the effects of these factors on prognosis *(Grade D).*
8. Future studies on the role of genetic polymorphisms and their modifying effect of lifestyle risk factors should take a more systematical high-throughput approach instead of a SNP by SNP approach. International collaboration will be necessary to reach sufficient power for such studies while avoiding many false positive associations *(Grade D).*

II. STAGING AND GRADING

1. The WHO/ISUP, now the WHO 2004, should be the only classification system used to diagnose bladder lesions. Although initially there had been conflicting reports of how well the category of papillary urothelial neoplasm of low malignant potential correlates with prognosis, subsequent studies have shown differences in prognosis and progression from low grade papillary carcinoma *(Grade B).*
2. Substaging of T1 tumor based on muscularis mucosa invasion should not be universally adopted or advocated to pathologists *(Grade D).*
3. For pT1 tumors, the presence or absence of muscular propria should be reported *(Grade B).*
4. For pT1 tumors, pathologists should provide assessment of the depth of lamina propria invasion or extent of the disease *(Grade B).*
5. There is little evidence supporting the substaging of T2 tumor based on the depth of muscularis propria invasion. Distinction between pT2a and pT2b tumor is unnecessary *(Grade B).*
6. Tumor size should be included in the subclassification of pT2 tumors *(Grade C).*
7. Distinction between pT3a and pT3b tumor is unnecessary *(Grade C).*
8. Subclassification of patients who have prostatic urethral involvement, based on the presence or absence of stromal invasion, is recommended *(Grade D).*

III. DIAGNOSIS

1. Currently there is no evidence available to show that bladder cancer screening is helpful in improving the survival. However, further studies are warranted to evaluate the true value of bladder cancer screening *(Grade C).*
2. Screening should probably be confined to patients at high risk for bladder cancer *(Grade C).*
3. Screening may consist of a yearly urine cytology and dipstick for hematuria *(Grade C).*
4. There is no correlation between the number of red cells per high power field seen on urine microscopy and the diagnosis of bladder cancer *(Grade B).*
5. Nearly all patients with bladder cancer diagnosed on cystoscopy have either some form of microhematuria or macroscopic hematuria. Hence, patients with microscopic or macroscopic hematuria require further evaluation such as flexible cystoscopy *(Grade D).*
6. Microscopic hematuria in patients with bladder cancer is variable and intermittent and hence a single negative urinalysis for hematuria does not exclude bladder cancer *(Grade C).*
7. In patients with irritative voiding symptoms such as dysuria, frequency, and urgency, bladder cancer, particularly carcinoma in situ, must be ruled out *(Grade C).*

8. It is recommended that the cytopathologist should use uniform nomenclature; currently, the 1998 WHO/ISUP Consensus classification is widely accepted *(Grade C).*
9. Bladder wash cytology provides better diagnostic yield than voided urine cytology (*Grade B).*
10. When a cystoscopy is performed, the residual urine should be collected for cytology. A thorough cystoscopy with minimal manipulation should be performed, which should be followed by a formal bladder lavage. Both specimens should be sent for cytopathology *(Grade D).*
11. Urine cytology is best used for the follow-up of patients with urothelial neoplasms in order to diagnose high grade tumor recurrence *(Grade C).*
12. Routine IVU is unnecessary in the initial assessment of bladder cancer; however, many patients undergo this examination as part of a hematuria evaluation *(Grade B).*
13. For invasive bladder tumors,
    a. Metastatic evaluation should include chest radiograph, liver function tests, and alkaline phosphatase *(Grade C).*
    b. Abdominal and pelvic imaging (MR or CT) is not accurate for staging of the primary bladder tumor, but may be useful when metastatic disease is suspected. *(Grade B).*
    c. Bone scan is unnecessary in all cases, but it should be performed in the presence of bone pain or elevated alkaline phosphatase *(Grade B).*
14. The shape, size, and location of the tumor should be documented explicitly as this provides important prognostic information *(Grade C).*
15. Carcinoma in situ may present as velvety erythematous patches. The endoscopist should specifically look for these changes and all suspicious lesions should be biopsied *(Grade C).*
16. Appearance of the base of the tumor, whether sessile or pedunculated, should be documented, as this finding often predicts the invasiveness of the tumor *(Grade C).*
17. Fluorescence cystoscopy improves the detection rates of carcinoma in situ *(Grade B).*
18. Fluorescence-guided transurethral resection of bladder tumor decreases the chance of residual tumor *(Grade B).*
19. Though fluorescence cystoscopy appears promising, further multicentric studies are required before it can be accepted in to routine clinical practice *(Grade C).*
20. At the present time, there is insufficient information to recommend a specific resection technique or method of pathologic evaluation of TURBT specimens. Urologists and pathologists should select systems with which they feel comfortable *(Grade D).*
21. During TURBT, complete tumor resection should be attempted except for diffuse carcinoma in situ *(Grade C).*
22. During TURBT, bladder perforation should be avoided *(Grade C).*
23. When resecting the ureteral orifice, cutting current should be used. Avoid coagulation of the ureteral orifice. Three to 6 weeks after resecting the ureteral orifice, obtain a functional study to check for stenosis *(Grade C).*
24. Aggressive resection of a tumor in a bladder diverticulum can lead to perforation. Low grade, noninvasive tumors in a diverticulum may be treated by transurethral resection or fulguration with or without intravesical therapy *(Grade C).*
25. A second TURBT should be performed in all patients with a high grade Ta lesion or any T1 lesion *(Grade B).*
26. Separate tumor base and margin biopsies should be performed during TURBT *(Grade C).*
27. The suggested optimal timing of repeat TURBT is within 1 to 4 weeks after the first resection *(Grade C).*
28. Routine random bladder biopsies are not recommended *(Grade C).*
29. Patients with positive urine cytology and normal bladder should undergo random bladder biopsies *(Grade B).*
30. In patients undergoing partial cystectomy, random bladder biopsies are recommended *(Grade C).*
31. If cold cup biopsies are performed, the biopsy site should be cauterized thoroughly *(Grade C).*
32. Routine prostatic urethral biopsy is not indicated. Prostatic urethral resection biopsy is indicated in cases of multifocal urothelial carcinoma of the bladder, CIS, and visible abnormalities of the prostatic urothelium *(Grade B).*
33. Prostatic urethral biopsies should be performed using electrocautry loop resection including the 5 and 7 o'clock positions of the verumontanum *(Grade B).*

REFERENCES

1. Parkin DM, Whelan SL, Felay J, Teppo L, Thomas DB. Cancer Incidence in Five Continents. Lyon, IARC: 2002.
2. Ferlay, Bray, Pisani, and Parkin. GLOBOCAN 2000: Cancer Incidence, Mortality and Prevalence Worldwide, Version 1.0. IARC CancerBase No. 5. 2001. Lyon, IARC Press.
3. Mungan NA, Aben KK, Schoenberg MP, Visser O, Coebergh JW, Witjes JA, Kiemeney LA. Gender differences in stage-adjusted bladder cancer survival. Urology 2000;55(6):876-880.
4. Cantor KP, Lynch CF, Johnson D. Bladder cancer, parity, and age at first birth. Cancer Causes Control 1992;3(1):57-62.
5. Green A, Beral V, Moser K. Mortality in women in relation to their childbearing history. BMJ 1988;297(6645):391-395.
6. Miller AB, Barclay TH, Choi NW, Grace MG, Wall C, Plante M, Howe GR, Cinader B, Davis FG. A study of cancer, parity and age at first pregnancy. J Chronic Dis 1980;33(10):595-605.
7. Plesko I, Preston-Martin S, Day NE, Tzonou A, Dimitrova E, Somogyi J. Parity and cancer risk in Slovakia. Int J Cancer 1985;36(5):529-533.
8. Reid LM, Leav I, Kwan PW, Russell P, Merk FB. Characterization of a human, sex steroid-responsive transitional cell carcinoma maintained as a tumor line (R198) in athymic nude mice. Cancer Res 1984;44(10):4560-4573.
9. Prout GR, Jr., Wesley MN, McCarron PG, Chen VW, Greenberg RS, Mayberry RM, Edwards BK. Survival experience of black patients and white patients with bladder carcinoma. Cancer 2004;100(3):621-630.
10. Schairer C, Hartge P, Hoover RN, Silverman DT. Racial differences in bladder cancer risk: a case-control study. Am J Epidemiol 1988;128(5):1027-1037.
11. SEER. Cancer Statistics Review, 1975-2001. Ries LAG, Eisner MP, Kosary CL, Hankey BF, Miller BA, Clegg L, Marrioto A, Feuer EJ and Edwards BK. 2004. Bethesda, MD, National Cancer Institute.
12. Foster F. New Zealand Cancer Registry report. Natl Cancer Inst Monogr 1979(53):77-80.
13. Marcus PM, Hayes RB, Vineis P, Garcia-Closas M, Caporaso NE, Autrup H, Branch RA, Brockmoller J, Ishizaki T, Karakaya AE, Ladero JM, Mommsen S, Okkels H, Romkes M, Roots I, Rothman N. Cigarette smoking, N-acetyltransferase 2 acetylation status, and bladder cancer risk: a case-series meta-analysis of a gene-environment interaction. Cancer Epidemiol Biomarkers Prev 2000;9(5):461-467.
14. Vineis P and Simonato L. Proportion of lung and bladder cancers in males resulting from occupation: a systematic approach. Arch Environ Health 1991;46(1):6-15.
15. Markowitz SB and Levin K. Continued epidemic of bladder cancer in workers exposed to ortho-toluidine in a chemical factory. J Occup Environ Med 2004;46(2):154-160.
16. Popp W, Schmieding W, Speck M, Vahrenholz C, Norpoth K. Incidence of bladder cancer in a cohort of workers exposed to 4-chloro-o-toluidine while synthesising chlordimeform. Br J Ind Med 1992;49(8):529-531.
17. Schulte PA, Ringen K, Hemstreet GP, Ward E. Occupational cancer of the urinary tract. Occup Med 1987;2(1):85-107.
18. Steenland K and Palu S. Cohort mortality study of 57,000 painters and other union members: a 15 year update. Occup Environ Med 1999;56(5):315-321.
19. Marrett LD, Hartge P, Meigs JW. Bladder cancer and occupational exposure to leather. Br J Ind Med 1986;43(2):96-100.
20. Gaertner RR and Theriault GP. Risk of bladder cancer in foundry workers: a meta-analysis. Occup Environ Med 2002;59(10):655-663.
21. Romundstad P, Haldorsen T, Andersen A. Lung and bladder cancer among workers in a Norwegian aluminium reduction plant. Occup Environ Med 2000;57(7):495-499.
22. Theriault G, Tremblay C, Cordier S, Gingras S. Bladder cancer in the aluminium industry. Lancet 1984;1(8383):947-950.
23. Boffetta P and Silverman DT. A meta-analysis of bladder cancer and diesel exhaust exposure. Epidemiology 2001;12(1):125-130.
24. Silverman DT, Hoover RN, Mason TJ, Swanson GM. Motor exhaust-related occupations and bladder cancer. Cancer Res 1986;46(4 Pt 2):2113-2116.
25. Kogevinas M, 't MA, Cordier S, Ranft U, Gonzalez CA, Vineis P, Chang-Claude J, Lynge E, Wahrendorf J, Tzonou A, Jockel KH, Serra C, Porru S, Hours M, Greiser E, Boffetta P. Occupation and bladder cancer among men in Western Europe. Cancer Causes Control 2003;14(10):907-914.
26. Zheng T, Cantor KP, Zhang Y, Lynch CF. Occupation and bladder cancer: a population-based, case-control study in Iowa. J Occup Environ Med. 2002;44(7):685-691.
27. Ranmuthugala G, Pilotto L, Smith W, Vimalasiri T, Dear K, Douglas R. Chlorinated drinking water and micronuclei in urinary bladder epithelial cells. Epidemiology 2003;14(5):617-622.
28. Cantor KP, Hoover R, Hartge P, Mason TJ, Silverman DT, Altman R, Austin DF, Child MA, Key CR, Marrett LD. Bladder cancer, drinking water source, and tap water consumption: a case-control study. J Natl Cancer Inst 1987;79(6):1269-1279.
29. Cantor KP, Lynch CF, Hildesheim ME, Dosemeci M, Lubin J, Alavanja M, Craun G. Drinking water source and chlorination byproducts. I. Risk of bladder cancer. Epidemiology 1998;9(1):21-28.
30. Doyle TJ, Zheng W, Cerhan JR, Hong CP, Sellers TA, Kushi LH, Folsom AR. The association of drinking water source and chlorination by-products with cancer incidence among postmenopausal women in Iowa: a prospective cohort study. Am J Public Health 997;87(7):1168-1176.
31. King WD, Marrett LD. Case-control study of bladder cancer and chlorination by-products in treated water (Ontario, Canada). Cancer Causes Control 1996;7(6):596-604.
32. Koivusalo M, Hakulinen T, Vartiainen T, Pukkala E, Jaakkola JJ, Tuomisto J. Drinking water mutagenicity and urinary tract cancers: a population-based case-control study in Finland. Am J Epidemiol 1998;148(7):704-712.
33. McGeehin MA, Reif JS, Becher JC, Mangione EJ. Case-control study of bladder cancer and water disinfection methods in Colorado. Am J Epidemiol 1993;138(7):492-501.
34. Vena JE, Graham S, Freudenheim J, Marshall J, Zielezny M, Swanson M, Sufrin G. Drinking water, fluid intake, and bladder cancer in western New York. Arch Environ Health 1993;48(3):191-198.
35. Wilkins JR, III, Comstock GW. Source of drinking water at home and site-specific cancer incidence in Washington County, Maryland. Am J Epidemiol. 1981;114(2):178-190.
36. IARC. Some chemicals that cause tumors of the kidney or urinary bladder in rodents and some other substances. 1999. Lyon, International Agency for Research on Cancer Scientific Publications. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, vol 73.
37. Villanueva CM, Cantor KP, Cordier S, Jaakkola JJ, King WD, Lynch CF, Porru S, Kogevinas M. Disinfection byproducts and bladder cancer: a pooled analysis. Epidemiology 2004;15(3):357-367.
38. Lynch CF, Woolson RF, O'Gorman T, Cantor KP. Chlorinated drinking water and bladder cancer: effect of misclassification on risk estimates. Arch Environ Health 1989;44(4):252-259.

39. Cordier S, Clavel J, Limasset JC, Boccon-Gibod L, Le Moual N, Mandereau L, Hemon D. Occupational risks of bladder cancer in France: a multicentre case-control study. Int J Epidemiol 1993;22(3):403-411.
40. Hartge P, Harvey EB, Linehan WM, Silverman DT, Sullivan JW, Hoover RN, Fraumeni JF, Jr. Unexplained excess risk of bladder cancer in men. J Natl Cancer Inst 1990;82(20):1636-1640.
41. Balchak SK, Hedge JM, Murr AS, Mole ML, Goldman JM. Influence of the drinking water disinfection by-product dibromoacetic acid on rat estrous cyclicity and ovarian follicular steroid release in vitro. Reprod Toxicol 2000;14(6):533-539.
42. Nieuwenhuijsen MJ, Toledano MB, Eaton NE, Fawell J, Elliott P. Chlorination disinfection byproducts in water and their association with adverse reproductive outcomes: a review. Occup Environ Med 2000;57(2):73-85.
43. Guengerich FP, Shimada T. Activation of procarcinogens by human cytochrome P450 enzymes. Mutat Res 1998;400(1-2):201-213.
44. Meibohm B, Beierle I, Derendorf H. How important are gender differences in pharmacokinetics? Clin Pharmacokinet 2002;41(5):329-342.
45. Raucy JL, Kraner JC, Lasker JM. Bioactivation of halogenated hydrocarbons by cytochrome P4502E1. Crit RevToxicol 1993;23(1):1-20.
46. Tanaka E. Gender-related differences in pharmacokinetics and their clinical significance. J Clin Pharm Ther 1999;24(5):339-346.
47. Chen CJ, Chuang YC, You SL, Lin TM, Wu HY. A retrospective study on malignant neoplasms of bladder, lung and liver in blackfoot disease endemic area in Taiwan. Br J Cancer 1986;53(3):399-405.
48. Anawar HM, Akai J, Mostofa KM, Safiullah S, Tareq SM. Arsenic poisoning in groundwater: health risk and geochemical sources in Bangladesh. Environ Int 2002;27(7):597-604.
49. Steinmaus C, Yuan Y, Bates MN, Smith AH. Case-control study of bladder cancer and drinking water arsenic in the western United States. Am J Epidemiol 2003;158(12):1193-1201.
50. Kantor AF, Hartge P, Hoover RN, Narayana AS, Sullivan JW, Fraumeni JF, Jr. Urinary tract infection and risk of bladder cancer. Am J Epidemiol 1984;119(4):510-515.
51. McCredie M, Stewart JH, Ford JM, MacLennan RA. Phenacetin-containing analgesics and cancer of the bladder or renal pelvis in women. Br J Urol 1983;55(2):220-224.
52. McCredie M, Stewart JH, Day NE. Different roles for phenacetin and paracetamol in cancer of the kidney and renal pelvis. Int J Cancer 1993;53(2):245-249.
53. Travis LB, Curtis RE, Glimelius B, Holowaty EJ, Van Leeuwen FE, Lynch CF, Hagenbeek A, Stovall M, Banks PM, Adami J, et al. Bladder and kidney cancer following cyclophosphamide therapy for non-Hodgkin's lymphoma. J Natl Cancer Inst 1995;87(7):524-530.
54. Kaldor JM, Day NE, Kittelmann B, Pettersson F, Langmark F, Pedersen D, Prior P, Neal F, Karjalainen S, Bell J, et al. Bladder tumours following chemotherapy and radiotherapy for ovarian cancer: a case-control study. Int J Cancer 1995;63(1):1-6.
55. Bedwani R, Renganathan E, El Kwhsky F, Braga C, Abu Seif HH, Abul AT, Zaki A, Franceschi S, Boffetta P, La Vecchia C. Schistosomiasis and the risk of bladder cancer in Alexandria, Egypt. Br J Cancer 1998;77(7):1186-1189.
56. Gelfand M, Weinberg RW, Castle WM. Relation between carcinoma of the bladder and infestation with Schistosoma haematobium. Lancet 1967;i:1249-1251.
57. Lucas SB. Squamous cell carcinoma of the bladder and schistosomiasis. East Afr Med J 1982;59(5):345-351.
58. Mustacchi P and Shimkin MD. Cancer of the bladder and infestation with Schistosoma haematobium. J Natl Cancer Inst 1958;20:825-842.
59. Cheever AW. Schistosomiasis and neoplasia. J Natl Cancer Inst 1978;61(1):13-18.
60. Tawfik HN. Carcinoma of the urinary bladder associated with schistosomiasis in Egypt: the possible causal relationship. Princess Takamatsu Symp 1987;18:197-209.
61. Netter F. Kidneys, Ureters, and Urinary Bladder. The Ciba Collection of Medical Illustrations. 1979.
62. La Vecchia C and Negri E. Nutrition and bladder cancer. Cancer Causes Control 1996;7(1):95-100.
63. Riboli E and Norat T. Epidemiologic evidence of the protective effect of fruit and vegetables on cancer risk. Am J Clin Nutr 2003;78(3 Suppl):559S-569S.
64. Hennekens CH, Buring JE, Manson JE, Stampfer M, Rosner B, Cook NR, Belanger C, LaMotte F, Gaziano JM, Ridker PM, Willett W, Peto R. Lack of effect of long-term supplementation with beta carotene on the incidence of malignant neoplasms and cardiovascular disease. N Engl J Med 1996;334(18):1145-1149.
65. The Alpha-Tocopherol BCCPSG. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. N Engl J Med 1994;330(15):1029-1035.
66. Michaud DS, Pietinen P, Taylor PR, Virtanen M, Virtamo J, Albanes D. Intakes of fruits and vegetables, carotenoids and vitamins A, E, C in relation to the risk of bladder cancer in the ATBC cohort study. Br J Cancer 2002;87(9):960-965.
67. Steinmaus CM, Nunez S, Smith AH. Diet and bladder cancer: a meta-analysis of six dietary variables. Am J Epidemiol 2000;151(7):693-702.
68. Jensen OM. Cancer morbidity and causes of death among Danish brewery workers. Int J Cancer 1979;23(4):454-463.
69. Hartge P, Hoover R, West DW, Lyon JL. Coffee drinking and risk of bladder cancer. J Natl Cancer Inst 1983;70(6):1021-1026.
70. Jensen OM, Wahrendorf J, Knudsen JB, Sorensen BL. The Copenhagen case-control study of bladder cancer. II. Effect of coffee and other beverages. Int J Cancer 1986;37(5):651-657.
71. Sala M, Cordier S, Chang-Claude J, Donato F, Escolar-Pujolar A, Fernandez F, Gonzalez CA, Greiser E, Jockel KH, Lynge E, Mannetje A, Pohlabeln H, Porru S, Serra C, Tzonou A, Vineis P, Wahrendorf J, Boffetta P, Kogevina M. Coffee consumption and bladder cancer in nonsmokers: a pooled analysis of case-control studies in European countries. Cancer Causes Control 2000;11(10):925-931.
72. Vineis P. Hypothesis: coffee consumption, N-acetyltransferase phenotype, and cancer. J Natl Cancer Inst 1993;85(12):1004-1005.
73. Armstrong B and Doll R. Bladder cancer mortality in diabetics in relation to saccharin consumption and smoking habits. Br J Prev Soc Med 1975;29(2):73-81.
74. Takayama S, Sieber SM, Adamson RH, Thorgeirsson UP, Dalgard DW, Arnold LL, Cano M, Eklund S, Cohen SM. Long-term feeding of sodium saccharin to nonhuman primates: implications for urinary tract cancer. J Natl Cancer Inst 1998;90(1):19-25.
75. Sturgeon SR, Hartge P, Silverman DT, Kantor AF, Linehan WM, Lynch C, Hoover RN. Associations between bladder cancer risk factors and tumor stage and grade at diagnosis. Epidemiology 1994;5(2):218-225.
76. Kunze E, Chang-Claude J, Frentzel-Beyme R. Life style and occupational risk factors for bladder cancer in Germany. A case-control study. Cancer 1992;69(7):1776-1790.
77. Mills PK, Beeson WL, Phillips RL, Fraser GE. Bladder cancer in a low risk population: results from the Adventist Health Study. Am J Epidemiol 1991;133(3):230-239.

78. Michaud DS, Spiegelman D, Clinton SK, Rimm EB, Curhan GC, Willett WC, Giovannucci EL. Fluid intake and the risk of bladder cancer in men. N Engl J Med 1999;340(18):1390-1397.

79. Turesky RJ, Freeman JP, Holland RD, Nestorick DM, Miller DW, Ratnasinghe DL, Kadlubar FF. Identification of aminobiphenyl derivatives in commercial hair dyes. Chem Res Toxicol 2003;16(9):1162-1173.

80. La Vecchia C, Tavani A. Epidemiological evidence on hair dyes and the risk of cancer in humans. Eur J Cancer Prev 1995;4(1):31-43.

81. Hennekens CH, Speizer FE, Rosner B, Bain CJ, Belanger C, Peto R. Use of permanent hair dyes and cancer among registered nurses. Lancet 1979;1(8131):1390-1393.

82. Thun MJ, Altekruse SF, Namboodiri MM, Calle EE, Myers DG, Heath CW, Jr. Hair dye use and risk of fatal cancers in U.S. women. J Natl Cancer Inst 1994;86(3):210-215.

83. Gago-Dominguez M, Castelao JE, Yuan JM, Yu MC, Ross RK. Use of permanent hair dyes and bladder-cancer risk. Int J Cancer 2001a;91(4):575-579.

84. Henley SJ, Thun MJ. Use of permanent hair dyes and bladder-cancer risk. Int J Cancer 2001;94(6):903-906.

85. Andrew AS, Schned AR, Heaney JA, Karagas MR. Bladder cancer risk and personal hair dye use. Int J Cancer 2004;109(4):581-586.

86. Gago-Dominguez M, Chan KK, Ross RK, Yu MC. Permanent hair dues and bladder cancer risk. Int J Cancer 2001b;94:905-906.

87. Gago-Dominguez M, Bell DA, Watson MA, Yuan JM, Castelao JE, Hein DW, Chan KK, Coetzee GA, Ross RK, Yu MC. Permanent hair dyes and bladder cancer: risk modification by cytochrome P4501A2 and N-acetyltransferases 1 and 2. Carcinogenesis 2003;24(3):483-489.

88. Bartsch H, Malaveille C, Friesen M, Kadlubar FF, Vineis P. Black (air-cured) and blond (flue-cured) tobacco cancer risk. IV: Molecular dosimetry studies implicate aromatic amines as bladder carcinogens. Eur J Cancer 1993;29A(8):1199-1207.

89. Bell DA, Taylor JA, Paulson DF, Robertson CN, Mohler JL, Lucier GW. Genetic risk and carcinogen exposure: a common inherited defect of the carcinogen-metabolism gene glutathione S-transferase M1 (GSTM1) that increases susceptibility to bladder cancer. J Natl Cancer Inst 1993;85(14):1159-1164.

90. Engel LS, Taioli E, Pfeiffer R, Garcia-Closas M, Marcus PM, Lan Q, Boffetta P, Vineis P, Autrup H, Bell DA, Branch RA, Brockmoller J, Daly AK, Heckbert SR, Kalina I, Kang D, Katoh T, Lafuente A, Lin HJ, Romkes M, Taylor JA, Rothman N. Pooled analysis and meta-analysis of glutathione S-transferase M1 and bladder cancer: a HuGE review. Am J Epidemiol 2002;156(2):95-109.

91. Watson P, Lynch HT. Extracolonic cancer in hereditary nonpolyposis colorectal cancer. Cancer 1993;71(3):677-685.

92. Kiemeney LA, Schoenberg M. Familial transitional cell carcinoma. J Urol 1996;156(3):867-872.

93. Goldgar DE, Easton DF, Cannon-Albright LA, Skolnick MH. Systematic population-based assessment of cancer risk in first-degree relatives of cancer probands. J Natl Cancer Inst 1994;86(21):1600-1608.

94. Kramer AA, Graham S, Burnett WS, Nasca P. Familial aggregation of bladder cancer stratified by smoking status. Epidemiology 1991;2(2):145-148.

95. Kiemeney LA, Moret NC, Witjes JA, Schoenberg MP, Tulinius H. Familial transitional cell carcinoma among the population of Iceland. J Urol 1997;157(5):1649-1651.

96. Aben KKH, Witjes JA, Schoenberg MP, Hulsbergen-van-de-Kaa C, Verbeek AL, Kiemeney LA. Familial aggregation of urothelial cell carcinoma. Int J Cancer 2002;98(2):274-278.

97. Lichtenstein P, Holm NV, Verkasalo PK, Iliadou A, Kaprio J, Koskenvuo M, Pukkala E, Skytthe A, Hemminki K. Environmental and heritable factors in the causation of cancer—analyses of cohorts of twins from Sweden, Denmark, and Finland. N Engl J Med 2000;343(2):78-85.

98. Czene K, Lichtenstein P, Hemminki K. Environmental and heritable causes of cancer among 9.6 million individuals in the Swedish Family-Cancer Database. Int J Cancer 2002;99(2):260-266.

99. Aben KKH, Cloos J, Koper NP, Braakhuis BJ, Witjes JA, Kiemeney LA. Mutagen sensitivity in patients with familial and non-familial urothelial cell carcinoma. Int J Cancer 2000;88(3):493-496.

100. Guo Z, Linn JF, Wu G, Anzick SL, Eisenberger CF, Halachmi S, Cohen Y, Fomenkov A, Hoque MO, Okami K, Steiner G, Engles JM, Osada M, Moon C, Ratovitski E, Trent JM, Meltzer PS, Westra WH, Kiemeney LA, Schoenberg MP, Sidransky D, Trink B. CDC91L1 (PIG-U) is a newly discovered oncogene in human bladder cancer. Nat Med 2004 Apr;10(4):374-381.

101. Schoenberg M, Kiemeney L, Walsh PC, Griffin CA, Sidransky D. Germline translocation t(5;20)(p15;q11) and familial transitional cell carcinoma. J Urol 1996;155(3):1035-1036.

102. Fletcher O, Easton D, Anderson K, Gilham C, Jay M, Peto J. Lifetime risks of common cancers among retinoblastoma survivors. J Natl Cancer Inst 2004;96(5):357-363.

103. Aveyard P, Adab P, Cheng KK, Wallace DM, Hey K, Murphy MF. Does smoking status influence the prognosis of bladder cancer? A systematic review. BJU Int 2002;90(3):228-239.

104. Wakai K, Ohno Y, Obata K, Aoki K. Prognostic significance of selected lifestyle factors in urinary bladder cancer. Jpn J Cancer Res 1993;84(12):1223-1229.

105. Epstein JI, Amin MB, Reuter VR, Mostofi FK. The World Health Organization/International Society of Urological Pathology consensus classification of urothelial (transitional cell) neoplasms of the urinary bladder. Bladder Consensus Conference Committee. Am J Surg Pathol. 1998 Dec;22(12):1435-1448.

106. Taylor DC, Bhagavan BS, Larsen MP, Cox JA, Epstein JI. Papillary urothelial hyperplasia. A precursor to papillary neoplasms. Am J Surg Pathol 1996;20:1481-1488.

107. Swierczinski SL, Epstein JI. Prognostic significance of atypical papillary urothelial hyperplasia. Hum Pathol. 2002 May;33(5):512-517.

108. Althausen AF, Prout GRJ, Dal JJ. Noninvasive papillary carcinoma of the bladder associated with carcinoma in-situ. J Urol 1976;116:575-580.

109. Farrow GM, Utz DC, Rife CC. Morphological and clinical observations of patients with early bladder cancer treated with total cystectomy. Cancer Res 1976;36:2495-2501.

110. Koss LG. Mapping of the urinary bladder: Its impact on the concepts of bladder cancer. Hum Pathol 1979;10:533-548.

111. Smith G, Elton RA, Beynon LL, Newsam JE, Chisolm GD, Hargreave TB. Prognostic significance of biopsy results of normal-looking mucosa in cases of superficial bladder cancer. Br J Urol 1983;55:665-669.

112. Heney NM, Ahmed S, Flanagan MJ, Frable W, Corder MP, Hafermann MD, Hawkins IR. Superficial bladder cancer: progression and recurrence. J Urol 1983;130:1083-1086.

113. Hofstäder F, Delgado R, Jakse G, Judmaier W. Urothelial dysplasia and carcinoma in situ of the bladder. Cancer 1986; 57:356-361.

114. Eble JN, Young RH. Benign and low-grade papillary lesions of the urinary bladder: a review of the papilloma-papillary carcinoma controversy and a report of 5 typical papillomas. Semin Diagn Pathol 1989;6:351-371.

115. Broders AC. Epithelium of the genito-urinary organs. Ann Surg 1922;75:574-604.

116. Bergkvist A, Ljungqvist A, Moberger G. Classification of bladder tumours based on the cellular pattern. Acta Chir Scand 1965;130:371-378.

117. Mostofi FK, Sobin LH, Torloni H. Histological typing of urinary bladder tumours. International classification of tumors 19. World Health Organization. Geneva, 1973.

118. Ooms ECM, Anderson WAAD, Alons CL, Boon ME, Veldhuizen RW. Analysis of the performance of pathologists in the grading of bladder tumors. Hum Pathol 1983;14:140-143.

119. Jordan AM, Weingarten J, Murphy WM. Transitional cell neoplasms of the urinary bladder. Can biologic potential be predicted from histologic grading? Cancer 1987;60:2766-2774.

120. Malmström PU, Busch C, Norlén BJ. Recurrence, progression and survival in bladder cancer: A retrospective analysis of 232 patients with 5-year follow-up. Scand J Urol Nephrol 1987;21:185-195.

121. Abel PD, Henderson D, Bennett, Hall RR, Williams G. Differing interpretations by pathologists of the pT category and grade of transitional cell cancer of the bladder. Br J Urol 1988;62:339-342.

122. Carbin BE, Ekman P, Gustafson H, Christensen NJ, Silfversward C, Sandstedt B. Grading of human urothelial carcinoma based on nuclear atypia and mitotic frequency. II. Prognostic importance. J Urol 1991;145:972-976.

123. McKenney JK, Amin MB, Young RH. Urothelial (transitional cell) papilloma of the urinary bladder: A clinicopathologic study of 25 cases. Mod Pathol 2002;15:174A.

124. Cheng L, Newman RM, Bostwick DG. Papillary urothelial neoplasms of low malignant potential. Cancer 1999;86:2102-2108.

125. Desai S, Lim SD, Jimenez RE, Chun T, Keane TE, McKenney JK, Zavala-Pompa A, Cohen C, Young RH, Amin MB. Relationship of cytokeratin 20 and CD44 protein expression with WHO/ISUP grade in pTa and pT1 papillary urothelial neoplasia. Mod Pathol 2000;13:1315-1323.

126. Alsheikh A, Mohamedali Z, Jones E, Masterson J, Gilks CB. Comparison of the WHO/ISUP classification and cytokeratin 20 expression in predicting the behavior of low-grade papillary urothelial tumors. Modern Pathology 2001;14:267-272.

27. Holmang S, Andius P, Hedelin H, Wester K, Busch C, Johansson SL. Stage progression in Ta papillary urothelial tumors: relationship to grade, immunohistochemical expression of tumor markers, mitotic frequency and DNA ploidy. J Urol 2001;165:1124-1130.

128. Pich A, Chiusa L, Formiconi A, Galliano D, Bortolini P, Navone R. Biologic differences between noninvasive papillary urothelial neoplasms of low malignant potential and low grade (grade 1) papillary carcinomas of the bladder. Am J Surg Pathol 2001;25:1528-1533.

129. Cina SJ, Lancaster-Weiss KJ, Lecksell K, Epstein JI. Correlation of Ki-67 and p53 with the new World Health Organization/International Society of Urological Pathology Classification System for Urothelial Neoplasia. Arch Pathol Lab Med 2001;125:646-651.

130. Samaratunga H, Makarov, DV, Epstein JI. Comparison of WHO/ISUP and WHO classification of non-invasive papillary urothelial neoplasms for risk of progression. Urology 2002; 60(2):315-319.

131. Eble JN, Sauter G, Epstein JI, Sesterhenn IA. (Eds): World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of the Urinary System and Male Genital Organs. IARC Press: Lyon 2004.

132. Lopez-Beltran A, Cheng L. Stage pT1 bladder carcinoma: diagnostic criteria, pitfalls and prognostic significance. Pathology Dec 2003;35(6):484-491.

133. Pathologists of the French Association of Urology Cancer Committee. Lamina propria microinvasion of bladder tumors, incidence on stage allocation (pTa vs pT1): recommended approach. World J Urol 1993;11:161-164.

134. Tosoni I, Wagner U, Sauter G, Egloff M, Knonagel H, Alund G, Bannwart F, Mihatsch MJ, Gasser TC, Maurer R. Clinical significance of interobserver differences in the staging and grading of superficial bladder cancer. BJU Int 2000;85:48-53.

135. Bol MG, Baak JP, Buhr-Wildhagen S, Kruse AJ, Kjellevold KH, Janssen EA, Mestad O, Ogreid P. Reproducibility and prognostic variability of grade and lamina propria invasion in stages Ta, T1 urothelial carcinoma of the bladder. J Urol 2003;169:1291-1294.

136. Pagano F, Garbeglio A, Milani C, Bassi P, Pegoraro V. Prognosis of bladder cancer. I. Risk factors in superficial transitional cell carcinoma. Eur Urol 1987;13(3):145-149.

137. Younes M, Sussman J, True LD. The usefulness of the level of the muscularis mucosae in the staging of invasive transitional cell carcinoma of the urinary bladder. Cancer 1990;66:543-548.

138. Hasui Y, Osada Y, Kitada S, Nishi S. Significance of invasion to the muscularis mucosae on the progression of superficial bladder cancer. Urology 1994;43:782-786.

139. Angulo JC, Lopez JI, Grignon DJ, Sanchez-Chapado M. Muscularis mucosa differentiates two populations with different prognosis in stage T1 bladder cancer. Urology 1995;45:47-53.

140. Platz CE, Cohen MB, Jones MP, Olson DB, Lynch CF. Is microstaging of early invasive cancer of the urinary bladder possible or useful? Mod Pathol 1996;11:1035-1039.

141. Holmang S, Hedelin H, Anderstrom C, Holmberg E, Johansson SL. The importance of the depth of invasion in stage T1 bladder carcinoma: a prospective cohort study. J Urol 1997;157:800-804.

142. Hermann GG, Horn T, Steven K. The influence of the level of lamina propria invasion and the prevalence of p53 nuclear accumulation on survival in stage T1 transitional cell bladder cancer. J Urol 1998;159:91-94.

143. Cheng L, Weaver AL, Neumann RM, Schere BG, Bostwick DG. Substaging of T1 bladder carcinoma based on the depth of invasion measured by micrometer: a new proposal. Cancer 1999;86:1035-1043.

144. Cheng L, Weaver AL, Bostwick DG. Predicting extravesical extension of bladder carcinoma: a novel method based on micrometer measurement of the depth of invasion in transurethral resection specimens. Urology 2000;55:668-672.

145. Cheng L, Neumann RM, Weaver AL, Spotts BE, Bostwick DG. Predicting cancer progression in patients with stage T1 bladder carcinoma. J Clin Oncol 1999;17:3182-3187.

146. Cheng L, Neumann RM, Scherer BG, Weaver AL, Leibovich BC, Nehra A, Zincke H, Bostwick DG. Tumor size predicts the survival of patients with pathologic stage T2 bladder carcinoma: a critical evaluation of the depth of muscle invasion. Cancer 1999;85:2638-2647.

147. Roehrborn CG, Sagalowsky AI, Peters PC. Long-term patient survival after cystectomy for regional metastastic transitional cell carcinoma of the bladder. J Urol 1991;146:36-39.

148. Quek ML, Stein JP, Clark PE, Daneshmand S, Miranda G, Cai J, Groshen S, Cote RJ, Lieskovsky G, Quinn DI, Skinner DG. Microscopic and gross extravesical extension in pathological staging of bladder cancer. J Urol 2004;171:640-645.

149. Esrig D, Freeman JA, Elmajian DA, Stein JP, Chen SC, Groshen S, Simoneau A, Skinner EC, Lieskovsky G, Boyd SD, Cote RJ, Skinner DG. Transitional cell carcinoma involving the prostate with a proposed staging classification for stromal invasion. J Urol 1996;156:1071-1076.

150. Pagano F, Bassi P, Ferrante GL, Piazza N, Abatangelo G, Pap-

pagallo GL, Garbeglio A. Is stage pT4a (D1) reliable in assessing transitional cell carcinoma involvement of the prostate in patients with a concurrent bladder cancer? A necessary distinction for contiguous or noncontiguous involvement. J Urol 1996;155:244-247.

151. Wilson JMG, Jungner G. Principles and practice of screening for disease. Public Health Papers 1968;34:1-163.

152. Schulte PA. Screening for bladder cancer in high-risk groups: delineation of the problem. J Occup Med 1990;32(9):789-792.

153. Lawrence WF, Messing EM, Bram LL. Cost-effectiveness of screening for bladder cancer using chemical reagent strips to detect microscopic hematuria. J Urol 1995;153 (April suppl):477a (abstract # 995).

154. Ellwein LB. Bladder cancer screening: lesions from a biologically based model of bladder cancer progression and therapeutic intervention. J Occup Med 1990;32(9):806-811.

155. Mason TJ and Vogler WJ. Bladder cancer screening at the DuPont Chambers Works: a new initiative. J Occup Med 1990;32(9):874-877.

156. Felknor SA, Delclos GL, Lerner SP, Burau KD, Wood SM, Lusk CM, Jalayer AD. Bladder cancer screening program for a petrochemical cohort with potential exposure to beta-napthylamine. J Occup Environ Med 2003;45:289-294.

157. Marsh GM, Callahan C, Pavlock D, Leviton LC, Talbott EO, Hemstreet G. A protocol for bladder cancer screening and medical surveillance among high risk groups: the Drake Health Registry experience. J Occup Med 1990;32(9):881-886.

158. Ward E, Halperin W, Thun M, Grossman HB, Fink B, Koss L, Osorio AM, Schulte P. Screening workers exposed to 4,4'-methylenebis(2-chloroaniline) for bladder cancer by cystoscopy. J Occup Med 1990;32(9):865-868.

159. Theriault GP, Tremblay CG, Armstrong BG. Bladder cancer screening among primary aluminum production workers in Quebec. J Occup Med 1990;32(9):869-872.

160. Goessl C, Knispel HH, Miller K, Klan R. Is routine excretory urography necessary at first diagnosis of bladder cancer? J Urol 1997;157(2):480-481.

161. Hiatt RA, Ordonez JD. Dipstick urinalysis screening, asymptomatic microhematuria, and subsequent urologic cancers in a population-based sample. Cancer Epidemiol Biomarkers Prev 1994;3(5):439-449.

162. Britton JP, Dowell AC, Whelan P. Dipstick hematuria and bladder cancer in men over 60: results of a community study. Br Med J 1989;299:1010-1012.

163. Messing EM, Young TB, Hunt VB, Newton MA, Bram LL, Vaillancourt A, Hisgen WJ, Greenberg EB, Kuglitsch ME, Wegenke JD. Hematuria home screening: repeating test results. J Urol 1995;154(1):57-61.

164. Britton JP, Dowell AC, Whelan P, Harris CM. A community study of bladder cancer screening by the detection of occult urinary bleeding. J Urol 1992;148:788-790.

165. Whelan P, Britton JP, Dowell AC. Three-year follow-up of bladder tumors found on screening. Br J Urol 1993;72(6):893-896.

166. Mayfield MP, Whelan P. Bladder tumors detected on screening: results at 7 years. Br J Urol 1998;82(6):825-828.

167. Messing EM, Young TB, Hunt VB, Gilchrist KW, Newton MA, Bram LL, Hisgen WJ, Greenberg EB, Kuglitsch ME, Wegenke JD. Comparison of bladder cancer outcome in men undergoing hematuria home screening versus those with standard clinical presentations. Urology 1995;45(3):387-396.

168. Messing EM and Vaillancourt A. Hematuria screening for bladder cancer. J Occup Med 1990;32:838-845.

169. Kretschmer HL. Hematuria-A clinical study based on 933 consecutive cases. Surg Gynecol Obstet 1925;40:683.

170. Varkarakis MJ, Gaeta J, Moore RH, Murphy GP. Superficial bladder tumor. Aspects of clinical progression. Urology 1974;4:414-420.

171. Lee LW and Davis E Jr. Gross urinary hemorrhage: a symptom, not a disease. JAMA 1953;153:782-784.

172. Mohr DN, Offord KP, Owen RA, Melton J III. Asymptomatic microhematuria and urologic disease. A population-based study. JAMA 1986;256:224-229.

173. Golin AL and Howard RS. Asymptomatic microscopic hematuria. J Urol 1980;124:389-391.

174. Sultana SR, Goodman CM, Byrne DJ, Baxby K. Microscopic haematuria: urological investigation using a standard protocol. Br J Urol 1996;78:691-698.

175. Cummings KB, Barone JG, Ward WS: Diagnosis and staging of baldder cancer. Urol Clin North Am 1992;19:455-465.

176. Guidelines for the cancer related checkup: Recommendations and Rationale. New York, American Cancer Society, 1981.

177. Jewett HJ. Cancer of the bladder. Diagnosis and staging. Cancer 1973;32:1072-1074.

178. Utz DC and Farrow GM. Carcinoma in situ of the urinary tract. Urol Clin North Am 1984;11:735-740.

179. Murphy WM, Grignon DJ, Perlman EJ. Tumors of the kidney, bladder, and related urinary structures. Atlas of Tumor Pathology, 4th Series, Fascicle 1. Washington, DC. Armed Forces Institute of Pathology; 2004.

180. Cheng L, Darson M, Cheville JC, Neumann RM, Zincke H, Nehra A, Bostwick DG. Urothelial papilloma of the bladder. Clinical and biologic implications. Cancer 1999;86:2098-2101.

181. McKenney JK, Desai S, Cohen C, Amin MB. Discriminatory immunohistochemical staining of urothelial carcinoma in situ and non-neoplastic urothelium: an analysis of cytokeratin 20, p53, and CD44 antigens. Am J Surg Pathol 2001;25:1074-1078.

182. Holmang S, Hedelin H, Anderstrom C, Holmberg E, Busch C, Johansson SL. Recurrence and progression in low grade papillary urothelial tumors. J Urol 1999;162:702-707.

183. Farrow GM and Utz DC. Observations on microinvasive transitional cell carcinoma of the urinary bladder. Clinics Oncol 1982;1:609-615.

184. Orozco RE, Martin AA, Murphy WM. Carcinoma in-situ of the urinary bladder. Clues to host involvement in human carcinogenesis. Cancer 1994;74:115-122.

185. Farrow GM, Utz DC, Rife CC, Greene LF. Clinical observations on sixty-nine cases of in-situ carcinoma of the urinary bladder. Cancer Res 1977;37:2794-2798.

186. Murphy WM. Urinary cytopathology. Chicago: ASCP Press; 2000.

187. Soloway MS, Murphy WM, Johnson DE, Farrow GM, Paulson DG, Garnick MB. Initial evaluation and response criteria for patients with superficial bladder cancer. Report of a workshop. Br J Urol 1990;66:380-385.

188. Schwalb DM, Herr HW, Fair WR. The management of clinically unconfirmed positive urinary cytology. J Urol 1993;150:1751-1756.

189. Malik S and Murphy WM. Monitoring patients for bladder neoplasms: what can be expected of urinary cytology consultations in clinical practice? Urology 1999;54:62-66.

190. Murphy WM, Crabtree WN, Jukkola AF, Soloway MS. The diagnostic value of urine versus bladder washing in patients with bladder cancer. J Urol 1981;126:320-322.

191. Renshaw AA. Subclassifying atypical urinary cytology specimens. Cancer 2000; 90:222-229.

192. Grégoire M, Fradet Y, Meyer F, Tetu B, Bois R, Bedard G, Charrois R, Naud A. Diagnostic accuracy of urinary cytology and

deoxyribonucleic acid flow cytometry and cytology on bladder washings during followup for bladder tumors. J Urol 1997;157:1660-1664.

193. Crosby JH, Allsbrook WC Jr, Koss LG, Bales CE, Witherington R, Schulte PA, Hemstreet G 3rd, Ringer K. Cytologic detection of urothelial cancer and other abnormalities in a cohort of workers exposed to aromatic amines. Acta Cytol 1991;35:263-268.

194. Koss LG, Deitch D, Ramanathan R, Sherman AB. Diagnostic value of cytology of voided urine. Acta Cytol 1985;29:810-816.

195. Rife CC, Farrow GM, Utz DC. Urine cytology of transitional cell neoplasms. Urol Clin N Am 1970;6:599-612.

196. Wiener HG, Vooijs GP, Hof-Grootenboer BV. Accuracy of urinary cytology in the diagnosis of primary and recurrent bladder cancer. Acta Cytol 1993;37:163-169.

197. Páez A, Coba JM, Murillo N, Fernandez P, de la Cal MA, Lujan M, Berenguer A. Reliability of the routine cytological diagnosis in bladder cancer. Eur Urol 1999;35:228-232.

198. Murphy WM, Soloway MS, Jukkola AF, Crabtree WN, Ford KS. Urinary cytology and bladder cancer. The cellular features of transitional cell neoplasms. Cancer 1984;53:1555-1565.

199. Dean PJ and Murphy WM. Importance of urinary cytology and future role of flow cytometry. Urology (suppl) 1985;26:11-15.

200. Baltaci S, Süzer O, Özer G, Gö?üs O. The efficacy of urinary cytology in the detection of recurrent bladder tumors. Int Urol Nephol 1996;28:649-653.

201. Sack MJ, Artymyshyn RL, Tomaszewski JE, Gupta PK. Diagnostic value of bladder wash cytology, with special reference to low grade urothelial neoplasms. Acta Cytol 1995;39:187-194.

202. Zein T, Wajsman Z, Englander LS, Gamarra M, Lopez C, Huben RP, Pontes JE.Evaluation of bladder washings and urine cytology in the diagnosis of bladder cancer and its correlation with selected biopsies of the bladder mucosa. J Urol 1984;132:670-671.

203. Raab SS, Slagel DD, Jensen CS, Teague MW, Savell VH, Ozkutlu D, Lenel JC, Cohen MB. Low-grade transitional cell carcinoma of the urinary bladder: application of select cytologic criteria to improve diagnostic accuracy. Mod Pathol 1996;9:225-232.

204. Bastacky S, Ibrahim S, Wilczynski SP, Murphy WM. The accuracy of urinary cytology in daily practice. Cancer 1999;87:118-128.

205. Mora LB, Nicosia SV, Pow-Sang JM, Ku NK, Diaz JI, Lockhart J, Einstein A. Ancillary techniques in the followup of transitional cell carcinoma: a comparison of cytology, histology and deoxyribonucleic acid image analysis cytometry in 91 patients. J Urol 1996;156:49-55.

206. Golijanin D, Shapiro A, Pode D. Immunostaining of cytokeratin 20 in cells from voided urine for detection of bladder cancer. J Urol 2000;164:1922-1925.

207. Planz B, Striepecke E, Jakse G, Böcking A. Use of Lewis X antigen and deoxyribonucleic acid image cytometry to increase sensitivity of urinary cytology in transitional cell carcinoma of the bladder. J Urol 1998;159:384-388.

208. Mao L, Schoenberg MP, Scicchitano M, Erozan YS, Merlo A, Schwab D, Sidransky D. Molecular detection of primary bladder cancer by microsatellite analysis. Science 1996;271:659-662.

209. Pfister C, Chautard D, Devonec M, Perrin P, Chopin D, Rischmann P, Bouchot O, Beurton D, Coulange C, Rambeaud JJ. Immunocyt test improves the diagnostic accuracy of urinary cytology: results of a French multicenter study. J Urol 2003;169:921-924.

210. Sánchez-Carbayo M, Urrutia M, Silva JM, Romani R, Gonzalez de Buitrago JM, Navajo JA. Comparative predictive values of urinary cytology, urinary bladder cancer antigen, Cyfra 21-1 and NMP 22 for evaluating symptomatic patients at risk for bladder cancer. J Urol 2001;165:1462-1467.

211. Katz RL, Sinkre PA, Zhang HH, Kidd L, Johnston D. Clinical significance of negative and equivocal urinary bladder cytology alone and in combination with DNA image analysis and cystoscopy. Cancer 1997;81(6):354-364.

212. Konety BR, Getzenberg RH. Urine based markers of urological malignancy. J Urol 2001;165:600-611.

213. Glas AS, Roos D, Deutekom M, Zwinderman AH, Bossuyt PMM, Kurth KH. Tumor markers in the diagnosis of primary bladder cancer. A systematic review. J Urol 2003;169:1975-1982.

214. Iczkowski KA, Katz G, Cascione CJ. Postoperative bladder washing cytology after transurethral resection. Acta Cytol 2004;48:380-384.

215. Bubendorf L, Grilli B, Sauter G, Mihatsch MJ, Gasser TC, Dalquen P. Multiprobe FISH for enhanced detection of bladder cancer in voided urine specimens and bladder washings. Am J Clin Pathol 2001;116:79-86.

216. Dalquen P, Kleiber B, Grilli B., Herzog M, Bubendorf L, Oberholzer M. DNA image cytometry and fluorescence in situ hybridization for noninvasive detection of urothelial tumors in voided urine. Cancer 2002;96:374-379.

217. Sarosdy MF, Schellhammer P, Bokinsky G, Kahn P, Chao R, Yore L, Zadra J, Burzon D, Osher G, Bridge JA, Anderson S, Johansson SL, Lieber M, Soloway M, Flom K. Clinical evaluation of a multi-target fluorescent in situ hybridization assay for detection of bladder cancer. J Urol 2002;168:1950-1954.

218. Righi E, Rossi G, Ferrari G, Dotti A, De Gaetani C, Ferrari P, Trentini GP. Does p53 immunostaining improve diagnostic accuracy in urine cytology? Diagn Cytopathol 1997;17:436-439.

219. Friedrich MG, Hellstern A, Hautmann SH, Graefen M, Conrad S, Huland E, Huland H. Clinical use of urinary markers for the detection and prognosis of bladder carcinoma: a comparison of immunocytology with monoclonal antibodies against Lewis X and 486p3/12 with the BTA stat and NMP 22 tests. J Urol 2002;168:470-474.

220. van der Poel HG, Boon ME, van Stratum P, Ooms EC, Wiener H, Debruyne FM, Witjes JA, Schalken JA, Murphy WM. Conventional bladder wash cytology performed by four experts versus quantitative image analysis. Mod Pathol 1997;10:976-982.

221. Murphy WM, Takezawa K, Maruniak NA. Interobserver discrepancy using the 1998 World Health Organization/International Society of Urologic Pathology classification of urothelial neoplasms: practical choices for patient care. J Urol 2002;168:968-972.

222. Herranz-Amo F, Diez-Cordero JM, Verdu-Tartajo F, Bueno-Chomon G, Leal-Hernandez F, Bielsa-Carrillo A. Need for intravenous urography in patients with primary transitional carcinoma of the bladder? Eur Urol 1999;36(3):221-224.

223. Yousem DM, Gatewood OM, Goldman SM, Marshall FF. Synchronous and metachronous transitional cell carcinoma of the urinary tract: prevalence, incidence, and radiographic detection. Radiology 1988;167(3):613-618.

224. Hatch TR and Barry JM. The value of excretory urography in staging of bladder cancer. J Urol 1986;135:49.

225. Lantz EJ, Hattery RR. Diagnostic imaging of urothelial cancer. Urol Clin North Am 1984;11(4):567-583.

226. Barentsz JO, Witjes JA, Ruijs JHJ. What is new in bladder cancer imaging. Urol Clin North Am 1997;24(3):583-602.

227. Voges GE, Tauschke E, Stockle M, Alken P, Hohenfellner R. Computerized tomography: an unreliable method for accurate staging of bladder tumors in patients who are candidates for radical cystectomy. J Urol 1989;142(4):972-974.

228. Paik ML, Scolieri MJ, Brown SL, Spirnak JP, Resnick MI. Limitations of computerized tomography in staging invasive bladder cancer before radical cystectomy. J Urol 2000; 163 (6): 1693-1696.

229. Nurmi M, Katevuo K, Puntala P. Reliability of CT in preoperative evaluation of bladder carcinoma. Scan J Urol Nephrol 1988;22:125-128.

230. Barentsz JO, Jager GJ, van Vierzen PB, Witjes JA, Strijk SP, Peters H, Karssemeijer N, Ruijs SH. Staging urinary bladder cancer after transurethral biopsy: value of fast dynamic contrast-enhanced MR imaging. Radiology 1996; 201 (1):185-193.

231. Herr HW. Routine CT scan in cystectomy patients: does it change management? J Urol 1996;47(3):324-325.

232. Lerner SP and Skinner DG. Radical cystectomy for bladder cancer. In Vogelzang NJ, Scardino PT, Shipley WU, Coffey DS (eds): Genitourinary Oncology, 2nd edition, Philadelphia: Lippincott Williams & Wilkins, 2000: 424-447.

233. Lindner A and deKernion JB. Cost-effective analysis of pre-cystectomy radioisotope scans. J Urol 1982;128(6):1181-1182.

234. Berger GL, Sadlowski RW, Sharpe JR, Finney RP. Lack of value of routine preoperative bone and liver scans in cystectomy candidates. J Urol 1981;125(5):637-639.

235. Brismar J and Gustafson T. Bone scintigraphy in staging of bladder carcinoma. Acta Radiol 1988;29(2):251-252.

236. Utz DC, Schmitz SE, Fugelso PD, Farrow GM. A clinicopathologic evaluation of partial cystectomy for carcinoma of the urinary bladder. Cancer. 1973;32:1075-1077.

237. Mulders PFA, Meyden APVD, Doesburg WH, Oosterhof GON, Debruyne FMJ, and members of the Dutch southeastern urological collaborative group. Prognostic factors in pT1-pT1 superficial bladder tumors treated with intra vesical instillations. Br J Urol 1994;73:403-408.

238. Jakse G, Loidl W, Seeber G, Hofstadter F. Stage T1 grade 3 transitional cell carcinoma of the bladder: an unfavorable tumor? J Urol 1987;137:39-43.

239. Abel PD, Hall RR, Williams G. Should pT1 transitional cell cancers of the bladder still be classified as superficial? Br J Urol 1988;62:235-239.

240. Lutzeyer W, Rubben H, Dahm H. Prognostic parameters in superficial bladder cancer: an analysis of 315 cases. J Urol 1981;127:250-252.

241. Dalesio O, Schulman CC, Sylvester R, De Pauw M, Denis L, Smith P, Viggiano G. Prognostic factors in superficial bladder tumors. a study of the European Organization for Research on Treatment of Cancer: Genitourinary Tract Cancer Cooperative Group. J Urol 1983;Apr 129(4):730-733.

242. Witjes JA, v d Meijden APM, Collette L, Sylvester R, Debruyne FMJ, van Aubel A, Witjes WPJ. Long-term follow-up of an EORTC randomized prospective trial comparing intravesical bacille Calmette-Guérin-RIVM and mitomycin C in superficial bladder cancer. EORTC GU Group and the Dutch South East Cooperative Urological Group. European Organisation for Research and Treatment of Cancer Genito-Urinary Tract Cancer Collaborative Group. Urology 1998;52(3):403-410.

243. Grimm MO, Steinhoff C, Simon X, Spiegelhalder P, Ackermann R, Vögeli TA. Effect of routine repeat transurethral resection for superficial bladder cancer: a long-term observational study. J Urol Aug 2003;170(2 Pt 1):433-437.

244. Klan R, Loy V, Huland H. Residual tumor discovered in routine second transurethral resection in patients with stage T1 transitional cell carcinoma of the bladder. J Urol 1991;146:316-318.

245. Fitzpatrick JM, West AB, Butler MR, Lane V, O´Flynn JD. Superficial bladder tumors (stage pTa grades 1 and 2): the importance of recurrence pattern following initial resection. J Urol 1986;135:920-922.

246. Whitmore WFJr and Bush IM. Ultraviolet cystoscopy in patients with bladder cancer. J Urol 1966;95:201.

247. Vicente J, Chéchile G, Algaba F. Value of in vivo mucosa-staining test with methylene blue in the diagnosis of pretumoral and tumoral lesions of the bladder. Eur Urol 1987;13:15-16.

248. Kriegmair M, Baumgartner R, Knuechel R, Steinbach P, Ehsan A, Lumper W, Hofstädter F, Hofstetter A. Fluorescence photodetection of neoplastic urothelial lesions following intravesical instillation of 5-aminolevulinic acid. Urology Dec 1994;44(6):836-841.

249. Kriegmair M, Zaak D, Stepp H, Stepp H, Baumgartner R, Knuechel R, Hofstetter A. Transurethral Resection and surveillance of bladder cancer supported by 5-aminolevulinic acid-induced fluorescence endoscopy. Eur Urol April 1999;36:386-392.

250. Kriegmair M, Baumgartner R, Knuechel R, Stepp H, Hofstadter F, Hofstetter A. Detection of early bladder cancer by 5-aminolevulinic acid induced porphyrin fluorescence. J Urol 1996;155:105-110.

251. Jichlinski, Forrer M, Mizeret J, Glanzmann T, Braichotte D, Wagnieres G, Zimmer G, Guillou L, Schmidlin F, Graber P. Clinical evaluation of a method for detecting superficial surgical transitional cell carcinoma of the bladder by light-induced fluorescence of protoporphyrin IX following the topical application of 5-aminolevulinic acid: preliminary results. Lasers Surg Med 1997;20:402-408.

252. König F, McGovern FJ, Larne R, Enquist H, Schomacker KT, Deutsch TF. Diagnosis of bladder carcinoma using protoporphyrin IX fluorescence induced 5-aminolevulinic acid. BJU Int 1999;83:129-135.

253. Filbeck T, Roessler W, Knuechel R, Straub M, Kiel HJ, Wieland WF. Clinical results of the transurethreal resection and evaluation of superficial bladder carcinomas by means of fluorescence diagnosis after intravesical instillation of 5-aminolevulinic acid. J Endourol 1999;13:117-121.

254. Riedl C, Plas E, Pfluger H. Fluorescence detection of bladder tumors with 5-aminolevulinic acid. J Endourol 1999; 13(10): 755-759.

255. De Dominicis C, Liberti M, Perugia G, De Nunzio C, Sxiobica F, Zuccala A, Sarkozy A, Iori F. Role of 5-aminolevulinic acid in the diagnosis and treatment of superficial bladder cancer: improvement in diagnostic sensitivity. Urology 2001; 57(6):1059-1062.

256. Filbeck T, Roessler W, Knuechel R, Straub M, Kiel HJ, Wieland WF. 5-aminolevulinic acid-induce fluorescence endoscopy applied at secondary transurethral resection after conventional resection of primary superficial bladder tumors. Urology 1999;53(1):77-81.

257. Zaak D, Frimberger D, Stepp H, Wagner S, Baumgartner R, Schneede P, Siebels M, Knuechel R, Kriegmair M, Hofstetter A. Quantification of 5-aminolevulinic acid induced fluorescence improves the specificity of bladder cancer detection. J Urol Nov 2001;166:1665-1669.

258. Zaak D, Hungerhuber E, Schneede P, Stepp H, Frimberger D, Corvin S, Schmeller N, Kriegmair M, Hofstetter A, Knuechel R. Role of 5-aminolevulinic acid in the detection of urothelial premalignant lesions. Cancer Sept 2002;95(6):1234-1238.

259. Zaak D, Kriegmair M, Stepp H, Stepp H, Baumgartner R, Oberneder R, Schneede P, Corvin S, Frimberger D, Knuechel R, Hofstetter A. Endoscopic detection of transitional cell carcinoma with 5-aminolevulinic acid – results of 1012 fluorescence endoscopies. Urology 2001;57(4):690-694.

260. Schmidbauer J, Witjes F, Schmeller N, Donat R, Susani M, Marberger M, Members of the Hexvix PCB301/01 Study group. Improved detection of urothelial carcinoma in situ with hexaminolevulinate fluorescence cystoscopy. J Urol Jan 2004; 171:135-138.

261. Filbeck T, Pichlmeier U, Knuechel R, Wieland WF, Roessler W. Do patients profit from 5-aminolevulinic acid-induced fluorescence diagnosis in transurethral resection of bladder carcinoma? Urology 2002;60(6):1025-1028.

262. Kriegmair M, Zaak D, Rothenberger KH, Rassweiler J, Jocham D, Eisenberger F, Tauber R, Stenzl A, Hofstetter A. Transurethral resection for bladder cancer using 5-aminolevulinic acid induced fluorescence endoscopy versus white light endoscopy. J Urol Aug 2002;168:475-478.

263. Riedl CR, Daniltchenko D, Koenig F, Simak R, Loening SA, Pflueger H. Fluorescence endoscopy with 5-aminolevulinic acid reduces early recurrence rate in superficial bladder cancer. J Urol April 2001;165:1121-1123.

264. Filbeck T, Pichlmeier U, Knuechel R, Wieland WF, Roessler W. Clinically relevant improvement of recurrence-free survival with 5-aminolevulinic acid induced fluorescence diagnosis in patients with superficial bladder tumors. J Urol July 2002;168:67-71.

265. Filbeck T, Pichlmeier U, Knuechel R, Wieland WF, Rößler W. Senkung des Rezidivrisikos oberflächlicher Harnblasenkarzinome mittels 5-Aminolävulinsäure- induzierter Fluoreszenzdiagnostik. Urologe A April 2003;42:1366-1373.

266. Shelfo SW, Brady JD, Soloway MS. Transurethral resection of bladder cancer. Atlas of the Urologic Clinics of North America 1997;5(2):1-14.

267. Milner WA. Transurethral biopsy: an accurate method of determining the true malignancy of bladder carcinoma. J Urol 1949;61(5):917-923.

268. Kolozsky Z. Histopathological “self control” in transurethral resection of bladder tumors. Br J Urol 1991;67:162-164.

269. Soloway MS and Patel J. Surgical techniques for endoscopic resection of bladder cancer. Urol Clin North Am 1992; 19(3):467-471.

270. Saito S. Transurethral en bloc resection of bladder tumors. J Urol 2001;166:2148-2150.

271. Lodde M, Lusuardi L, Palmero S, Signorelo D, Maier K, Hohenfellner R, Pycha A. En bloc transurethral resection of bladder tumors: use and limits. Urology 2003;62:1089-1091.

272. Ukai R, Kawashita E, Ikeda H. A new technique for transurethral resection of superficial bladder tumor in 1 piece. J Urol 2000;163:878-879.

273. Solsona E, Iborra I, Ricos JV, Monros JL, Dumont R. Feasibility of transurethral resection for muscle infiltrating carcinoma of the bladder: prospective study. J Urol 1992;147:1513-1515.

274. Reynolds LR, Schulte TL, Hammer HJ. Bladder tumors – a clinical evaluation of radical transurethral management. J Urol 1949;61(5):912-916.

275. Davis JP. Ureteral injury by transurethral electroresection and coagulation. J Urol 1952;68(1):168-177.

276. Posta B, Streit B, Schmauzer J. Transurethral resection of the carcinomatous ureteral orifice. Int Urol Nephrol 1980; 12 (1):23-35.

277. Kisbenedek L, Szeldeli P, Balogh F. Vesicoureteral reflux following transurethral resection of bladder tumors at the ureteral orifice. Eur Urol 1982;8:9-10.

278. Gottfries A, Nilsson S, Sundin T, Viklund LG. Late effects of transurethral resection of bladder tumors at the ureteric orifice. Scand J Urol Nephrol 1975;9:32-35.

279. Amar AD. Ureterovesical junction obstruction following transurethral resection. Br J Urol 1965;37:307-313.

280. Rees RWM. The effect of transurethral resection of the intravesical ureter during removal of bladder tumors. Br J Urol 1969;41:2-5.

281. Freed SZ. Vesicoureteral reflux following transurethral resection of bladder tumors. J Urol 1976;116:184-187.

282. Palou J, Farina LA, Villavicencio H, Vicente J. Upper tract urothelial tumor after transurethral resection for bladder tumor. Eur Urol 1991;21(2):110-114.

283. De Torres Mateos JA, Banus Gassol JM, Palou Redorta J, Morote Robles J. Vesicorenal reflux and upper urinary tract transitional cell carcinoma after transurethral resection of recurrent superficial bladder carcinoma. J Urol 1987;138(1):49-51.

284. Amar AD and Das S. Upper urinary tract transitional cell carcinoma in patients with bladder carcinoma and associated vesicoureteral reflux. J Urol 1985;133(3):468-471.

285. Amar AD and Das S. Vesicoureteric reflux in patients with bladder tumors. Br J Urol 1983;55:483-487.

286. Gonzalez Martin M, Sousa Escandon A, Busto Castanon L, Gomez Veiga F, Chantada Abal V, Serrano Barrientos J. Endoscopic treatment of vesicoureteral reflux following transurethral resection of a vesical carcinoma by Teflon injection. Eur Urol 1991;19(4):291-294.

287. Hobika JH and Clarke BG. Use of neuromuscular blocking drugs to counteract thigh-adductor spasm induced by electrical shocks of obturator nerve during transurethral resection of bladder tumors. J Urol 1961;85(3):295-296.

288. Prentiss RJ, Harvey GW, Bethard WF, Boatwright DE, Pennington RD. Massive adductor muscle contraction in transurethral surgery: cause and prevention; development of new electrical circuitry. J Urol 1965;93:263-271.

289. Augspurger RR and Donohue RE. Prevention of obturator nerve stimulation during transurethral surgery. J Urol 1980; 123: 170-172.

290. Redman JF, McGinnis TB, Bissada NK. Management of neoplasms in vesical diverticula. Urology 1976;7(5):492-494.

291. Golijanin D, Yossepowitch O, Beck SD, Sogani P, Dalbagni G. Carcinoma in a bladder diverticulum: presentation and treatment outcome. J Urol 2003;170(5):1761-1764.

292. Melekos MD, Asbach HW, Barbalias GA. Vesical diverticula: etiology, diagnosis, tumorigenesis, and treatment. Urology 1987;30(5):453-457.

293. Dick A, Barnes R, Hadley H, Bergman RT, Ninan CA. Complications of transurethral resection of bladder tumors: prevention, recognition and treatment. J Urol 1980;124:810-811.

294. Herr HW. The value of a second transurethral resection in evaluating patients with bladder tumors. J Urol Jul 1999;162(1):74-76.

295. Dutta SC, Smith JA, Jr., Shappell SB, Coffey CS, Chang SS, Cookson MS. Clinical under staging of high risk nonmuscle invasive urothelial carcinoma treated with radical cystectomy. J Urol Aug 2001;166(2):490-493.

296. Zurkirchen MA, Sulser T, Gaspert A, Hauri D. Second transurethral resection of superficial transitional cell carcinoma of the bladder: a must even for experienced urologists. Urol Int 2004;72(2):99-102.

297. Brauers A, Buettner R, Jakse G. Second resection and prognosis of primary high risk superficial bladder cancer: is cystectomy often too early? J Urol Mar 2001;165(3):808-810.

298. Schips L, Augustin H, Zigeuner RE, Galle G, Habermann H, Trummer H, Pummer K, Hubmer G. Is repeated transurethral resection justified in patients with newly diagnosed superficial bladder cancer? Urology Feb 2002;59(2):220-223.

299. May M, Nitzke T, Helke C, Vogler H, Hoschke B. Significance of the time period between diagnosis of muscle invasion and radical cystectomy with regard to the prognosis of transitional cell carcinoma of the urothelium in the bladder. Scand J Urol Nephrol 2004;38(3):231-235.

300. Sanchez-Ortiz RF, Huang WC, Mick R, Van Arsdalen KN, Wein AJ, Malkowicz SB. An interval longer than 12 weeks between the diagnosis of muscle invasion and cystectomy is associated

with worse outcome in bladder carcinoma. J Urol 2003 Jan;169(1):110-115.

301. Van Gils-Gielen RJ, Witjes WP, Caris CT, Debruyne FM, Witjes JA, Oosterhof GO.Risk factors in carcinoma in situ of the urinary bladder. Dutch South East Cooperative Urological Group. Urology 1995 Apr;45(4):581-586.

302. May F, Treiber U, Hartung R, Schwaibold H. Significance of random bladder biopsies in superficial bladder cancer. Eur Urol 2003 Jul;44(1):47-50.

303. Mufti GR and Singh M.Value of random mucosal biopsies in the management of superficial bladder cancer. Eur Urol 1992;22(4):288-293.

304. Fujimoto N, Harada S, Terado M, Sato H, Matsumoto T. Multiple biopsies of normal-looking urothelium in patients with superficial bladder cancer: Are they necessary? Int J Urol 2003 Dec;10(12):631-635.

305. Van der Meijden A, Oosterlinck W, Brausi M, Kurth KH, Sylvester R, de Balincourt C. Significance of bladder biopsies in Ta,T1 bladder tumors: a report from the EORTC Genito-Urinary Tract Cancer Cooperative Group. EORTC-GU Group Superficial Bladder Committee. Eur Urol 1999 Apr;35(4):267-271.

306. Taguchi I, Gohji K, Hara I, Gotoh A, Yamada Y, Yamanaka K, Okada H, Arakawa S, Kamidono S. Clinical evaluation of random biopsy of urinary bladder in patients with superficial bladder cancer. Int J Urol 1998 Jan;5(1):30-34.

307. Levi AW, Potter SR, Schoenberg MP, Epstein JI. Clinical significance of denuded urothelium in bladder biopsy. J Urol 2001 Aug;166(2):457-460.

308. Ende N, Woods LP, Shelley HS. Carcinoma originating in ducts surrounding the prostatic urethra. Am J Clin Pathol 1963;40:183-189.

309. Bates HR. Transitional cell carcinoma of the prostate. J Urol 1969;101:206-207.

310. Schellhammer PF, Bean MA, Whitmore WF. Prostatic involvement by transitional cell carcinoma: pathogenesis, patterns and prognosis. J Urol 1977;118:399-403.

311. DePaepe ME, Andre R, Mahadevia P. Urethral involvement in patients with bladder cancer. A study of 22 cystectomy specimens. Cancer 1990;65:1237-1241.

312. Muezzinoglu B, Mootha R, Chakraborty S, et al. Prostatic involvement by transitional cell carcinoma of the urinary bladder. US Can Acad Pathol 1997;76:83, abstract.

313. Nixon RG, Chang SS, Lafleur BJ, Smith JA, Cookson MS. Carcinoma in situ and tumor multifocality predict the risk of prostatic urethral involvement at radical cystectomy in men with transitional cell carcinoma of the bladder. J Urol 2002 Feb;167(2 Pt 1):502-505.

314. Solsona E, Iborra I, Ricos JV, Monros JL, Dumont R, Casanova J, Calabuig C. Recurrence of superficial bladder tumors in prostatic urethra. Eur Urol 1991;9(2):89-92.

315. Sakamoto N, Tsuneyoshi M, Naito S, Kumazawa J. An adequate sampling of the prostate to identify prostatic involvement by urothelial carcinoma in bladder cancer patients. J Urol 1993 Feb;149(2):318-321.

316. Freeman JA, Tarter TA, Esrig D, Stein JP, Elmajian DA, Chen SC, Groshen S, Lieskovsky G, Skinner DG. Urethral recurrence in patients with orthotopic ileal neobladders. J Urol 1996;156:1615-1619.

317. Iselin CE, Robertson CN, Webster GD, Viewig J, Paulson DF. Does prostate transitional cell carcinoma preclude orthotopic bladder reconstruction after radical cystoprostatectomy for bladder cancer? J Urol 1997;158:2123-2126.

Committee 2

Cytology And Tumor Markers: Tumor Markers Beyond Cytology

Chair

V. B. Lokeshwar (USA)

Members

T. Habuchi (Japan)

H. B. Grossman (USA)

W. M. Murphy (USA)

G. P. Hemstreet, III (USA)

S. H. Hautmann (Germany)

A. V. Bono (Italy)

R. H. Getzenberg (USA)

P. Goebell (Germany)

B. J. Schmitz-Dräger (Germany)

M. Marberger (Austria)

J. A. Schalken (Netherlands)

E. Messing (USA)

Y. Fradet (Canada)

M. J. Droller (USA)

CONTENTS

Cytology And Tumor Markers: Tumor Markers Beyond Cytology

V. B. Lokeshwar

T. Habuchi, H. B. Grossman , W. M. Murphy, G. P. Hemstreet, III, S. H. Hautmann, A. V. Bono, R. H. Getzenberg, P. Goebell, B. J. Schmitz-Dräger, M. Marberger, J. A. Schalken, E. Messing, Y. Fradet, M. J. Droller

The search for finding new cancer diagnostic tests or improving existing ones is driven by the appeal of being able to detect every symptomatic and asymptomatic cancer patient, monitoring tumor recurrence, and predicting prognosis. If the diagnostic test or marker is noninvasive, reliable, and inexpensive, it will significantly improve the clinical applicability of the marker. In case of bladder cancer, there is an impetus for developing an accurate and noninvasive bladder tumor marker(s) because such a marker(s) could be an important adjunct in screening, initial diagnosis, surveillance for recurrence, detection of early progression, and prediction of prognosis [1]. Unlike prostate cancer, bladder cancer is almost never found as an incidental cancer on autopsy [2]. Patients with bladder cancer present themselves to urologists with symptoms such as painless hematuria in the absence of any urinary tract infection and irritative voiding [3,4].

This mode of detection may be acceptable for the approximately 70% of urothelial carcinomas that are low grade papillary tumors, which have little propensity to invade and metastasize [1,3,5,6]. However, the majority of patients with high grade bladder cancer, at the time of initial presentation, have tumors that invade the lamina propria (stage T1) and beyond [1,3-6]. These patients have a high risk of developing distant metastasis and death despite aggressive treatment of the disease. In these patients, early detection of bladder tumors, before they become muscle–invasive, will improve survival. Bladder tumors recur frequently; typically 40% to 80% of patients with bladder cancer will have a recurrence within 3 years following initial treatment [5]. Furthermore, tumors that recur may be of higher grade or stage. Thus, patients with bladder cancer usually undergo 3- to 6-month surveillance.

Cystoscopy, the gold standard for the detection of bladder cancer, is invasive and relatively expensive (Medicare reimbursement cost in the US: $200-$300) [7]. In fact, due to the lifelong need for recurrence monitoring by cystoscopy and the treatment of recurrent tumors, the cost per bladder cancer patient from diagnosis to death is the highest among all cancers ($96,000 to $187,000 per patient in the United States) [8].

Voided urine cytology is a highly specific, noninvasive adjunct to cystoscopy **(Figure 1)**. It has good sensitivity for detecting high grade bladder tumors,

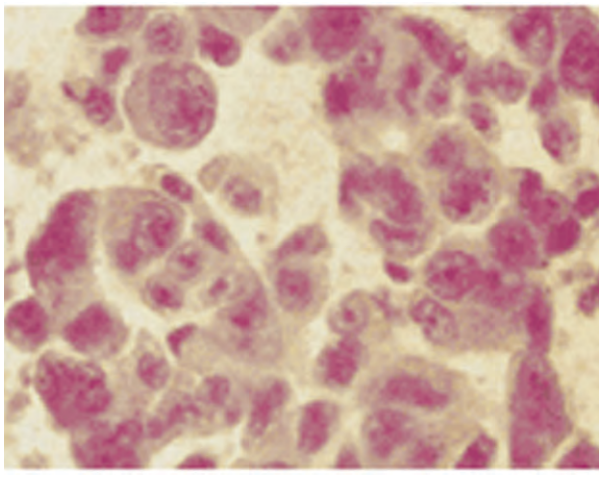


Figure 1. Positive cytology

but has poor sensitivity to detect low grade disease. Furthermore, the accuracy of cytology depends upon the reviewer's expertise, and it is relatively expensive and not readily available in all countries. Thus, a noninvasive, highly sensitive and specific marker(s) for detecting bladder cancer would decrease the morbidity associated with cystoscopy, improve patient quality of life, and decrease costs by substituting a less expensive, noninvasive test for the more expensive endoscopic procedure.

In this review on markers, cytology, and molecular biology, the panel presents a critical analysis of the recent literature and provides recommendations on various areas in bladder cancer management where markers will be useful, requirements of an ideal bladder tumor marker, and different tumor markers that are being evaluated for bladder cancer diagnosis, surveillance, and prognostic predictions.

I. STANDARD CARE FOR BLADDER CANCER DETECTION AND SURVEILLANCE

1. Detection

Bladder cancer may be diagnosed incidentally or because of symptoms. The main symptom of bladder cancer is hematuria, but in some patients irritative symptoms are present from the very beginning. Incidental cancer is usually found on ultrasound, performed either for hematuria or irritative symptoms, or for screening or symptoms unrelated to the urinary tract. Ultrasound reveals filling defects, informs about the postvoid residual urine, and shows some upper tract patterns. It may give some information about bladder capacity, useful to suspect the presence of carcinoma in situ (CIS) [9].

The clinical diagnosis of bladder cancer is usually made by flexible or rigid cystoscopy. Techniques of rigid and flexible cystoscopy are intuitively different. The observer accustomed only to rigid scopes, which offer various angles of observation, may be in some way disoriented with flexible instruments that have zero degree optics only. The main difference is that flexible scopes are active instruments because their tip curvature can vary between +210 to –120 degrees, allowing an easy exploration of all vesical areas. The limit of these types of instruments is that the irrigation channel is of small diameter, and, therefore, in the presence of hematuria the observation can be more difficult in comparison to rigid scopes [10]. It is helpful to draw bladder diagrams showing the number and extent of lesions. Bimanual examination under anesthesia (EAU) is useful in staging. The finding of a 3-dimensional mass on EUA after transurethral resection indicates the presence of extravesical spread.

In other cases, the detection of a superficial bladder tumor is the result of an intravenous urography (IVU) performed for various reasons when the late cystogram shows a filling defect within the bladder, in the case of papillary tumors. This exam cannot, however, diagnose a CIS. Once the clinical diagnosis is made, the rationale for performing an IVU is to exclude an obstructive uropathy and upper tract papillary tumors [11]. However, personal experience suggests that its routine use may be neither necessary nor cost-effective.

The further step in diagnosis is the pathologic examination of resected specimens performed on productive or flat suspicious lesions. Pathology definitively confirms the diagnosis and is mandatory for the correct staging of the disease.

2. Surveillance

Because of the frequency of recurrence, endoscopic surveillance is essential after tumor resection, intravesical prophylaxis or treatment, and during the maintenance prophylaxis period. Surveillance consists of periodic endoscopies. Schedules of endoscopies vary according to patients' risk factors. The schedule recommended by the EORTC for patients with low- to intermediate-risk disease is cystoscopy at 3-month intervals for the first 2 years, at 4-month intervals for the next 2 years, and yearly thereafter. This schedule also applies to patients in whom no recurrence is seen during the follow-up. In case of recurrence, the follow-up starts again with the same scheme adopted after the first diagnosis and might even be modified according to the recurrence patterns and pathology. This is because a tumor belonging to the low-risk category can progress in grade or stage or both. For example, a superficial Ta lesion may recur and progress toward submucosa infiltration [T1] and, in addition, CIS may appear. The duration of surveillance is debated: in some centers lifelong follow-up is recommended. For the high-risk group, an early re-TURBT or bladder mapping is frequently performed (1-3 months), and control cystoscopies are continued at 3-month intervals.

The main rationale for such strict follow-up procedures is the natural history of the disease. The vast majority of cases, which at first observation are

defined as “superficial” (70%-80%), show a high rate of recurrence, varying from 40% to 80% [12]. For instance, the mean 5-year recurrence rate for low-risk patients treated with transurethral resection alone is 46%, but it can reach 80% if the patients are followed for about 20 years [13]. The assumption is that frequent cystoscopies allow the treatment of the recurrences at a very early stage, thus lowering the further recurrence rate and possibly reducing the progression to muscle-invasive disease. Rates of progression of superficial disease is variable, again depending on the tumor category at first presentation, being about 5% for TaG1 tumors and 20% to 50% for T1 and G3 tumors [14,15]. Endovesical prophylaxis with chemotherapeutic agents increases the disease-free intervals and time to progression in progressive disease, but does not alter the progression rate and survival [16]. On the contrary, BCG prophylaxis and treatment act favorably in that sense in cases with high-risk tumors [17].

As far as imaging during the follow-up is concerned, its validity is questioned. In fact the rate of upper tract recurrences is reported low, at less than 2% [18]. Imaging can be useful when multiple resections of recurrent low grade tumors have been performed to assess bladder retraction due to scars and its impact on the upper tract.

Summary

Standard care of bladder cancer detection includes cystoscopy and pathologic examination of biopsy specimens. Standard care of bladder cancer surveillance consists of periodic cystoscopies, schedules of which vary according to the risk factors of the disease.

II. BLADDER TUMOR MARKERS: WHY DO WE NEED THEM?

A noninvasive and accurate bladder tumor marker may be used for bladder cancer screening and recurrence monitoring.

1. Tumor Markers and Bladder Cancer Screening

A bladder screening program, like any other cancer program, should be feasible, inexpensive, and accurate, and should promote early detection. In case of bladder cancer, detection of high grade tumors before they become invasive (i.e., detection at stages ≤ T1b) would result in improved prognosis [2,5]. The prevalence of bladder cancer in the general population is low (0.001%) [19]; however, it increases with age. In prospective community screening studies the prevalence of bladder cancer among asymptomatic men above the age of 50 is about 0.67% to 1.13% [20-27]. Given that high grade bladder tumors account for about 15% to 30% of all bladder tumors, the prevalence of high grade bladder tumors in the general population would be even lower. Thus, screening the whole population for bladder cancer, with the possibility of detecting too many false positives (each requiring an expensive work-up), would not be cost-effective.

Bladder cancer screening may be cost-effective among individuals who are at a higher risk for bladder cancer. In population cohort studies, cigarette smoking; occupational exposures to aniline dyes, aromatic amines, benzidine, and arsenic; parasitic infections (e.g., *Schistosoma haematobium*), chronic bacterial infections, chronic catheterization, and possibly even geographical region (such as Northeast United States vs. Western United States), have been shown to increase the risk for bladder cancer [28-34]. The risk for bladder cancer is even higher when smoking is combined with other known bladder carcinogens (e.g., > 80 µg arsenic per day in drinking water of smokers) or genetic polymorphisms [35]. For example, polymorphisms in N-acetyl transferase-2 (NAT-2; slow acetylator phenotype), glutathione-S-transferase (GSTM1 null phenotype), and manganese superoxide dismutase genes increase the risk for developing bladder cancer among smokers [36,37]. The mean time for the development of bladder cancer, following exposure to bladder carcinogens, is about 18 years [2]. Therefore, early detection of bladder cancer prior to the occurrence of muscle-invasive disease may be possible if a single or panel of bladder tumor markers is used for screening the high risk population.

When using a bladder tumor marker for screening, it is essential that the marker have a low false positive rate. This will avoid unnecessary anxiety to patients and expensive work-up incurred due to false positive results. One of the possible ways to identify false positive results would be to have the knowledge of conditions and diseases that give rise to a false positive result on a particular marker, and then screening the population for those conditions along with screening for the tumor marker. For example, when screening a population for bladder cancer using

hemoglobin dipstick (detects hematuria), information on the history of or active episodes of stone disease, urinary tract infection, cystitis, etc., would be useful to identify false positive results. In a bladder cancer screening study, involving 401 Department of Energy workers who had a possible exposure to bladder carcinogens, the majority of the positive cases on the BTA-Stat test had an abnormal urinalysis (i.e., 2+ to 3+ protein on dipstick, microhematuria, presence of leukocytes, history of cystitis, and others) and cystoscopy revealed no evidence of bladder cancer in some of them [38].

Currently, the data on the feasibility, accuracy, and cost analysis, as well as the challenges of bladder cancer screening, are available from a series of community-based hematuria detection trials [20-27]. For example, in an initial study of 533 individuals over the age of 50, Messing et al. evaluated the efficacy of hemoglobin dipstick self-testing once a week for 1 year to detect bladder and other urologic malignancies [21]. The compliance rate in this study (individuals who completed the 1-year testing protocol and the questionnaire on health and sociodemographic information) was 44%. Out of the 44 patients who had hematuria, 5 were subsequently detected to have bladder cancer and 3 to have renal cell carcinoma. Thus, although the prevalence of bladder cancer in the entire study population was 2.13%, in patients with hematuria it was fivefold higher (11.4%). Interestingly, in this study, among the individuals who declined to participate, 4 urologic cancers were detected 18 to 30 months after completion of the study, suggesting that hematuria screening offers an early detection advantage [23]. In a subsequent study, Messing et al. solicited 2932 individuals, out of which 1736 agreed to a 14-day hematuria testing protocol and 1340 individuals finally completed the study [20]. In this study, the prevalence of bladder cancer in the total population, 0.67%, was lower than what was observed in the earlier yearlong weekly hematuria testing protocol. The prevalence of bladder cancer among patients with hematuria (3.2%) was also lower than that observed in the 1-year protocol. One of the reasons for this difference could be that patients with urologic malignancies have intermittent hematuria, and, therefore, the chance of detecting it would be higher if testing was conducted over a longer period of time. In a screening trial of 578 men over the age of 60, Britton et al. found that 13% of the men were positive for hematuria on a single dipstick test, and an additional 9% were detected when testing was continued once a week for 10 weeks [27]. In this trial, the prevalence of bladder cancer in the entire cohort was 0.69%, but among men with hematuria it was 3%. The benefits of repeat hematuria testing were evaluated in a large community screening trial by Messing et al. In this study, 1055 men who were negative on first hematuria 14-day testing protocol were solicited for retesting in a second 14-day testing protocol after 9 months. The compliance rate in the second phase of the study was much higher, at 81.1% [24]. The prevalence of bladder cancer in phase II of the study in the total population was 0.82%. However, in the hematuria-positive individuals it was 18.4%. If the results of both first time detection of hematuria (Phase I) and Phase II studies are combined, the frequency of bladder cancer detection among hematuria-positive patients increases to about 22% [8]. In several of these community screening trials, the detection of bladder cancer by hemoglobin dipstick was found to be independent of tumor grade [20-27], suggesting that if the hematuria 14-day screening protocol is conducted at regular intervals among individuals above the age of 50, it may result in early detection of bladder cancer.

Contrary to the findings of Messing et al. and Britton et al., Hiatt et al., in an epidemiological retrospective outcomes study involving 20 571 men aged 35 years or older and women aged 55 years or older, found that the relative risk of urologic cancers was not significantly elevated among individuals positive for asymptomatic microhematuria when compared to those with negative results [39]. The sensitivity and specificity of a single dipstick urinalysis for microhematuria to indicate urologic cancers within 3 years were 2.9% and 96.7%, respectively. Based on these results, the authors conclude that screening for microhematuria among asymptomatic men is not recommended. However, since hematuria is intermittent among patients with urological cancers and data show that a substantial percentage of individuals with a first negative test show a positive test result during subsequent testing, the results based on a single hematuria dipstick test may not be accurate [27,28,39].

Cost analysis for bladder cancer screening was also performed at the end of several of the above discussed screening studies. Messing et al. reported that the average cost of phase I screening, per participant, was between $52.32 and $90.96 [20,21]. However, the cost of phase II screening was low, at $22.76. The average cost per bladder cancer detected was $12,960 in Phase I screening and $2,783 in Phase II.

Since hematuria also detects other malignancies, the cost per serious disease found is even lower, $1,935 in Phase I and $1,299 in Phase II [24]. These cost comparisons compare with other mass screenings for diseases such as breast cancer [24]. However, it should be noted that the cost of hematuria screening might be higher than what was predicted nearly 10 years ago when these studies were conducted. It is also noteworthy that none of the bladder tumor markers available today are as inexpensive as the hemoglobin dipstick test, and, therefore, the cost of bladder cancer screening using other bladder tumor markers could be higher depending upon the number of false positive cases and the need for repeating the test due to spurious results.

One prospective cohort study evaluated the usefulness of bladder tumor markers for screening high risk populations. Hemstreet et al. assessed the risk for the development of bladder cancer in a group of 1788 Chinese workers who were exposed to benzidine by developing a biomarker profile [40]. This biomarker profile included the analysis of DNA ploidy, G-actin, and tumor-associated antigen P-300. Although the biomarker profile placed only 21% of the exposed workers in a high or moderate risk group, 87% of the bladder cancer cases in the entire cohort were found in this group, and all of the tumors were clinically organ-confined [40,41]. More interestingly, a positive biomarker profile occurred 15 to 33 months before the clinical detection of bladder cancer. This study demonstrates that screening a high risk population using biomarkers may offer an early detection advantage. If early diagnosis translates into detection of tumors prior to progression, clinicians may be able to manage bladder cancer patients with bladder preservation treatments and prolong the time to cystectomy. Parekattil et al. have developed a neural network using urine levels of nuclear matrix protein-22, monocyte chemoattractant protein-1, and urinary intercellular adhesion molecule-1 to identify patients with bladder cancer. This algorithm has 100% sensitivity and 75% specificity for identifying patients who will require cystoscopy, patients who have bladder cancer, and patients who have muscle-invasive disease. Interestingly, they suggest that screening of potential bladder cancer patients with this neural network may save 41% of the cost of conventional bladder cancer diagnosis [42].

Summary

The use of tumor markers to screen the general population might not be cost-effective due to the low prevalence of bladder cancer in the general population. Screening of high-risk populations, including populations above the age of 50 (using hematuria detection) may be cost-effective and can offer an early detection advantage. More studies with accurate markers are needed to establish the role (if any) of tumor markers in bladder cancer screening.

2. Tumor Markers and Bladder Cancer Recurrence

Individuals with bladder cancer are at significant risk for developing another bladder tumor. Clinically, these subsequent neoplasms are all called recurrences and a distinction is not made between second primary tumors and growth of occult residual disease (polyclonal vs. monoclonal). Cystoscopy is the conventional method for following these people and has excellent sensitivity and specificity in experienced hands. Furthermore, it enables the excision of recurrent tumors without an open surgical procedure. However, cystoscopy has its limits and is particularly poor for detecting CIS. Furthermore, the use of fluorescence cystoscopy strongly suggests that this investigative technique results in more complete tumor resection [43]. Conventional indicators of recurrence such as grade, stage, and multicentricity provide useful indications of the risks of recurrence in a population at risk but have poor predictive value on an individual basis [44].

Biomarkers can improve the surveillance of patients with recurrent bladder cancer who are currently being assessed by periodic cystoscopy by improving the detection of occult or missed disease or identifying patients who, despite abnormal appearing urothelium, do not have bladder cancer. Tests with high specificity and high positive predictive value will be most useful for indicating the need for random biopsies when no disease is seen. Tests with high sensitivity and high negative predictive value are useful for avoiding biopsies and perhaps decreasing the frequency of cystoscopic surveillance. Currently, the test with greatest specificity for the detection of occult CIS is urine cytology [45]. However, urine cytology is not an easy test to perform and is associated with significant variability. Soluble urinary markers for bladder cancer have a lower specificity

and are not indicators for random biopsy [46]. A fluorescence in situ hybridization (FISH) assay (UroVysion) demonstrates increased risk for tumor recurrence when it is positive and the cystoscopy is negative [47]. However, the clinical utility of this observation appears low because most patients will still be free of detectable tumor 1 year later. The alternative use of markers uses the high negative predictive value of tests with high sensitivity. When the UroVysion assay and cystoscopy are negative, the risk of recurrence is very low in the ensuing 6 months. Other markers also have high negative predictive value. For example, the combination of cytology and DD23 has a negative predictive value of 90% [48]. Although evidence is meager, the current data suggest that many of the currently available markers could be used to clarify the meaning of an abnormal appearing bladder and would be more informative when they are negative than when they are positive.

Surveillance for recurrent bladder cancer is performed using an arbitrary schedule. Conceivably, validated biomarkers could be used to individualize the cystoscopic interval based on periodic noninvasive testing. There are obvious benefits and risks to this use of biomarkers. The benefits include fewer invasive procedures (cystoscopy with or without biopsy) and less expense. Retrospective data suggest that this can be accomplished [49]. However, this use of biomarkers also has some risk, and the risk is not based on a normal distribution. The risk to the individual being followed by a biomarker-based strategy is asymptotic. The greatest risk would be missing a high grade tumor that could metastasize and be fatal. A risk with significant but lower impact on the patient would be missing a superficial tumor that would progress but be cured with cystectomy. A third and lower risk is missing small superficial tumors that could be treated in the office setting by fulguration but now require transurethral resection in the operating room. An obvious concern is low probability that any biomarker will always exhibit 100% sensitivity. Nevertheless, this approach of providing individualized surveillance appears feasible. The risk of a serious adverse event (death from bladder cancer or need for cystectomy) is related to tumor biology and time to surveillance. It is important to recall that even with regular scheduled surveillance these events still occur. Fortunately, biomarkers have their greatest sensitivity for high grade tumors. If this did not provide enough reassurance of the limited risk with this approach, patients with grade 3 tumors could be maintained on the conventional surveillance schedule. The second risk is related to time. Even low to moderate grade tumors can eventually cause problems and require cystectomy. For this reason, a biomarker based follow-up strategy is not meant to replace but to decrease the frequency of cystoscopy. The periodicity of this fail-safe cystoscopy needs to be determined and validated in a prospective study, but presumably would be between 6 and 12 months. While the existing data and retrospective analyses suggest that this approach is reasonable and cost- effective, safety (the risks of metastasis and cystectomy) cannot be effectively modeled. A prospective study is needed and is likely to validate this approach and usher in a new era for the surveillance of bladder cancer.

Summary

Currently available biomarkers have good sensitivity, particularly for high grade bladder cancer, and moderate to good specificity. The general use of these markers focuses on positive predictive value, which in a group of individuals at high risk for recurrence is moderate to good. A second but often neglected use of biomarkers takes advantage of their negative predictive value. Several of the currently available biomarkers have high negative predictive values and could be used to prolong the cystoscopic interval, particularly in patients with low-risk bladder cancer. A prospective trial is needed to determine the cost savings, change in quality of life, and safety of this strategy.

III. IDEAL TUMOR MARKER

Several criteria have been established to assess the usefulness of a substance as a marker for the diagnosis and surveillance of cancer. The attributes of an ideal tumor marker include technical ease of assaying, low intra-assay and interassay variability, and high accuracy [6,50]. In this section, we will discuss the attributes of an ideal tumor marker by considering the development of a hypothetical bladder tumor marker, MDVL. Consider that MDVL is a secreted protein synthesized by normal urothelial cells; however, its expression is fourfold to eightfold elevated in bladder tumor cells. Two highly specific monoclonal antibodies are available for MDVL and, using these antibodies, MDVL can be detected in the cul-

ture-conditioned media of bladder cancer cells, bladder tumor tissues, and urine specimens. MDVL transcripts can also be detected in tumor cells and exfoliated cells by real time-polymerase chain reaction (RT-PCR) analysis. In the following paragraphs, we will discuss how one can evaluate whether MDVL is a useful bladder tumor marker, and whether it can be developed into a clinically applicable diagnostic test.

1. Technical Simplicity of Detection

Since cystoscopy is invasive and patients consider it uncomfortable, the main argument for designing a bladder tumor marker is that it be noninvasive. Of possibly greater importance, given our increasing understanding of the molecular aspects of bladder cancer, is the possibility of identifying markers that might be used to characterize and predict the biological potential of a particular diathesis. It is relatively easy to design a bladder cancer test, since many "molecular determinants" of bladder tumor growth and invasion are released into urine when it comes in contact with the tumor during storage in the bladder. Thus, many bladder cancer tests, such as BTA-Stat/TRAK, UBC-Rapid, UBC-IRMA, BLCA-4, HA-HAase, NMP-22, and survivin detect soluble markers released in urine (product inserts of BTA-Stat/TRAK, NMP-22, UBC) [51,52]. In addition, tests such as UroVysion (multicolor FISH), uCyt+™, microsatellite DNA analysis, telomerase, DD23, etc., detect either genetic alterations or cell-surface antigens that may indicate biologic characteristics of a particular cancer. These tests require exfoliated tumor cells in voided urine specimens or in bladder wash specimens as the starting material [6,48,51,52]. Since our hypothetical bladder tumor marker MDVL is secreted in urine, a urine-based sandwich ELISA (enzyme-linked immunosorbent assay) can be developed using the 2 monoclonal antibodies to detect levels of MDVL protein. In addition, an RT-PCR assay can be developed to detect the expression of MDVL transcript in exfoliated cells for diagnosing bladder cancer.

A point-of-care assay for the measurement of bladder cancer is desirable, since the diagnosis can be made immediately in a physician's office. Of the various tests designed for detecting bladder cancer, hematuria detection, BTA-Stat, NMP-22 (point-of-care test), and UBC-Rapid are dipstick tests and can be performed in the urologist's office. Other tests such as BTA-TRAK, NMP-22 (original), telomerase (TRAP assay and hTERT RT-PCR), uCyt+™, UroVysion, HA-HAase, BLCA-4, microsatellite DNA alterations, Quanticyt nuclear karyometry, and DD23 marker are either ELISAs, RT-PCR, or microscopic image analysis and require that urine specimens be sent to a central laboratory for assay. In the case of our hypothetical marker MDVL, a qualitative point-of-care sandwich dip-test, a quantitative ELISA, and an RT-PCR assay can be developed.

2. Reliability

Accuracy of a marker or diagnostic test is influenced by how much variation the test or marker displays during testing. The variation may result from specimen stability, conditions of specimen storage, or variation and shelf life of test reagents. For any bladder tumor marker, including our hypothetical marker MDVL, variability can be calculated by determining the intraclass and interclass correlations. The intraclass correlation can be evaluated by assaying the marker in the same specimen at multiple times in a single experiment, followed by computing one-way analysis of variance. If the intraclass correlation approaches 1.0, it indicates that the assay has low intra-assay variability. For calculating the interclass variability, the marker can be assayed using the same sample but in different experiments. Pearson's correlation analysis is performed on test results; if the Pearson's r approaches 1.0, it indicates that the marker has low variability.

3. Statistical parameters for evaluating marker efficiency

a) Contingency Table

Accuracy and reliability are the most critical parameters that determine the usefulness of a marker in diagnosing bladder cancer. This is because a false positive result leaves patients with unnecessary anxiety and the prospect of further costly and invasive testing. Contrarily, a false negative result provides patients a false sense of security and exposes them to the risk that their disease may progress and not be detected, resulting in a poorer prognosis. Since we must apply statistical measures for assessing the usefulness of markers, it may be useful for the reader to define some of the terminologies that are applied. The efficacy of a bladder cancer marker is analyzed by testing it in both populations with and without bladder cancer. The test inferences are then analyzed using a "2 x 2" contingency analysis. For example, we can measure MDVL concentrations in urine specimens from 200 individuals. Among these, 100 are patients with bladder cancer and 100 are control individuals either with other conditions that may produce

falsely positive assay results (see below) or with no clinical problems. When the MDVL test is performed, the test inferences will fall into 1 of the 4 compartments of the contingency table. True positives (TP) will be positive MDVL results in those individuals who have bladder cancer. False negatives (FN) will be negative MDVL results in those individuals who have bladder cancer. Correspondingly, true negatives (TN) will be negative MDVL results in those individuals who do not have bladder cancer, while false positives (FP) will be positive MDVL results in those individuals who do not have bladder cancer. Based on these 4 populations, one can determine the sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of the marker. These contingency tables are used to evaluate the statistical significance in cross-sectional, retrospective, and prospective studies.

b) Sensitivity

In our example, the sensitivity of the MDVL marker is defined as the percentage of bladder cancer patients in whom the test is positive. It is calculated from the contingency table as TP/(TP + FN) x 100. The false negative rate is just the opposite; it is calculated as FN/(TP + FN) x 100. For an ideal tumor marker, the sensitivity and false negative rate should approach 100% and 0%, respectively. Low sensitivity (higher false negative rate) of a marker may increase the risk for bladder cancer progression due to missed diagnosis [1,6,51]. However, it is important to understand that the sensitivity of a marker depends upon the population in which it is evaluated [53]. For example, the hypothetical marker MDVL may show 90% sensitivity to detect large high grade and advanced tumors, but show less sensitivity to detect low grade and recurrent tumors, which usually are smaller in size [46,53]. This may be the case for many urine-based markers since a large volume bladder tumor would ensure the secretion of large concentrations of different markers or the shedding of large numbers of tumor cells into the urine. In this regard, several markers (BTA-Stat/TRAK, NMP-22, UBC, telomerase (TRAP assay), microsatellite DNA analysis, UroVysion, and uCyt+™) have been found to have lower sensitivity to detect low grade and low stage tumors when compared to high grade, high stage tumors [46,55-65]. In addition, several tumor markers have lower sensitivities for detecting recurrent tumors than primary tumors because of the smaller size of recurrent tumors [54,55]. Interestingly, patients with bladder cancer appear to be reluctant to switch from cystoscopy to relying solely on a non-invasive urine test as a standard mode of surveillance if the test has a more than 10% false negative rate [66]. Therefore, for our hypothetical marker MDVL to become clinically useful, in terms of the sensitivity issue, it will have to be tested in multi-center trials and in heterogeneous community settings that include bladder cancer patients with primary and recurrent bladder cancers of different grades and stages.

c) Specificity

Specificity is equally as important as sensitivity when evaluating the usefulness of a marker. Specificity is defined as the percentage of individuals without the disease in whom the test is negative, and is calculated as TN/(TN + FP) x 100. The false positive rate is the reverse of specificity, and is calculated as FP/(TN + FP) x 100. For the ideal tumor marker, the specificity and false positive rates should approach 100% and 0%, respectively. As is the case for sensitivity, specificity of a marker depends on the composition of the study population. For example, many bladder cancer markers have greater than 90% specificity among healthy individuals, but have low specificity among patients with hematuria or lower urinary tract infection and inflammation. For example, specificities of BTA-Stat/TRAK and NMP-22 tests vary depending upon the degree of hematuria and inflammatory conditions [67-69, BTA-Stat/TRAK product inserts]. Knowledge of conditions other than bladder cancer that may cause a positive result may reduce anxiety and eliminate the need for further assessment. In evaluating the specificity of our hypothetical marker MDVL, the control population should include patients with a variety of benign urologic conditions.

d) Deciding Cutoff Limits for Sensitivity and Specificity Determinations (ROC Curve)

When a diagnostic test involves quantitative measurement of a particular marker, a cutoff limit is set to distinguish between positive and negative inferences. If the cutoff limit is set too high, the marker will be very specific, but the sensitivity will decrease. Conversely, if the cutoff limit is set too low, the marker will have high sensitivity, but the specificity will suffer due to increased false positive cases. For example, the sensitivity of BTA-TRAK varies between 58% and 77% at a threshold level of 14 U/mL, which is the cutoff limit recommended by the manufacturer. The specificity of the test at this threshold level varies between 54% and 75% [70-72]. However, at a cutoff limit of 1300 U/mL, the specificity of the test increases to 95%, but its sensi-

tivity decreases to 13% [29]. Similarly, the sensitivity and specificity of the NMP-22 test vary in different studies, which may be a reflection of the various thresholds used in these studies (3.6 U/mL-12 U/mL) [6,51].

Choosing the correct cutoff limit depends upon the type of population in which the marker will be tested. This is determined by generating a receiver operating characteristic (ROC) curve. To generate an ROC curve, the sensitivity and specificity values of a test or marker at different cutoff limits are calculated. The ROC curve is plotted as sensitivity versus specificity. If a marker is to be used for monitoring recurrence, the cutoff limit may be set at the lower end, such that the marker has high sensitivity and reasonable specificity. If a bladder cancer marker is used for screening, the cutoff limit could be set at the higher end, such that the number of false positive cases is decreased. Since the prevalence of bladder cancer in the general population is low, this is the approach that has been applied as a corollary. For the hypothetical marker MDVL, urinary levels are measured using an ELISA, and therefore, an ROC curve can be generated to determine the cutoff limit. There will be a trade-off between sensitivity and specificity, depending upon whether MDVL is to be used for monitoring bladder cancer recurrence or for screening a high-risk population for cancer.

e) Accuracy

Accuracy of a tumor marker or test is a function of both sensitivity and specificity. It is expressed as a percentage and calculated as (TP + TN)/total number of study individuals X 100. Since both sensitivity and specificity are valid only for the population in which the marker is tested, accuracy of a marker is also dependent on the study population and the cutoff limit used for calculating the sensitivity and specificity of the marker.

f) Positive and Negative Predictive Values

The other 2 terms that are often used for evaluating the usefulness of a marker are positive predictive value (PPV) and negative predictive value (NPV). Both PPV and NPV are dependent on the prevalence of the disease in a study population. PPV is defined as the percent of individuals in whom the test or marker is positive and the disease is present. It is calculated as TP/(TP + FP) x 100. NPV is defined as the percent of individuals in whom the test is negative and the disease is not present. NPV is calculated as TN/(TN + FN) x 100. Since PPV and NPV depend upon disease prevalence in a population, these values can be either high or low in different populations, even if a marker has the same sensitivity and specificity in those different populations [6,53]. Therefore, extrapolating the PPV and NPV obtained in a study population and applying them to the general population is not only incorrect, but may prove to be costly, misleading, and, therefore, not without risk.

In the following examples, we illustrate this concept using our hypothetical marker MDVL. In the first example, MDVL has 85% sensitivity and 85% specificity to detect bladder cancer and is being tested in a study population of 1000 individuals. In this scenario, the 1000 individuals are part of a community-based screening program. The SEER/NCI (Surveillance, Epidemiology, and End Results/National Cancer Institute) database indicates that the prevalence of bladder cancer in the general population is 0.1% [19]. Assuming a prevalence of 0.1% in our study population, the PPV and NPV of MDVL will be 0.56% and 99.99%, respectively. This means that less than 1% of individuals who test positive on MDVL will have bladder cancer.

In the second example, let us consider a population of 1000 individuals who are 65 years or older. Two-thirds of bladder cancer cases occur above the age of 65 years [73,74]. Britton et al. and Messing et al., when screening a general population for hematuria, found that the prevalence of bladder cancer among individuals above the age of 50 or 60 years is higher, about 0.7% [20,27]. Thus, considering a 0.7% prevalence of bladder cancer in this group of individuals, the PPV and NPV of MDVL will be 4% and 99.9%, respectively. These examples demonstrate that screening the general population for bladder cancer in the real world will be costly, regardless of a marker's sensitivity.

The risk of bladder cancer among smokers, painters, and industry workers exposed to arylamines is three- to sixfold higher than it is in unexposed individuals [29,31,34,75-78]. The risk is even higher if smoking or occupational exposure to bladder carcinogens is combined with other risk factors, including genetic polymorphism [29,75,77,79,80]. For example, in a case-control study, smokers with polymorphisms in glutathione S-transferase (GST) M1 and T1 genes (GST M1- or GST T1-null phenotypes) were found to have about a threefold increased risk of bladder cancer when compared to controls or smokers with wild type genes [81]. Similarly, in a case control study, heavy smokers were found to have a sevenfold increased risk of bladder cancer if they also had polymorphisms in folate metabolic genes, such as methylene-tetrahydrofolate reductase (MTHFR)-TT or CT phenotypes or methionine synthase (2756 A-

G) phenotype [82]. Among permanent hair dye users, the risk of bladder cancer is increased threefold if they have N-acetyltransferase 2 slow acetylator phenotype [83]. In a study by Hemstreet et al., the total incidence of bladder cancer among a moderate to high-risk group of Chinese workers exposed to benzidine (as defined by the biomarker profile) was fourfold higher than that in the entire cohort of workers who were either exposed or unexposed to benzidine [40]. Assuming a 4.5% prevalence due to increased risk, the hypothetical marker MDVL, with 85% sensitivity and 85% specificity, would have 21.1% PPV and 95.5% NPV.

An interesting comparison is that of PSA screening and prostate cancer detection. In various screening studies, regardless of whether total PSA or free PSA to total PSA ratio is used to detect prostate cancer, the PPV of PSA varies between 17% and 36% (assuming an incidence of about 3%) [84-86]. Widespread acceptance of PSA screening for prostate cancer has been based on the suggestions that screening for prostate cancer is medically beneficial and economically feasible. However, this assumption has not been without controversy. The controversy is centered on the basic premise that elevated PSA does not actually reflect the presence of cancer and that the diagnosis of clinically nonsignificant prostate cancer is costly economically, as well as emotionally and psychologically devastating. Therefore, implementation of a screening program for bladder cancer would require general acceptance of a particular marker (or panel of markers) by both urologists and their patients in a global sense.

An important objective for use of a noninvasive marker in surveillance for bladder cancer is to increase the interval between cystoscopic examinations without missing any tumor recurrence [46]. In the absence of a well-accepted biomarker, bladder cancer patients now undergo cystoscopy at scheduled intervals. A false positive test or marker inference resulting in cystoscopic examination is of lesser concern than a false negative inference that may lead to tumor progression [87]. The prevalence of bladder cancer among patients with a history of bladder cancer varies between 26% and 70% [7]. In the last example, assuming the prevalence of bladder cancer at 35%, the PPV and NPV of MDVL among patients with a history of bladder cancer will be 75.3% and 91.3%. Thus, a noninvasive marker with high sensitivity and reasonably good specificity may have a place in the management of recurrent bladder cancer.

4. Biochemical Markers and the Dilemma of Early Detection

Currently, cystoscopy is the gold standard for detecting bladder cancer, with urine cytology serving as a useful adjunct for high grade disease. Cystoscopy visualizes the tumor mass. Urine cytology evaluates malignancy based on cellular and nuclear morphology. In contrast, various noninvasive biochemical and molecular markers can detect tumor-associated molecules in the nano- or picomolar range (e.g., ELISAs, dipstick tests) or can identify a single abnormal cell (e.g., immunocytochemistry, RT-PCR, and FISH). Therefore, many of these markers could conceivably detect bladder tumors before they were clinically documented. Such “false positive” results would create a dilemma for urologists: should they offer treatment that might produce side effects or wait until the tumor becomes cystoscopically visible, when it may have progressed in grade or stage [6,51]?

The significance of false positive results in identifying the presence of a bladder tumor within a specified time can be evaluated by calculating risk ratio and odds ratio (OR). For example, Hemstreet et al. suggested that the risk of developing bladder cancer among biomarker positive individuals was high, with the risk ratio for various markers ranging between 16 and 38 and the OR ranging between 40 and 46 [40]. The biomarker profile in this study predicted the presence of bladder cancer 15 to 33 months before actual clinical detection of the disease. In another study, where a cohort of 70 patients was followed for bladder tumor recurrence over a period of 4 years, the HA-HAase test had 91% sensitivity, 70% specificity, 87% accuracy, 92% PPV, and 67% NPV to detect recurrence. Interestingly, out of the 14 false positive cases, 6 recurred within 5 months, whereas only 4 out of the 33 true negative cases recurred during the same period. Thus, a “false positive” HA-HAase test carried a 3.5-fold increased risk of tumor recurrence within 5 months (risk ratio = 3.5). In this study, usefulness of the HA-HAase test and the BTA-Stat to monitor bladder tumor recurrence was compared in a subset of 26 patients [38]. In that subset, an apparently false positive HA-HAase test carried a tenfold risk of recurrence (risk ratio = 10.2), whereas a false positive BTA-Stat test did not indicate a risk of recurrence within 5 months (risk ratio = 1.4). Similarly, in some studies, the UroVysion test has been shown to predict recurrence. Skacel et al. reported that 8 out of 9 FISH-positive patients with

atypical cytology but negative biopsy had biopsy-proven bladder cancer in 12 months [88]. These examples indicate that evaluating a marker's performance based solely on cystoscopy observations may be misleading and ultimately inaccurate [89].

An accurate knowledge of genitourinary conditions that may cause false positive results in a biomarker test, measuring quantitative changes in levels of a marker rather than simply noting its presence or absence, repeat testing, improving the clinical means of confirming malignancy, and testing the marker in large community settings will help clinicians decide on the best course of action when a biomarker is positive in the absence of a visible tumor in the bladder. Such information may complement the information provided in assessing risk ratio and OR.

Summary

For a biomarker to be clinically useful, it should have technical simplicity, reliability and high accuracy (i.e., high sensitivity and specificity). However, in addition to high sensitivity and specificity, the usefulness of a marker will depend on the population in which it is used. If a marker is to be used for bladder cancer screening, it should have high specificity and high PPV in order to avoid unnecessary anxiety and expense due to too many false positive results. If a marker is to be used for monitoring bladder tumor recurrence, it should have high sensitivity and high NPV in order to detect each and every case of bladder cancer.

The physician's dilemma related to the possible early detection of bladder cancer by biomarkers could be decreased by examining the risk of developing bladder cancer in a specified time when a biomarker is positive in the context of other conditions which may result in a false positive biomarker test.

The overall acceptance of a noninvasive test for bladder cancer in clinical decision-making would not only depend upon its performance, but also on physician and patient willingness to accept its usefulness.

IV. GOOD CLINICAL PRACTICE IN MARKER DEVELOPMENT

As we begin our discussion into tumor markers for bladder cancer, it is important to define our terminology. The search for determinants ("biomarkers") to better understand the biology of cancer, to improve the detection and monitoring tumors in patients, and to predict the outcome and response to treatment of cancer has been the focus of much research. Considering the relative incidence and mortality from bladder cancer, there are an amazing number of markers that have been explored. Part of this relates to the unique situation found in the bladder and the many bodily fluids that are accessible for analyzing bladder markers. These materials include urine, serum, and cytologic cells, as well as biopsy samples.

Urine is probably the most unique environment in which to study tumor markers. The urine is an environment that very few organs have exposure to and, therefore, identifying markers in the urine often leads to higher specificity than those found in serum samples. The urine is also a harsh environment for many proteins, allowing for the subtraction of many proteases and other types of degrading enzymes, which often make it difficult to develop assays for markers. While this environment is unfriendly for many proteins, it does provide stability to those that are able to survive in it and, therefore, allows an opportunity to focus on this unique set of proteins. In addition, cells are also located within the urine allowing cytology and cytologic examination. These cells represent unique looks into the bladder in a noninvasive fashion. Therefore, many markers are being developed to better examine these cells and to determine their biologic features implicating the propensity to act as malignant cells.

The serum is an environment that has not been well-explored in bladder cancer, mainly because of the fact that urine has been an easier environment in which to study unique changes that may be associated with the bladder. There are some markers that are being identified in the serum of individuals with bladder cancer, but these are typically markers of advanced or metastatic disease.

Unfortunately, the results of such biomarker studies are often inconsistent and sometimes contradictory. Recognized problems include different methods of performing assays, the use of different subsets of patients (difference in stage or treatment) and endpoints (e.g. local vs. distant recurrence vs. survival), and inadequate study design, leading to incompatible data sets. This has impeded understanding the role of new markers. Since replication and independent confirmation are hallmarks of the scientific method, the implementation of standards and conventions is essential for the comparison and integration of studies conducted at different institutions and different times.

As you will read in this chapter, the work on tumor markers in general but, specifically, those in bladder cancer that will be discussed here, is often made difficult to discern based upon the fact that there is no common terminology in place for authors to describe where their work really stands and where given biomarkers are in their developmental phases. This has made it often difficult for clinicians to interpret whether a marker is ready to be used in the clinic or still needs much additional investigation.

1. Aims of Marker Studies

In establishing the utility of a marker for clinical use, investigators must demonstrate that (a) the marker can be reliably and consistently measured, (b) the marker has good sensitivity and specificity so it can, with reasonably high probability, identify patients with a better or worse prognosis or with a greater or lesser likelihood of having a specified condition, and (c) the use of the marker will improve outcome by targeting therapeutic or diagnostic interventions. It should also be emphasized that the development and understanding of new tumor markers is best accomplished as part of a clinical and biological model with study designs that reflect the underlying mechanisms of cancer development and/or progression, including knowledge of specific pathways.

As in the setting of clinical trials research, there is a need to standardize different phases of tumor marker development, and to develop general guidelines and protocols for broadly accepted (or at least understood) principles of conducting and reporting translational marker studies.

To address the absence of standards, Altman et al. proposed a series of guidelines for validation/confirmatory marker studies. [90] Points discussed by Altman were extended and discussed in separate articles and studies: for example, sample size considerations [91,92], requirements for validation of prognostic models [93], and comparison of classification systems in terms of prognostic value. [94] In addition, Simon and Altman and others have suggested methods of classifying the stages or phases of tumor marker development [95-99]. Drew and colleagues extended the list of goals to include a fourth type of study in marker development, which aims to evaluate treatment effects on subsets of patients identified by a marker or factor [99]. Not emphasized in these recommendations and classifications is the prerequisite and fundamental requirement of assay validation.

2. Phases of Marker Studies

Although there has been discussion for establishing general methodological principles and guidelines for design, conduct, analysis, and reporting of marker studies (analogous to those for clinical trials), these have not been widely implemented, and there are no well-recognized prototypes or models that can be used to design marker studies. Those studying bladder cancer, because of many of its properties as described above, have really been quite fortunate in that a number of leading scientists from a wide range of disciplines have chosen to focus on this disease as a template for development of biomarkers to improve the diagnosis, prevention, and treatment of this disease. As a result, 4 phases can be defined through which markers are developed:

a) Phase I: Assay Development and Evaluation of Clinical Prevalence (Feasibility Studies)

A reproducible and optimized assay is the essential prerequisite prior to the application to clinical samples. This should be complemented with feasibility studies documenting the prevalence and expression of the markers of interest and examining their association with demographic and clinical characteristics in a representative study cohort (target population).

b) Phase II: Evaluation Studies for Clinical Utility

These studies may include the further optimization of the assay methods and/or interpretation of the assay results, to address a defined logistic/practical issue. The ultimate goal of this phase of investigation is to refine hypotheses and to define standards that can be used to perform the Phase III studies. It is essential that the results of Phase II studies translate into standards and criteria that can be used by other investigators.

c) Phase III: Confirmation Studies

Phase II findings are replicated, and hypotheses generated previously are tested with sufficient power in a larger defined clinical setting in an independent, prospective cohort of patients. The clinical utility of a given marker assay, its performance, and interpretation is established in that phase.

d) Phase IV: Validation and Technology Transfer as Application Studies

The aims of Phase IV studies are (a) to transfer the techniques and established methods of the assays and other aspects of the technology and (b) to evaluate the ability of other investigators and clinicians at other institutions to apply these methods and interpret the results. The Phase IV study is the final step in the translational research process, in which a given biomarker is incorporated into clinical practice.

3. Implementation of Phases of Marker Development

Often with Phase I and Phase II studies, there are single institutions with resources to perform these investigations. However, a multi-institutional approach offers many advantages even in these initial phases. Adequately sized and representative samples of patients may be easier to achieve in a large collaborative network with sufficient numbers of specimens to define and select the most appropriate set of samples. In addition, identifying sources of variability during these phases of biomarker development is required for correctly designing the next Phase III study and for confirming the conclusions reached in this evaluation phase.

With this fertile environment for developing tumor markers, many markers have been analyzed for Phase I. Typically, these first analyses involve the comparison of alterations in tumor tissue to normal adjacent tissue and/or to normal controls. However, it has to be of note that field effects are an established integral part of the development of bladder cancer, which warrants not only to include “normal” adjacent tissue but also tissue and samples from healthy individuals as important controls during this early phase of studies. Often at this stage, the test is protein-based including immunohistochemistry, immunoblotting, and other techniques. Alternatively, DNA-based or nucleic acid-based approaches can be used. Unfortunately, many investigations of potential markers do not exceed this phase and therefore are not developed into clinical assays.

The phase II of assay development is the step in which the biomarker typically moves from the individual research laboratory to a more clinically related laboratory that has more expertise related to clinical assays. The primary goal of this phase of development is to determine important characteristics of the assay. The first is referred to as the sensitivity or the true positive rate. This is the indication related to the number of, for example, bladder cancer cases that the assay is able to detect. If it is able to detect 100% of the cases, then the sensitivity or the true positive rate is 100%. In addition to the true positive rate, at this phase the false positive rate, the specificity of the assay, is analyzed. This helps to estimate how many individuals without bladder cancer are actually being detected positive with the given marker. Finally, if the assay allows, an ROC curve for the marker should be performed. These curves allow for identification of both the true sensitivity and specificity of the assay.

For the successful completion of Phase III and Phase IV studies of marker development, it is most likely that in the future only an international multi-institutional network will be able to perform this last required step. These phases aim to provide insight to understand the interrelationships between a given marker and the intrinsic prognosis for a patient, the effects of treatment, and effects on quality of life. As a result, these studies become more complex and require both larger numbers of patients and a sufficiently heterogeneous, yet representative, sample of patients. Furthermore, markers are often most useful in a well-defined subset of patients, and even large single center studies may have insufficient statistical power to detect these effects in the subset. Finally, since independent data sets are needed for all validation studies, accruing new patients or collaborating with other groups can only accomplish these later phase studies. The establishment of a collaborative network would clearly facilitate these essential interactions.

Summary

As you will see from this chapter, there are many markers that are in various phases of development for bladder cancer. With this in mind, there are now a number of exciting markers that are at different stages of development and are moving into clinical utility. In addition, consensus of general methodological principles and guidelines for design, conduct, analysis, and reporting of marker studies is warranted and can be achieved. This will enhance the development of more effective therapy and foster the integration of new tools and strategies that will help standardize their use in pathological and clinical applications.

V. URINE CYTOLOGY: THE STANDARD NONINVASIVE BLADDER TUMOR MARKER

The most efficacious approach to the detection of a bladder neoplasm is to identify the tumor cells themselves. At present, the only well-established way to achieve this goal is through consultation with a pathologist, asked to interpret tissue specimens or urinary samples. The pathologic interpretation of urinary samples is included in the discussion of markers both for comparison and completeness, but it is essential to emphasize that "urine cytology" is not a laboratory test and that the entities being detected using this method are not markers of a tumor, but the cellular components of the tumor itself.

Pathologic assessment of a randomly voided urine specimen is the standard noninvasive method in current use. Often called simply "urine cytology," this approach is used primarily to monitor patients with a history of "bladder cancer" for the detection of new urothelial tumors. These new bladder neoplasms are traditionally called "recurrences" but they are usually not at the same site as the index lesion and may not be the same grade or stage as the initial lesion. Urine cytology requires no patient preparation, inexpensive equipment, and very little time. It does require trained preparatory personnel and pathologists who can maintain their expertise through examination of large numbers of specimens and who are willing to render unequivocal judgments.

The clinical value of voided urine cytology is usually assessed in terms of specificity and sensitivity, that is, the likelihood that the method can identify the absence or presence of a bladder neoplasm. The positive and negative predictive values of a voided urine interpretation can also be calculated and are probably more important to patient care. Considering that urine cytology is used primarily to stimulate additional studies and sometimes to alter topical therapy and that other methods of detection are available, the reliability of an interpretation is arguably more important than the total number of cases identified. In this regard, cytology has a favorable record, at least for aggressive carcinomas, with false positive and false negative results being very few.

Voided urine cytology has a high specificity - that is, the method is good at determining the absence of a bladder tumor and false positive interpretations are unusual [100-105]. Values for specificity approach 100% in many studies. The method is not as good for detecting the presence of a neoplasm, where the false negative rate is higher. A wide range of figures have appeared in the literature but most reports have recorded sensitivities in the range of 35% to 65%. Urine cytology is especially valuable for differentiating high grade urothelial carcinomas from low grade urothelial neoplasms, a feat that "markers" have not yet achieved. Even in studies where the adequacy of sampling has not been addressed, high grade carcinomas have been detected with sensitivities and positive predictive values in the range of 80% to 90% of cases [100-102,106,107]. This is especially important when the patient's neoplasm is progressing from low to high grade. In contrast, low grade neoplasms are not readily identified using voided urine cytology [52,101,102,106,108,109]. Sensitivities in the range of 20% are commonly recorded, and few studies have documented figures higher than 60%. The difficulty in pathologic recognition of the disaggregated cells of low grade urothelial neoplasms is almost certainly due to the absence of anaplastic changes in these tumors. Very few low grade urothelial neoplasms are malignant and their cells reflect this fact. One might even contend that a "positive" cytology result rendered on cells emanating from a papillary urothelial neoplasm of low malignant potential (G1) is an interpretive error and that "negative," or perhaps "reactive," is a more accurate diagnosis.

Whatever the indicator of success, the results of urine cytology must be understood in light of two important factors of bladder cancer: sampling error and tumor load. Neither random voided urines, nor bladder washings for that matter, contain tumor cells

in each and every specimen, even when tumors are present in the bladder. In at least one study, 23% of washings obtained from patients with biopsy-proven, high grade urothelial carcinomas in their bladders contained no tumor cells [110]. Most data document a 20% decrease in diagnostic yield for voided urines compared to bladder washings [105,107]. Thus, a negative urine cytology result cannot necessarily be construed as a deficiency in the method when compared to other approaches. Further, urothelial neoplasms may be so small that they cannot be detected by either cystoscopy or selected site biopsies. Many instances of a positive urine cytology that required months for histologic correlation have been recorded [108,111]. Therefore, a positive cytology that is not associated with an immediate cystoscopic or histologic correlation cannot necessarily be considered an interpretive error.

The cytologic features of urothelial neoplasms have been described and illustrated by many authors in numerous publications and are well known to nearly all cytopathologists who are responsible for interpreting urinary specimens [112-118]. As with other medical fields, differences of opinion for any particular specimen might occur but concentrating on education as a means to increase the sensitivity of the method is unlikely to be any more productive in the future than it has been in the past. More success might be achieved by recognizing the role of urine cytology in the initial detection and monitoring of those urothelial neoplasms that are commonly called "bladder cancer."

Summary

"Urine cytology" is not a laboratory test; it is the interpretation (opinion) of a pathologist concerning the nature of cells disaggregated from their environment in the urothelium. Urinary specimens do not always contain a representative sample of the bladder and may not contain tumor cells even when a tumor is present. Urinary specimens may contain tumor cells when the tumor load is too small for recognition by other methods. Voided urines usually contain fewer and less well-preserved cells than bladder washings. The diagnostic yield of urine cytology is increased if at least 3 samples are obtained. The diagnostic yield of urine cytology depends upon many factors in addition to the acumen of the pathologist. Since the endpoint of urine cytology is to identify the tumor cells themselves, the predictive value of a positive result is very high. The sensitivity and specificity of urine cytology are very high for potentially aggressive urothelial neoplasms, those with the ability to invade and metastasize. The sensitivity and specificity of urine cytology are low for urothelial neoplasms that lack the ability to disseminate, primarily because these tumors are not malignant and should not be included among neoplasms labeled "bladder cancer."

VI. BLADDER TUMOR MARKERS FOR DIAGNOSIS AND MONITORING RECURRENCE

In the following section, we discuss various bladder cancer markers and tests that are commercially available, or have shown potential to be clinically useful. **Table 1** lists all of these tests and markers. The tumor makers are divided into 2 categories, soluble urine markers and cell-associated markers, depending upon whether urine specimens or exfoliated cells in urine are used in the assay.

1. Soluble Urine Markers

a) Hematuria Detection

1. Introduction

Microscopic hematuria is common among asymptomatic adults. In community screening studies, 14% to 22% of men age 50 years and older have hematuria and approximately 33% to 57% of the hematuria positive individuals have progressive urologic diseases that require immediate medical attention [20-27]. The most common finding among individuals presenting with urinary tract malignancies is hematuria, seen in about 85% of bladder cancer patients and 40% of renal carcinoma patients [117]. In a case-control study involving the follow-up of 1046 patients with a physician's diagnosis of asymptomatic hematuria, Friedman et al. found that hematuria may be present in a higher proportion of cases than controls, 5 to 6 years before the clinical diagnosis of urothelial malignancy [118]. Hematuria due to urothelial cancers is intermittent, may be grossly visible or only visible on microscopic examination, and is independent of tumor grade and stage [23,117].

Several community-screening studies have been conducted to test the usefulness of hematuria screen-

Table 1. Current Bladder Tumor Markers for Detection and Surveillance

Test/Marker	Marker Detected	Specimen	Assay Type	Marker Type	Manufacturer	% Sensitivity	% Specificity
Cytology	Tumor cells	Voided urine, Barbotage specimen	Microscopy	Cell morphology	Diagnostic Reference Laboratories	11-76	> 90
Hematuria detection	A: Hemoglobin B: Red blood cells	A: Voided urine B: Voided urine	A: Dipstick B: Interference-contrast microscopy or Red blood cell analyzer	A: Soluble protein B: Red blood cell morphology	A: Bayer Corp. B: -	A: 50-90 B: ~ 100	A: Low B: ~ 100
BTA-Stat	Complement factor H-related protein (and also Complement factor H)	Voided urine	Dipstick immuno-assay	Soluble antigen	Bard/Bion Diagnostics	36-89, low sensitivity for low-grade tumors, low-tumor volume	50-70, low specificity among benign urologic conditions
BTA-TRAK	Complement factor H-related protein (and also Complement factor H)	Voided urine	Sandwich ELISA	Soluble antigen	Bard/Bion Diagnostics	57-83 Sensitivity value depends on cutoff limit selection	~ 50 in benign urologic conditions; ~ 90% healthy individuals
NMP-22	Nuclear mitotic apparatus protein	Voided urine	Sandwich ELISA (Newer version: a point-of-care device)	Soluble antigen	Matritech, Inc.	47-100, sensitivity value depends on cutoff limit selection, tumor volume and patient population	55-80, specificity depends on presence of benign urologic conditions
BLCA-4	Nuclear matrix protein	Voided urine	ELISA (using a rabbit polyclonal antibody)	Soluble antigen	Eichrom Technologies	96.4	100 in healthy individuals; 81 in other urologic conditions

Table 1. Current Bladder Tumor Markers for Detection and Surveillance (Continued)

Survivin	A member of inhibitors of apoptosis gene family	Voided urine	Bio-dot test (dot blot assay using a rabbit polyclonal antibody)	Soluble antigen	-	100	87-100
UBC	Cytokeratin 8 and 18 (cytoskeletal proteins)	Voided urine	Sandwich ELISA or a point-of-care test	Soluble antigen	IDL Biotech.	36-79, may be low to detect Ta, T1 tumors	88-92, may be low in benign urologic conditions
Cytokeratin 20	Cytoskeletal protein	Exfoliated cells	RT-PCR or immunocy-tology	mRNA or cell-associated protein	-	82-87	55-70, low in benign urologic conditions
CYFRA 21-1	Cytokeratin 19 (a cytoskeletal protein)	Voided urine	Immunorad-iometric assay or electrochemi -luminescent immuno-assay	Soluble antigen	Bio International; Roche Diagnostics	75-97; ~55 to detect G1 tumors	67-71, low for urolithiasis, stenosis, BPH, and UTI
HA-HAase	Hyaluronic acid and hyaluronidase	Voided urine	ELISA-like assays using a biotinylated HA-binding protein	2 Soluble matrix components	-	88-94	Overall 84; 63-71 in recurrent tumors: 60 false positives turn true positive in 5 months
Microsatellit e DNA test	Microsatellite markers on chromosomes	Exfoliated cells	Genomic DNA PCR	Genomic DNA	-	72-97	> 95% in healthy individuals; false positives if BPH, cystitis
Telomerase (TRAP assay)	Enzyme activity	Exfoliated cells	TRAP assay	Cell-associated enzyme	Intergen, Oncor?	70-90, but as low as 7-46 (enzyme unstable in urine)	60-70, low if UTI, urolithiasis, or inflammation present

Table 1. Current Bladder Tumor Markers for Detection and Surveillance (Continued)

Telomerase (hTERT)	hTERT	Exfoliated cells	RT-PCR (conventional or real-time)	mRNA for hTERT	-	83-95, but as low as 24	60-70, low if UTI, urolithiasis, or inflammation present
ImmunoCyt	Carcinoembryonic antigen, 2 bladder tumor cell-associated mucins	Exfoliated cells	Immunocyto-chemistry	Cell-surface antigen	DiagnoCure, Inc.	38-90, low for low grade tumors, and recurrent tumors?	73-80, low if microhema-turia, BPH, cystitis present
DD23	185-kDa tumor-associated antigen	Exfoliated cells	Immunocyto-chemistry	Cell-surface antigen	Urocor	73-100	33-67.5
Quanticyt	Mean nuclear shape and DNA content	Exfoliated cells	Computerize d analysis of light microscopy images	Nucleus, DNA	-	Quanticyt	Mean nuclear shape and DNA content
UroVysion	Alterations in chromosomes 3, 7, 17, and 9p21	Exfoliated cells	Multi-colored, multi-probe FISH	Denatured chromosoma l DNA	Vysis	68-87, low for low grade tumors (36-55)	> 90

ing for detecting bladder cancer in the general population. As discussed in the Tumor Markers and Screening section, Messing et al. and Britton et al. showed that although the prevalence of bladder cancer among men over the age of 49 years is about 0.7%, the prevalence of bladder cancer among individuals with asymptomatic microhematuria varies between 3% and 18% [20,21,24,27]. Consistent with the intermittent nature of hematuria, Messing et al. have shown the benefits of repeat hematuria testing after a 9-month interval among men over the age of 50 to detect urologic malignancies (i.e., cancers of the bladder, kidney, and prostate) [24]. Wakui and Shigai conducted a prospective screening study involving a 3-year follow-up of 21 372 adults being tested for hematuria [117]. Of the 912 individuals who were positive for hematuria, 1 case of bladder cancer was detected [117]. In a prospective cohort study, Murakami et al. discovered 24 cases of urinary tract cancers among 1034 individuals positive for microhematuria and 4 more cases within 3 years of testing [119]. Furthermore, in this and another study, 22% of the hematuria positive individuals had significant urological diseases requiring treatment [119,120]. Mohr et al., in a population-based study, followed 781 residents over a 10-year period for microhematuria and found 8 patients with urothelial cancers and 5 with prostate cancer [121]. The reason for the low prevalence of bladder or other urinary tract cancers in patients with hematuria is that hematuria may arise due to inflammatory conditions, urinary tract infection, stone disease, benign prostate hyperplasia (BPH), and many other conditions that produce blood in the urinary tract [39, 117, 118, 121, 122].

2. Methodology

When evaluated in the general population, microscopic appearance of red blood cells (RBCs) (< 3 to 5 RBCs per high power field) may be evident in many individuals without any underlying clinical or pathological condition [50]. To formulate policy statements and recommendations for the evaluation of asymptomatic microhematuria in adults, The American Urological Association (AUA) convened the Best Practice Policy Panel on Asymptomatic Microscopic Hematuria [123]. The panel recommended that the definition of microscopic hematuria is 3 or more RBCs per high power microscopic field in urinary sediment from 2 of 3 properly collected urinalysis specimens.

Although counting of RBCs under a high power field is the standard method to detect microscopic hematuria, the results of this method may vary because of a number of factors. For example, initial, total, or terminal specimens are more likely to yield positive results than are midstream specimens [23]. RBC detection also depends on the methods used to prepare the specimens for microscopic examinations including whether an immediate or an old specimen was examined, the volume of the aliquot used, the speed and duration of centrifugation, the methods of decanting supernatants, and the volume used to resuspend the sediment, as well as interobserver and intraobserver variation [23]. If the specific gravity of urine is less than 1.008 (quite common in well-hydrated individuals), more than 96% of RBCs may lyse prior to microscopic examination, yielding false negative results [23].

Detection of hemoglobin using a hemoglobin dipstick is another way of detecting hematuria. The hemoglobin dipstick test is easy to use, inexpensive, requires little training, and does not require the presence of intact RBCs. Several community studies involving home hematuria testing have shown that the hemoglobin dipstick test is suitable for testing in a convenient, natural setting (by the patient in the privacy of his or her home or in the physician's office), which enhances the detection of intermittently bleeding lesions [23]. The test is available over the counter in any pharmacy and costs about 60¢ per test. A sample is recorded as positive when any hemoglobin is present (trace, small, moderate, or large). Considering that hematuria screening may also detect other serious diseases, the cost of detecting a true positive case through such screening could be as low as $1300 [22].

3. Results

Earlier studies have reported that hematuria detection has high sensitivity (90%-95%) for diagnosing bladder cancer [20-27]. However, more recent studies have reported a significantly lower sensitivity for hemoglobin dipstick testing (46%-74%) [42,58,124,125]. A likely explanation for this discrepancy is that hematuria testing was performed repeatedly in the earlier studies, but was done only once in the later studies. Since hematuria is intermittent in nature, repeat testing increases the sensitivity of the hemoglobin dipstick test.

To reduce unnecessary cost and morbidity associated with further work-up, evaluation of RBC morphology by phase contrast microscopy has been suggested [117,126]. Schramek et al. separated individuals with asymptomatic hematuria based on RBC morphology,

which was examined by an interference-contrast microscope [126]. In the dysmorphic cell group (193 individuals), with a median follow-up of 42 months, no cases of urological malignancies were found. However, in the eumorphic/mixed cell group (123 individuals), 13 cases of urological malignancies were found. In a prospective screening study, Wakui and Shiigai used RBC volume distribution curves (RDC) generated by an automated blood cell analyzer to divide 912 subjects with a positive hemoglobin dipstick into 2 groups [117]. Group 1 consisted of 38 individuals who showed normocytic or mixed cell patterns, which are predictors of urinary tract cancer. Among group 1 individuals, a single case of bladder cancer was found (1 in 38; incidence rate 2.6%). However, no bladder cancer cases were detected in group 2 individuals (n = 869), who showed a microcytic pattern on RDC. The microcytic pattern probably arises due to urinary tract infection or glomerular disorders. Thus, the RDC method appears to reduce the total work-up cost by 93.8% when compared to a conventional setting that involves a full evaluation of all cases of hematuria [117]. Georgopoulos et al. suggested that the assessment of erythrocyte morphology should be carried out at pH < 7.0 and at osmolarity ≥ 700 mOsmol/kg [127]. Under these conditions, if more than 90% of cells are dysmorphic, the blood pressure is normal, and there is no proteinuria, hematuria is most likely renoparenchymal, requiring only routine check-ups twice a year. However, if more than 90% of cells are eumorphic, microhematuria is most likely post-renal and requires a full work-up [127].

Summary

Hematuria detection is a useful first-line marker to detect urologic diseases including urologic malignancies. Hematuria screening for detection of bladder cancer and other urologic malignancie shas high sensitivity but low specificity due to a low prevalence of urologic malignancies among patients with hematuria. Hematuria testing by hemoglobin dipstick is reliable and superior to microscopic examination of RBCs. Newer techniques that help to distinguish between hematuria originating from malignancy or other disorders/infections should help to improve specificity without changing sensitivity.

b) BTA-Stat and BTA-TRAK

1. Introduction

The BTA (bladder tumor antigen)-Stat and BTA–TRAK tests detect a complement factor H-related protein in urine. In addition to being present in the urine of patients with bladder cancer, this complement factor H-related protein is produced and secreted by several bladder and renal cancer cell lines [128,129]. The complement factor H-related protein has an almost identical amino acid composition and function as the human complement factor H protein [128,129]. Indeed, both monoclonal antibodies that are used in BTA-Stat and BTA-TRAK tests also detect the complement factor H protein. The difference between BTA-Stat and BTA-TRAK tests is that the BTA-Stat is a qualitative point-of-care test, whereas BTA-TRAK is quantitative, requiring testing in a diagnostic laboratory.

2. Methodology

The BTA-Stat is an immunoassay performed by placing 5 drops of urine in the sample well of the test device and allowing it to react for exactly 5 minutes. A visible red line in the test window indicates a positive result, while a line in the control widow indicates that the test is working correctly. BTA-TRAK is a standard ELISA that quantitatively measures the amounts of a complement factor H-related protein and complement factor H in urine (BTA-TRAK product insert). Both BTA-Stat and BTA-TRAK tests can be purchased from Polymedco Inc., New York, NY, and Mentor Urology.

3. Results

The sensitivity of the BTA-Stat test reported in several cohort and case-control studies ranges from as low as 9.3% to as high as 89% [38,47,55,56,58-60,105,124,130-135]. The sensitivity of the BTA-Stat test to detect low grade tumors is low, ranging between 13% and 55%. For G2 and G3 bladder tumors, it varies between 36% to 67% and 63% to 90%, respectively. The specificity of the BTA-Stat test among healthy individuals is more than 90%. However, it has low specificity (about 50%) among patients with urinary tract infections, urinary calculi (90% positive on BTA-Stat) [136], nephritis, renal stones, cystitis, benign prostatic hyperplasia, hematuria, and 2+ to 3+ protein on urine dipstick [38,67,138,139]. The reason why the BTA-Stat test has lower specificity among patients with any one of the several benign genitourinary conditions is that

the test detects both the complement factor H-related protein and complement factor H (BTA-Stat product insert). Complement factor H is present in human serum at high concentrations (0.5 mg/cc), and, therefore, the BTA-Stat test might be falsely positive in many benign conditions that cause hematuria. Indeed, Oge et al. showed that if urine is spiked with blood, the specificity of the BTA-Stat varies depending upon the severity of hematuria: 80% for microscopic hematuria and 24% for gross hematuria [67]. Nasuti et al. found an 84% false positive rate for BTA-Stat among patients with symptoms of dysuria, incontinence, and hematuria [139]. The BTA-Stat product insert includes a list of benign conditions in which the test should not be performed.

Both cohort and case-control prospective and retrospective studies have explored the usefulness of the BTA-Stat test as a prognostic marker. For example, Raitanen et al. reported that bladder cancer patients with positive BTA-Stat tests have shorter disease-free survivals [140]. However, the same group reported that, while 16% of the false positive cases on the BTA-Stat had a recurrence, the majority of the false positive cases were due to intravesical therapy or infection [8]. Similarly, van Rhijn et al. showed that a positive BTA-Stat test does not predict recurrence in cases with a negative cystoscopy and biopsy [56]. Lokeshwar et al. found that a false positive BTA-Stat result does not carry any significant risk (risk ratio = 1.4, OR = 1.5) for recurrence within 5 months [38]. Other studies have also shown that false positive BTA-Stat inferences do not predict bladder cancer recurrence [59,60,141].

In various case-control and cohort studies, the sensitivity of BTA-TRAK ranges from 52% to 83% [72,129,142-144]. However, in a recent study that followed the recommendations of the European Group on tumor markers, the sensitivity of the BTA-TRAK was 8% to 17% to detect both primary tumors and recurrence [144]. As in the case of BTA-Stat, the sensitivity of the BTA-TRAK is higher for detecting high grade and high stage tumors [46,70-72]. Multicenter studies and cohort studies have shown that the sensitivity of the BTA-TRAK test also varies depending upon the cutoff limit used on the test [70-72,144].

Among patients with benign conditions, the specificity of the BTA-TRAK is low, about 50%. For example, levels of bladder tumor antigen above 72 mU/mL are often obtained in patients with hematuria [143]. The reason for this is that the BTA-TRAK test also detects complement factor H, which is abundantly present in blood. Considering this possibility, the manufacturer recommends that BTA-TRAK should be used only with information available for the clinical evaluation of the patient and other diagnostic procedures, and that the test should not be used as a screening test (BTA-TRAK product insert).

According to BTA product inserts, the FDA has approved both BTA-Stat and BTA-TRAK tests for use as aids in the management of bladder cancer in combination with cystoscopy.

Summary

Several case-control and cohort studies have shown that the sensitivity of BTA-Stat and BTA-TRAK tests varies between 9.3% and 89% and is dependent on tumor grade, stage, and size. The sensitivity of BTA-Stat and BTA-TRAK also depends upon whether the tumors are primary or recurrent. The specificity of BTA-Stat and BTA-TRAK is high among healthy individuals but is low among patients with various benign genitourinary conditions.

c) NMP-22

1. Introduction

Nuclear matrix proteins (NMP) are part of the internal structural framework of the cell nuclei [145]. This non-chromatin structure supports nuclear shape, organizes DNA, and plays an important role in DNA replication, transcription, and gene expression [146,147]. NMP-22 is a nuclear mitotic apparatus that is involved in the proper distribution of chromatin to daughter cells during cellular replication [148]. NMP-22 is present at a relatively low level in the interphase nuclear matrix. However, it is probably released from the nuclei of tumor cells during apoptosis.

2. Methodology

The NMP-22 test, which is manufactured by Matritech Inc. (Matritech, Newton, MA, USA), is a quantitative microtiter sandwich ELISA that uses 2 antibodies, each of which recognizes a different epitope of the nuclear mitotic apparatus [6]. This assay usually needs a laboratory with trained technicians and is not a point-of-care test. Because the NMP-22 test is quantitative, it is important to note the cutoff used in any particular study [6]. Although the manufacturer's recommended cutoff value is 10 units/mL, variable cutoff limits ranging from 7 to 27 units/mL have been applied, depending on the opti-

mum sensitivity and specificity of the receiver operating curve [141,149-151]. Recently, a point-of-care NMP-22 assay has become available, which involves addition of 4 drops of urine in a point-of-care device and reading the results 30 to 50 minutes later [152].

3. Results

In most studies, the subjects were patients with newly-diagnosed bladder cancer with no previous history of urothelial cancers, and controls were selected from patients with benign urologic conditions or those with hematuria with no evidence of urothelial or other urologic cancers. The sensitivity has ranged from 47% to 100%, most often falling between 60% and 70% [69,125,131,153-160]. The specificity is between 60% and 90%, depending on the cutoff value used [69,125,131,149,153,154,156-158]. The positive predictive value of this test has been reported to be as low as 34% to as high as 76%, while the negative predictive value varies from 77.9% to 98% [69,141,150,151,154]. It should be noted that these studies mostly dealt with patients without a history of bladder cancer treatment.

In general, the NMP-22 test has a higher sensitivity than cytology, especially in the case of low grade and stage tumors, because the test is less influenced by tumor grade and stage. However, there is a slight increase in sensitivity with increase in tumor grade. For example, Del Nero found in grades 1, 2, and 3 urothelial cancer of the bladder, sensitivities of 69%, 86%, and 90%, respectively [158]. Others have found similar results with the increasing T stage of the tumor, with a sensitivity of 71% in stage Ta and T1, increasing to 93% in stages T2 to T4 [161].

The usefulness of the NMP-22 test in monitoring recurrences in treated bladder cancer patients was assessed in several studies. Soloway et al. used NMP-22 to predict tumor recurrence after transurethral bladder tumor resection at subsequent cystoscopy in 90 patients [153]. With the cutoff value at 10 units/mL, they found 69.7% overall sensitivity and 78.5% specificity. In addition, the test was 100% sensitive for detecting invasive tumors. Boman et al. reported 45% sensitivity and 65% specificity, and claimed that the low sensitivity and specificity was due to the relatively small size of recurrent tumors, indicating the usefulness of the NMP-22 test for monitoring recurrence is questionable [135]. Miyanaga et al. reported 18.6% sensitivity and 85.1% specificity in 51 patients with recurrent tumors among 156 follow-up cases [130]. They also concluded that the low sensitivity was due to the small size of recurrent tumors and presence of urinary WBC. They further recommended that the cutoff value for monitoring recurrence be set at 5.0 U/mL, which resulted in 48.8% sensitivity and 66.6% specificity. Sanchez-Carbayo et al. found 80.6% sensitivity and 92.6% specificity in 31 recurrent bladder cancer patients among 106 cases with a previous bladder cancer history, and 65.0% sensitivity and 91.9% specificity in 24 recurrent bladder cancer patients among 126 cases under intravesical adjuvant instillation therapy [162]. Although the results were superior to voided cytology, Friedrich et al. showed that 2 of 25 (8%) false positive patients later suffered from tumor recurrence while 2 of 36 (5.6%) true negative patients had tumor recurrence, indicating that an abnormal NMP-22 test is not predictive of future recurrence [163]. In summary, in follow-up studies after endoscopic treatment, overall sensitivity ranges from 45% to 81%, and specificity ranges from 65% to 93% [153,130,135,162]. Lower sensitivity in the follow-up setting than in freshly diagnosed cases is presumably caused by a relatively higher percentage of low grade tumors with low tumor volume among recurrent superficial tumors at follow-up.

Analysis of all of the data clearly shows that the NMP-22 test is superior to cytology for detection of grade 1 and 2 bladder cancer in terms of sensitivity, but that it offers lower specificity. To overcome this low specificity, Sharma et al. evaluated the causes of false positive tests in order to exclude patients with these results from testing and, thus, improve the specificity of the tests [157]. In 278 symptomatic patients, including 34 (12%) confirmed bladder cancer cases, they showed an overall sensitivity and specificity of 82.4% and 82.0%. They identified the following 6 criteria for excluding patients: benign inflammatory conditions (infections, etc.), renal or bladder calculi, foreign bodies (stents or nephrostomy tubes), bowel interposition, other genitourinary cancer, and instrumentation. When patients with these problems were excluded, specificity increased to 95.6%. With the same exclusion criteria, Ponsky et al. also showed an increase in specificity to 99.2%, whereas the overall sensitivity and specificity were 88.5% and 83.9% without the exclusions [69].

At the present time, not many studies have been conducted on the point-of-care NMP-22 test. However, recently in a large prospective multi-center study that involved 1331 study individuals, the point-of-care NMP-22 test had 55.7% sensitivity and 85.7% specificity to detect bladder cancer. As in the case of NMP-22 ELISA, the sensitivity of the point-of-care test also increased with tumor grade and stage [152].

Summary

The NMP-22 test may provide adjunctive information in monitoring bladder cancer recurrence. Although sensitivity data appear promising, the sensitivity is not high enough to eliminate current cystoscopic evaluation in both fresh and follow-up patients. Because of the relatively low specificity, its routine use for the detection of bladder cancer is not recommended. If use of this test is limited according to certain exclusion criteria (see above), the test may be valuable in the detection of fresh bladder cancer or monitoring patients with a previous history of bladder cancer.

d) BLCA-4 and BLCA-1

1. Introduction

One approach to identifying novel tumor markers relies on trying to understand and utilize some of the hallmarks of the bladder cancer cell, in order to develop assays which detect protein components that are specific for the disease. One of the fundamental changes that occur in a cancer cell is alteration in cell and nuclear shape. These alterations are utilized by the pathologist to identify cancer cells on microscopic examination. All cancer cells undergo these characteristic changes, and they are considered to be defining aspects of the tumorigenic process. Since changes in nuclear shape are characteristic of the cancer cell, Getzenberg et al. have focused on understanding nuclear structure as an underlying framework for the observed changes in nuclear shape. In addition, it is known that a number of processes are altered within the cancer cell that can be traced back to changes within nuclear structure. In cancer cells, it is common to find rearrangements, translocations, and other chromosomal events, which are atypical for normal cells. In addition, genetic instability, in which genes that may be differentiation-related may be turned off, whereas embryonic or other types of genes may be turned on, is commonplace in the cancer cell. The hypothesis of the Getzenberg laboratory is that not only are changes in nuclear structure reflective of the characteristic changes in nuclear shape observed by the pathologist in a cancer cell but that these changes in nuclear structure may also result in some of the loss of fidelity of these nuclear processes, which are known to rely upon nuclear structure for organization and function. The group has performed proteomic analysis of the nuclear structural components, termed the nuclear matrix, in order to determine differences in these components between cancer and normal cells. The group has previously identified a series of these nuclear structural alterations, characteristic of bladder cancer, which are not found in individuals that do not have the disease [164]. One of these markers, BLCA-4 is found throughout the bladder in people with bladder cancer, including both tumor as well as normal regions, but is not found in the bladders of individuals without the disease. This marker, therefore, may reflect a type of “field effect” that has been observed at the genetic level by a number of investigators. Recent studies by Dr. Getzenberg’s group have revealed that this marker appears to be a transcriptional regulator, which may play an active role in the regulation of gene expression within bladder cancer [165].

2. Methodology and Results

Utilizing 2 different forms of ELISA, Konety et al. has been successful in detecting BLCA-4 in the urine of patients with bladder cancer. The first assay that was developed was an indirect assay. Urine samples from patients diagnosed with bladder cancer, along with normal controls, were collected and tested with the indirect ELISA that we developed. This assay requires no stabilization. In the initial clinical trial of 106 individuals, using a prospectively-defined cutoff based upon the first 3 tumor and normal samples, we demonstrated a sensitivity of 96.4% and a specificity of 100% [164,166]. Furthermore, in this study the authors demonstrated that this assay was able to detect almost all of the individuals who were not considered to be positive for bladder cancer by cytology. In order to examine the expression of this and other markers in a high-risk population for the development of bladder cancer, the Getzenberg group has been studying individuals with spinal cord injuries. It is known that individuals with spinal cord injuries have up to a 460-fold increased risk for developing bladder cancer and as many as 1 in 10 individuals with spinal cord injuries actually develop the disease [167]. In addition, this population represents a difficult group in which to utilize bladder cancer markers since the presence of cystitis and other types of inflammation within the bladder is common.

While the indirect assay that was developed revealed both high sensitivity and specificity, it was necessary to develop a higher throughput test that did not require urine precipitation and which used a sandwich assay taking advantage of monoclonal antibodies. This type of assay would provide for a higher throughput clinical test. This assay neither requires urine precipitation nor consideration of the amount of protein that is found in the sample. Ideal charac-

teristics of a tumor marker include high sensitivity and specificity for disease, accuracy, precision, rapid turn-around time, and ease of measuring at a low cost. In order to accomplish the rapid turn-around time, it was necessary to develop the immunoassay on straight voided urine samples rather than concentrating the proteins by ethanol precipitation. In tandem, a sandwich-based immunoassay was developed by utilizing several antibodies (both monoclonal and polyclonal) raised against BLCA-4. The advantage of this assay is that any number of different sources of antibodies can be added to the captured antigen, provided that the species in which it was produced is not the same as the capture antibody. More specifically, the enzyme conjugated anti-species antibody should not react with the antibodies used to capture the antigen.

In order to test the sandwich-based immunoassay on populations of patients that would reflect specificity and sensitivity issues for the detection of bladder cancer, a large number of samples representing unique patient groups were assayed [168]. This study included patients with biopsy-confirmed bladder cancer (Group A), individuals that had identified benign urologic conditions (Groups B and C), individuals with the most prevalent urologic cancer, prostate cancer (Group D), and normal individuals (Group E). A training set was used to establish a cut-off that was then applied to the sample set being tested. The results from the trial, which examined 168 individuals, demonstrated a sensitivity of 89% and a specificity of 100% in this complex mixture of samples [168]. A large national clinical trial is currently underway to validate these studies and determine the utility of this marker in diagnosing bladder cancer.

BLCA-4 is just 1 of the 6 nuclear structural proteins that has been identified, which are expressed only in bladder cancer. Many nuclear structural proteins have now been sequenced. Meyers et al. have studied one such protein, BLCA-1, and found that it is a potentially valuable marker for bladder cancer. The expression of BLCA-1 is different from that of BLCA-4 described above. BLCA-1 is expressed only in the tumor areas of the bladder and is not expressed in normal adjacent tissue or in normal bladder tissue. An immunoassay which detects BLCA-1 in straight urine samples from individuals with bladder cancer with high sensitivity and specificity has been developed. The urine levels of this marker also appear to be increased with higher tumor stages, another distinction from BLCA-4 [169].

Summary

BLCA-4 is a potentially useful marker for the detection of bladder cancer, as it detects bladder cancer with both high sensitivity and specificity. BLCA-1 is another potentially useful marker for bladder cancer that is currently under investigation. Large multi-center clinical trials will validate the efficacy of these potentially useful markers.

e) Survivin

1. Introduction

Survivin is an anti-apoptotic protein that is a member of the inhibition of apoptosis protein (IAP) gene family [170,171]. It is overexpressed in a wide range of malignancies, including carcinoma of the bladder urothelium, and it can be detected in the urine of patients with bladder cancer. Various studies have been performed on the relevance of survivin in the diagnosis of bladder cancer. Ku et al. used immunohistochemistry to study the expression of survivin in bladder cancer and found high expression of survivin in 58% (51 of 88) of superficial bladder cancer cases [172]. Lehner reported nuclear staining in 58% (26 of 45) of bladder cancer tissues and in 14.3% of CIS tissues. No nuclear staining was observed in normal bladder mucosa. Interestingly, patients with bladder cancer and a nuclear pattern of survivin localization had a greater period of disease-free survival (27.2 months) than was observed in patients with urothelial carcinoma that showed no nuclear staining for survivin (9.9 months); however, the differences were not statistically significant [173]. Gazzaniga et al. used RT-PCR analysis and showed that the survivin transcript is expressed in 30% of bladder tumor tissues [174]. Using similar analysis, Schultz et al. found survivin mRNA expression in 100% of the bladder tumor tissues examined [175].

2. Methodology

The survivin urine test is a bio-dot test in which urine samples are blotted as dots on nitrocellulose membranes, and survivin present in the samples is detected using a rabbit polyclonal anti-survivin antibody and standard dot-blot detection reagents.

3. Results

In initial studies with relatively small numbers of patients with bladder cancer, the survivin dot-blot assay had 100% sensitivity [176,177]. Its specificity among normal individuals and patients with benign genitourinary conditions is 100% and 87%, respec-

tively [7,8]. Recently, Shariat et al. showed that higher urinary survivin levels are associated with increased risk of bladder cancer and higher grade tumors [178]. In that study, which involved 117 bladder cancer patients and 97 controls, the survivin-dot-blot assay had 64% sensitivity and 93% specificity. In a study of 25 patients, Hausladen reported that urinary survivin levels were higher in patients in whom urothelial carcinoma recurred compared with those who achieved remission after treatment with BCG or mitomycin C [179]. In this study, survivin had 100% sensitivity and 78% specificity. In addition to the survivin dot blot assay, Schultz et al. have used RT-PCR on exfoliated cells to detect survivin mRNA expression in bladder washing specimens. Their results show that survivin mRNA copy number is a predictor of bladder tumor recurrence [180].

Summary

A limited number of studies show that survivin may be a potentially useful marker in the detection of bladder cancer. However, more cohort studies are needed to evaluate this marker.

f) Cytokeratins

Cytokeratins are intermediate filament type cytoskeletal proteins that have been tested as bladder tumor markers in many studies. In human cells, a total of 20 cytokeratins have been identified and their expression reflects the type and differentiation state of the epithelial cells [181]. The expression of cytokeratins 8, 18, 19, and 20 at the protein or mRNA level has been evaluated as a bladder cancer marker. Since cytokeratins are intracellular proteins, the detection of these proteins in urine is possible only when they are released in urine following cell death. UBC tests and CYFRA 21-1 are urine tests that detect cytokeratin 8 and 18 and a cytokeratin 19 fragment, respectively. There is no test that detects soluble cytokeratin 20 protein in urine. Cytokeratin 20 mRNA expression is detected by RT-PCR in exfoliated cells in urine or in bladder wash specimens.

1. UBC Tests

UBC-Rapid and UBC-ELISA tests manufactured by IDL Biotech, Borläbger, Sweden, detect the presence of cytokeratin 8 and 18 in the urine of bladder cancer patients [182,183]. UBC-Rapid is a point-of-care test, whereas UBC-ELISA (i.e., UBC-IRMA) is a 2-hour sandwich ELISA test. The manufacturer suggested cutoff limit for UBC-IRMA is 12 ng/mL. In several retrospective cohort and case-control studies, the sensitivity of UBC tests to detect bladder cancer (both primary and recurrent) varies between 35% and 79% [55,58,184-187]. In a retrospective case-control study, Boman et al. studied the effect of tumor size, grade, and stage on the sensitivity of the UBC-Rapid test [55]. The UBC-Rapid test had slightly higher sensitivity (53%) to detect small new tumors (≤ 10 mm) than to detect small recurrent tumors. The difference between the detection of new versus recurrent tumors was most striking in TaG1 and TaG2 tumors. Consistent with these observations, several studies have also reported lower sensitivity of UBC to detect low grade and low stage tumors. The sensitivity of UBC to detect G1, G2, and G3 bladder tumors is 13% to 60%, 42% to 79%, and 35% to 75%, respectively [55, 57, 58, 182-184]. In retrospective cohort studies, Mungan et al. and Schroeder et al. reported 21% to 25% sensitivity of UBC-Rapid to detect stage Ta tumors and CIS. Mungan et al. concluded that the UBC has insufficient diagnostic value for detecting superficial bladder cancer [57]. In studies that compared different bladder tumor markers, UBC tests had lower sensitivity than other markers, including cytology [55, 57, 58, 182, 183, 185, 187,188].

In addition to the UBC tests, a combined use of DNA and cytokeratin 8 and 18 flow-cytometry on exfoliated cells, together with the measurement of cytokeratin 8 and 18 levels by UBC for detecting recurrent bladder cancer has been suggested [187]. This technique increased the sensitivity of UBC from 77% when used alone, to 89% when used in combination with DNA analysis. However, the combination had a higher false positive rate among individuals with benign urological diseases and patients undergoing intravesical therapy [187]. In most studies, the specificity of UBC test varies between 65% and 75%

2. Cytokeratin 20

The expression of cytokeratin 20 is restricted to superficial and, occasionally, intermediate cells of the normal urothelium [1]. Aberrant cytokeratin 20 expression is present in bladder cells and in other urothelial cancer cells [181]. Immunohistochemistry and RT-PCR techniques have been used to evaluate the expression of cytokeratin 20 at the protein and mRNA level in bladder tissues and exfoliated cells. In a prospective cohort study involving only bladder cancer patients, Harnden et al. observed that cytokeratin 20 expression examined by immunohistochemistry could be used to distinguish between non-invasive papillary urothelial tumors that recur and those that do not [189]. In this study, the only factor that had a significant effect on the outcome of patients in terms of recurrence was cytokeratin 20

expression [189]. McKenney et al. have suggested the use of cytokeratin 20 along with p53 as immunohistochemical markers for distinguishing CIS from reactive atypia [190].

In mostly case-control retrospective studies, cytokeratin 20 expression in bladder cancer patients has been studied using an RT-PCR assay [191-196]. In these studies, cytokeratin 20 RT-PCR has 78% to 87% sensitivity to detect bladder cancer with a strong correlation between tumor keratin and cytokeratin-positive tumor cells in urine [191-195]. In addition, Rotem et al., in a case-control retrospective study, reported that 44% of the false positive cases detected by the cytokeratin 20 RT-PCR assay recurred within 6 months [192]. The specificity of cytokeratin 20 RT-PCR among healthy individuals and patients with clinical conditions other than bladder cancer varies between 55.7% and 80% [191-195]. Finding that cytokeratin 20 can a have false positive rate of 44.3%, Cassel et al. concluded that cytokeratin 20 expression is not specific for malignancy, and, therefore, its use as a potential marker for bladder cancer should be carefully evaluated [193].

The cytokeratin 20 RT-PCR assay is found to detect as few as 2 bladder cells per milliliter of blood and has been suggested as a promising approach for the early detection of systemic progression of bladder cancer [191]. However, Gazzaniga et al. found that blood samples from only 17% of bladder cancer patients were positive for cytokeratin 20 on RT-PCR [195]. In addition, the high sensitivity of any RT-PCR assay using peripheral blood may also be associated with low specificity [193].

Cytokeratin 20 immunocytochemistry has been evaluated as an adjunct marker for atypical cytology. For example, in a retrospective cohort study, Lin et al. reported that cytokeratin 20 immunocytochemistry detected bladder cancer in atypical cytology cases with biopsy proven bladder cancer with 94.4% sensitivity. The false positive rate of this staining was 37.8% [196]. Golijanin et al., in a cohort of new patients presenting with microhematuria and patients with a history of bladder cancer, also reported a high sensitivity (82%) and specificity (76%) for detecting bladder cancer using 5% cytokeratin 20 positive cells as the cutoff limit to detect bladder cancer [100]. The sensitivity of cytokeratin 20 was very similar in detecting primary and recurrent tumors. However, in this study the sensitivity to detect bladder cancer according to tumor grade was 56.5%, 93%, and 92% for G1, G2, and G3 bladder tumors, respectively [100]. Thus, although cytokeratin 20 immunocytology improves the overall sensitivity of cytology, this technique still misses 43% of low grade bladder tumors. Since the sensitivity of cytology to detect high grade tumors is high, an added value of cytokeratin 20 immunocytology may be justified only if it can improve the sensitivity of cytology for detecting low grade bladder tumors.

3. CYFRA 21-1

Cytokeratin 19 is expressed in normal urothelium. Since urothelial cells exfoliate, lysed cells release cytokeratin 19 in urine [1]. CYFRA 21-1 is a soluble fragment of cytokeratin 19 that is measured either by a solid phase sandwich immunoradiometric assay (Cis Bio international, Gif-sur-Yvette, France) or an electrochemiluminescent immunoassay with the Elec sys 2010 system (Roche Diagnostics), and the levels of cytokeratin 19 are normalized to urinary creatinine [104]. Pariente et al., in a retrospective cohort study, found that CYFRA 21-1 levels in bladder cancer patients, patients with other urologic conditions, and normal controls are 154.4 ng/mL, 22.3 ng/mL, and 2.4 ng/mL, respectively [197]. Using a cutoff value of 4 ng/mL, the sensitivity and specificity of CYFRA 21-1 assay to detect bladder cancer were 96.9% and 67.2%, respectively. In this study, patients with urolithiaisis and urinary tract infection had high urinary levels of cytokeratin 19. In another study, Sanchez-Carbayo et al. reported 75.5% sensitivity and 71% specificity for detecting bladder cancer; using the electrochemiluminescent assay for measuring CYFRA 21-1 levels [197]. In this study, the sensitivity of the CYFRA 21-1 test to detect G1, G2, and G3 tumors was 54.5%, 66.7%, and 88.2%, respectively. However, in various urologic conditions such as urolithiasis, stenosis, benign prostate hyperplasia, and urinary tract infections, the false positive rate is around 33%.

Summary

Based on several cohort and case-control studies, UBC tests appear to have low sensitivity to detect both low grade and low stage tumors. The overall sensitivity of these tests is also lower than several other bladder tumor markers. In addition, cytokeratin markers show high false positive rate among individuals with a wide range of clinical disorders.

Based on the conclusions of case-control studies, detection of cytokeratin 20 by RT-PCR assay, immunocytology, or immunohistochemistry

appears to be a useful marker to detect bladder cancer. However, lower specificity of cytokeratin 20 markers reported in some studies indicate that the identification of benign conditions that cause aberrant expression of cytokeratin 20 may help to improve the clinical applicability of this marker. In addition, cytokeratin 20 immunocytochemistry may not improve the sensitivity of cytology in detecting low grade tumors.

At the present time, there is limited data available on CYFRA 21-1 and thus recommendations cannot be made on this marker. In addition, this marker may have high false positive rate in various benign urologic conditions.

In general, the utility of cytokeratin markers for detecting bladder cancer will depend upon improving the sensitivity of these markers to detect low grade tumors and reducing the high false positive rate seen in several urologic conditions other than bladder cancer.

g) HA-HAase Test

1. Introduction

This test measures urinary levels of hyaluronic acid (HA) and hyaluronidase (HAase) using 2 very similar ELISA-like assays [38,198,199]. HA is a glycosaminoglycan that regulates cell adhesion, migration, and proliferation [200,201]. HA is known to promote tumor metastasis, and its concentration is elevated in several tumors including colon, esophagus, breast, prostate, and bladder [198,201,202]. Small fragments of HA are angiogenic and are generated when HAase degrades HA [203]. HA fragments are detected in the urine and tumor tissues of patients with high grade bladder cancer [202,204, 205]. HYAL1-type HAase has been shown to be the major tumor-derived HAase secreted by tumor cells [202,204,206].

2. Methodology

The HA test is based on the competition binding principle, in which HA present in urine competes with HA-coated microtiter wells to bind to a biotinylated bovine nasal cartilage HA-binding protein. Following incubation, the unbound HA-binding protein is washed off, and the HA-binding protein bound to microtiter wells is measured using an avidin-biotin detection system [199]. The HA present in each urine sample (ng/mL) is determined from a standard graph. To account for differences due to the hydration status of individuals, urinary HA levels are normalized to total urinary protein and are expressed as ng HA/mg protein. For the HA test, urinary HA levels ≥ 500 ng/mg (cutoff limit) constitute a positive test [198,204].

The HAase test measures HAase activity in urine. HAase present in urine degrades HA that is coated on microtiter well plates. Following incubation, the degraded HA is washed off and the HA remaining on the microtiter well plates is measured using the same biotinylated HA binding protein and the avidin-biotin detection system as the HA test. Urinary HAase levels (mU/mL) are determined from a standard graph and normalized to total urinary protein (mg/mL). For the HAase test, urinary HAase levels at or above 10 mU/mL constitute a positive test [198,199,207].

3. Results

In an initial case-control study, urinary HA, measured using the HA test, was found to be elevated 2.5- to 6.5-fold in patients with bladder cancer, regardless of tumor grade [8]. HAase levels measured using the HAase test were preferentially elevated (three- to sixfold) in the urine of patients with G2 and G3 bladder cancer [207]. In a case-control study involving 504 individuals (261 bladder cancer patients and 243 control individuals), the HA test had 83.1% sensitivity and 90.1% specificity to detect bladder cancer, regardless of the tumor grade [199]. In the same study, the HAase test had 81.5% sensitivity and 83.8% specificity for detecting G2 and G3 bladder cancer. Combining these 2 tests into the HA-HAase test resulted in bladder cancer detection with higher overall sensitivity (91.9%), with 86.4%, 95.7%, and 93.3% sensitivity to detect G1, G2, and G3 bladder tumors, respectively (*Level 3,* [199]). The HA-HAase test also detected both superficial (stages Ta, T1, and CIS) and invasive (stages ≥ T2) tumors with 87% to 100% sensitivity, respectively. The overall specificity of the HA-HAase test in this study was 84% [199]. The control population included normal healthy individuals; patients with genitourinary conditions such as stone disease, BPH, microhematuria, urinary tract infection, and cystitis; and patients with a history of bladder cancer but no evidence of disease at the time of testing. In a retrospective cohort study involving 83 bladder tissues and 34 urine specimens, Hautmann et al. demonstrated a close correlation between elevated HA and HYAL1 levels in bladder tumor tissues and a positive HA-HAase urine test. The authors concluded that in patients with bladder cancer tumor-associated HA and HYAL1 are secreted in urine, which results in a positive HA-HAase test [208].

The ability of the HA-HAase test to monitor bladder cancer recurrence was compared with that of BTA-Stat in a prospective cohort study of patients with recurrent bladder cancer [38]. In this study, the HA-HAase and BTA-Stat tests had 94% and 61% sensitivity, 63% and 74% specificity, and 87% and 64% accuracy, respectively. More interestingly, a false positive HA-HAase test carried a tenfold increased risk (risk ratio = 10.2) for tumor recurrence within 5 months, whereas a false positive BTA-Stat test did not carry any statistically significant risk for tumor recurrence within the same time frame (risk ratio = 1.4) [38].

Recently, 2 retrospective cohort studies compared the accuracy of the HA-HAase test with cytology and biomarkers such as BTA-Stat, hematuria detection, UBC-Rapid, and Immunocyt [58,64]. In the study by Schroeder et al., involving 138 urine specimens, HA-HAase test, cytology, BTA-Stat, hemoglobin dipstick, and UBC-Rapid had 88.1%, 70.6%, 52.5%, 50.8%, and 35.6% sensitivities, respectively (*Level 2,* [58]). The tests had 81% (HA-HAase), 81% (cytology), 76.7% (BTA-Stat), 78.2% (hemoglobin dipstick), and 75% (UBC-Rapid) specificities [13]. Among various tests and cytology, the HA-HAase test had the highest sensitivity in detecting both low grade, low stage and high grade, high stage tumors. Hautmann et al., in a study of 94 consecutive patients, found that the sensitivity of the HA-HAase urine test (83.3%) was significantly higher than the Immunocyt (63%) [64]. In that study, both tests had comparable specificity (HA-HAase 78.1%; Immunocyt 75%). The combination of both the HA-HAase and Immunocyt tests had 93.3% sensitivity without a significant decrease in specificity [64].

Srougi et al. compared accuracy of the HA test (hyaluronic acid detection test part of the HA-HAase test), UroVysion, BTA-Stat, and cytology in a prospective study involving bladder cancer patients with either primary or recurrent tumors [209]. The specificity of these tests was determined in patients with a history of bladder cancer but no evidence at the time of testing and in patients with benign prostate hyperplasia. The sensitivity of the HA test was the highest (83%) followed by BTA-Stat (75%), UroVysion (73%), and cytology (67%). The combination of HA test with UroVysion had 95% sensitivity to detect bladder cancer. The specificity of all of the tests were comparable to each other, although the HA test had slightly higher specificity than all of the tests.

Summary

Case-control and cohort studies show that the HA-HAase test is a promising method for detecting new onset and recurrent bladder tumors. The test has high sensitivity to detect low grade, low stage and high grade, high stage tumors. This test may also be useful in screening a high-risk population for bladder cancer. The accuracy of this test needs to be evaluated in larger multicenter trials.

2. Cell-based Markers

a) Microsatellite Analysis

1. Introduction

Microsatellites are highly polymorphic short tandem DNA repeats (mostly 2 to 4 base pairs each) found throughout the human genome [210]. Two types of "microsatellite alteration" can be found in many cancers. One is the loss of heterozygosity (LOH=allelic deletion), which is a hallmark of inactivation of tumor suppressor genes and can be detected in exfoliated cancer cells in urine, as well as in bladder tumor tissues [211-213]. The other is a somatic alteration of microsatellite repeat length in cancer cells, which can be detected as "microsatellite instability" or "a new allele" [211-213]. "LOH" and "microsatellite instability" can be used as markers of neoplasia and are known as "microsatellite alteration."

One of the most common genetic changes in bladder cancer is LOH on chromosome 9 [214]. Chromosomes 4p, 8p, 9p, 11p, and 17p also often display LOH in bladder cancer [214-217]. While LOH on chromosome 9p and 9q is found regardless of tumor grade and stage, LOH on other chromosomes is generally detected more frequently in tumors with higher grade or stage. Microsatellite instability can be detected as a result of genomic instability in cancer cells. Although microsatellite instability tends to be found more frequently in advanced bladder cancers, it was found frequently in low grade, low stage tumors when more microsatellite markers were used.

2. Methodology

To detect microsatellite alterations in the urine of patients with bladder cancer, DNA is extracted from cells in urine sediment, and then the samples are analyzed with PCR using DNA primers for a panel of known microsatellite markers. It has been reported that detection of microsatellite instability requires a ratio of tumor DNA to contaminating normal DNA

of more than 0.5% [217], whereas the detection of LOH requires at least 20% tumor DNA [218]. Generally, the more microsatellite markers used, the higher the sensitivity achieved. In addition, the number of loci at which LOH is found in bladder cancer increases as tumor grade or stage increases [214-216]. As for microsatellite instability, it also tends to be found more frequently in advanced cancer [219-222]. It is important to use a substantial number of microsatellite markers (15 to 20) at different loci to achieve high sensitivity.

3. Results

Several case-control studies, which analyzed voided urine specimens using 13 to 60 microsatellite markers, have been conducted. However, in most of these studies 15 to 20 microsatellite markers were used [56,213,222-234]. The overall sensitivity from these studies was 72% to 97% and overall specificity was 80% to 100%. One study indicated that the presence of cystitis or BPH may cause false positive results [221]. Although these studies demonstrated high sensitivity and specificity, all involved small numbers of patients, particularly in the control groups. Therefore, it remains to be clarified whether high specificity is maintained even in patients with benign inflammatory or neoplastic diseases.

As for tumor grade and stage, one study indicated that sensitivity increased somewhat as grade and stage became higher [226]. In addition, van Rhijn found that microsatellite markers missed all of the 11 Ta tumors that were included in the study [56]. However, in most studies an association between the sensitivity, tumor grade, and stage was not observed. Since the number of loci with microsatellite alterations found in each case increases in higher grade or stage tumors, it is, again, important to use an appropriate number (15 to 20) of microsatellite markers. As for the follow-up settings, high sensitivity was observed consistently in both primary and recurrent tumors [56, 222, 226].

4. Novel Methodology

More recently, activating FGFR3 mutations have been shown to be detected frequently in low grade superficial bladder caners [220]. Van Rhijn et al. showed that the combination of microsatellite analysis and the FGFR3 mutation analysis enhanced the sensitivity of the urine detection system and the sensitivity was 89%, compared with 71% for negative FGFR3 mutations [220]. The study also demonstrated no relationship between the test positivity and tumor grade and stage and multiplicity [220].

Using a DNA chip (HuSNP chip) that can discriminate different alleles by single nucleotide polymorphisms, the presence of LOH at nearly 1500 loci can be examined at once. Although experimental at present, Hoque et al. demonstrated that LOH at 24 or more loci could be detected with 100% sensitivity in 31 patients, while the alterations were not found in 9 control subjects and 4 of 5 patients with hematuria. [235]. Using a DNA chip assay is a promising method for detection of genomic alterations from urine specimens.

While the mutation of known oncogenes and tumor suppressor genes could be detected from urine specimens [236,237], the complicated methodology hampers its routine clinical application. Nonetheless, it has been demonstrated that tumor-specific hypermethylation at CpG sites can be detected by methylation-specific PCR, which may be able to detect only 0.1% to 0.001% of tumor cells among normal cells [238]. However, the methodology is still time-consuming and requires expensive equipment and trained personnel at present.

Summary

Microsatellite analysis demonstrates excellent sensitivity and specificity, independent of tumor grade and stage, tumor multiplicity, or previous history of bladder cancer. In spite of the superiority of this analysis, a need for expensive equipment and trained personnel with up-to-date techniques and protocols hampers the routine use of this analysis in clinical settings. To date, no results from a large-scale prospective study have been published. If the analysis can be automated and replicated by others, it might have a significant role in urine-based bladder cancer screening or follow-up. A large-scale prospective study employing automated analysis of a panel of microsatellite markers has recently been initiated through the NCI Early Detection Research Network in the USA. At present, microsatellite analysis of urine is experimental and not recommended for either detection or follow-up in routine clinical settings.

b) Telomerase

1. Introduction

Telomeres are nucleotide sequences at the 3' end of the lagging (5' to 3') strand of DNA that remain uncopied after each cycle of DNA replication [239]. In mammals, an array of tandem repeats of the

sequence TTAGGG forms telomeres, which are specialized heterochromatin structures that act as protective caps at the end of chromosomes [240]. The function of telomeric sequences is believed to be protection of chromosomal ends and maintenance of genomic stability.

Telomerase is a ribonucleoprotein that catalyzes the addition of telomeric repeats to the 3' end of chromosome DNA [241], thereby preventing the loss of telomeric sequences, reconstituting the ends of chromosomes after cell division and circumventing the damage that occurs in normal adult somatic cells during successive mitosis. This enzyme is a complex containing a protein subunit and an RNA component. The RNA subunit of human telomerase, called hTER or hTR, provides the template for telomeric repeat synthesis. The active site of the protein subunit contains the catalytic activity of the enzyme called hTERT in humans, and is functionally homologous to the reverse transcriptase (RT) of retroviruses [241].

Telomerase is active during human embryogenesis, but downregulated at tissue differentiation [242]. In normal tissues, low levels of telomerase activity have been found in proliferating cells [4]. More than 90% of human cancer is telomerase-positive, whereas most normal tissues or benign tumors contain low or undetectable telomerase activity [243]. From these results, many investigators have tried to use the presence of telomerase activity as a novel and useful tumor marker with a relevant diagnostic capability.

2. Methodology

An important improvement in telomerase detection was the development of the telomeric repeat amplification protocol assay (TRAP assay) [244]. This highly sensitive assay is based on polymerase chain reaction (PCR) amplification of in vitro telomerase reaction products. First, TTAGGG repeats are synthesized and amplified by PCR utilizing the telomerase in target tissues or specimens [244]. The PCR products are then analyzed on gels. Commercially available kits (the TRAPeze by Appligene® Oncor and a kit by Boehringer Mannheim) provide optimized sets of primers and reagents for telomerase detection. The test must be done in a reference laboratory with specialized equipment and trained personnel. Because the TRAP assay is a complex procedure with a PCR amplification step, it is particularly sensitive to potential inhibitors of PCR reaction, therefore causing false negative results.

Because the conventional TRAP assay provides qualitative information only, that is, positive versus negative, several variations to this protocol have been proposed to improve the sensitivity of the assay and transform this qualitative method into a procedure for obtaining quantitative information on telomerase activity [245,246].

Besides the TRAP assay, 3 major components of human telomerase - human telomerase RNA (hTERC), telomerase-associated protein (TEP1), and a catalytic subunit of telomerase (hTERT) - have been identified [247]. The gene cloning of these components enabled a different approach to the detection of telomerase activity based on the measurement of specific mRNA by an RT-PCR technique. Although the relationship between the expression of this mRNA and enzyme activity has not been completely elucidated [248], hTERT mRNA expression is closely associated with telomerase activity and is a rate-limiting determinant of telomerase [247-250].

3. Results

• Application in Urothelial Cancer

- General Description

Studies have demonstrated that telomerase may be detected in bladder cancer tissue and in the urine of patients with bladder cancer. Telomerase activity has been shown to be present in more than 85% (mostly over 90%) of bladder cancer tissues, regardless of tumor grade and stage [251-255].

Telomerase activity in exfoliated cells collected in normally voided urine or in bladder washings can be detected using this highly sensitive TRAP assay. The overall sensitivity of urine-based TRAP assays for detection of bladder cancer is mostly between 70% and 90% [125,149,252,256-258], although much lower sensitivity was reported in some studies [255, 259,260].

Generally, the TRAP assay has shown better sensitivity than cytology, with slightly lower specificity [150, 255]. When patients with inflammatory conditions or benign urologic disease are included as normal controls, specificity may be lower because of the contaminating benign cells with telomerase activity (for example, lymphocytes). It should be noted that most of the above studies were performed on patients with documented bladder cancer (mostly fresh cases) as positive controls.

• Detection of Recurrent Bladder Cancers

Only a few studies have focused on telomerase detection in the follow-up setting after endoscopic treatment. In 42 patients with a previous history of

bladder cancer, a low sensitivity of 29% (10 of 35) was found by the TRAP assay using voided urine [261]. Low sensitivity (35%) in follow-up settings was also reported by Dalbagni et al. [259]. Although Wu et al. suggested that the recurrence rate for patients with a positive TRAP assay using urine after transurethral resection (TUR) was higher than that of those with negative activity (50% vs. 17.7%), they later reported that the positive telomerase activity after TUR was not associated with recurrence [260, 262]. Although the telomerase assay demonstrated high sensitivity in a cohort of documented fresh bladder cancer patients, it is not known whether this high sensitivity is achieved in follow-up settings, in which most of the recurrent tumors are small and of low grade.

• Voided Urine or Bladder Washings?

In a few studies, the sensitivity of the TRAP assay was compared between voided urine and bladder washing fluid. While Kinoshita et al. showed a significantly higher sensitivity using bladder washings than voided urine (55% vs. 84%) with no difference in specificity [255], Gelmini et al. showed no difference between the 2 groups (82% in both) [15]. Higher sensitivity using bladder washings was also observed in another study [263].

• Alternative Methods to the TRAP Assay

As described before, recent molecular cloning of the telomerase components enabled a different approach to the detection of telomerase activity, that is, the measurement of specific mRNA by an RT-PCR technique. Although the relationship between the expression of each mRNA and enzyme activity has not been completely elucidated [248], the hTERT mRNA expression is well associated with telomerase activity and is a rate-limiting determinant of telomerase [247,249,250]. Bialkowska-Hobrzanska et al. showed that hTERT mRNA detection in urine specimens had a higher sensitivity than the conventional TRAP (94.3% vs. 48.6%), with a slightly lower specificity (92% vs. 100%) [264]. Using washing fluid specimens, Isurugi et al. showed that overall sensitivity for hTERT detection by RT-PCR was 75.6%, varying from 52%, 80%, and 94% for grade 1, 2, and 3 tumors, respectively [265]. Using a real time-quantitative RT-PCR assay for hTERT mRNA, de Kok et al. reported that both 100% sensitivity and specificity were achieved, and a higher hTERT mRNA level was found in tumors with higher grade and stage [266]. High sensitivity (92%) and specificity (94%) with hTERT mRNA detection from voided urine samples were further reported by Melissourgos et al. [267]. Although the sensitivity of the hTERT mRNA detection by RT-PCR seems to be higher, it should be noted that substantial variation in the sensitivity and specificity still occurs according to the sample collection and processing procedures, RT-PCR conditions, and the presence of RT-PCR inhibitors or non-malignant cells in urine samples.

Summary

Despite the excellent results of telomerase detection using the TRAP assay, some problems have hampered its widespread use in clinical settings. Telomerase was not grade sensitive, but false positive results were obtained in cases of chronic or severe bladder inflammation due to the presence of lymphocytes. False negative results may be obtained depending on the sample collection and processing procedures, and the presence of PCR inhibitors or ribonuclease [268]. Basically, telomerase detection requires immediate urine processing within 24 hours. Since at least 50 cells expressing telomerase are required to ensure reliable detection of telomerase by the TRAP assay [252], tumor volume may be one of the significant determinants of sensitivity, and there will be a higher rate of false negative results when detecting small tumors, especially in follow-up settings after endoscopic treatment. Improvements in the assay technique (for example, hTERT mRNA detection by a real time-quantitative RT- PCR assay) and adherence to more stringent conditions should address these problems in the future.

c) uCyt™

1. INTRODUCTION

Immunocytology is based upon the visualization of tumor-associated antigens in urothelial carcinoma cells using monoclonal antibodies. Over the last 2 decades, a variety of monoclonal antibodies have been evaluated for their potential in the diagnosis of bladder cancer. Today, the uCyt™ assay is the most frequently used immunocytological test.

2. METHODOLOGY

uCyt™ is a commercially available immunocytological assay based upon microscopic detection of tumor-associated cellular antigens in urothelial cells by immunocytochemistry (Diagnocure Inc., Quebec, Canada). Triple antibody labeling is performed using fluorescein-labeled monoclonal antibodies M344 and LDQ10 directed against sulfated mucinglyco-

proteins and a Texas-red linked monoclonal antibody 19A211 against glycosylated forms of high molecular carcinoembryonic antigens (hmCEA). Specific technical requirements for this assay are a high quality fluorescence microscope and a cytocentrifuge. Apart from this, the assay can easily be performed even in smaller peripheral laboratories. On-site training, significant experience, and regular quality control are mandatory. The time-consuming microscopic examination of the slides remains a disadvantage. Despite the observer-dependence, reproducibility is good.

3. RESULTS

Several reports addressing the test performance have been published (**Tables 2 and 3**). Analyzing the results reported for immunocytology, the broad variation specifically concerning test sensitivity ranging between 38% and 100% is remarkable (**Table 3**). Specificity ranges between 75% and 90%. The reasons for these differences may be manifold and largely due to patient selection. However, it should be noted that immunocytology is an observer-dependent technique requiring a broad personal experience and constant quality control [269]. This may be one explanation for the observation that those groups performing this test on a routine basis tend to have results superior to those with a limited experience.

Summary

With an average sensitivity and specificity of approximately 80%, the uCyt™ assay is superior to conventional urine cytology and clearly belongs in the group of the most promising diagnostic markers for bladder cancer. A prospective evaluation to further assess the role of this test in the management of bladder cancer appears worthwhile.

Table 2. Sensitivity and Specificity of Immunocytology (uCyt™) and Cytology in the Diagnosis of Bladder Cancer: Summary of Literature

			Sensitivity/Specificity (%)	
Author (year)	**Stage/grade**	**n**	**uCyt™**	**Cytology**
Mian et al. (1999) [270]	G1	25	84	4
	G2	25	88	52
	G3	29	97	79
	Controls	135/167	79	98
Olsson and Zackrisson (2001) [271]	G1	8	100	
	G2	14	100	55
	G3	8	100	
	Negative	83	69	NR
Lodde et al. (2003) [272]	G1	20	85	5
	G2	18	100	55
	G3	13	92	85
	Controls	40	80	96
Feil et al. (2003) [273]	Ta low grade	11	18	27
	T1 high grade	8	38	38
	T2 high grade	7	71	43
	Controls	87	84	92
Pfister et al. (2003) [109]	G1	31	61	18
	G2	40	76	46
	G3	68	77	64
	Controls	162/170	84.7	93.2
Hautmann et al. (2004) [64]	G1	4	75	50
	G2	15	47	53
	G3	11	82	82
	Controls	64	75	80
Schmitz-Dräger et al. (2004)*	G1/2 (LMP)	7	71	NR
	G3	9	89	NR
	Controls	144	90	NR

* - personal communication, NR – not reported

Table 3. Overall Sensitivity and Specificity of Immunocytology (uCyt™) and Cytology in the Diagnosis of Bladder Cancer: Summary of Literature

Author (year)	Sensitivity (%)		Specificity (%)	
	uCyt™	Cytology	uCyt™	Cytology
Mian et al. (1999) [270]	68/79 (86)	37/79 (47)	107/135 (79)	164/167 (98)
Olsson and Zackrisson (2001) [271]	30/30 (100)	16/30 (55)	57/83 (69)	NR
Lodde et al. (2003) [272]	47/51 (92)	22/51 (43)	32/40 (80)	38/40 (96)
Pfister et al. (2003) [109]	101/139 (73)	67/139 (48)	137/162 (85)	158/170 (93)
Feil et al. (2003) [273]	10/26 (38)	9/26 (35)	73/87 (84)	80/87 (92)
Hautmann et al. (2004) [64]	19/30 (63)	22/30 (73) 4	3/64 (75)	51/64 (80)
Present series (2004)	13/16 (81)	NR	129/144 (90)	NR
Overall	**288/371 (78)**	**173/355 (49)**	**578/715 (81)**	**491/528 (93)**
Fradet et al. (2002) [274]*	394/438 (90)	235/438 (54)	760/1055 (72)	NR

NR – not reported, * - Combined analysis of 5 trials

d) DD23

1. Introduction

A monoclonal antibody called DD23 was first reported in 1992 [275]. This IgG1 murine monoclonal antibody resulted from the immunization of a BALB/c mouse with a fresh human bladder cancer. Initial results demonstrated binding to 32 of 40 bladder cancers and 9 of 16 breast cancers. It did not bind to normal ureter or bladder.

2. Methodology and Results

Initial clinical evaluation utilized quantitative fluorescence image analysis (QFIA). In a case-control study, DD23 testing by QFIA was evaluated on voided urine from 41 asymptomatic controls, 34 symptomatic controls, and 41 patients with bladder cancer [276]. The sensitivity for bladder cancer was 85% with a specificity of 95%. No significant difference was seen between symptomatic and asymptomatic control populations, including patients with a history of bladder cancer who were free of disease.

UroCor, Inc. licensed the DD23 monoclonal antibody, and the analytic method was converted to an alkaline phosphatase immunohistochemical assay. In 2002, a prospective cohort study evaluated the usefulness of DD23 in bladder cytology specimens from 308 patients [48]. Of these specimens, 164 were voided urine, 49 were catheterized urine, and 95 were bladder barbotage specimens. DD23 and cytology were assessed in routine alcohol-fixed specimens. The overall sensitivity for cytology and DD23 was 66% and 81%, respectively. The specificity of cytology and DD23 was 85% and 60%, respectively. The combination of cytology and DD23 had a sensitivity of 85%, specificity of 55%, positive predictive value of 43%, and negative predictive value of 90%. Combining DD23 with cytology increased the sensitivity for both low grade and high grade bladder cancers. For low grade cancers, the sensitivities of cytology, DD23, and the combination were 32%, 72%, and 76%, respectively. For high grade cancers, the sensitivities of cytology, DD23, and the combination were 85%, 87%, and 95%.

A single institution cohort study evaluated DD23 and cytology in 151 specimens from 81 patients with a history of urothelial carcinoma of the bladder [277]. A positive DD23 assay was defined as the presence of 3+ chromogenic cytoplasmic staining in at least one urothelial cell. The overall sensitivity of cytology, DD23, and the combination was 44%, 70%, and 78%, respectively. The overall specificity of cytology, DD23, and the combination was 92%, 60%, and 59%, respectively. Cytology, DD23, and the combination exhibited higher sensitivity but lower specificity in bladder barbotage specimens compared with voided urine specimens. DD23 exhibited a sensitivity of 95% and a specificity of 33% in patients with a history of intravesical therapy.

Summary

DD23 is a monoclonal antibody that detects a protein dimer expressed on bladder cancer cells. It is meant to be used with urine cytology and is performed by one laboratory, Dianon (LabCorp). This combination improves the detection of bladder cancer, especially low grade disease. The 90% negative predictive value suggests that the combination of DD23 and cytology could be used to decrease the frequency of cystoscopy. Prospective validation of this concept is needed.

e) Quanticyt Nuclear Karyometry

1. Introduction

Quanticyt is an automated quantitative karyometric cytology system that enables objective interpretation of nuclear features (i.e., nuclear shape and DNA content) in light microscopy images. Based on the nuclear features, individuals are stratified in various risk groups for bladder cancer.

2. Methodology

The test involves staining of a cytospin preparation of ethanol-polyethylene glycol fixed bladder wash specimens. The nuclear images observed under a light microscope are transferred to a computerized image analysis system. Samples are assessed for mean nuclear shape (MPASS) and DNA content (2c deviation index or 2cDI) parameters using an internal lymphocyte standard [4,160,278-280]. Based on the Quanticyt results, the study individuals are identified as being at low-, intermediate-, or high-risk for bladder cancer.

3. Results

In 2 studies, the Quanticyt test had 59% and 69% sensitivity, respectively, for detecting bladder cancer, while the specificity was 70% [280,281]. The test had 57%, 56%, and 85% sensitivity to detect G1, G2, and G3 bladder cancer, respectively. Witjes et al. reported an 82.6% and 50% prognostic NPV and PPV, respectively, for Quanticyt [160]. Van Rhijn et al. found that among the 105 high-risk patients identified by Quanticyt, malignancy was found in 54 patients [279]. Furthermore, a 2cDI ≥ 2.00 was a significant predictor of CIS, invasive bladder cancer, and progression. Thus, a 2cDI > 2.00 can be used to further stratify patients with high-risk invasive bladder cancer [279]. Van der Poel et al., in a retrospective study of 614 patients and 5832 bladder wash specimens, suggested that consecutive cytology and Quanticyt analyses of bladder wash specimens improve the rate of detection of high grade tumors [282]. However, in that study, the risk score of the first sample was not predictive of recurrence. It was only after 5 samples that the rate of finding invasive disease was 10% among individuals classified as high-risk by Quanticyt [282]. However, a study by Wiender et al. indicates that Quanticyt may overestimate the risk for bladder abnormalities, and, therefore, has a lower specificity than bladder wash cytology and voided urine cytology [281]. Some samples may also be eliminated due to too few urothelial cells, or if the sample has an abundance of leukocytes and erythrocytes.

Summary

Quanticyt nuclear karyometry measures mean nuclear shape (MPASS) and DNA content (2c deviation index or 2cDI) parameters and stratifies patients into low-, intermediate-, or high-risk for bladder cancer. The analysis requires sophisticated instrumentation, bladder wash specimens, and technical expertise. In some cases, the test may overestimate the risk for bladder cancer. At the present time, general applicability of this marker is limited.

f) Multi-target Multi-color FISH Assay (UroVysion Test)

1. Introduction

Cytogenetic studies reveal frequent alterations in chromosomes 1, 3, 4, 7, 8, 9, 11, 17, etc., in urothelial cancers [283,284]. Recently, Junker et al., in a retrospective study involving archival bladder cancer specimens, evaluated the frequency of the loss of heterozygosity (LOH) for various chromosomes. The LOH was the highest for chromosome 9p (54.9%), followed by 9q (49.3%), 13q (40.8%), 14q (40.8%), 10q (39.4%), 17p (39.4%), 8p (38%), 21q (36.6%), 11p (31%), 18q (23.9%), 4q (21.1%), 3p (16.9%), 6q (14.1%), and 1q (8.1%). Deletion in chromosome 9p21 at the p16 gene locus has been identified as an early event in bladder cancer development [284]. Chromosomal abnormalities can be detected by FISH. FISH assay involves binding (i.e., hybridization) of specific fluorescently-labeled DNA probes to chromosome centromeres or unique loci on the chromosomes that are altered in tumor cells. This hybridization allows detection of cells with a fluorescence microscope and recording system. For detecting bladder cancer cells, FISH assay is per-

formed on exfoliated cells. The sensitivity of a multi-colored multi-probe with FISH assay is better than a single probe.

2. Methodology

UroVysion test is a multi-target multi-color FISH assay that uses peri-centromeric fluorescent probes for chromosomes 3, 7, and 17, and a locus specific probe for the 9p21 region (P16 locus). The test involves fixing of exfoliated cells from 10 to 50 mL of urine specimens and placing them in wells of 12-well slides. The cells are incubated with denatured Chromosome Enumeration Probe (CEP) 3 (spectrum red), CEP7 (spectrum green), CEP17 (spectrum aqua), and Locus Specific Identifier (LSI) 9p21 (spectrum gold). The slides are counterstained and observed under a fluorescence microscope (UroVysion/Abott Laboratories insert). The criteria for detecting bladder cancer include finding 5 or more urinary cells with gains of 2 or more chromosomes, or 10 or more cells with gain of a single chromosome (such as trisomy 7). Homozygous detection of 9p21 locus in greater than 20% of epithelial cells is considered a positive result [124,285]. However, currently there are no universally accepted criteria for determining the positivity of a FISH test. For example, Friedrich et al. discarded specimens with less than 100 cells/slide and considered a specimen as positive if 20% of the cells gained 2 or more chromosomes or 40% of cells gained or lost one chromosome (i.e., 9p21 [59,60]. Skacel et al. considered a specimen as positive if 5 or more cells gained 2 or more chromosomes (3, 7, or 17) or 10% or more of cells had trisomy of 1 of the chromosomes 3, 7, or 17 or 12 or more cells showed the loss of the 9p21 locus [88]. Dalquen et al. discarded samples with less than 25 cells and considered a sample as positive if 3 or more cells showed a gain of 3 or more copies of chromosomes 3, 7, and 17 and a heterozygous or homozygous loss of the 9p21 locus [286]. In addition, some studies have used only 2 of the 4 probes provided in the UroVysion test to ascertain the presence of bladder cancer [287].

3. Results

In initial case-control cohort studies, the sensitivity of the UroVysion test to detect bladder cancer was 81% to 84% [288,289]. These groups reported an overall sensitivity of 81% and a specificity of 96% for detecting bladder cancer. However, in those studies, the sensitivity of the UroVysion assay was low in detecting low grade tumors (36%) and was not very different from that of voided urine cytology (27%) [289]. In recent case-control and cohort studies, some of which also compared the sensitivity of UroVysion to other markers, the sensitivity of the UroVysion test varied between 69% and 87% [47,59-61,124,286]. These studies report a low sensitivity of UroVysion to detect low grade (36%-57%) and low stage (62%-65%) tumors [47, 60-61,124,287]. The test has high sensitivity to detect high grade and high stage tumors (83%-97%) and also to detect CIS (about 100%) [47,59-61,124,286]. The specificity of the UroVysion test reported in various studies is high and varies between 89% and 96% [47,59-61,124,286]. The test also has high specificity among patients who have a variety of benign genitourinary conditions, including microhematuria, benign prostatic hyperplasia, infections, and inflammation [47,124,288].

In some studies, the UroVysion test has been shown to predict recurrence. For example, Skacel et al., in a retrospective cohort study, reported that 8 of 9 FISH-positive patients with atypical cytology but negative biopsy had biopsy-proven bladder cancer in 12 months [88]. Bubendorf et al., in a case-control study, reported that 4 of the 5 false positive patients on the UroVysion had a recurrence within 8 months; however, none of the true negative cases recurred within 18 months. It should be noted that the criteria used in the Bubendorf study to detect abnormal cells were different from those suggested by the manufacturer [287]. Furthermore, Bubendorf et al. concluded that the optimal criteria to define a FISH-positive result are not absolutely clear and that not all FISH aberrations are equally important [287]. Noting the high sensitivity of the UroVysion test to detect chromosomal abnormalities, Veeramachaneni et al., in a cohort study, concluded that a positive FISH test may indicate frank neoplastic urothelial transformation, or it may merely be an indicator of unstable urothelium capable of or primed for malignant transformation, thus detecting patients at significant risk [290].

Summary

Based on case-control and cohort studies, the UroVysion test appears to be a promising test for detecting bladder cancer. It may have an ability to detect bladder tumor recurrence prior to its clinical detection. However, it is important to develop a consensus for the criteria used for the evaluation of abnormal cells. The test also has low sensitivity to detect low grade bladder tumors. Furthermore, at this time, it is not clear whether a positive UroVysion indicates both the neoplastic transformation (i.e., presence of bladder cancer) and an unstable urothelium primed for malignant transformation.

VII. COMPARATIVE ANALYSIS OF BLADDER TUMOR MARKERS (2000-2004)

Several studies have compared sensitivity and specificity of a variety of markers with each other and with cytology. Most of the markers have significantly higher sensitivity than cytology to detect bladder cancer. The sensitivity of many markers also varies with tumor grade, stage, and size. Depending upon the population that is evaluated, some markers show specificity comparable to cytology in side-by-side comparison studies. Many markers show lower specificity among patients with benign urologic conditions such as cystitis, urinary tract infection, hematuria, urolithiasis, and BPH. **Table 4** summarizes some of the comparative studies conducted between 2000 and 2004 that allow us to compare the performance of different markers evaluated in the same study population.

Giannopoulas et al., in a cohort study of 213 patients, compared the efficacies of the urinary UBC-IRMA, NMP-22, and BTA-Stat tests [291]. The study population included new patients, as well as patients who previously had superficial bladder cancer. For the NMP-22 test, the authors' used 8 U/mL as the cutoff limit, which is lower than the cutoff limit suggested by the manufacturer (10 U/mL). The cutoff value used for UBC-IRMA was the same as that suggested by the manufacturer. The overall sensitivity and specificity were 72.9% and 64.6% for the BTA-Stat, 63.5% and 75% for NMP-22, and 80.5% and 80.2% for the UBC test, respectively. The UBC test also detected low grade and low stage bladder cancer with higher sensitivity and specificity than NMP-22 and BTA-Stat. The sensitivities of BTA-Stat and NMP-22 increased significantly with tumor grade, but the sensitivity of UBC-IRMA increased only marginally. Based on these results, the authors concluded that UBC might be a better diagnostic marker for bladder cancer than NMP-22 and BTA-Stat.

Mian et al. compared the accuracy of the UBC tests (IRMA and Rapid) with BTA-Stat and NMP-22 in 2 separate retrospective cohort studies [183,186]. The first study involved 183 patients, 57 suspected of having bladder cancer and 123 with a history of bladder cancer. The BTA-Stat and UBC-Rapid tests had 52.8% and 66% sensitivities, respectively, for detecting bladder cancer [183]. The sensitivities of both UBC-Rapid and BTA-Stat to detect low grade tumors were low, at 38.8% for the BTA-Stat and 44.4% for UBC, respectively. The specificities of the BTA-Stat and UBC were 70% and 90%, respectively.

In the second study, when comparing the performances of the UBC-IRMA and the NMP-22 among patients with symptoms suggestive of bladder cancer, Mian et al. used 10 U/mL cutoff for the NMP-22 test and 12 μg/L cutoff for the UBC-IRMA [186]. UBC-IRMA had a slightly higher sensitivity (64.8%) than the NMP-22 (55.5%) in detecting bladder cancer. While the sensitivity of UBC-IRMA for detecting G1, G2, and G3 bladder tumors (66.6%, 60%, and 68.7%) was very similar, the sensitivity of NMP-22 was slightly higher for detecting G3 tumors (50%, 50%, and 68.7%). The specificities of NMP-22 and UBC-IRMA were 79% and 92%, respectively. However, both tests had a higher positive rate among patients with cystitis or benign lesions of the urinary tract. Based on both studies, Mian et al. concluded that although the UBC tests (Rapid and IRMA) are superior to both the BTA-Stat and the NMP-22 tests, all of these tests can be used only to lower the number of cystoscopies while monitoring recurrence, not to replace it completely [183,186].

In a case-control retrospective study involving 112 symptomatic bladder cancer patients and 75 patients with benign genitourinary conditions, Sánchez-Carbayo et al. compared the diagnostic potential of the UBC-IRMA, NMP-22, and CYFRA 21-1 tests with cytology and microhematuria [104]. In this study, the authors also compared the diagnostic characteristics of urinary tumor markers with or without normalization to urinary creatinine. In the absence of normalization, the UBC-IRMA, CYFRA 21-1, and NMP-22 tests had 69.4%, 67.3%, and 61.2% sensitivities and 91.3%, 88.4%, and 89.9% specificities, respectively. Normalization to creatinine increased the sensitivity of CYFRA 21-1 (75.5%) and NMP-22 (73.5%), however, it decreased the specificity significantly (NMP-22, 68.1% and CYFRA 21-1, 71%). The increased sensitivity and decreased specificity could also be due to the use of different cutoff limits when the values of the markers were normalized to creatinine than when non-normalized values were used. All 3 markers had significantly higher sensitivity than cytology (35.4%) and microhematuria (55.1%). However, the majority of the false negatives were among patients with G1 tumors and superficial bladder cancer. The sensitivity of all 3 markers for detecting G1 tumors varied between 27% and 54%, regardless of whether the marker levels were normalized to creatinine. The false positive rate for all 3 markers among patients with benign genitourinary conditions (such as BPH, urinary tract infection, stenosis, and

lithiasis) was between 23% and 39%, either with or without normalization to urinary creatinine. Therefore, although the combination of the NMP-22, UBC, and BTA-Stat tests will improve the sensitivity of bladder cancer detection, it will significantly impact the specificity and the positive predictive value of the combination.

In 2 case-control retrospective studies, Boman et al. compared the performances of the BTA-Stat, NMP-22, and UBC-IRMA with bladder wash cytology in detecting new tumors and tumor recurrence among a total of 250 study patients [55,135]. The cutoff limits for NMP-22 and UMC-IRMA in these 2 studies were 4 U/mL and 1 ng/mL, respectively. The first study documents that there is a large difference in size between new tumors (median size 15 mm) and recurrent tumor (median size 6.5 mm) and that new tumors tend to have higher grade and stage than recurrent tumors [135]. The sensitivity of all 3 markers for detecting new tumors was higher (NMP-22, 65%, BTA-Stat, 75% and UBC-IRMA, 60%) than that for detecting recurrent tumors (NMP-22, 45%, BTA-Stat, 55% and UBC-IRMA, 40%). The sensitivity of bladder wash cytology for detecting both new and recurrent tumors was about 40%. The difference in the sensitivity of the 3 markers for detecting new and recurrent tumors disappeared when the tumors in both categories were differentiated with respect to size, grade, and stage. Thus, all 3 markers had a lower sensitivity for detecting smaller superficial tumors. In the second study, Boman et al. compared the sensitivity of NMP-22, UBC-IRMA, flow cytometry, and bladder wash cytology to detect different sizes of tumors (≤ 10 mm to ≥ 31 mm). Sensitivity of NMP-22 was about 75% among tumor sizes ≤ 10 mm to 21 to 30 mm, but it increased to 93% when tumors were ≥ 31 mm. The sensitivity of BTA-Stat and UBC-IRMA increased from about 55% to 100% between tumor sizes ≤ 10 mm and ≥ 31 mm. Interestingly, the sensitivity of bladder wash cytology also increased from 35% to 85% between tumor sizes ≤ 10 mm and ≥ 31 mm. Based on these studies, the authors concluded that NMP-22, UBC-IRMA, and BTA-Stat markers or any combination of them cannot replace follow-up cystoscopy, mainly because most recurrent tumors are small. Another point to consider is that if the purpose of noninvasive tumor markers is to detect bladder tumors before they become invasive, the tumor markers should have a reasonably high sensitivity for detecting small, superficial tumors.

Gutierrez-Banos et al. compared the efficacies of the NMP-22, BTA-Stat, and cytology in a cohort of 150 symptomatic patients and patients with a history of bladder cancer [292]. The sensitivities of NMP-22 at 6 U/mL and 10 U/mL were 84.2% and 76.3%, respectively. The sensitivities of NMP-22 to detect G1, G2, and G3 bladder tumors were 68.7%, 75.9%, and 100%, respectively at 6 U/mL cutoff and 50%, 69%, and 96.8%, respectively, at 10 U/mL cutoff. The sensitivities of the BTA-Stat and cytology for detecting bladder cancer were 72.3% and 69.7%, respectively. The sensitivities for detecting G1, G2, and G3 tumors were 56.2%, 62.1%, and 90.3%, respectively, for the BTA-Stat and 43.8%, 62.1%, and 90.3%, respectively, for cytology. The specificities of the BTA-Stat (89.2%), NMP-22 (86.5%, 6 U/mL, and 90.5%, 10 U/mL), and cytology (93.2%) were comparable. Based on these results, the authors suggested using 6 U/mL as a cutoff for the NMP-22 test. However, this conclusion should not be generalized because, in the study by Boman et al., NMP-22 had low sensitivity (65% for detecting new tumors and 45% for detecting recurrent tumors) even when a cutoff value of 4 U/mL was used [135]. Since in the Gutierrez-Banos study all tests including cytology had higher sensitivity for detecting bladder cancer, it is possible that the study patients might have had larger tumors, which are more readily detected by the markers.

In a retrospective cohort study involving 94 new patients suspected of having bladder cancer and 102 patients with a history of bladder cancer, Casetta et al. compared the usefulness of the BTA-TRAK and NMP-22 with urine cytology performed on 3 consecutive samples to detect bladder cancer. This is the only study where the sensitivity of cytology was higher than the tumor makers under study [293]. The overall sensitivities of the NMP-22 (cutoff 11 U/mL), BTA-TRAK (cutoff 60 U/mL), and cytology were 56%, 57%, and 59.3%, respectively. When “dubious results” on cytology were considered as positive cases, the sensitivity of cytology increased to 73.3%. The sensitivity of the 2 tumor markers was not different in the 2 groups, and it did not improve by lowering the cutoff values on both tests. Based on these results, the authors concluded that urine cytology performed on 3 samples outperforms the NMP-22 and BTA-Stat tests. The authors also observed that the diagnostic advantage of cytology over the 2 urine tests was maintained even when the patients were stratified according to tumor grade.

Table 4. Comparative Studies of Tumor Markers

Study	Cytology	BTA-Stat	BTA-TRAK	CYFRA 21-1	HA-HAase	HA Test	Hemo-globin
Giannopoulas et al. [291]							
Sensitivity		72.90%					
G1		50%					
G2		73.30%					
G3		88.40%					
Superficial		65.30%					
Invasive		95%					
Specificity		64.60%					
Mian et al. (a) [183]							
Sensitivity		52.80%					
G1		38.80%					
G2		52.60%					
G3		68.70%					
Superficial		52.10%					
Invasive		70%					
Specificity		70%					
Mian et al. (b) [186]							
Sensitivity							
G1							
G2							
G3							
Superficial							
Invasive							
Specificity							
Sanchez-Carbayo et al. [104]							
Sensitivity	35.40%			75.50%			8.70%
G1				54.50%			
G2				66.70%			
G3				88.20%			
Superficial				61.20%			
Invasive				100%			
Specificity	97.20%			71%			99.20%
Boman et al. (a) [135]							
Sensitivity							
Primary tumors		75%					
Recurrent tumors		55%					
Specificity							
Primary tumors		75%					
Recurrent tumors		54%					

Table 4. Comparative Studies of Tumor Markers (Continued)

Immunocyt	Lewis X Ag	486p3/12	NMP-22	Telom. (TRAP)	Telom. (hTERT)	UBC-Rapid	UBC-IRMA	UroVysion
			63.50%				80.50%	
			50%				70%	
			55.50%				80%	
			81.40%				88.40%	
			57.10%				76.50%	
			90%				85%	
			75%				80.20%	
						66%		
						44.40%		
						78.90%		
						75%		
						65%		
						80%		
						90%		
			55.50%				64.80%	
			50%				66.60%	
			50%				60%	
			68.70%				68.70%	
			54.10%				58%	
			70%				80%	
			79%				92%	
			73.50%				69.40%	
			36.40%				27.30%	
			66.70%				73.30%	
			82.30%				82.30%	
			67.60%				58.80%	
			100%				88.90%	
			68.10%				87%	
			65%				60%	
			45%				40%	
			74%				75%	
			64%				72%	

Table 4. Comparative Studies of Tumor Markers (Continued)

Study	Cytology	BTA-Stat	BTA-TRAK	CYFRA 21-1	HA-HAase	HA test	Hemo-globin
Boman et al. (b) [35]							
Sensitivity	42%	78%					
G1	8%	62%					
G2	43%	82%					
G3	77%	96%					
Superficial	32.60%	75.30%					
Invasive	73%	100%					
Specificity	97%	73%					
Halling et al. [124]							
Sensitivity		78%					74%
G1		50%					42%
G2		72%					60%
G3		91%					97%
Superficial		72.70%					54%
Invasive		94%					89%
Specificity		74%					51%
Sarosdy et al. [47]							
Sensitivity	26%	50%					
G1	18%	27%					
G2	44%	78%					
G3	41%	72%					
Superficial	31.80%	53.30%					
Invasive	33%	67%					
Specificity*	71%	75%					
Babjuk et al. [185]							
Sensitivity	33.30%	74.40%	75.60%				
G1	3.70%	59.30%	59.30%				
G2	40.70%	74.10%	77.80%				
G3	58.30%	91.70%	91.70%				
Superficial	29.30%	69%	72.40%				
Invasive	45%	90%	85%				
Specificity	100%	87.10%	72.60%				
Gutierrez-Banos et al. [292]							
Sensitivity	69.70%	72.30%					
G1	43.80%	56.20%					
G2	62.10%	62.10%					
G3	90.30%	90.30%					
Superficial	55.70%	62%					
Invasive	85.70%	92.90%					
Specificity	93.20%	89.20%					

Table 4. Comparative Studies of Tumor Markers (Continued)

Immunocyt	Lewis X Ag	486p3/12	NMP-22	Telom. (TRAP)	Telom. (hTERT)	UBC-Rapid	UBC-IRMA	UroVysion
			75%				64%	
			73%				61%	
			72%				65%	
			81%				67%	
			73%				60%	
			100%				91%	
			73%				73%	
				46%				81%
				30%				36%
				48%				76%
				49%				97%
				42.90%				75.60%
				31%				95%
				91%				96%
								71%
								55%
								78%
								94%
								73.30%
								100%
								89%/94%
						48.70%	70.50%	
						33.30%	59.30%	
						51.90%	74.10%	
						62.50%	79.20%	
						44.80%	70.70%	
						60%	70%	
						79.30%	64.50%	
			76.30%					
			50%					
			69%					
			96.80%					
			65.20%					
			92.90%					
			90.50%					

Table 4. Comparative Studies of Tumor Markers (Continued)

Study	Cytology	BTA-Stat	BTA-TRAK	CYFRA 21-1	HA-HAase	HA test	Hemo-globin
Friedrich et al. [60]							
Sensitivity		67%					
G1		43%					
G2		70%					
G3		92%					
Superficial		69%					
Invasive		100%					
Specificity		78%					
Toma et al. [59]							
Sensitivity	84.60%	66.60%					
G1	42.90%	42.90%					
G2	87%	70.40%					
G3	75%	91.70%					
Superficial	NA	46.60%					
Invasive	80%	100%					
Specificity	80%	78.20%					
Serreta et al. [138]							
Sensitivity		60.80%	62.50%				
G1		50%	50%				
G2		50%	100%				
G3		67%	55%				
Superficial		50%	66.70%				
Invasive		100%	50%				
Specificity		64.70%	79.40%				
Lokeshwar et al. [38]							
Recurrent tumors							
Sensitivity		60.70%			94%		
G1		72.70%			90.90%		
G2		52.40%			100%		
G3		61.50%			92.30%		
Superficial		70.10%			94.70%		
Invasive		62.50%			87.50%		
Specificity		74%			63%*		
Schroeder et al. [58]							
Sensitivity	70.60%	52.50%			88.10%		50.80%
G1	50%	25%			75%		50%
G2	75%	46.10%			84.60%		50%
G3	72.70%	73.90%			95.70%		56.50%
Superficial	77.80%	45.70%			84.70%		58.70%
Invasive	50%	72.70%			100%		54.50%
Specificity	81%	76.70%			81%		78.20%

Table 4. Comparative Studies of Tumor Markers (Continued)

Immunocyt	Lewis X Ag	486p3/12	NMP-22	Telom. (TRAP)	Telom. (hTERT)	UBC-Rapid	UBC-IRMA	UroVysion
	96%	69%	69%					68%
	100%	86%	43%					57%
	96%	74%	70%					63%
	92%	42%	83%					83%
	97.40%	77%						64%
		33%						83%
	33%	76%	65%					89%
78.30%	95.50%	68.60%	68.50%					
85.70%	100%	85.70%	42.90%					
73.90%	96.30%	74.10%	70.40%					
83.30%	91.70%	41.70%	83.30%					
83.30%	83.40%	33.30%	83.30%					
73.80%	32.80%	76.40%	65.20%					
			70%					
			42.80%					
			63.10%					
			89.60%					
			69.80%					
			83.30%					
			55.50%					
						35.60%		
						12.50%		
						42.30%		
						34.80%		
						34.80%		
						36.4%		
						75%		

Table 4. Comparative Studies of Tumor Markers (Continued)

Study	Cytology	BTA-Stat	BTA-TRAK	CYFRA 21-1	HA-HAase	HA test	Hemo-globin
Hautmann et al. [64]							
Sensitivity	73.30%				83.30%		
G1	75%				50%		
G2	53.30%				87%		
G3	81.80%				91%		
Superficial	68%				80%		
Invasive	100%				100%		
Specificity	80%				78%		
Srougi et al. [209]							
Sensitivity	67%	75%				80%	
LMP	0%	33%				67%	
Low grade	59%	68%				82%	
High grade	78%	84%				82%	
Ta+ CIS	76%	73.70%				70.70%	
pT1-T4	83%	97%				89%	
Specificity	75%	71%				83%	
Bialkowska-Hobrzanska [263]							
Sensitivity	61.90%						
G1	20%						
G2	80%						
G3	66.60%						
Ta + CIS	54.50%						
T1 + T2	70%						
Specificity							

Table 4. Comparative Studies of Tumor Markers (Continued)

Immunocyt	Lewis X Ag	486p3/12	NMP-22	Telom. (TRAP)	Telom. (hTERT)	UBC-Rapid	UBC-IRMA	UroVysion
63.30%								
75%								
46.70%								
81.80%								
60%								
80%								
75%								
								73%
								0%
								45%
								94%
								73.70%
								97%
								79%
				48.60%	94.30%			
				10%	80%			
				44.40%	100%			
				85.70%	100%			
				33.30%	88.90%			
				64.70%	100%			
				100%	100%			

Serretta et al. compared the efficacy of the NMP-22, BTA-Stat, and BTA-TRAK tests in a cohort study of 170 patients, who were being followed for recurrent superficial bladder tumors [138]. The NMP-22, BTA-Stat, and BTA-TRAK tests had sensitivities of 55%, 62%, and 79%, respectively, for detecting bladder cancer recurrence. In this study, approximately 52% of patients were receiving adjuvant intravesical chemotherapy. All 3 tests showed higher false positive rates among these patients. This is not surprising, since during the course of chemotherapy there is cell death (releasing NMP-22 in urine) as well as inflammatory reaction (possibly causing the BTA-Stat and TRAK tests to be positive), which could lead to positive NMP-22, BTA-Stat and BTA-TRAK tests. The authors of this study concluded that bladder cancer monitoring using certain noninvasive tests should not be carried out during intravesical treatment.

As discussed in the earlier section, an RT-PCR assay that amplifies the human telomerase reverse transcriptase (hTERT) may be a better alternative to the TRAP assay for detecting bladder cancer. Bialkowska-Hobrzanska et al., in a prospective study involving a small number of bladder cancer patients (n = 35), directly compared the TRAP assay and hTERT/GAPDH RT-PCR to detect bladder cancer in a study of 35 patients [263]. In the hTERT/GAPDH RT-PCR assay, the hTERT message amplification is normalized to the amplification of GAPDH (a housekeeping gene), which eliminates disparity in results due to different amounts of exfoliated cells in different samples, differences in RNA extraction, etc. In this study the hTERT/GAPDH RT-PCR outperformed the TRAP assay by almost twofold, in terms of sensitivity (94.3% for hTERT/GAPDH versus 48.6% for TRAP assay, $P < 0.001$). The TRAP assay (43.8% and 52.6%) and hTERT (100% and 89.5%) had similar sensitivities in detecting primary and recurrent tumors. The sensitivity of urine cytology in this study was 61.9%. The hTERT/GAPDH had a significantly higher sensitivity (90%) in detecting G1 and G2 tumors than the TRAP assay (25%) and urine cytology (58.3%). The overall specificities of the hTERT/GAPDH RT-PCR (92%), TRAP assay (100%), and urine cytology (100%) were comparable. Thus, in this small study, the hTERT/GAPDH RT-PCR was significantly better than the TRAP assay for detecting bladder cancer.

In contrast to the Bialkowska-Hobrzanska study, de Kok et al. found that the sensitivity of the TRAP assay (29%) and hTERT real-time (i.e., quantitative) RT-PCR (24%) was poor [261]. The authors concluded that several variables including interlaboratory differences in sample storage and sample processing and the presence of occult blood may lead to poor reproducibility of the TRAP assay and hTERT RT-PCR. In this study, only patients with bladder cancer were studied, and, hence, evaluation of specificity was not performed.

In a case-control study involving 44 bladder cancer patients and 26 age-matched controls with a wide variety of clinical disorders, Cassel et al. evaluated the performance of TRAP-ELISA and cytokeratin-20 RT-PCR to detect bladder cancer [193]. The clinical disorders included BPH, perichondroitis, renal colic, bilateral inguinal hernia, epilepsy, prostatectomy, impotence, facialis, and bowel obstruction. In this study, the telomerase activity and cytokeratin-20 RT-PCR had 84.1% and 81.8% sensitivity, respectively, for detecting bladder cancer. However, among the urological and non-urological cases, the specificity of telomerase activity (24.1%) and cytokeratin-20 (55.2%) was low. These results demonstrate that telomerase activity and cytokeratin-20 expression are not specific for malignancy and may be detected in many benign cases. Therefore, the use of these molecules as potential markers for bladder cancer needs to be carefully evaluated.

Halling et al., in a case-control study of 265 individuals which included 146 patients with a history of bladder cancer and 119 benign genitourinary conditions, compared the sensitivity and specificity of BTA-Stat, UroVysion, hemoglobin dipstick testing, and the telomerase TRAP assay. The sensitivities of UroVysion (81%), BTA-Stat (78%), and hemoglobin dipstick (74%) were similar but that of telomerase was low (36%). The sensitivity of all tests to detect G1 tumor was low and ranged between 30% and 50%; UroVysion had 36% sensitivity to detect G1 tumors. Except for telomerase, the sensitivity of the other 3 tests increased with both tumor grade and stage. The specificity of UroVysion was the highest (96%), followed by telomerase (91%), BTA-Stat (74%), and hemoglobin dipstick (51%). Based on these studies, the authors concluded that the UroVysion test is a promising new marker for the detection of bladder cancer [124].

In a case-control prospective multi-center study involving 176 patients with a history of bladder cancer and 265 control individuals (both healthy individuals and patients with non-bladder cancer conditions), Sarosdy et al. compared the performance of BTA-Stat, UroVysion, and voided urine cytology [47]. In contrast to the study by Halling et al., the UroVysion test had significantly higher sensitivity

(71%) than BTA-Stat (50%), with cytology having 26% sensitivity. The specificity of only UroVysion test was reported in this study and was very high (94.6%). Consistent with earlier reports, UroVysion (55%), BTA-Stat (27%), and cytology (18%) had low sensitivities to detect low grade tumors. However, the sensitivity of BTA-Stat and UroVysion increased with tumor grade and stage. In BCG-treated patients, the sensitivities of both UroVysion (55%) and BTA-Stat (41%) were lower than cytology (60%). The specificity of UroVysion in BCG-treated patients (89%) was not only higher than BTA-Stat (75%), but was also higher than cytology (71%). Based on these studies, Sarosdy et al. concluded that the sensitivity of UroVysion is at least comparable to BTA-Stat and has specificity comparable to cytology.

Friedrich et al. and Toma et al. compared the sensitivity and specificity of Lewis X antigen and 486p3/12 markers with BTA-Stat, NMP-22, UroVysion, and Immunocyt [59,60]. In both studies, the criteria to detect a positive UroVysion test were different from those reported in studies by Halling et al. and Sarosdy et al. [47,60]. In a cohort of 103 patients which included 55 first time patients suspected of having bladder cancer and 48 patients with a history of bladder cancer, Friedrich et al. found that the sensitivity of Lewis X Ag was the highest (96%), followed by NMP-22/486p3/12 (both at 69%), UroVysion (68%), and BTA-Stat (67%). However, Lewis X Ag had the lowest specificity. The specificity of UroVysion was the highest (89%), followed by BTA-Stat (78%), 486p3/12 (76%), NMP-22 (65%), and Lewis X Ag (33%). The sensitivities of all markers increased with tumor grade and stage, particularly in BTA-Stat, NMP-22, and UroVysion. Toma et al. conducted a cohort study involving 126 patients among whom there were 47 patients suspected of bladder cancer and 79 patients with a history of bladder cancer. For the Immunocyt test, 1 or more cells with red and/or green fluorescence was taken as a positive inference. The sensitivity of Lewis X Ag was the highest (95.5%), followed by cytology (84.6%), Immunocyt (78.3%), UroVysion (68.8%), 486p3/12 (68.6%), NMP-22 (68.5%), and BTA-Stat (66.6%). As observed in the study by Friedrich et al., the specificity of UroVysion was the highest (89.1%), followed by cytology (80%), BTA-Stat (78.2%), 486p3/12 (76.4%), Immunocyt (73.8%), NMP-22 (65.2%), and Lewis X Ag (32.8%) [15]. Except for Lewis X Ag, the sensitivity of all markers including cytology increased with tumor grade. These studies show that, although Lewis X Ag is a sensitive marker for detecting bladder cancer, it is not very specific, and that the UroVysion test has low sensitivity to detect low grade tumors.

Lokeshwar et al. compared the performance of the HA-HAase test with the BTA-Stat in 26 patients with a history of bladder cancer, which were followed over a 4-year period (111 urine specimens). [38] These patients were monitored over a course of 4 years. The HA-HAase and BTA-Stat tests had 94% and 61% sensitivity, 63% and 74% specificity, and 87% and 64% accuracy, respectively. The HA-HAase and the BTA-Stat tests had 89% and 88% PPV and 77% and 38% NPV for detecting bladder cancer. The HA-HAase test had 91%, 100%, and 92.3% sensitivity for detecting G1, G2, and G3 bladder tumors, respectively. The BTA-Stat test showed 73%, 52%, and 62% sensitivity for detecting G1, G2, and G3 bladder tumors. In this study, 60% of the false positive cases on the HA-HAase test recurred within 4.7 months. However, during the same time period, only 12% of the true negative cases recurred. Thus, a false positive HA-HAase test carried a ten-fold risk of recurrence within 4.7 months (risk ratio = 10.2; OR = 24; $P = 0.004$). In contrast, a false positive BTA-Stat test did not carry any significant risk of recurrence within 4.7 months (risk ratio = 1.4, OR = 1.5; $P = 0.756$). This study concluded that the HA-HAase test is superior to the BTA-Stat in monitoring and predicting future bladder cancer recurrence. In the same study, a comparison between the performance of the HA-HAase and BTA-Stat tests was conducted for screening of 401 former Department of Energy workers who had a possible exposure to bladder carcinogens for at least 1 year. The HA-HAase and BTA-Stat tests were positive among 14% and 17% of the individuals, respectively. Sixty-three percent of the positives on the BTA-Stat compared to only 25% of the positives on the HA-HAase test had abnormal urinalyses or benign urologic conditions. It should be noted that even after a rigorous follow-up, only 29 individuals positive on either 1 or both HA-HAase and BTA-Stat tests underwent cystoscopy and only 20, who were negative for bladder cancer, reported back the results. This study suggests that noninvasive tests with low false positive rates could be used for bladder cancer screening. But, more importantly, it also reveals some of the challenges in terms of patient follow-up when conducting screening trials involving biomarkers.

Schroeder et al. compared the accuracy of HA-HAase, BTA-Stat, UBC-Rapid, hemoglobin dipstick, and cytology to detect bladder cancer in a retrospective cohort study involving 138 urine specimens from 115 patients suspected of bladder cancer

[58]. The sensitivity of the HA-HAase test (88.1%) was the highest followed by cytology (70.6%), BTA-Stat (52.5%), hemoglobin dipstick (50.8%), and UBC-Rapid (35.6%). The specificities of all markers were comparable: HA-HAase/cytology was 81%, hemoglobin dipstick 78.2%, BTA-Stat 76.7%, and UBC-Rapid 75%. The sensitivities of all markers increased with tumor grade; the most striking increase was observed for BTA-Stat (G1, 25%; G2, 46.1%; and G3, 73.9%). The sensitivity of BTA-Stat also increased with tumor stage. Based on these results, the authors concluded that the HA-HAase test is superior to cytology, BTA-Stat, hemoglobin dipstick, and UBC-Rapid for detecting bladder cancer.

Hautmann et al., in a retrospective cohort study involving 94 consecutive patients, compared the accuracies of cytology, Immunocyt, and the HA-HAase test. The prevalence of bladder cancer in this study was 31%, and it included mostly patients with recurrence. The sensitivity of the HA-HAase urine test (83.3%) was significantly higher than Immunocyt (63.3%) and cytology (73%). Among patients without bladder cancer, the majority were patients with a history of bladder cancer, and the specificities of all of the 3 markers were comparable (HA-HAase test, 78.1%; Immunocyt, 75%; and cytology, 79.7%) [64].

Srougi et al. compared the accuracy of the HA test (hyaluronic acid detection test part of the HA-HAase test), UroVysion, BTA-Stat, and cytology in a prospective study involving bladder cancer patients with either primary or recurrent tumors [209]. The specificity of these tests was determined in patients with a history of bladder cancer but no evidence at the time of testing and patients with benign prostatic hyperplasia. The sensitivity of the HA test was the highest (83%), followed by BTA-Stat (75%), UroVysion (73%), and cytology (67%). The specificity of all of the tests was comparable among patients with a history of bladder cancer and benign prostatic hyperplasia: 86% versus 79% for HA, 82% versus 76% for UroVysion, 70% versus 72% for BTA-Stat, and 74% versus 74% for cytology. The combination of the HA test and UroVysion test had the highest sensitivity at 95%. This is interesting since the combination of the HA test with the HAase test (HA-HAase test) also has greater than 90% sensitivity [198,199]. This study found that the UroVysion test has high sensitivity to detect high grade tumors (94%). The HAase test has been shown to preferentially detect high grade tumors [198,199]. This may be the reason why the combination of the HA test with either UroVysion or HAase test has higher sensitivity than the individual tests alone.

Van Rhijn et al. compared the efficacy of microsatellite DNA testing with the BTA-Stat and voided urine cytology in 93 patients [56]. The microsatellite DNA analysis, BTA-Stat, and cytology had 74%, 56%, and 22% sensitivities and 82%, 79%, and 95% specificities, respectively. In this study, data on the comparative analyses of the sensitivity of microsatellite DNA analysis, BTA-Stat, and cytology according to tumor grade and stage were not presented. However, microsatellite DNA analysis missed all 11 TaG1 tumors. Interestingly, 55% of the false positive cases on the microsatellite DNA test recurred within 6 months. In contrast, only 11.6% of the true negative cases recurred during that time. Thus, the corrected specificity of the test is 94%. It should be noted, however, that 14 patients were eliminated from the study either due to insufficient DNA quality or abundance of leukocytes, both of which render the results of microsatellite testing unreliable. Based on these results, the authors concluded that microsatellite analysis, a DNA test in urine, reliably signals the presence of recurrent bladder cancer, sometimes even before cystoscopic evidence of disease.

Summary

Comparative studies show that noninvasive tests are more sensitive than cytology. Some of these tests can also detect bladder cancer recurrence before it can be detected clinically. Thus, noninvasive tests with a high sensitivity and reasonable specificity can be used in a surveillance setting to reduce the number of cystoscopies performed each year for monitoring bladder tumor recurrence.

A few studies have evaluated the usefulness of bladder tumor markers in a screening setting. The use of noninvasive tests for screening a high-risk population could be made economically sound by choosing noninvasive tests that have high specificity and reasonable sensitivity. Furthermore, concurrently performing urinalyses on each specimen and having knowledge about patients' clinical histories might reveal conditions that could render a false positive result on the noninvasive tests.

VIII. PROGNOSTIC MARKERS FOR BLADDER CANCER

(Including markers for predicting recurrence, progression, disease-specific survival, and response to chemotherapy and radiotherapy).

The current clinical and pathological parameters, such as tumor grade, stage, and vascular and lymphatic extension, provide important prognostic information, yet still have limited ability to predict tumor recurrence, progression, development of metastases, and response to therapy or survival. A substantial number of potential molecular markers for the prediction of clinical course and outcome have been identified by recent studies of molecular biology and genetics. However, no single marker is reliable enough to predict the clinical course and outcome of bladder cancers and to replace standard clinical and pathological parameters.

For new candidate prognostic markers or tests to be of clinical use, they must add some predictive capacity beyond what standard clinical and pathologic parameters offer. To achieve this goal, at the least, using sufficient numbers of subjects in the relevant staging and grading categories, a multivariate analysis to determine each marker's prognostic independence is required [294]. It is noteworthy that the same criteria that apply to an ideal tumor also apply to prognostic markers. However, at the present time none of the prognostic markers have been tested as rigourously as have been many of the diagnostic urine markers. In particular, few prospective trials have been conducted to test the performance of potential prognostic markers in side-by-side comparisons. Unlike definitive strategies that are in place for the development of diagnostic markers for bladder cancer, there is a lack of strategies for the development of prognostic markers. The performance of a prognostic marker may also be complicated due to the impact of therapy on the course of the disease. These probably are some of the reasons why prognostic markers have not been implemented in the management of patients with bladder cancer.

In this section, representative bladder cancer prognostic markers are presented, and the relevant literatures focusing on prognostic significance are summarized, while extensive description of the biological role of each marker is omitted.

1. Chromosomal Alterations and Allelic Deletion (Loss of Heterozygosity)

• *DNA and FISH Analysis*

Recent advances in molecular genetic methodologies, such as loss of heterozygosity (LOH) analysis, FISH analysis, and comparative genomic hybridization, have made it possible to identify the loss of several potential tumor suppressor genes in bladder cancer. Pycha et al. examined chromosome 7, 9, and 17 alterations using FISH, and p53 positivity in 190 muscle-invasive bladder cancer cases (94 urothelial carcinomas and 96 squamous cell carcinomas). Although numerical chromosomal alterations were associated with progression-free survival, the alterations were not independent prognostic factors for disease progression [295]. LOH studies have shown that the loss of 17p, 3p, 13q, 18q, or 10q is found more frequently in high grade, high stage bladder cancer [283]. However, no large prospective study has demonstrated that this type of genetic analysis has prognostic value in patients with bladder cancer. The complicated laboratory process required in this type of analysis has hampered wide application in clinical settings and a large scale study to date.

2. Oncogenes

a) EGFR (Epidermal Growth Factor Receptor)

Several investigators have shown a positive association between overexpression of EGFR and high grade, high stage bladder cancer, indicating that EGFR expression identified by IHC (immunohistochemistry) is an independent prognostic factor in patients with advanced bladder cancer [296-299]. Furthermore, the prospective evaluation of 212 patients with newly diagnosed bladder cancer confirmed EGFR expression as an independent predictor of survival and stage progression [300]. In contrast, although the EGFR expression by IHC was one of the significant predictors of progression in patients with Ta or T1 bladder tumors by univariate analysis, it was not a significant predictor by multivariate analysis [301]. Furthermore, EGFR expression by IHC was seen in 86% of 43 invasive bladder cancer cases treated by cystectomy and had no prognostic significance [302].

b) HER-2

The product of the HER-2/neu (c-erb-B2) oncogene was found to be expressed frequently in urinary bladder carcinoma [303], and overexpression of HER-2

protein was shown to correlate with increased tumor grade, cancer-specific survival, and incidence of metastatic disease, and was an independent prognostic factor in a retrospective IHC study of 88 patients with muscle-invasive bladder cancer [304]. Kruger et al. also reported that HER-2 product was a significant and independent prognostic factor of tumor-specific survival in patients with muscle-invasive bladder cancer by multivariate analysis [305]. Other authors, however, found, in evaluations of 95 and 89 patients [306,307], that determination of HER-2 by IHC provided no additional prognostic information over tumor stage and grade for bladder cancer. In an IHC study of 80 cases of muscle-invasive bladder cancer treated by radical cystectomy, there was no significant difference in the median survival between HER-2-negative patients and HER-2-positive patients (P = 0.46) [308]. In addition, they showed no significant difference in the median survival between patients with HER-2-negative lymph nodes and those with HER-2-positive lymph nodes (P = 0.39) [308]. Therefore, it was claimed that HER-2 overexpression did not predict survival when analyzed by its presence either in the primary tumor or in the regional lymph node metastasis [308].

In summary, the level of expression and the prognostic significance of HER-2 protein in urothelial cancer varies among different studies, with some revealing no prognostic relevance and others suggesting a better or worse prognosis [309].

c) H-Ras

Mutations in the H-Ras gene at codons 12 and 61 have been implicated in the development and progression in up to 10% of bladder cancers [310]. However, no study has shown any prognostic value in the presence of mutation. A potential prognostic role of cH-Ras protein overexpression in cancer patients has been suggested by Fontana et al., in which the overexpression was correlated with early recurrence in patients with superficial Ta or T1 bladder cancer [311]. However, this prognostic effect was not clearly shown in other studies, and contradictory results have been observed as well [312, 313].

d) Bcl-2

Shiina et al. found no significant correlation between bcl-2 expression by IHC and overall survival in 77 patients who received cystectomy [314]. In an analysis of 109 patients with invasive bladder carcinoma treated with preoperative radiation therapy without concurrent chemotherapy, Pollack et al. demonstrated that bcl-2 overexpression was significantly associated with disease progression and upstaging of the tumor during radiation therapy [23]. However, bcl-2 overexpression had no significant effect on response to a combination of platinum-based chemotherapy and radiation therapy [315,316]. In patients treated with TUR, bcl-2 expression did not offer any prognostic information in predicting either recurrence or progression over conventional prognostic factors [317].

e) MDM-2

Although amplification of the mdm-2 gene is infrequently seen in bladder cancer [318], mdm-2 overexpression by IHC has been reported in 20% to 30% of bladder tumors (n = 87) [319]. However, the prognostic value of mdm-2 overexpression remains unknown.

f) FGFR3

Molecular genetic analyses have shown the frequent presence of FGFR3 point mutation in bladder cancers, especially in those with a low grade and stage phenotype [320,321]. The presence of FGFR3 mutation might be a prognostic variable [30]. However, no large study to determine whether FGFR3 mutation has significant prognostic independence is available at present.

g) c-myc

Although c-myc overexpression has been reported more frequently in high grade tumors, no correlation with recurrence, progression, or survival has been demonstrated [323-325].

3. Tumor Suppressor Genes

a) p53

The tumor suppressor p53 plays a key role in regulating cell cycle progression and apoptosis under genotoxic conditions. The p53 gene mutations are the most common genetic defect in human cancers [326]. Mutated p53 protein often results in a prolonged half-life compared to the wild-type p53 and accumulates in the cell nuclei; it can be detected by IHC. The comparison of p53 detection by IHC and molecular analysis, including the PCR-SSCP method and DNA sequencing, has shown that p53 accumulation correlates with the mutated p53 gene [327]. However, there may be a considerable number of discordant cases of p53 gene mutation confirmed by DNA sequencing and “altered p53” judged by IHC [328]. Owing to the complicated process of molecular analysis, many groups have investigated the prognostic value of p53 by IHC. However, a recent study

of the Bladder Cancer Marker Network showed that, although there was a high degree of agreement for negative p53 expression or strongly p53-positive samples, a high level of variability between laboratories and observers existed in the gray zone of low p53 positivity between 1% and 20% [294]. Taken together, one should be cautious in interpreting a large amount of literature concerning the association between p53 expression by IHC and clinical outcome.

1. p53 as a Marker in Patients With Muscle-Invasive Bladder Cancer

One large study of 253 patients treated by radical cystectomy indicated that p53 positivity in the nucleus by IHC was an independent predictor of recurrence and overall survival in a multivariable analysis stratified according to grade, pathologic stage, and lymph node status [329]. However, in a cohort of 59 patients with pathologically confirmed lymph node-positive bladder cancer treated with cystectomy, p53 positivity was not predictive of disease-free survival in node-positive disease [330]. In a study of 212 bladder cancer patients, a multivariate survival analysis indicated p53 positivity had no independent prognostic value over clinical stage and mitotic index [331]. The Bladder Cancer Marker Network also evaluated a series of 109 patients with G2 or G3, T2 to T3 disease and found no prognostic value of p53 staining [332]. In a study of 109 patients with pT2N0M0 bilharzial-related bladder cancer, p53, along with MIB-1(Ki-67), Bcl-x, and BAX, was an independent predictor for progression-free survival in urothelial carcinoma group (n = 49), and p53 positivity and PCNA were independent predictors in the squamous cell carcinoma group (n = 60) [333]. Among the contradictory results of many studies of p53 status as a prognostic variable in muscle-invasive bladder cancer, Schmitz-Dräger et al. reviewed all published literature on the association of p53 positivity and prognosis of bladder cancer patients in a recent meta-analysis [334]. In only 2 out of the 7 trials in muscle-invasive bladder cancer was p53 regarded as an independent prognostic marker of disease progression [42].

2. p53 as a Prognostic Marker in Patients With Tis to T1 Bladder Cancer

In a study including 43 patients with T1 bladder cancer, patients having tumors with 20% or more tumor cells with p53 positivity had a significantly lower progression-free interval [335], and this finding was supported by several other studies. In a more recent study of 175 patients with T1 bladder cancer, p53 positivity was one of the independent cancer-related survival variables [336]. In 102 high-risk patients with Tis to T1 tumors treated with BCG, p53 overexpression was shown to be an independent predictor of recurrence [337]. Furthermore, in a study including 198 Tis to T1 patients who received adjuvant or therapeutic BCG therapy, p53 positivity after BCG therapy was the only independent marker of disease progression in a subgroup of patients with residual disease after BCG therapy [338].

While the above-mentioned studies have demonstrated a significant predictive value in p53 expression in patients with Tis to T1 bladder cancer, there are several studies that indicate absence of such predictive value. Peyromaure et al. reported that p53 positivity had no predictive value for recurrence and progression in 29 patients with T1G3 tumors treated with TUR followed by intravesical BCG [339]. The role of p53 positivity as an independent predictive marker in patients with BCG-treated superficial bladder cancer was also denied in another study [340]. In a study of 93 patients with G1 or G2, Ta to T1 bladder cancer, the Ki-67 labeling index, but not p53 positivity or Bcl-2 overexpression, was the only significant prognostic indicator for recurrence in univariate and multivariate analyses [341]. The absence of a role of p53 positivity as an independent prognostic variable for recurrence or progression in Ta or T1 bladder cancer has been reported in several studies [342-344].

The role of p53 positivity as an independent prognostic marker in Tis or T1 bladder cancer patients with or without BCG treatment has not been clearly demonstrated at present.? However, a meta-analysis by Schmitz-Dräger et al. showed about a 50% rate of positive multivariate analyses of p53 positivity as a prognostic marker of progression in T1 bladder cancer [334].

3. p53 as a Response Marker to Chemotherapy or Radiotherapy

A study in 111 patients with invasive bladder cancer treated with neoadjuvant MVAC therapy suggested that p53-positive tumors have a lower response to chemotherapy [345]. In support of this finding, Kakehi et al. reported that p53-negative tumors responded favorably to cisplatin-based combination chemotherapy in a cohort of 60 muscle-invasive or metastatic bladder cancer patients [346].

In another study of 60 patients treated with cisplatin-based systemic chemotherapy for locally advanced and/or metastatic urothelial cancer, p53 negativity

was correlated with complete or partial remission following inductive chemotherapy, indicating that tumors with intact p53 responded significantly better [347]. In contrast, one preliminary study showed that p53-positive tumors responded better to adjuvant chemotherapy in patients treated by radical cystectomy [348]. In 50 primary bladder cancers with metastatic lesions, p53 positivity was not correlated with response to cisplatin-based chemotherapy or surviva [349].

Despite the lack of consistent published results with regard to p53 status and response to chemotherapy, appropriate studies using p53 with or without other markers may be particularly helpful in treatment decisions as they relate to using neoadjuvant and adjuvant chemotherapy. One large prospective study is currently enrolling patients with p53-positive organ-confined bladder cancer treated by radical cystectomy with randomization to chemotherapy or observation.

In a study of 109 patients treated preoperatively with 50 Gy radiation therapy followed by radical cystectomy, p53 positivity was not correlated with radiation response or overall survival. Ogura et al. also showed no significant correlation between p53 positivity and radiosensitivity in 60 patients with muscle-invasive bladder cancer [350]. In another study of 131 patients with T2 to T4 bladder cancer treated with external full-dose radiotherapy, multivariate analysis indicated that the T category (T2 or T3 vs. T4), histological grade, and p21 expression, but not p53 positivity, were independent prognostic factors for overall survival [351]. The lack of association between p53 positivity and response to radiation therapy was also found in 2 other studies [315,352]. The results of these studies show the lack of prognostic value of p53 expression with respect to radiation response in bladder cancer.

4. Combination of p53 and Other Potential Markers

Because of the significance of p53 alterations in high grade and advanced bladder cancers, the significance of p53 expression combined with other potential markers was explored in several studies. Cote et al. examined p53 and Rb protein expression by IHC in bladder cancers from 185 patients who underwent radical cystectomy, and reported that patients having tumors with both p53 and Rb alterations had significantly increased rates of recurrence ($P < 0.0001$) and survival ($P < 0.0001$) compared to those with no alterations, and patients with alterations in only 1 of these proteins had intermediate rates of recurrence and survival [353]. In another study examining p53 and Rb expression in 59 Ta or T1 bladder cancers, there was more marked increase in progression ($P = 0.00005$) and decreased overall survival ($P = 0.0004$) in patients having tumors with alterations in both, after controlling for tumor stage, tumor grade, and suspicion of vascular invasion [354]. These studies suggest an independent yet synergistic role for p53 and Rb expression in the progression of bladder cancer.

More recently, Chatterjee et al. examined p53, p21, and pRb expression in 154 patients with high grade superficial or muscle-invasive bladder cancers, and reported that the number of altered markers (p53, p21, and pRB) were significantly associated with time to recurrence and overall survival by multivariate analysis [355]. In another study examining p53, p21, pRB, and p16 expression in bladder cancers in 80 patients who underwent radical cystectomy, the incremental number of altered markers was independently associated with an increased risk of bladder cancer progression and mortality [356].

Although these studies are retrospective and relatively small in number of subjects, these results indicate that the analysis of the interaction of different cell cycle regulatory proteins in combination with p53 will further increase the benefit of p53 determination as a prognostic marker.

b) Rb

In a small cohort of 38 patients with muscle-invasive tumors, Cordon-Cardo et al. reported that overall survival, independent of stage, was higher in patients with pRb-normal tumors than in those with pRb-altered (negative or weak) tumors [357]. Logothetis et al. also reported a significantly poorer tumor-free survival rate in those who had a tumor with an altered Rb protein in 43 patients with locally-advanced bladder cancer treated by surgery and chemotherapy [358]. In an IHC study of 45 patients with T1 bladder tumors, loss of Rb protein expression combined with altered p53 expression was associated with significantly poorer progression-free survival [359].

4. Cell Cycle Regulators

a) p21

In an IHC study for p21 and p53 expression in 242 patients who underwent cystectomy, multivariate analysis showed that p21 IHC labeling was an independent predictor of tumor recurrence and survival [68]. Furthermore, patients with p53-altered/p21-

negative tumors demonstrated a higher rate of recurrence and worse survival compared with those with p53-altered/p21-positive tumors [360]. In 96 patients with superficial urothelial carcinoma, multivariate analysis indicated that negative p21 expression was an independent predictor of reduced overall survival, but not of disease-free survival [361]. In contrast, Lipponen et al. reported that low p21 positivity was associated with a better prognosis for Ta and T1 tumors (n = 186), although not significantly [362]. In a multicenter study of 207 patients with superficial (Ta or T1) bladder cancer, p21 expression by IHC provided no additional prognostic information compared with established prognostic factors for predicting the risk of tumor recurrence and progressive disease [363]. Furthermore, high p21 expression (>10%) was associated with shorter recurrence-free intervals in 47 patients with superficial bladder cancer who were treated with 6 weekly intravesical BCG instillations [363]. Therefore, to date, the role of p21 expression as a prognostic variable remains controversial and unknown.

b) p27

In 120 consecutive cases of urothelial carcinoma, p27 levels were significantly higher in low grade, superficial, papillary, and slowly-proliferating tumors [364]. Decreased p27 expression was associated with poor overall and post-relapse survival, and the Ki-67/p27 status had the strongest bearing on the overall survival of patients with muscle-invasive tumors in a multivariate analysis [72]. In a series of 96 patients with superficial (pTa or T1) bladder cancer, low p27 expression by IHC was significantly correlated with decreased disease-free survival (P = 0.0003 by log-rank test) and overall survival and was an independent predictor of reduced disease-free survival, second only to tumor stage [365]. In 145 consecutive bladder cancer patients, low IHC p27 expression levels were independent predictors of shortened disease-free and overall survival in multivariate analysis [366]. Furthermore, significant correlations were found between low IHC p27 expression and early recurrence in 86 patients with superficial disease (Ta or T1) [366].

c) Ki-67 (MIB-1)

The Ki-67 antigen detected by IHC, using the monoclonal antibodies Ki-67 and MIB-1, accumulates in the nuclei of proliferating cells from the G1 phase to mitosis, but not in the nuclei of quiescent or resting cells [367]. There are a large number of studies that define Ki-67 as an independent prognostic marker of bladder cancer progression and recurrence in multivariate analysis. In 159 patients with Ta or T1 bladder cancer, a high Ki-67 index (≥18%) and multifocality were significantly related to recurrence and progression-free survival and were independent prognostic factors in the multivariate analysis [368]. In a study examining the prognostic value of MIB-1 score, p53, EGFR, mitotic index, and papillary status in 207 patients with Ta or T1 bladder cancer, only MIB-1 score and papillary status were independent predictors of progressive disease- and cancer-specific survival by multivariate analysis [369]. Stavropoulos et al. evaluated p53, bcl-2, and Ki-67 expression in 58 Ta or T1 patients, and found that the Ki-67 index was the only independent prognostic factor for recurrence in patients treated with TUR alone [370]. A study in 114 bladder cancer patients showed that Ki-67 expression, as well as tumor stage and p53 positivity, provides independent prognostic information in relation to progression-free and disease-specific survival in multivariate analysis [371]. In a cohort of 192 patients with apparently superficial Ta or T1 urothelial carcinoma, only Ki-67 and multifocality were found to be independent prognostic factors of recurrence in multivariate analysis, whereas p53 positivity was not significant [342]. In an analysis of 319 patients, Ki-67 index was an independent prognostic variable of recurrence of large pTa or T1 tumors [343]. Furthermore, in a study examining Ki-67, bcl-2, and p53 expression in 93 cases of primary, low grade, superficial bladder cancer, the Ki-67 labeling index was the only significant prognostic indicator in predicting tumor recurrence in univariate and multivariate analysis [341].

These documents rather consistently indicate that Ki-67 expression is a promising marker for recurrence and progression in superficial bladder cancer. Larger prospective studies with a standardized method and positive criteria, especially of the cutoff value of the labeling index, may be warranted. In addition, Ki-67 expression as a prognostic marker in patients with locally-advanced or metastatic bladder cancer remains unconfirmed.

d) Cyclin D1 and E

Although cyclin D1 is a positive regulator of the cell cycle, Sgambato et al. reported that patients with Ta or T1 tumors with low cyclin D1 expression, along with low p27 and high Ki-67 expression, had extremely high rates of recurrence [372]. In an IHC study of 392 bladder specimens, cyclin D1 positivity was not linked to a risk of recurrence or tumor progression, in patients with either pTa or pT1 tumors [373]. In a multicenter IHC study of 207 patients with superficial (Ta or T1) bladder cancer, the cyclin

D1 expression level was an independent predictor of tumor recurrence, but provided no additional prognostic information for predicting the risk of progressive disease [363].

A study using a tissue microarray of 2317 specimens from 1842 patients with bladder cancer, staged Ta through T3, demonstrated that low cyclin E expression was associated with poor overall survival in all patients, but had no prognostic impact independent of stage [82]. In a cohort of 145 consecutive bladder cancer patients, low cyclin E expression was one of the independent predictors of overall survival [366].

5. Angiogenesis-related Factors

Although numerous angiogenic factors have been described, the relative importance of individual angiogenic factors in the majority of tumor types remains largely unclear.

a) VEGF

Vascular endothelial growth factor (VEGF) is present in higher concentrations in the urine of patients with bladder cancer than in that of controls, and urinary VEGF levels as determined by ELISA are correlated with tumor recurrence rates in patients with Ta and T1 disease [375]. On the other hand, in a study of 185 patients with pTa or T1 tumors, VEGF expression by IHC was not correlated with a risk of tumor recurrence or with patient survival [376]. Inoue et al. reported that VEGF expression as determined by in situ hybridization was an independent prognostic factor for disease recurrence by multivariate analysis in 55 patients with muscle-invasive bladder cancer treated with neoadjuvant MVAC chemotherapy and radical cystectomy [85].

b) Thrombospondin-1 (TSP-1)

TSP-1 is an extracellular matrix glycoprotein that is a potent inhibitor of angiogenesis. An IHC study evaluating thrombospondin-1 expression in 163 cystectomy specimens showed that decreased TSP-1 expression was an independent predictor of disease recurrence and overall survival after stratifying for tumor stage, lymph node status, and histologic grade [378]. Interestingly, TSP-1 expression was significantly associated with p53 expression status and microvessel density counts [378].

c) COX-2

One IHC study of 108 patients treated with radical cystectomy reported that COX-2 expression was found in 31% of the cases and was correlated with local invasion, lymphovascular invasion, and recurrence [379]. However, its expression was not an independent prognostic marker for survival [379]. An IHC study including 39 patients with CIS and 34 with stage T1 tumors showed that COX-2 expression was not associated with clinical outcome in the T1 patients [380]. In the CIS patients, COX-2 expression was significantly associated with disease recurrence using cutoffs of 0% and greater than 10% positive cells and with disease progression using a greater than 20% cutoff [88]. In another small study of 37 patients with initial T1G3 bladder cancer, who had undergone complete TUR followed by 6 weeks of intravesical instillation of BCG, COX-2 expression was a statistically significant variable in predicting both recurrence and disease progression [381].

6. Extracellular Matrix, Adhesion Molecules, Cell Surface Markers, and Related Proteins

a) Matrix Metalloproteinase (MMP) and Tissue Inhibitors of Matrix Metalloproteinase (TIMP)

A preliminary study evaluating the expression of MMP-2, TIMP-2, and membrane-type matrix metalloproteinase-1 (MT1-MMP) by RT-PCR analysis in 41 bladder cancer patients indicated that high levels of MMP-2, TIMP-2, and MT-1-MMP expression were strongly associated with decreased survival [382]. In a study of 97 urothelial cancer patients, the serum MMP-2/TIMP-2 ratio, as determined by enzyme immunoassay, was a significant and independent indicator of recurrence in advanced urothelial cancer patients in univariate and multivariate analyses [383]. It remains unknown whether evaluation of the balance between the activity of MMPs and that of their inhibitors (i.e., TIMP) in serum or tissues can provide distinct information regarding progression in patients with bladder cancer.

b) E-cadherin

Decreased E-cadherin expression is generally correlated with increased muscle invasion and distant metastasis as well as with higher tumor grade and stage in patients with bladder cancer [384,385]. E-cadherin expression has been associated with overall survival and recurrence-free survival [384,386-388] In a cohort of 77 patients who underwent radical cystectomy, E-cadherin expression by IHC was significantly associated with disease progression and cancer-specific survival, and E-cadherin and stage were independent predictors of disease progression [389].

c) CD44

CD44 is a widely expressed cell surface adhesion molecule involved in cell–cell and cell–matrix interactions. The variant exons (CD44v) are expressed differentially according to cell and tissue type. Recent data suggest that the ratio of the mRNA level of the splice variant form of CD44 (=CD44v6-10) to that of standard CD44 was closely associated with the presence of tumor or with tumor progression [390,391], indicating that the CD44 mRNA variant may be a potential marker for bladder cancer screening.

d) Urokinase-type Plasminogen Activator (u-PA)

Hasui et al. evaluated u-PA content in tumor tissue in 52 patients undergoing TUR, and the multivariate analysis indicated that elevated u-PA content was the most important risk factor for invasion and metastasis, compared with tumor stage, grade, multiplicity, and size [392]. In a study including 51 patients who underwent radical cystectomy, preoperative plasma uPA level, but not urinary uPA level, was independently associated with metastases to regional lymph nodes, lymphovascular invasion, disease progression, and disease-specific survival [393].

e) Multidrug Resistance (MDR)-related Proteins (as a response marker)

Several multidrug resistance (MDR)-related proteins, such as P-glycoprotein (P-gp), multidrug resistance protein 1 (MRP1), breast cancer resistance protein (BCRP), and lung cancer resistance-related protein/major vault protein (LRP/MVP), have been identified. The relationship between chemo-resistance and the expression level of these proteins has been investigated in many studies [394-398]. However, no large study to date has provided conclusive data on their evaluation as chemosensitivity markers in clinical settings.

Summary

Although significant correlations between various laboratory markers and tumor progression have been demonstrated, these tests have not been adopted into standard practice yet and should not significantly influence treatment decisions for individual patients.

The usefulness of the currently available molecular markers as independent prognostic markers still has to be determined in large prospective comparative studies.

Among the markers described in this section, p53 and Ki-67 labeling seem to be the most extensively studied and may be promising molecular markers in predicting recurrence as well as progression of bladder cancer. However, even for p53 and Ki-67, the data is still heterogeneous, because of the lack of definitive criteria for test positivity, a clearly defined patient population, required clinical and pathological standard tests for the staging and grading of each tumor, and clearly defined endpoints and statistical methods.

As for the methodology, recent advances in molecular biology have provided various promising techniques for exploiting and developing new markers, including DNA and tissue microarray technologies. However, these techniques still require specialized personnel and equipment and are time-consuming. From this point of view, IHC is rather simple and is the most widely used method for prognostic markers. However, as stated above, the results of different authors have to be interpreted carefully since IHC is a multistep procedure, with variations of antibodies and condition of tissue sections, antibody concentrations, and incubation periods occurring among different institutions. Furthermore, standardized criteria for “positivity” should be established for each marker. Therefore, multicenter studies for standardization of IHC detection methods and judgment are ulti mately necessary for their successful and consistent application. For example, in the case of p53, a multicenter study of the Bladder Cancer Marker Network indicated that, although there was a high degree of agreement for p53-negative samples or strongly p53-positive samples, a high level of variability between laboratories and observers existed in the gray zone of low p53 positivity, between 1% and 20% [1].

Although some molecular markers (e.g., p53, Ki-67) may be promising in predicting recurrence as well as progression of bladder cancer, the results of multi-center studies with a standardized methodology and cohort of patients are required to apply these molecular markers to routine clinical decision-making.

X. OVERALL SUMMARY

Heterogeneity of bladder tumors to invade and metastasize and their frequent recurrence pose a challenge for the physicians who treat bladder cancer patients and for the researchers who work on bladder

cancer diagnosis, recurrence, and treatment-related areas. For the majority of new bladder cancer cases, investigation begins when patients are symptomatic (for example, with hematuria or irritative voiding). This mode of detection is often inadequate for nearly 15% to 30% of these new cases that have high-grade bladder cancer, since the tumor is already in the invasive stage at the time of diagnosis. Patients with bladder cancer usually are followed on a 3- to 6-month surveillance schedule, since bladder tumors frequently recur. The current mode of detecting bladder cancer involves cystoscopy, which is an invasive and relatively expensive procedure. Voided urine cytology, the standard noninvasive marker, is highly tumor specific and has good sensitivity to detect high grade tumors. However, its sensitivity to detect low grade tumors is low, its accuracy depends upon a pathologist's expertise, and it is not readily available in all countries.

Noninvasive tests that detect tumor-associated molecules (such as enzymes, sugar polymers, and tumor cell-associated proteins), altered gene expression, or chromosomal alterations would be useful for detecting bladder cancer, evaluating its grade, monitoring recurrence, and predicting prognosis.

Due to the low prevalence of bladder cancer, screening of the general population for bladder cancer using noninvasive tests is not cost-effective. However, noninvasive tests may be effective in screening and in early detection of bladder cancer among high-risk individuals. The most practical use of noninvasive tests would be for monitoring bladder cancer recurrence and reducing the number of surveillance cystoscopies performed each year.

For a noninvasive test to become clinically useful, it should be easy to perform, have low-intra-assay and interassay variability, have minimum requirements for sample handling and preparation, and be reliable. A noninvasive test should have high sensitivity and specificity in order to minimize the false negative and false positive cases, respectively. Due to highly sensitive detection methods, many noninvasive tests might detect a bladder tumor before it becomes clinically visible. The risk ratio and the odds ratio calculated for the false positive results on a noninvasive test should help physicians in making treatment decisions based on positive test results in the absence of clinical evidence of bladder cancer.

Several tumor markers and tests such as hemoglobin dipstick, BTA-Stat, BTA-TRAK, NMP-22, HA-HAase, BLCA-4, cytokeratins (18, 19 and 20), DD23, Immunocyt, survivin, Quanticyt, microsatellite analysis, telomerase (TRAP assay and hTERT RT-PCR), and UroVysion have been tested for their clinical usefulness. Some of these markers have also been compared with each other and/or with cytology. Case-control and cohort studies show that most of these markers have significantly higher sensitivity than cytology, and some also have the ability to detect bladder tumor recurrence before it becomes clinically visible. However, cytology is the superior marker in terms of specificity, although some markers in limited numbers of studies have specificity equivalent to that of cytology. As we learn more about these markers through clinical trials and have a better understanding of the conditions that cause false positive or false negative results, it should be possible to select a single marker or a combination of markers that can accurately detect bladder cancer.

Several proliferation and metastasis-associated molecules such as p53, Ki67, Rb, EGF-receptors, E-cadherin, cyclins, p21/WAF1, Kip1, and apoptosis-related molecules have shown potential in providing prognostic information related to metastasis, recurrence, and overall survival and cancer-specific survival. However, the results of many studies are contradictory, and there is no accurate marker as yet. The ability to predict prognosis will improve as our understanding of the biology of bladder cancer and of the basis of molecular heterogeneity among bladder tumors of the same histologic grade and stage improves. Development of reliable and accurate detecting methods will also improve the acceptability of prognostic markers among physicians.

The field of noninvasive bladder tumor markers and prognostic indicators is rapidly expanding. Although none of the noninvasive markers or tests can replace cystoscopy, at the present time, certainly many markers together with cystoscopy can improve the current practice of managing bladder cancer patients. Several bladder cancer markers have higher sensitivity, specificity, positive predictive value and negative predictive value for detecting bladder cancer than PSA has for detecting prostate cancer. Ultimately, the confidence of both physicians and patients to accept tumor markers in the management of bladder cancer patients will decide whether any of the current, or yet to be discovered, markers will reach the status as a "PSA for bladder cancer " [399].

RECOMMENDATION

I. STANDARD CARE FOR BLADDER CANCER DETECTION AND SURVEILLANCE

1. Cystoscopy and pathologic examination of biopsy specimens is the standard of care for the detection of bladder cancer.
2. Periodic cystoscopies are the standard of care for surveillance. Surveillance schedules vary according to the risk factors of the disease.

II. BLADDER TUMOR MARKERS : WHY DO WE NEED THEM?

1. Screening of high-risk, but not the general population, using bladder tumor markers can offer early detection advantage and save medical costs.
2. More studies are needed to identify accurate markers for bladder cancer screening.
3. Bladder tumor markers with high negative predictive values can be used in monitoring recurrence, not to replace cystoscopy, but to prolong the interval between examinations.
4. Prospective trials are needed to determine the cost savings, change in quality of life, and safety of this strategy.

III. IDEAL TUMOR MARKER

1. For a biomarker to be clinically useful, it should have technical simplicity, reliability, and high accuracy (i.e., high sensitivity and specificity).
2. A clinically useful marker should have high positive predictive value to avoid unnecessary work-up due to false positive results.
3. A biomarker should have a high negative predictive value in order to avoid the risk of bladder cancer progression due to missed tumor detection.
4. The physician's dilemma related to the possible early detection of bladder cancer by biomarkers could be decreased by examining the risk of developing bladder cancer in a specified time when a biomarker is positive.

IV. GOOD CLINICAL PRACTICE IN MARKER DEVELOPMENT

1. Efforts should be supported to standardize tumor marker development.
2. General guidelines and protocols for broadly accepted principles of the design of marker studies should be developed and made available for discussion to reach consensus.
3. Different phases of tumor marker development for conducting, reporting, and reviewing translational marker studies should be followed.
4. Indicating the developmental stage of a given marker may help to identify its usefulness for either further evaluation or clinical application.

V. URINE CYTOLOGY: THE STANDARD NONINVASIVE BLADDER TUMOR MARKER

1. Urine cytology is the standard noninvasive method for detecting bladder cancer.
2. The diagnostic yield of urine cytology is increased if at least 3 samples are analyzed.
3. Bladder washings may be better than voided urine for the evaluation of exfoliated urothelial cells.
4. Cytology has high sensitivity and negative predictive value to detect high grade bladder tumors.
5. Cytology has low sensitivity and negative predictive value to detect low grade bladder neoplasms.
6. Cytology has superior specificity than most of the currently available bladder tumor markers.

VI. BLADDER TUMOR MARKERS FOR DIAGNOSIS AND MONITORING RECURRENCE

1. Soluble Urine Markers

a) Hematuria Detection

1. Hematuria detection is a useful first-line marker to detect urologic diseases including urologic malignancies.
2. In general, hematuria detection has high sensitivity but low specificity to detect bladder cancer.

However, the sensitivity of hematuria detection may suffer due to the intermittent nature of hematuria.

3. Hematuria testing by hemoglobin dipstick is reliable and superior to microscopic examination of RBCs.

b) BTA-Stat and BTA-TRAK

1. The sensitivity of BTA-Stat and BTA-TRAK tests is dependent on tumor grade, stage, and size.

2. The specificity of BTA-Stat and BTA-TRAK is high among healthy individuals but is low among patients with various benign genitourinary conditions.

c) NMP-22

1. The NMP-22 test may provide adjunctive information in monitoring bladder cancer recurrence.

2. The sensitivity of NMP-22 is not high enough to eliminate current cystoscopy for bladder cancer detection and monitoring recurrence.

3. Due to relatively low specificity, its routine use for the detection of bladder cancer is not recommended.

d) BLCA-4 and BLCA-1

1. BLCA-4 is a potentially useful marker for the detection of bladder cancer, as it detects bladder cancer with both high sensitivity and specificity.

2. Large multicenter clinical trials will validate the efficacy of these potentially useful markers.

e) Survivin

• Due to the limited number of studies conducted on this marker, which involved relatively small numbers of patients with bladder cancer and relevant controls, recommendations cannot be made at this time.

f) Cytokeratins

1. The UBC-Rapid and UBC-IRMA tests may have limited clinical applicability due to lower sensitivity to detect bladder cancer when compared to other bladder tumor markers.

2. Cytokeratin-20 (RT-PCR or immunohistochemistry) may be a useful marker to detect bladder cancer.

3. Limited data are available on CYFRA 21-1 and thus recommendations cannot be made on this marker.

4. Since cytokeratin markers have high false positive rates when several urologic conditions other than bladder cancer are present, the clinical utility of these markers may be limited.

g) HA-HAase test

1. The HA-HAase test has high sensitivity and specificity to detect both primary and recurrent bladder tumors and to evaluate their grade.

2. This test may provide an early detection advantage.

3. The accuracy of this potentially useful test needs to be evaluated in larger multicenter trials.

2. CELL-BASED MARKERS

a) Microsatellite Analysis

• The clinical applicability of these markers is limited at this time because of the lack of consensus on the types and number of markers to be used, as well as a need for expensive equipment and trained personnel for conducting the analysis.

b) Telomerase

1. Telomerase detection by TRAP assay or hTERT RT-PCR has higher sensitivity than conventional cytology regardless of tumor grade and stage.

2. TRAP assay or hTERT RT-PCR are not recommended in routine clinical settings because of the lack of standardization of sample processing, complicated laboratory procedures, and the lack of standardized methods to eliminate factors which cause false positive and false negative results.

c) u-Cyt™

1. The uCyt™ assay is superior to conventional urine cytology and appears to be a promising diagnostic marker for bladder cancer.

2. The uCyt™ assay is an observer-dependent technique requiring a broad personal experience and constant quality control.

3. Prospective trials designed to evaluate the role of this test in the management of bladder cancer appear worthwhile.

d) DD23

1. This immunocytology-based test has high sensitivity but low specificity to detect bladder cancer.

2. The combination of DD23 with cytology could be used to decrease the frequency of cystoscopy.

3. A prospective trial to evaluate the usefulness of a combination of DD23 and cytology should be conducted.

e) Quanticyt Nuclear Karyometry

1. This is a useful marker to stratify patients into low-, intermediate-, or high-risk for bladder cancer.

2. Due to the requirement for sophisticated instrumentation, bladder wash specimens, and technical expertise, the general applicability of this marker is limited.

f) UroVysion Test

1. The UroVysion test appears to be a promising test for detecting bladder cancer and monitoring its recurrence. However, the test has low sensitivity to detect low grade bladder tumors.

2. Development of a consensus for the criteria used for the evaluation of abnormal cells is needed to improve the test's clinical applicability.

3. UroVysion is an observer-dependent technique requiring trained personnel, sophisticated instrumentation, and constant quality control.

4. A positive UroVysion may be indicative of both the neoplastic transformation (i.e., presence of bladder cancer) and an unstable urothelium primed for malignant transformation.

VII. COMPARATIVE ANALYSIS OF BLADDER TUMOR MARKERS

1. Several noninvasive tests are more sensitive than cytology.

2. Noninvasive tests with a high sensitivity and reasonable specificity can be used in a surveillance setting to reduce the number of cystoscopies performed each year for monitoring bladder tumor recurrence.

3. Due to the limited amount of data, no tumor marker can be recommended for use in bladder cancer screening at this time.

VIII. PROGNOSTIC MARKERS FOR BLADDER CANCER

Although some molecular markers (e.g., p53, Ki-67) may be promising in predicting recurrence as well as progression of bladder cancer, the results of multicenter studies with a standardized methodology and cohort of patients are required to apply these molecular markers to routine clinical decision-making.

ACKNOWLEDGMENTS: We acknowledge the editorial assistance of Dr. Adrienne Carmack. This work was supported for the following grants: NCI/NIH R01 CA-72821-06A2 [Vinata B. Lokeswhar, PhD].

REFERENCES

1. Droller MJ. Cancer heterogeneity and its biologic implications in the grading of urothelial carcinoma. J Urol 2001;165:696–697.
2. Lee R and Droller MJ. The natural history of bladder cancer. Implications for therapy. Urol Clin North Am 2000;27:1 - 13, vii.
3. Amling CL. Diagnosis and management of superficial bladder cancer. Curr Probl Cancer 2000;25:219-278.
4. van der Poel HG and Debruyne FM. Can biological markers replace cystoscopy? An update. Curr Opin Urol 2001;11:503-509.
5. Heney NM. Natural history of superficial bladder cancer. Prognostic features and long-term disease course. Urol Clin North Am 1992;19:429-433.
6. Lokeshwar VB and Soloway MS. Current bladder tumor tests: does their projected utility fulfill clinical necessity? J Urol 2001;165:1067-1077.
7. Lotan Y and Roehrborn CG. Cost-effectiveness of a modified care protocol substituting bladder tumor markers for cystoscopy for the followup of patients with transitional cell carcinoma of the bladder: a decision analytical approach. J Urol 2002;167:75-79.
8. Botteman MF, Pashos CL, Redaelli A, Laskin B, Hauser R. The health economics of bladder cancer: a comprehensive review of the published literature. Pharmacoeconomics 2003;21:1315-1330.
9. Datta SN, Allen GM, Evans R, Vaughton KC, Lucas MG. Urinary tract ultrasonography in the evaluation of haematuria—a report of over 1,000 cases. Ann R Coll Surg Engl 2002;84:203-205.
10. Pope AJ and Wickham JE. A user's guide to flexible cystoscopy. Br J Urol 1991;68:10-14.
11. Nijima T, Denis L, Pontes E, Alfthan O, Akaza H, Jaeger N, Kotake T, Ohi Y, Fujime N. Diagnostic work-up. in: Denis L, Nijima T, Prout G, Schroeder FH eds. Developments in bladder cancer. A Liss Publ New York, pp 211 – 222.
12. Cutler SJ, Heney NM, Friedell GH. Longitudinal study of patients with bladder cancer: factors associated with disease recurrence and progression. in: Bladder Cancer. Bonney WW, Prout G. eds. AUA monographs vol 1. Williams and Wilkins publ. Baltimore, 1982.
13. Fitzpatrick JM, West AB, Butler MR, Lane V., O'Flynn ID. Special bladder tumors (stage pTa, grade 1and 2): the importance of recurrence pattern following initial resection. J Urol 1986;135:920-922.
14. Heney NM, Ahmed S, Flanagan MJ, Frable W., Corder MP, Hafermann MD, Hawkins IR. Superficial bladder cancer: progression and recurrence. J Urol 1983;130:1083-1086.
15. Kaubisch S, Lum BL, Reese J, Freiha F, Torti FM. Stage T1 bladder cancer: grading is the primary determinant for risk of muscle invasion J Urol 1991;146:28-31.
16. Pawinski A, Sylvester R, Kurth KH, Bouffioux C, van der Meijden A, Pasrmar MK, Bijnens L. A combined analysis of EORTC and MRC randomized clinical trials for the prophylactic treatment of Ta-T1 bladder cancer. J Urol 1995;153:1934-1941.
17. Lamm DL. BCG immunotherapy for transitional cell carcinoma of the bladder Oncol 1995;9:947-952.
18. Walzer Y and Soloway MS. Should the followup of patients with bladder cancer include routine excretory urography? J Urol 1983;130:672-673.
19. Ries LAG, Eisner MP, Kosary CL, et al. (eds.): SEER Cancer Statistics Review, 1975 – 2001, National Cancer Institute. Bethesda, Maryland, http:// seer. cancer. gov/csr/ 1975 2001/ ,2004.
20. Messing EM, Young TB, Hunt VB, Roecker EB, Vaillancourt AM, Hisgen WJ, Greenberg EB, Kuglitsch ME, Wegenke JD. Home screening for hematuria: results of a multiclinic study. J Urol 1992;148:289-292.
21. Messing EM, Young TB, Hunt VB, Wehbie JM, Rust P. Urinary tract cancers found by homescreening with hematuria dipsticks in healthy men over 50 years of age. Cancer 1989;64:2361-2367.
22. Messing EM, Young TB, Hunt VB, Gilchrist KW, Newton MA, Bram LL, Hisgen WJ, Greenberg EB, Kuglitsch ME, Wegenke JD. Comparison of bladder cancer outcome in men undergoing hematuria home screening versus those with standard clinical presentations. Urology 1995;45:387-396; discussion 396-397.
23. Messing EM and Vaillancourt A. Hematuria screening for bladder cancer. J Occup Med 1990;32:838-845.
24. Messing EM, Young TB, Hunt VB, Newton MA, Bram LL, Vaillancourt A, Hisgen WJ, Greenberg EB, Kuglitsch ME, Wegenke JD. Hematuria home screening: repeat testing results. J Urol 1995 Jul;154(1):57-61.
25. Whelan P, Britton JP, Dowell AC. Three-year follow-up of bladder tumours found on screening. Br J Urol 1993;72:893-896.
26. Britton JP, Dowell AC, Whelan P, Harris CM. A community study of bladder cancer screening by the detection of occult urinary bleeding. J Urol 1992;148:788-790.
27. Britton JP, Dowell AC, Whelan P. Dipstick haematuria and bladder cancer in men over 60: results of a community study. BMJ 1989;299:1010-1012.
28. Hodder SL, Mahmoud AA, Sorenson K, Weinert DM, Stein RL, Ouma JH, Koech D,King CH. Predisposition to urinary tract epithelial metaplasia in Schistosoma haematobium infection. Am J Trop Med Hyg 2000;63:133-138.
29. Zeegers MP, Kellen E, Buntinx F, van den Brandt PA. The association between smoking, beverage consumption, diet and bladder cancer: a systematic literature review. World J Urol 2004;21:392-401.
30. Talaska G. Aromatic amines and human urinary bladder cancer: exposure sources and epidemiology. J Environ Sci Health Part C Environ Carcinog Ecotoxicol Rev 2003;21:29-43.
31. Skipper PL, Tannenbaum SR, Ross RK, Yu MC. Nonsmoking-related arylamine exposure and bladder cancer risk. Cancer Epidemiol Biomarkers Prev 2003;12:503-507.
32. Tripathi A, Folsom AR, Anderson KE. Iowa Women's Health Study: Risk factors for urinary bladder carcinoma in postmenopausal women. The Iowa Women's Health Study. Cancer 2002;95:2316-2323.
33. Pashos CL, Botteman MF, Laskin BL, Redaelli A. Bladder cancer: epidemiology, diagnosis, and management. Cancer Pract 2002;10:311-322.
34. Castelao JE, Yuan JM, Skipper PL, Tannenbaum SR, Gago-Dominguez M, Crowder JS, Ross RK, Yu MC. Gender- and smoking-related bladder cancer risk. J Natl Cancer Inst 2001;93:538-545.
35. Steinmaus C, Yuan Y, Bates MN, Smith AH. Case-control study of bladder cancer and drinking water arsenic in the western United States. Am J Epidemiol 2003;158:1193-1201.
36. Giannakopoulos X, Charalabopoulos K, Baltogiannis D, Chatzikiriakidou A, Alamanos Y, Georgiou I, Evangelou A, Agnantis N, Sofikitis N. The role of N-acetyltransferase-2 and glutathione S-transferase on the risk and aggressiveness of bladder cancer. Anticancer Res 2002;22:3801-3804.
37. Hung RJ, Boffetta P, Brennan P, Malaveille C, Gelatti U, Placidi D, Carta A,Hautefeuille A, Porru S. Genetic polymorphisms of MPO, COMT, MnSOD, NQO1, interactions with environmental

exposures and bladder cancer risk. Carcinogenesis 2004;25:973-978.

38. Lokeshwar VB, Schroeder GL, Selzer MG, Hautmann SH, Posey JT, Duncan RC Watson R, Rose L, Markowitz S, Soloway MS. Bladder tumor markers for monitoring recurrence and screening comparison of hyaluronic acid-hyaluronidase and BTA-Stat tests. Cancer 2002;95:61-72.

39. Hiatt RA and Ordonez JD. Dipstick urinalysis screening, asymptomatic microhematuria, and subsequent urological cancers in a population-based sample. Cancer Epidemiol Biomarkers Prev 1994;3:439-443.

40. Hemstreet GP 3rd, Yin S, Ma Z, Bonner RB, Bi W, Rao JY, Zang M, Zheng Q, Bane B, Asal N, Li G, Feng P, Hurst RE, Wang W. Biomarker risk assessment and bladder cancer detection in a cohort exposed to benzidine. J Natl Cancer Inst 2001;93:427-436.

41. Gazdar AF and Czerniak B. Filling the void: urinary markers for bladder cancer risk and diagnosis. J Natl Cancer Inst 2001;93:413-415.

42. Parekattil SJ, Fisher HA, Kogan BA. Neural network using combined urine nuclear matrix protein-22, monocyte chemoattractant protein-1 and urinary intercellular adhesion molecule-1 to detect bladder cancer. J Urol 2003;169:917-920.

43. Filbeck T, Pichlmeier U, Knuechel R, Wieland WF, Roessler W. Clinically relevant improvement of recurrence-free survival with 5-aminolevulinic acid induced fluorescence diagnosis in patients with superficial bladder tumors. J Urol 2002;168:67-71.

44. Kiemeney LA, Witjes JA, Heijbroek RP, Verbeek AL, Debruyne FM. Predictability of recurrent and progressive disease in individual patients with primary superficial bladder cancer. J Urol 1993;150:60-64.

45. Bastacky S, Ibrahim S, Wilczynski SP, Murphy WM. The accuracy of urinary cytology in daily practice. Cancer 1999;87:118-128.

46. Lotan Y and Roehrborn CG. Sensitivity and specificity of commonly available bladder tumor markers versus cytology: results of a comprehensive literature review and meta-analyses.Urology 2003;61:109-118.

47. Sarosdy MF, Schellhammer P, Bokinsky G, Kahn P, Chao R, Yore L, Zadra J, Burzon D, Osher G, Bridge JA, Anderson S, Johansson SL, Lieber M, Soloway M, Flom K. Clinical evaluation of a multi-target fluorescent in situ hybridization assay for detection of bladder cancer. J Urol 2002;168:1950-1954.

48. Sawczuk IS, Pickens CL, Vasa UR, Ralph DA, Norris KA, Miller MC, Ng AY, Grossman HB, Veltri RW. DD23 Biomarker. A prospective clinical assessment in routine urinary cytology specimens from patients being monitored for TCC. Urol Oncol 2002;7:185-190.

49. Nam RK, Redelmeier DA, Spiess PE, Sampson HA, Fradet Y, Jewett MAS. Comparison of ;molecular and conventional strategies for followup of superficial bladder cancer using decision-analysis. J Urol 2000;163:752-757.

50. Droller MJ. Bladder cancer: Stat-of-the-art-care. CA: A cancer journal for clinicians 1998;48:269-284.

51. Lokeshwar VB and Civantos F. Tumor markers: Current Status. In American Cancer Society Atlas of Clinical Oncology: Bladder Cancer (Droller MJ (ed)) Ontario Canada: Hamilton, 2004: pp: 160–205.

52. Konety BR and Getzenberg RH. Urine based markers of urological malignancy. J Urol 2001;165:600-611.

53. Duncan RC, Cnapp RG, Miller MC III. Introductory Biostatistics for the health sciences. (2nd edition) John Wiley and Sons New York, NY, 1983.

54. Miyanaga N, Akaza H, Tsukamoto T, Ishikawa S, Noguchi R, Ohtani M, Kawabe K, Kubota Y, Fujita K, Obata K, Hirao Y, Kotake T, Ohmori H, Kumazawa J, Koiso K. Urinary nuclear matrix protein 22 as a new marker for the screening of urothelial cancer in patients with microscopic hematuria. Int J Urol 1999;6:173-177.

55. Boman H, Hedelin H, Jacobsson S, Holmang S. Newly diagnosed bladder cancer: the relationship of initial symptoms, degree of microhematuria and tumor marker status. J Urol 2002;168:1955-1959.

56. van Rhijn BW, Lurkin I, Kirkels WJ, van der Kwast TH, Zwarthoff EC. Microsatellite analysis—DNA test in urine competes with cystoscopy in follow-up of superficial bladder carcinoma: a phase II trial. Cancer 2001;92:768-775.

57. Mungan NA, Vriesema JL, Thomas CM, Kiemeney LA, Witjes JA. Urinary bladder cancer test: a new urinary tumor marker in the follow-up of superficial bladder cancer. Urology 2000;56:787-792.

58. Schroeder GL, Lorenzo-Gomez MF, Hautmann SH, Friedrich MG, Ekici S., Huland H. Lokeshwar VB. A side-by-side comparison of cytology and biomarkers, HA-HAase, hematuria detection, BTA-Stat, UBC-Rapid for bladder cancer detection J Urol 2004;172:1123-1126.

59. Toma MI, Friedrich MG, Hautmann SH, Jakel KT, Erbersdobler A, Hellstern A, Huland H. Comparison of the ImmunoCyt test and urinary cytology with other urine tests in the detection and surveillance of bladder cancer. World J Urol 2004;22:145-149.

60. Friedrich MG, Toma MI, Hellstern A, Pantel K, Weisenberger DJ, Noldus J, Huland H: Comparison of multitarget fluorescence in situ hybridization in urine with other noninvasive tests for detecting bladder cancer. BJU Int 2003;92:911-914.

61. Varella-Garcia M, Akduman B, Sunpaweravong P, Di Maria MV, Crawford ED. The UroVysion fluorescence in situ hybridization assay is an effective tool for monitoring recurrence of bladder cancer. Urol Oncol 2004;22:16-19.

62. Lodde M, Mian C, Wiener H, Haitel A, Pycha A, Marberger M. Detection of upper urinary tract transitional cell carcinoma with ImmunoCyt: a preliminary report. Urology 2001;58:362-366.

63. Feil G, Zumbragel A, Paulgen-Nelde HJ, Hennenlotter J, Maurer S, Krause S, Bichler KH, Stenzl A. Accuracy of the ImmunoCyt assay in the diagnosis of transitional cell carcinoma of the urinary bladder. Anticancer Res 2003;23:963-967.

64. Hautmann SH, Toma M, Lorenzo Gomez MF, Friedrich MG, Jäkel T, Michl U, Schroeder GL, Huland H, Lokeshwar VB. Immunocyt and the HA-HAase urine tests for the detection of bladder cancer: a side by side comparison. Eur Urol 2004;46:466-471.

65. Saad A, Hanbury DC, McNicholas TA, Boustead GB, Morgan S, Woodman AC. A study comparing various noninvasive methods of detecting bladder cancer in urine. BJU Int 2002 Mar; 89(4):369-373.

66. Vriesema JL, Atsma F, Kiemeney LA, Peelen WP, Witjes JA, Schalken JA. Diagnostic efficacy of the ImmunoCyt test to detect superficial bladder cancer recurrence. Urology 2001;58:367-371.

67. Oge O, Kozaci D, Gemalmaz H. The BTA stat test is nonspecific for hematuria: an experimental hematuria model. J Urol 2002;167:1318-1319; discussion 1319-1320.

68. Atsu N, Ekici S, Oge O, Ergen A, Hascelik G, Ozen H. False-positive results of the NMP22 test due to hematuria. J Urol 2002;167:555-558.

69. Ponsky LE, Sharma S, Pandrangi L, Kedia S, Nelson D, Agarwal A, Zippe CD. Screening and monitoring for bladder cancer: refining the use of NMP22. J Urol 2001;166:75-78.

70. Chautard D, Daver A, Bocquillon V, Verriele V, Colls P, Bertrand G, Soret JY. Comparison of the Bard Trak test with voided urine

cytology in the diagnosis and follow-up of bladder tumors. Eur Urol 2000;38:686-690.

71. Thomas L, Leyh H, Marberger M, Bombardieri E, Bassi P, Pagano F, Pansadoro V, Sternberg CN, Boccon-Gibod L, Ravery V, Le Guludec D, Meulemans A, Conort P, Ishak L. Multicenter trial of the quantitative BTA TRAK assay in the detection of bladder cancer. Clin Chem 1999;45:472-477.
72. Mahnert B, Tauber S, Kriegmair M, Schmitt UM, Hasholzner U, Reiter W, Hofmann K, Schmeller N, Stieber P. BTA-TRAK—a useful diagnostic tool in urinary bladder cancer? Anticancer Res 1999;19:2615-2619.
73. Gu J, Liang D, Wang Y, Lu C, Wu X. Effects of N-acetyl transferase 1 and 2 polymorphisms on bladder cancer risk in Caucasians. Mutat Res 2005;581:97-104.
74. Yu MC, Skipper PL, Tannenbaum SR, Chan KK, Ross RK. Arylamine exposures and bladder cancer risk. Mutat Res 2002;506-507:21-28.
75. Brauers A, Jakse G. Epidemiology and biology of human urinary bladder cancer. J Cancer Res Clin Oncol 2000;126:575-583.
76. Michaud DS, Clinton SK, Rimm EB, Willett WC, Giovannucci E. Risk of bladder cancer by geographic region in a U.S. cohort of male health professionals. Epidemiology 2001;12:719-726.
77. Pelucchi C, La Vecchia C, Negri E, Dal Maso L, Franceschi S. Smoking and other risk factors for bladder cancer in women. Prev Med 2002;35:114-120.
78. Gago-Dominguez M, Castelao JE, Yuan JM, Yu MC, Ross RK. Use of permanent hair dyes and bladder-cancer risk. Int J Cancer 2001;91:575-579.
79. Shen M, Hung RJ, Brennan P, Malaveille C, Donato F, Placidi D, Carta A, Hautefeuille A, Boffetta P, Porru S. Polymorphisms of the DNA repair genes XRCC1, XRCC3, XPD, interaction with environmental exposures, and bladder cancer risk in a case-control study in northern Italy. Cancer Epidemiol Biomarkers Prev 2003;12:1234-1240.
80. Jong Jeong H, Jin Kim H, Young Seo I, Ju Kim H, Oh GJ, Cheon Chae S, Sik Lim J, Taeg Chung H, Joong Kim J. Association between glutathione S-transferase M1 and T1 polymorphisms and increased risk for bladder cancer in Korean smokers. Cancer Lett 2003;202(2):193-199.
81. Hung RJ, Boffetta P, Brennan P, Malaveille C, Hautefeuille A, Donato F, Gelatti U, Spaliviero M, Placidi D, Carta A, Scotto di Carlo A, Porru S: GST, NAT, SULT1A1, CYP1B1 genetic polymorphisms, interactions with environmental exposures and bladder cancer risk in a high-risk population. Int J Cancer 2004;110:598-604.
82. Lin J, Spitz MR, Wang Y, Schabath MB, Gorlov IP, Hernandez LM, Pillow PC, Grossman HB, Wu X. Polymorphisms of folate metabolic genes and susceptibility to bladder cancer: a case-control study. Carcinogenesis 2004;25:1639-1647.
83. Gago-Dominguez M, Bell DA, Watson MA, Yuan JM, Castelao JE, Hein DW, Chan KK, Coetzee GA, Ross RK, Yu MC. Permanent hair dyes and bladder cancer: risk modification by cytochrome P4501A2 and N-acetyltransferases 1 and 2. Carcinogenesis 2003;24:483-489.
84. Kwiatkowski M, Huber A, Stamm B, Lehmann K, Wernli M, Hafeli A, Recker F. Features and preliminary results of prostate cancer screening in Canton Aargau, Switzerland. BJU Int 2003;92 Suppl 2:44-47.
85. Hugosson J, Aus G, Bergdahl S, Fernlund P, Frosing R, Lodding P, Pihl CG, Lilja H. Population-based screening for prostate cancer by measuring free and total serum prostate-specific antigen in Sweden. BJU Int 2003;92 Suppl 2:39-43.
86. Luboldt HJ, Bex A, Swoboda A, Husing J, Rubben H. Early Detection Project Group of the German Urological Association. Early detection of prostate cancer in Germany: a study using digital rectal examination and 4.0 ng/ml prostate-specific antigen as cutoff. Eur Urol 2001;39:131-137.
87. Grossman HB. Biomarkers for transitional cell carcinoma-pro. Urology 2001;57:847-848.
88. Skacel M, Fahmy M, Brainard JA, Pettay JD, Biscotti CV, Liou LS, Procop GW, Jones JS, Ulchaker J, Zippe CD, Tubbs RR. Multitarget fluorescence in situ hybridization assay detects transitional cell carcinoma in the majority of patients with bladder cancer and atypical or negative urine cytology. J Urol 2003;169:2101-2105.
89. Blumenstein BA, Ellis WJ, Ishak LM. The relationship between serial measurements of the level of a bladder tumor associated antigen and the potential for recurrence. J Urol 1999;161:57-60;discussion 60-61.
90. Altman DG, Lausen B, Sauerbrei W, Schumacher M. Dangers of using “optimal” cutpoints in the evaluation of prognostic factors. J Natl Cancer Inst 1994;86:829-835.
91. Schmoor C, Sauerbrei W, Schumacher M. Sample size considerations for the evaluation of prognostic factors in survival analysis. Stat Med 2000;19:441-452.
92. Pajak TF, Clark GM, Sargent DJ, McShane LM, Hammond ME. Statistical issues in tumor marker studies. Arch Pathol Lab Med 2000;124:1011-1015.
93. Altman DG and Royston P. What do we mean by validating a prognostic model? Stat Med 2000;19:453-473.
94. Begg CB, Cramer LD, Venkatraman ES, Rosai J. Comparing tumour staging and grading systems: a case study and a review of the issues, using thymoma as a model. Stat Med 2000;19:1997-2014.
95. Simon R and Altman DG. (1994) Statistical aspects of prognostic factor studies in oncology. Br J Cancer 1994;69:979-985.
96. McGuire WL. Breast cancer prognostic factors: evaluation guidelines. J Natl Cancer Inst 1991;83:154-155.
97. Stockler MR, Boyd NF, Tannock IF. Guide to Studies of Diagnostic Tests, Prognostic Factors, and Treatments. In: Tannock IF and Hill RP, editors. The Basic Science of Oncology. 3rd ed. McGraw-Hill; 1998.
98. Pepe MS, Etzioni R, Feng Z, Potter JD, Thompson ML, Thornquist M, Winget M, Yasui Y. Phases of Biomarker Development for Early Detection of Cancer. J Nat Cancer Inst 2001;93:1054-1061.
99. Drew PJ, Ilstrup DM, Kerin MJ, Monson JR. Prognostic factors: guidelines for investigation design and state of the art analytical methods. Surg Oncol 1998;7:71-76.
100. Golijanin D, Shapiro A, Pode D. Immunostaining of cytokeratin 20 in cells from voided urine for detection of bladder cancer. J Urol 2000;164:1922-1925.
101. Koss LG, Deitch D, Ramanathan R, Sherman AB. Diagnostic value of cytology of voided urine. Acta Cytol 1985;29:810-816.
102. Rife CC, Farrow GM, Utz DC. Urine cytology of transitional cell neoplasms. Urol Clini N Am 1970;6:599-612.
103. Murphy WM, Rivera-Ramirez I, Medina CA, Wright NJ, Wajsman Z. The bladder tumor antigen (BTA) test compared to voided urine cytology in the detection of bladder neoplasms. J Urol 1997;158:2102-2106.
104. Sánchez-Carbayo M, Urrutia M, Silva JM, Romani R, Gonzalez de Buitrago JM, Navajo JA. Comparative predictive values of urinary cytology, urinary bladder cancer antigen, CYFRA-A 21-1 and NMP 22 for evaluating symptomatic patients at risk for bladder cancer. J Urol 2001;165:1462-1467.
105. Glas AS, Roos D, Deutekom M, Zwinderman AH, Bossuyt PMM, Kurth KH. Tumor markers in the diagnosis of primary bladder cancer. A systemic review. J Urol 2003;169:1975-1982.
106. Wiener HG, Vooijs GP, Hof-Grootenboer BV. Accuracy of uri-

nary cytology in the diagnosis of primary and recurrent bladder cancer. Acta Cytol 1993;37:163-169.

107. Grégoire M, Fradet Y, Meyer F, Tetu B, Bois R, Bedard G, Charrois R, Naud A. Diagnostic accuracy of urinary cytology and deoxyribonucleic acid flow cytometry and cytology on bladder washings during followup for bladder tumors. J Urol 1997;157:1660-1664.

108. Murphy WM, Soloway MS, Jukkola AF, Crabtree WN, Ford KS. Urinary cytology and bladder cancer. The cellular features of transitional cell neoplasms. Cancer 1984;53:1555-1565.

109. Pfister C, Chautard D, Devonec M, Perrin P, Chopin D, Rischmann P, Bouchot O, Beurton D, Coulange C, Rambeaud JJ. Immunocyt test improves the diagnostic accuracy of urinary cytology: results of a French multicenter study. J Urol 2003;169:921-924.

110. Malik S, Murphy WM. Monitoring patients for bladder neoplasms: what can be expected of urinary cytology consultations in daily practice? Urology 1999;54:62-66.

111. Farrow GM, Utz DC, Rife CC, Greene LF. Clinical observations on sixty-nine cases of in-situ carcinoma of the urinary bladder. Cancer Res 1977;37:2794-2798.

112. Murphy WM. Urinary cytopathology. Chicago; ASCP Press; 2000.

113. Sack MJ, Artymyshyn RL, Tomaszewski JE, Gupta PK. Diagnostic value of bladder wash cytology with special reference to low grade urothelial neoplasms. Acta Cytol 1995;39:187-194.

114. Raab SS, Slagel DD, Jensen CS, Teague MW, Savell VH, Ozkutlu D, Lenel JC, Cohen MB. Low-grade transitional cell carcinoma of the urinary bladder: application of select cytologic criteria to improve diagnostic accuracy [corrected]. Mod Pathol 1996;9:225-232. Erratum in: Mod Pathol 1996;9:803.

115. Bastacky S, Ibrahim S, Wilczynski SP, Murphy WM. The accuracy of urinary cytology in daily practice. Cancer (Cancer Cytopathol) 1999;87:118-128.

116. Katz RL, Sinkre PA, Zhang HH, Kidd L, Johnston D. Clinical significance of negative and equivocal urinary bladder cytology alone and in combination with DNA image analysis and cystoscopy. Cancer 1997;81:354 -364.

117. Wakui M and Shiigai T. Urinary tract cancer screening through analysis of urinary red blood cell volume distribution. Int J Urol 2000;7:248-253.

118. Friedman GD, Carroll PR, Cattolica EV, Hiatt RA. Can hematuria be a predictor as well as a symptom or sign of bladder cancer? Cancer Epidemiol Biomarkers Prev 1996;5:993-996.

119. Murakami S, Igarashi T, Hara S, Shimazaki J. Strategies for asymptomatic microscopic hematuria: a prospective study of 1,034 patients. J Urol 1990;144:99-101.

120. Thompson IM. The evaluation of microscopic hematuria: a population-based study. J Urol 1987;138:1189-1190.

121. Mohr DN, Offord KP, Melton LJ 3rd. Isolated asymptomatic microhematuria: a cross-sectional analysis of test-positive and test-negative patients. J Gen Intern Med 1987;2:318-324.

122. Froom P, Froom J, Ribak J. Asymptomatic microscopic hematuria—is investigation necessary? J Clin Epidemiol 1997;50:1197-1200.

123. Grossfeld GD, Wolf JS Jr, Litwan MS, Hricak H, Shuler CL, Agerter DC, Carroll PR. Asymptomatic microscopic hematuria in adults: summary of the AUA best practice policy recommendations. Am Fam Physician 2001;63:1145-1154.

124. Halling KC, King W, Sokolova IA, Karnes RJ, Meyer RG, Powell EL, Sebo TJ,Cheville JC, Clayton AC, Krajnik KL, Ebert TA, Nelson RE, Burkhardt HM,Ramakumar S, Stewart CS, Pankratz VS, Lieber MM, Blute ML, Zincke H, Seelig SA,Jenkins RB, O'Kane DJ. A comparison of BTA stat, hemoglobin dipstick, telomerase and Vysis UroVysion assays for the detection of urothelial carcinoma in urine. J Urol 2002;167:2001-2006.

125. Ramakumar S, Bhuiyan J, Besse JA, Roberts SG, Wollan PC, Blute ML, O'KaneDJ. Comparison of screening methods in the detection of bladder cancer. J Urol 1999;161:388-394.

126. Schramek P, Schuster FX, Georgopoulos M, Porpaczy P, Maier M. Value of urinary erythrocyte morphology in assessment of symptomless microhaematuria. Lancet 1989;2:1316-1319.

127. Georgopoulos M, Schuster FX, Porpaczy P, Schramek P. Evaluation of asymptomatic microscopic haematuria—influence and clinical relevance of osmolality and pH on urinary erythrocyte morphology. Br J Urol 1996;78:192-196.

128. Kinders R, Jones T, Root R, Bruce C, Murchison H, Corey M, Williams L, Enfield D, Hass GM. Complement factor H or a related protein is a marker for transitional cell cancer of the bladder. Clin Cancer Res 1998;4:2511-2520.

129. Malkowicz SB. The application of human complement factor H-related protein (BTA TRAK) in monitoring patients with bladder cancer. Urol Clin North Am 2000;27:63-73, ix.

130. Miyanaga N, Akaza H, Tsukamoto S, Shimazui T, Ohtani M, Ishikawa S, Noguchi R, Manabe F, Nishijima Y, Kikuchi K, Sato K, Hayashi H, Kondo F, Shiraiwa H, Aoyama O. Usefulness of urinary NMP22 to detect tumor recurrence of superficial bladder cancer after transurethral resection. Int J Clin Oncol 2003;8:369-373.

131. Gutierrez Banos JL, del Henar Rebollo Rodrigo M, Antolin Juarez FM, Garcia BM. Usefulness of the BTA STAT Test for the diagnosis of bladder cancer. Urology 2001;57:685-689.

132. Walsh IK, Keane PF, Ishak LM, Flessland KA. The BTA stat test: a tumor marker for the detection of upper tract transitional cell carcinoma. Urology 2001;58:532-535.

133. Raitanen MP, Marttila T, Nurmi M, Ala-Opas M, Nieminen P, Aine R, Tammela TL. Human complement factor H related protein test for monitoring bladder cancer. J Urol 2001;165:374-377.

134. Raitanen MP, Marttila T, Kaasinen E, Rintala E, Aine R, Tammela TL. Sensitivity of human complement factor H related protein (BTA stat) test and voided urine cytology in the diagnosis of bladder cancer. J Urol 2000;163:1689-1692.

135. Boman H, Hedelin H, Holmang S. Four bladder tumor markers have a disappointingly low sensitivity for small size and low grade recurrence. J Urol 2002;167:80-83.

136. Wald M, Halachmi S, Amiel G, Madjar S, Mullerad M, Miselevitz I, MoskovitzB, Nativ O. Bladder tumor antigen stat test in non-urothelial malignant urologicconditions. Isr Med Assoc J 2002;4:174-175.

137. Heicappell R, Muller M, Fimmers R, Miller K. Qualitative determination of urinary human complement factor H-related protein (hcfHrp) in patients with bladder cancer, healthy controls, and patients with benign urologic disease. Urol Int 2000;65:181-184.

138. Serretta V, Pomara G, Rizzo I, Esposito E. Urinary BTA-stat, BTA-trak and NMP22 in surveillance after TUR of recurrent superficial transitional cell carcinoma of the bladder. Eur Urol 2000;38:419-425.

139. Nasuti JF, Gomella LG, Ismial M, Bibbo M. Utility of the BTA stat test kit for bladder cancer screening. Diagn Cytopathol 1999;21:27-29.

140. Raitanen MP, Kaasinen E, Rintala E, Hansson E, Nieminen P, Aine R, Tammela TL. Prognostic utility of human complement factor H related protein test (the BTA-stat Test). Br J Cancer 2001;85:552-556.

141. Poulakis V, Witzsch U, De Vries R, Altmannsberger HM, Manyak MJ, Becht E. A comparison of urinary nuclear matrix protein-22 and bladder tumour antigen tests with voided urinary

cytology in detecting and following bladder cancer: the prognostic value of false-positive results. BJU Int 2001;88:692-701.

142. Mattioli S, Seregni E, Caperna L, Botti C, Savelli G, Bombardieri E. BTA-TRAK combined with urinary cytology is a reliable urinary indicator of recurrent transitional cell carcinoma (TCC) of the bladder. Int J Biol Markers 2000;15:219-225.

143. Priolo G, Gontero P, Martinasso G, Mengozzi G, Formiconi A, Pelucelli G, Zitella A, Casetta G, Viberti L, Aimo G, Tizzani A. Bladder tumor antigen assay as compared to voided urine cytology in the diagnosis of bladder cancer. Clin Chim Acta 2001;305:47-53.

144. Mahnert B, Tauber S, Kriegmair M, Nagel D, Holdenrieder S, Hofmann K, ReiterW, Schmeller N, Stieber P. Measurements of complement factor H-related protein (BTA-TRAK assay) and nuclear matrix protein (NMP22 assay)—useful diagnostic tools in the diagnosis of urinary bladder cancer? Clin Chem Lab Med 2003;41:104-110.

145. Berezney R and Coffey DS. Identification of a nuclear protein matrix. Biochem Biophys Res Commun 1974;60:1410-1417.

146. Pardoll DM, Vogelstein B, Coffey DS. A fixed site of DNA replication in eucaryotic cells. Cell 1980;19:527-536.

147. Gordon JN, Shu WP, Schlussel RN, Droller MJ, Liu BC. Altered extracellular matrices influence cellular processes and nuclear matrix organizations of overlying human bladder urothelial cells. Cancer Res 1993;53:4971-4977.

148. Yang CH, Lambie EJ, Snyder M. NuMA: an unusually long coiled-coil related protein in the mammalian nucleus. J Cell Biol 1992;116:1303-1317.

149. Landman J, Chang Y, Kavaler E, Droller MJ, Liu BC. Sensitivity and specificity of NMP-22, telomerase, and BTA in the detection of human bladder cancer. Urology 1998;52:398-402.

150. Eissa S, Swellam M, Sadek M, Mourad MS, Ahmady OE, Khalifa A. Comparative evaluation of the nuclear matrix protein, fibronectin, urinary bladder cancer antigen and voided urine cytology in the detection of bladder tumors. J Urol 2002;168:465-469.

151. Friedrich MG, Hellstern, A, Hautmann SH, Graefen M, Conrad S, Huland E, Huland H. Clinical use of urinary markers for the detection and prognosis of bladder carcinoma: a comparison of immunocytology with monoclonal antibodies against Lewis X and 486p3/12 with the BTA STAT and NMP22 tests. J Urol 2002;168:470-474.

152. Grossman HB, Messing E, Soloway M, Tomera K, Katz G, Berger Y, Shen Y. Detection of bladder cancer using a point-of-care proteomic assay. JAMA 2005;293:810-816.

153. Soloway MS, Briggman V, Carpinito GA, Chodak GW, Church PA, Lamm DL, Lange P, Messing E, Pasciak RM, Reservitz GB, Rukstalis DB, Sarosdy MF, Stadler WM, Thiel RP, Hayden CL. Use of a new tumor marker, urinary NMP22, in the detection of occult or rapidly recurring transitional cell carcinoma of the urinary tract following surgical treatment. J Urol 1996;156:363-367.

154. Wiener HG, Mian C, Haitel A, Pycha A, Schatzl G, Marberger M. Can urine bound diagnostic tests replace cystoscopy in the management of bladder cancer? J Urol 1998;159:1876-1880.

155. Zippe C, Pandrangi L, Potts JM, Kursh E, Novick A, Agarwal A. NMP22: a sensitive, cost-effective test in patients at risk for bladder cancer. Anticancer Res 1999;19:2621-2623.

156. Stampfer DS, Carpinito GA, Rodriguez-Villanueva J, Willsey LW, Dinney CP, Grossman, HB, Fritsche HA, McDougal WS. Evaluation of NMP22 in the detection of transitional cell carcinoma of the bladder. J Urol 1998;159:394-398.

157. Sharma S, Zippe CD, Pandrangi L, Nelson D, Agarwal A. Exclusion criteria enhance the specificity and positive predictive value of NMP22 and BTA stat. J Urol 1999;162:53-57.

158. Del Nero A, Esposito N, Curro A, Biasoni D, Montanari E, Mangiarotti B, Trinchieri A, Zanetti G, Serrago MP, Pisani E. Evaluation of urinary level of NMP22 as a diagnostic marker for stage pTa-pT1 bladder cancer: comparison with urinary cytology and BTA test. Eur Urol 1999;35:93-97.

159. Serretta V, Lo Presti D, Vasile P, Gange E, Esposito E, Menozzi I. Urinary NMP22 for the detection of recurrence after transurethral resection of transitional cell carcinoma of the bladder: experience on 137 patients. Urology 1998;52:793-796

160. Witjes J A, van der Poel HG, van Balken MR, Debruyne FM, Schalken JA. Urinary NMP22 and karyometry in the diagnosis and follow-up of patients with superficial bladder cancer. Eur Urol 1998;33:387-391.

161. Sanchez-Carbayo M, Herrero E, Megias J, Mira A, Soria F. Evaluation of nuclear matrix protein 22 as a tumour marker in the detection of transitional cell carcinoma of the bladder. BJU Int 1999;84:706-713.

162. Sanchez-Carbayo M, Urrutia M, Gonzalez de Buitrago JM, Navajo JA. Utility of serial urinary tumor markers to individualize intervals between cystoscopies in the monitoring of patients with bladder carcinoma. Cancer 2001;92:2820-2828.

163. Friedrich MG, Hellstern A, Toma MI, Hammerer P, Huland H. Are false-positive urine markers for the detection of bladder carcinoma really wrong or do they predict tumor recurrence? Eur Urol 2003;43:146-150; discussion 150-151.

164. Konety BR, Nguyen TS, Dhir R, Day RS, Becich MJ, Stadler WM, Getzenberg RH. Detection of bladder cancer using a novel nuclear matrix protein, BLCA-4. Clin Cancer Res 2000;6:2618-2625.

165. Van Le TS, Myers J, Konety BR, Barder T, Getzenberg RH. Functional characterization of the bladder cancer marker, BLCA-4. Clin Cancer Res 2004;10:1384-1391.

166. Konety BR, Nguyen TS, Brenes G, Sholder A, Lewis N, Bastacky S, Potter DM,Getzenberg RH. Clinical usefulness of the novel marker BLCA-4 for the detection of bladdercancer. J Urol 2000;164:634-649.

167. Konety BR, Nguyen T-ST, Brenes G, Lewis N, Saul M, Nelson JB, Getzenberg RH. Evaluation of the Effect of Spinal Cord Injury (SCI) on serum PSA levels. Urology 2000;56:82-86.

168. Van Le T-ST, Miller R, Barder T, Babjuk M, Potter DM, Getzenberg RH. A highly specific urine-based marker of bladder cancer. Urology (Submitted, 2005).

169. Myers JM, Landsittel D, and Getzenberg RH: Utilization of the Nuclear Protein, BLCA-1, for the Detection of Bladder Cancer. Clin Cancer Res (2005, In Press)

170. Altieri DC. Survivin, versatile modulation of cell division and apoptosis in cancer. Oncogene 2003;22:8581-8589.

171. Altieri DC. The molecular basis and potential role of survivin in cancer diagnosis and therapy. Trends Mol Med 2001;7:542-547.

172. Ku JH, Kwak C, Lee HS, Park HK, Lee E, Lee SE. Expression of survivin, a novel inhibitor of apoptosis, in superficial transitional cell carcinoma of the bladder. J Urol 2004 Feb;171(2 Pt 1):631-635.

173. Lehner R, Lucia MS, Jarboe EA, Orlicky D, Shroyer AL, McGregor JA, Shroyer KR. Immunohistochemical localization of the IAP protein survivin in bladder mucosa and transitional cell carcinoma. Appl Immunohistochem Mol Morphol 2002 Jun;10(2):134-138.

174. Gazzaniga P, Gradilone A, Giuliani L, Gandini O, Silvestri I, Nofroni I, Saccani G, Frati L, Agliano AM. Expression and prognostic significance of LIVIN, SURVIVIN and other apoptosis-related genes in the progression of superficial bladder cancer. Ann Oncol 2003;14:85-90.

175. Schultz IJ, Kiemeney LA, Witjes JA, Schalken JA, Willems JL, Swinkels DW, de Kok JB. Survivin mRNA expression is elevat-

ed in malignant urothelial cell carcinomas and predicts time to recurrence. Anticancer Res 2003 Jul-Aug;23(4):3327-3331.

176. Smith SD, Wheeler MA, Plescia J, Colberg JW, Weiss RM, Altieri DC. Urine detection of survivin and diagnosis of bladder cancer. JAMA 2001;285:324-328.

177. Sharp JD, Hausladen DA, Maher MG, Wheeler MA, Altieri DC, Weiss RM. Bladder cancer detection with urinary survivin, an inhibitor of apoptosis. Front Biosci 2002;7:E36-E41.

178. Shariat SF, Casella R, Khoddami SM, Hernandez G, Sulser T, Gasser TC, Lerner SP. Urine detection of survivin is a sensitive marker for the noninvasive diagnosis of bladder cancer. J Urol 2004;171:626-630.

179. Hausladen DA, Wheeler MA, Altieri DC, Colberg JW, Weiss RM. Effect of intravesical treatment of transitional cell carcinoma with bacillus Calmette-Guerin and mitomycin C on urinary survivin levels and outcome. J Urol 2003 Jul;170(1):230-234.

180. Schultz IJ, Kiemeney LA, Karthaus HF, Witjes JA, Willems JL, Swinkels DW, Gunnewiek JM, de Kok JB. Survivin mRNA copy number in bladder washings predicts tumor recurrence in patients with superficial urothelial cell carcinomas. Clin Chem 2004;50:1425-1428.

181. Southgate J, Harnden P, Trejdosiewicz LK. Cytokeratin expression patterns in normal and malignant urothelium: a review of the biological and diagnostic implications. Histol Histopathol 1999;14:657-664.

182. Sanchez-Carbayo M, Herrero E, Megias J, Mira A, Soria F. Comparative sensitivity of urinary CYFRA 21-1, urinary bladder cancer antigen, tissue polypeptide antigen, tissue polypeptide antigen and NMP22 to detect bladder cancer. J Urol 1999;162:1951-1956.

183. Mian C, Lodde M, Haitel A, Vigl EE, Marberger M, Pycha A. Comparison of the monoclonal UBC-ELISA test and the NMP22 ELISA test for the detection of urothelial cell carcinoma of the bladder. Urology 2000;55:223-226.

184. Eissa S, Kenawy G, Swellam M, El-Fadle AA, Abd El-Aal AA, El-Ahmady O. Comparison of cytokeratin 20 RNA and angiogenin in voided urine samples as diagnostic tools for bladder carcinoma. Clin Biochem 2004 Sep;37(9):803-810.

185. Babjuk M, Kostirova M, Mudra K, Pecher S, Smolova H, Pecen L, Ibrahim Z,Dvoracek J, Jarolim L, Novak J, Zima T. Qualitative and quantitative detection of urinary human complement factor H-related protein (BTA stat and BTA TRAK) and fragments of cytokeratins 8, 18 (UBC rapid and UBC IRMA) as markers for transitional cell carcinoma of the bladder. Eur Urol 2002;41:34-39.

186. Mian C, Lodde M, Haitel A, Egarter Vigl E, Marberger M, Pycha A. Comparison of two qualitative assays, the UBC rapid test and the BTA stat test, in the diagnosis of urothelial cell carcinoma of the bladder. Urology 2000;56:228-231.

187. Sanchez-Carbayo M, Ciudad J, Urrutia M, Navajo JA, Orfao A. Diagnostic performance of the urinary bladder carcinoma antigen ELISA test and multiparametric DNA/cytokeratin flow cytometry in urine voided samples from patients with bladder carcinoma. Cancer 2001;92:2811-2819.

188. Eissa S, Swellam M, el-Mosallamy H, Mourad MS, Hamdy N, Kamel K, Zaglol AS,Khafagy MM, el-Ahmady O. Diagnostic value of urinary molecular markers in bladder cancer. Anticancer Res 2003;23:4347-4355.

189. Harnden P, Mahmood N, Southgate J. Expression of cytokeratin 20 redefines urothelial papillomas of the bladder. Lancet 1999;353:974-977.

190. McKenney JK, Desai S, Cohen C, Amin MB. Discriminatory immunohistochemical staining of urothelial carcinoma in situ and non-neoplastic urothelium: an analysis of cytokeratin 20, p53, and CD44 antigens. Am J Surg Pathol 2001;25:1074-1078.

191. Retz M, Lehmann J, Amann E, Wullich B, Roder C, Stockle M. Mucin 7 and cytokeratin 20 as new diagnostic urinary markers for bladder tumor. J Urol 2003;169:86-89.

192. Rotem D, Cassel A, Lindenfeld N, Mecz Y, Sova Y, Resnick M, Stein A. Urinary cytokeratin 20 as a marker for transitional cell carcinoma. Eur Urol 2000;37:601-604.

193. Cassel A, Rahat MA, Lahat N, Lindenfeld N, Mecz Y, Stein A. Telomerase activity and cytokeratin 20 as markers for the detection and followup of transitional cell carcinoma: an unfulfilled promise. J Urol 2001;166:841-844.

194. Buchumensky V, Klein A, Zemer R, Kessler OJ, Zimlichman S, Nissenkorn I: Cytokeratin 20: a new marker for early detection of bladder cell carcinoma? J Urol 1998;160:1971-1974.

195. Gazzaniga P, Gandini O, Giuliani L, Magnanti M, Gradilone A, Silvestri I, Gianni W, Gallucci M, Frati L, Agliano AM. Detection of epidermal growth factor receptor mRNA in peripheral blood: a new marker of circulating neoplastic cells in bladder cancer patients. Clin Cancer Res 2001;7:577-583.

196. Lin S, Hirschowitz SL, Williams C, Shintako P, Said J, Rao JY. Cytokeratin 20 as an immunocytochemical marker for detection of urothelial carcinoma in atypical cytology: preliminary retrospective study on archived urine slides. Cancer Detect Prev 2001;25:202-209.

197. Pariente JL, Bordenave L, Jacob F, Gobinet A, Leger F, Ferriere JM, Le Guillou M. Analytical and prospective evaluation of urinary cytokeratin 19 fragment in bladder cancer. J Urol 2000;163:1116-1169.

198. Lokeshwar VB and Block NL. HA-HAase urine test. A sensitive and specific method for detecting bladder cancer and evaluating its grade. Urol Clin North Am 2000;27:53-61.

199. Lokeshwar VB, Obek C, Pham HT, Wei D, Young MJ, Duncan RC, Soloway MS, Block NL. Urinary hyaluronic acid and hyaluronidase: markers for bladder cancer detection and evaluation of grade. J Urol 2000;163:348-356.

200. Lee JY and Spicer AP. Hyaluronan: a multifunctional, megaDalton, stealth molecule. Curr Opin Cell Biol 2000;12:581-586.

201. Delpech B, Girard N, Bertrand P, Courel MN, Chauzy C, Delpech A. Hyaluronan: fundamental principles and applications in cancer. J Intern Med 1997;242:41-48.

202. Lokeshwar VB, Rubinowicz D, Schroeder GL, Forgacs E, Minna JD, Block NL, Nadji M, Lokeshwar BL. Stromal and epithelial expression of tumor markers hyaluronic acid and HYAL1 hyaluronidase in prostate cancer. J Biol Chem 2001;276:11922-11932.

203. West DC and Kumar S. Hyaluronan and angiogenesis. Ciba Found Symp 1989;143:187-201; discussion 201-207;281-285.

204. Lokeshwar VB, Obek C, Soloway MS, Block NL. Tumor-associated hyaluronic acid: a newsensitive and specific urine marker for bladder cancer. Cancer Res 1997;57:773-777. Erratum, Cancer Res 1998;58:3191.

205. Franzmann EJ, Schroeder GL, Goodwin WJ, Weed DT, Fisher P, Lokeshwar VB. Expression of tumor markers hyaluronic acid and hyaluronidase (HYAL1) in head and neck tumors. Int J Cancer 2003;106:438-445.

206. Lokeshwar VB, Young MJ, Goudarzi G, Iida N, Yudin AI, Cherr GN, Selzer MG.Identification of bladder tumor-derived hyaluronidase: its similarity to HYAL1. Cancer Res1999;59:4464-4470.

207. Pham HT, Block NL, Lokeshwar VB. Tumor-derived hyaluronidase: a diagnostic urinemarker for high-grade bladder cancer. Cancer Res 1997;57:778-783. Erratum, Cancer Res1997;57:1622.

208. Hautmann SH, Lokeshwar VB, Schroeder GL, Civantos F, Duncan RC, Gnann R.Friedrich MG, Soloway MS. Elevated tissue expression of hyaluronic acid andhyaluronidase validates the

HA-HAase urine test for bladder cancer. J Urol2001;165:2068-2074.

209. Srougi M, Gattas G, Leite KR, Camara-Lopes, Nader HB, Passerotti CC, Ortiz V. Increasing the FISH detection of urothelial bladder carcinoma – A Brazilian experience comparing with BTA-Stat, hyaluronic acid and cytology in voided urine specimens. J Urol 2004;171 (Suppl 4):71 (269 Abstract).

210. Weber JL and May PE. Abundant class of human DNA polymorphisms which can be typed using the polymerase chain reaction. Am J Hum Genet 1989;44:388-396.

211. Mao L, Lee DJ, Tockman MS, Erozan YS, Askin F, Sidransky D. Microsatellite alterations as clonal markers for the detection of human cancer. Proc Natl Acad Sci USA 1994;91:9871-9875.

212 Mao L, Schoenberg MP, Scicchitano M Erozan YS, Merlo A, Schwab D, Sidransky D. Molecular detection of primary bladder cancer by microsatellite analysis. Science 1996;271:659-662.

213. Steiner G, Schoenberg MP, Linn JF Mao L, Sidransky D. Detection of bladder cancer recurrence by microsatellite analysis of urine. Nat Med 1997;3:621-624.

214. Knowles MA, Elder PA, Williamson M Cairns JP, Shaw ME, Law MG. Allelotype of human bladder cancer. Cancer Res 1994;54:531-538.

215. Habuchi T, Ogawa O, Kakehi Y Ogura K, Koshiba M, Hamazaki S, Takahashi R,Sugiyama T, Yoshida O. Accumulated allelic losses in the development of invasive urothelial cancer. Int J Cancer 1993;53:579-584.

216. Dalbagni G, Presti J, Reuter V, Fair WR, Cordon-Cardo C. Genetic alterations in bladder cancer. Lancet 1993;342:469-471.

217. Chen XQ, Stroun M, Magnenat JL, Nicod LP, Kurt AM, Lyautey J, Lederrey C,Anker P. Microsatellite alterations in plasma DNA of small cell lung cancer patients. Nat Med 1996;2:1033-1035.

218. Wang Y, Hung SC, Linn JF Steiner G, Glazer AN, Sidransky D, Mathies RA. Microsatellite-based cancer detection using capillary array electrophoresis and energy-transfer fluorescent primers. Electrophoresis 1997;18:1742-1749.

219. Sardi I, Bartoletti R, Occhini I, Piazzini M, Travaglini F, Guazzelli R, Montali E. Microsatellite alterations in superficial and locally advanced transitional cell carcinoma of the bladder. Oncol Rep 1999;6:901-905.

220. van Rhijn BW, Lurkin I, Chopin DK Kirkels WJ, Thiery JP, van der Kwast TH, Radvanyi F, Zwarthoff EC. Combined microsatellite and FGFR3 mutation analysis enables a highly sensitive detection of urothelial cell carcinoma in voided urine. Clin Cancer Res 2003;9:257-263.

221. Christensen M, Wolf H, Orntoft TF. Microsatellite alterations in urinary sediments from patients with cystitis and bladder cancer. Int J Cancer 2000;85:614 –617.

222. Seripa D, Parrella P, Gallucci M, Gravina C, Papa S, Fortunato P, Alcini A, Flammia G, Lazzari M, Fazio VM. Sensitive detection of transitional cell carcinoma of the bladder by microsatellite analysis of cells exfoliated in urine. Int J Cancer 2001;95:364-369.

223. Linn JF, Lango M, Halachmi S Schoenberg MP, Sidransky D. Microsatellite analysis and telomerase activity in archived tissue and urine samples of bladder cancer patients. Int J Cancer 1997;74:625-629.

224. Mourah S, Cussenot O, Vimont V, Desgrandchamps F, Teillac P, Cochant-Priollet B, Le Duc A, Fiet J, Soliman H. Assessment of microsatellite instability in urine in the detection of transitional-cell carcinoma of the bladder. Int J Cancer 1998;79:629-633.

225. Baron A, Mastroeni F, Moore PS, Bonetti F, Orlandini S, Manfrin E, Schiavone D, Migliorini F, Lusuardi L, Mobilio G, Scarpa A. Detection of bladder cancer by semi-automated microsatellite analysis of urine sediment. Adv Clin Path 2000;4:19-24.

226. Schneider A, Borgnat S, Lang H, Regine O, Lindner V, Kassem M, Saussine C, Oudet P, Jacqmin D, Gaub MP. Evaluation of microsatellite analysis in urine sediment for diagnosis of bladder cancer. Cancer Res 2000;60:4617-4622.

227. Sourvinos G, Kazanis I, Delakas D, Cranidis A, Spandidos DA. Genetic detection of bladder cancer by microsatellite analysis of p16, RB1 and p53 tumor suppressor genes. J Urol 2001;165:249-252.

228. Larsson PC, Beheshti B, Sampson HA Jewett MA, Shipman R. Allelic deletion fingerprinting of urine cell sediments in bladder cancer. Mol Diagn 2001;6:181-188.

229. von Knobloch R, Hegele A, Brandt H, Olbert P, Heidenreich A, Hofmann R. Serum DNA and urine DNA alterations of urinary transitional cell bladder carcinoma detected by fluorescent microsatellite analysis. Int J Cancer 2001;94:67-72.

230. Zhang J, Fan Z, Gao Y, Xiao Z, Li C, An Q, Cheng S. Detecting bladder cancer in the Chinese by microsatellite analysis: ethnic and etiologic considerations. J Natl Cancer Inst 2001;93:45-50.

231. Amira N, Mourah S, Rozet F, Teillac P, Fiet J, Aubin P, Cortesse A, Desgrandchamps F, Le Duc A, Cussenot O, Soliman H. Non-invasive molecular detection of bladder cancer recurrence. Int J Cancer 2002;101:293-297.

232. Berger AP, Parson W, Stenzl A Steiner H, Bartsch G, Klocker H. Microsatellite alterations in human bladder cancer: detection of tumor cells in urine sediment and tumor tissue. Eur Urol 2002;41:532-539v.

233. Neves M, Ciofu C, Larousserie F, Fleury J, Sibony M, Flahault A, Soubrier F, Gattegno B. Prospective evaluation of genetic abnormalities and telomerase expression in exfoliated urinary cells for bladder cancer detection. J Urol 2002;167:1276-1281

234. Dal Canto M, Bartoletti R, Travaglini F Piazzini M, Lodovichi G, Rizzo M, Selli C. Molecular urinary sediment analysis in patients with transitional cell bladder carcinoma. Anticancer Res 2003;23:5095-5100.

235. Hoque MO, Lee J, Begum S Yamashita K, Engles JM, Schoenberg M, Westra WH, Sidransky D. High-throughput molecular analysis of urine sediment for the detection of bladder cancer by high-density single-nucleotide polymorphism array. Cancer Res 2003;63:5723-5726.

236. Sidransky D, Von Eschenbach A, Tsai YC, Jones P, Summerhayes I, Marshall F, Paul M, Green P, Hamilton SR, Frost P, et al. Identification of p53 gene mutations in bladder cancers and urine samples. Science 1991;252:706-709.

237. Fitzgerald JM, Ramchurren N, Rieger K Levesque P, Silverman M, Libertino JA, Summerhayes IC. Identification of H-ras mutations in urine sediments complements cytology in the detection of bladder tumors. J Natl Cancer Inst 1995;87:29-133.

238. Esteller M, Sanchez-Cespedes M, Rosell R, Sidransky D, Baylin SB, Herman JG. Detection of aberrant promoter hypermethylation of tumor suppressor genes in serum DNA from non-small cell lung cancer patients. Cancer Res 1999;59:67-70

239. Holt SE, Shay JW, Wright WE. Refining the telomere-telomerase hypothesis of aging and cancer. Nat Biotechnol 1996;14:836-839.

240. Rhyu MS. Telomeres, telomerase, and immortality. J Natl Cancer Inst 1995;87:884-894.

241. Zakian VA. Life and cancer without telomerase. Cell 1997;91:1-3.

242. Wright WE, Piatyszek MA, Rainey WE, Byrd W, Shay JW. Telomerase activity in human germline and embryonic tissues and cells. Dev Genet 1996;18:173-179.

243. Broccoli D, Young JW, de Lange T. Telomerase activity in normal and malignant hematopoietic cells. Proc Natl Acad Sci USA 1995;92:9082-9086.

244. Kim NW, Piatyszek MA, Prowse KR, Harley CB, West MD, Ho

PL, Coviello GM, Wright WE, Weinrich SL, Shay JW. Specific association of human telomerase activity with immortal cells and cancer. Science 1994;266:2011-2015.

245. Kim NW and Wu F. Advances in quantification and characterization of telomerase activity by the telomeric repeat amplification protocol (TRAP). Nucleic Acids Res 1997;25:2595-2597.

246. Gelmini S, Caldini A, Becherini L, Capaccioli S, Pazzagli M, Orlando C. Rapid, quantitative nonisotopic assay for telomerase activity in human tumors. Clin Chem 1998;44:2133-2138.

247. Meyerson M, Counter CM, Eaton EN, Ellisen LW, Steiner P, Caddle SD, Ziaugra L, Beijersbergen RL, Davidoff MJ, Liu Q, Bacchetti S, Haber DA., Weinberg RA. hEST2, the putative human telomerase catalytic subunit gene, is up-regulated in tumor cells and during immortalization. Cell 1997;90:785-795.

248. Ulaner GA, Hu JF, Vu TH, Giudice LC, Hoffman AR. Telomerase activity in human development is regulated by human telomerase reverse transcriptase (hTERT) transcription and by alternate splicing of hTERT transcripts. Cancer Res 1998;58:4168-4172.

249. Feng J, Funk WD, Wang SS, Weinrich SL, Avilion AA, Chiu CP, Adams RR, Chang E, Allsopp RC, Yu J, et al. The RNA component of human telomerase. Science 1995;269:1236-1241

250. Ito H, Kyo S, Kanaya T, Takakura M, Koshida K, Namiki M, Inoue M. Detection of human telomerase reverse transcriptase messenger RNA in voided urine samples as a useful diagnostic tool for bladder cancer. Clin Cancer Res 1998;4:2807-2810.

251. Yoshida K, Sugino T, Tahara H, Woodman A, Bolodeoku J, Nargund V, Fellows G, Goodison S, Tahara E, Tarin D. Telomerase activity in bladder carcinoma and its implication for noninvasive diagnosis by detection of exfoliated cancer cells in urine. Cancer 1997;79:362-369.

252. Kavaler E, Landman J, Chang Y, Droller MJ, Liu BC. Detecting human bladder carcinoma cells in voided urine samples by assaying for the presence of telomerase activity. Cancer 1998;82:708-714.

253. Gelmini S, Crisci A, Salvadori B, Pazzagli M, Selli C, Orlando C. Comparison of telomerase activity in bladder carcinoma and exfoliated cells collected in urine and bladder washings, using a quantitative assay. Clin Cancer Res 2000;6:2771-2776.

254. Lancelin F, Anidjar M, Villette JM, Soliman A, Teillac P, Le Duc A, Fiet J, Cussenot O. Telomerase activity as a potential marker in preneoplastic bladder lesions. BJU Int 2000;85:526-531.

255. Kinoshita H, Ogawa O, Kakehi Y, Mishina M, Mitsumori K, Itoh N, Yamada H, Terachi T, Yoshida O. Detection of telomerase activity in exfoliated cells in urine from patients with bladder cancer. J Natl Cancer Inst 1997;89:724-730.

256. Lee DH, Yang SC, Hong SJ, Chung BH, Kim IY. Telomerase: a potential marker of bladder transitional cell carcinoma in bladder washes. Clin Cancer Res 1998;4:535-538.

257. Yokota K, Kanda K, Inoue Y, Kanayama H, Kagawa S. Semiquantitative analysis of telomerase activity in exfoliated human urothelial cells and bladder transitional cell carcinoma. Br J Urol 1998;82:727-732.

258. Cheng CW, Chueh SC, Chern HD. Diagnosis of bladder cancer using telomerase activity in voided urine. J Formos Med Assoc 2000;99:920-925.

259. Dalbagni G, Han W, Zhang ZF, Cordon-Cardon C, Saigo P, Fair WR, Herr H, Kim N, Moore MA. Evaluation of the telomeric repeat amplification protocol (TRAP) assay for telomerase as a diagnostic modality in recurrent bladder cancer. Clin Cancer Res 1997;3:1593-1598.

260. Wu XX, Kakehi Y, Takahashi T, Habuchi T, Ogawa O. Telomerase activity in urine after transurethral resection of superficial bladder cancer and early recurrence. Int J Urol 2000;7:210-217.

261. de Kok JB, van Balken MR, Ruers TJ, Swinkels DW, Klein Gunnewiek JM. Detection of telomerase activity in urine as a tool for noninvasive detection of recurrent bladder tumors is poor and cannot be improved by timing of sampling. Clin Chem 2000;46:2014-2015.

262. Wu XX, Kakehi Y, Nishiyama H, Habuchi T, Ogawa O. Telomerase activity in urine after transurethral resection is not a predictive marker for recurrence of superficial bladder cancer. Int J Urol 2003;10:117-118.

263. Bhuiyan J, Akhter J, O'Kane DJ. Performance characteristics of multiple urinary tumor markers and sample collection techniques in the detection of transitional cell carcinoma of the bladder. Clin Chim Acta 2003;331:69-77.

264. Bialkowska-Hobrzanska H, Bowles L, Bukala B, Joseph MG, Fletcher R, Razvi H. Comparison of human telomerase reverse transcriptase messenger RNA and telomerase activity as urine markers for diagnosis of bladder carcinoma. Mol Diagn 2000;5:267-277.

265. Isurugi K, Suzuki Y, Tanji S, Fujioka T. Detection of the presence of catalytic subunit mRNA associated with telomerase gene in exfoliated urothelial cells from patients with bladder cancer. J Urol 2002;168:1574-1577.

266. De Kok JB, Schalken JA, Aalders TW, Ruers TJ, Willems HL, Swinkels DW..Quantitative measurement of telomerase reverse transcriptase (hTERT) mRNA in urothelial cell carcinomas. Int J Cancer 2000;87:217-220.

267. Melissourgos N, Kastrinakis NG, Davilas I, Foukas P, Farmakis A, Lykourinas M. Detection of human telomerase reverse transcriptase mRNA in urine of patients with bladder cancer: evaluation of an emerging tumor marker. Urology 2003;62:362-367.

268. Liu BC and Loughlin KR. Telomerase in human bladder cancer. Urol Clin North Am 2000;27:115-123, x.

269. Beiche B, Ebert T, Schmitz-Dräger BJ. Immunzytologie in der Diagnostik des Urothelkarzinoms – ein reproduzierbares Testverfahren? Urologe A 2002;41 (Suppl 1):45.

270. Mian C, Pycha A, Wiener H, Haitel A, Lodde M, Marberger M. Immunocyt: a new tool for detecting transitional cell cancer of the urinary tract. J Urol 1999;161:1486-1489.

271. Olsson H and Zackrisson B. ImmunoCyt a useful method in the follow-up protocol for patients with urinary bladder carcinoma. Scand J Urol Nephrol 2001;35:280-282.

272. Lodde M, Mian C, Negri G, Berner L, Maffei N, Lusuardi L, Palermo S, Marberger M, Brössner C, Pycha A. Role of uCyt+ in the detection and surveillance of urothelial carcinoma. Urology 2003;61:243-247.

273. Feil G, Zumbragel A, Paulgen-Nelde HJ, Hennenlotter J, Maurer S, Krause S, Bichler KH, Stenzl A. Accuracy of the ImmunoCyt assay in the diagnosis of transitional cell carcinoma of the urinary bladder. Anticancer Res 2003;23:963-967.

274. Fradet Y. Recent advances in the management of superficial bladder tumors. Can J Urol 2002;9:1544-1550.

275. Grossman HB, Washington RW Jr, Carey TE, Liebert M. Alterations in antigen expressionin superficial bladder cancer. J Cell Biochem Suppl 1992;16I:63-68.

276. Bonner RB, Liebert M, Hurst RE, Grossman HB, Bane BL, Hemstreet GP 3rd. Characterization of the DD23 tumor-associated antigen for bladder cancer detection and recurrence monitoring. Cancer Epidemiol Biomarkers Prev 1996;5:971-978.

277. Gilbert SM, Veltri RW, Sawczuk A, Shabsigh A, Knowles DR, Bright S, O'Dowd GJ, Olsson CA, Benson MC, Sawczuk IS. Evaluation of DD23 as a marker for detection of recurrent transitional cell carcinoma of the bladder in patients with a history of bladder cancer. Urology 2003;61:539-543.

278. Vriesema JL, van der Poel HG, Debruyne FM, Schalken JA, Kok LP, Boon ME. Neural network-based digitized cell image diagnosis of bladder wash cytology. Diagn Cytopathol 2000;23:171-179.

279. van Rhijn BW, van der Poel HG, Boon ME, Debruyne FM, Schalken JA, Witjes JA. Presence of carcinoma in situ and high 2C-deviation index are the best predictors of invasive transitional cell carcinoma of the bladder in patients with high-risk Quanticyt. Urology 2000;55:363-367.

280. van der Poel HG, Van Balken MR, Schamhart DH, Peelen P, de Reijke T, Debruyne FM, Schalken JA, Witjes JA. Bladder wash cytology, quantitative cytology, and the qualitative BTA test in patients with superficial bladder cancer. Urology 1998;51:44-50.

281. Wiener HG, Mian C, Haitel A, Pycha A, Schatzl G, Marberger M. Can urine bound diagnostic tests replace cystoscopy in the management of bladder cancer? J Urol 1998;159:1876-1880.

282. van der Poel HG, van Rhijn BW, Peelen P, Debruyne FM, Boon ME, Schalken JA. Consecutive quantitative cytology in bladder cancer. Urology 2000;56:584-588.

283. Junker K, Boerner D, Schulze W, Utting M, Schubert J, Werner W. Analysis of genetic alterations in normal bladder urothelium. Urology 2003;62:1134-1138.

284. Knowles MA. What we could do now: molecular pathology of bladder cancer. Mol Pathol 2001;54:215-221.

285. Placer J, Espinet B, Salido M, Sole F, Gelabert-Mas A. Clinical utility of a multiprobe FISH assay in voided urine specimens for the detection of bladder cancer and its recurrences, compared with urinary cytology. Eur Urol 2002;42:547-552.

286. Dalquen P, Kleiber B, Grilli B, Herzog M, Bubendorf L, Oberholzer M. DNA image cytometry and fluorescence in situ hybridization for noninvasive detection of urothelial tumors in voided urine. Cancer 2002;96:374-379.

287. Bubendorf L, Grilli B, Sauter G, Mihatsch MJ, Gasser TC, Dalquen P. Multiprobe FISH for enhanced detection of bladder cancer in voided urine specimens and bladder washings. Am J Clin Pathol 2001;116:79-86.

288. Sokolova IA, Halling KC, Jenkins RB, Burkhardt HM, Meyer RG, Seelig SA, King W. The development of a multitarget, multicolor fluorescence in situ hybridization assay for the detection of urothelial carcinoma in urine. J Mol Diagn 2000;2:116-123.

289. Halling KC, King W, Sokolova IA, Meyer RG, Burkhardt HM, Halling AC, Cheville JC, Sebo TJ, Ramakumar S, Stewart CS, Pankratz S, O'Kane DJ, Seelig SA, Lieber MM, Jenkins RB. A comparison of cytology and fluorescence in situ hybridization for the detection of urothelial carcinoma. J Urol 2000;164:1768-1775.

290. Veeramachaneni R, Nordberg ML, Shi R, Herrera GA, Turbat-Herrera EA. Evaluation of fluorescence in situ hybridization as an ancillary tool to urine cytology in diagnosing urothelial carcinoma. Diagn Cytopathol 2003;28:301-307.

291. Giannopoulos A, Manousakas T, Gounari A, Constantinides C, Choremi-Papadopoulou H, Dimopoulos C. Comparative evaluation of the diagnostic performance of the BTA stat test, NMP22 and urinary bladder cancer antigen for primary and recurrent bladder tumors. J Urol 2001;166:470-475.

292. Gutierrez Banos JL, Rebollo Rodrigo MH, Antolin Juarez FM, Martin Garcia B. NMP22, BTA stat test and cytology in the diagnosis of bladder cancer: a comparative study. Urol Int 2001;66:185-190.

293. Casetta G, Gontero P, Zitella A, Pelucelli G, Formiconi A, Priolo G, Martinasso G, Mengozzi G, Aimo G, Viberti L, Tizzani A. BTA quantitative assay and NMP22 testing compared with urine cytology in the detection of transitional cell carcinoma of the bladder. Urol Int 2000;65:100-105.

294. McShane LM, Aamodt R, Cordon-Cardo C, Cote R, Faraggi D, Fradet Y, Grossman HB, Peng A, Taube SE, Waldman FM. Reproducibility of p53 immunohistochemistry in bladder tumors. National Cancer Institute, Bladder Tumor Marker Network. Clin Cancer Res 2000;6:1854-1864.

295. Pycha A, Mian C, Posch B, Haitel A, Mokhtar AA, El-Baz M, Ghoneim MA, Marberger M. Numerical chromosomal aberrations in muscle invasive squamous cell and transitional cell cancer of the urinary bladder: an alternative to classic prognostic indicators? Urology 1999;53:1005-1010.

296. Neal DE, Marsh C, Bennett MK, Abel PD, Hall RR, Sainsbury JR, Harris AL. Epidermal-growth-factor receptors in human bladder cancer: comparison of invasive and superficial tumours. Lancet 1985;1:366-368.

297. Messing EM. Clinical implications of the expression of epidermal growth factor receptors in human transitional cell carcinoma. Cancer Res 1990;50:2530-2537.

298. Nguyen PL, Swanson PE, Jaszcz W, Aeppli DM, Zhang G, Singleton TP, Ward S, Dykoski D, Harvey J, Niehans GA. Expression of epidermal growth factor receptor in invasive transitional cell carcinoma of the urinary bladder. A multivariate survival analysis. Am J Clin Pathol 1994;101:166-176.

299. Lipponen P and Eskelinen M. Expression of epidermal growth factor receptor in bladder cancer as related to established prognostic factors, oncoprotein (c-erbB-2, p53) expression and long-term prognosis. Br J Cancer 1994;69:1120-1125.

300. Mellon K, Wright C, Kelly P, Horne CH, Neal DE. Long-term outcome related to epidermal growth factor receptor status in bladder cancer. J Urol 1995;153:919-925.

301. Liukkonen T, Rajala P, Raitanen M, Rintala E, Kaasinen E, Lipponen P. Prognostic value of MIB-1 score, p53, EGFr, mitotic index and papillary status in primary superficial (Stage pTa/T1) bladder cancer: a prospective comparative study. The Finnbladder Group. Eur Urol 1999;36:393-400.

302. Ravery V, Grignon D, Angulo J, Pontes E, Montie J, Crissman J, Chopin D. Evaluation of epidermal growth factor receptor, transforming growth factor alpha, epidermal growth factor and c-erbB2 in the progression of invasive bladder cancer. Urol Res 1997;25:9-17.

303. Lipponen P, Eskelinen M, Syrjanen S, Tervahauta A, Syrjanen K: Use of immunohistochemically demonstrated c-erb B-2 oncoprotein expression as a prognostic factor in transitional cell carcinoma of the urinary bladder. Eur Urol 1991;20:238-242.

304. Sato K, Moriyama M, Mori S, Saito M, Watanuki T, Terada K, Okuhara E, Akiyama T, Toyoshima K, Yamamoto T, et al. An immunohistologic evaluation of C-erbB-2 gene product in patients with urinary bladder carcinoma. Cancer 1992;70:2493-2498.

305. Kruger S, Weitsch G, Buttner H, Matthiensen A, Bohmer T, Marquardt T, Sayk F, Feller AC, Bohle A. Overexpression of c-erbB-2 oncoprotein in muscle-invasive bladder carcinoma: relationship with gene amplification, clinicopathological parameters and prognostic outcome. Int J Oncol 2002;21:981-987.

306. Mellon JK, Lunec J, Wright C, Horne CH, Kelly P, Neal DE. C-erbB-2 in bladder cancer: molecular biology, correlation with epidermal growth factor receptors and prognostic value. J Urol 1996;155:321-326.

307. Underwood M, Bartlett J, Reeves J, Gardiner DS, Scott R, Cooke T. C-erbB-2 gene amplification: a molecular marker in recurrent bladder tumors? Cancer Res 1995;55:2422-2430.

308. Jimenez RE, Hussain M, Bianco FJ Jr., Vaishampayan U, Tabazcka P, Sakr WA, Pontes JE, Wood DP, Jr., Grignon DJ. Her-2/neu overexpression in muscle-invasive urothelial carcinoma of the bladder: prognostic significance and comparative analysis in primary and metastatic tumors. Clin Cancer Res 2001;7:2440-2447.

309. Gandour-Edwards R, Lara PN, Jr., Folkins AK, LaSalle JM, Beckett L, Li Y, Meyers FJ, DeVere-White R. Does HER2/neu expression provide prognostic information in patients with advanced urothelial carcinoma? Cancer 2002;95:1009-1015.

310. Knowles MA and Williamson M. Mutation of H-ras is infrequent in bladder cancer: confirmation by single-strand conformation polymorphism analysis, designed restriction fragment length polymorphisms, and direct sequencing. Cancer Res 1993;53:133-139.

311. Fontana D, Bellina M, Scoffone C, Cagnazzi E, Cappia S, Cavallo F, Russo R, Leonardo E. Evaluation of c-ras oncogene product (p21) in superficial bladder cancer. Eur Urol 1996;29:470-476.

312. Moriyama N, Umeda T, Akaza H, Taniguchi J, Kitamura T, Murakami T, Kawabe K, Aso Y. Expression of ras p21 oncogene product on human bladder tumors. Urol Int 1989;44:260-263.

313. Ye DW, Zheng JF, Qian SX, Ma YJ. Correlation between the expression of oncogenes ras and c-erbB-2 and the biological behavior of bladder tumors. Urol Res 1993;21:39-43.

314. Shiina H, Igawa M, Urakami S, Honda S, Shirakawa H, Ishibe T. Immunohistochemical analysis of bcl-2 expression in transitional cell carcinoma of the bladder. J Clin Pathol 1996;49:395-399.

315. Pollack A, Wu CS, Czerniak B, Zagars GK, Benedict WF, McDonnell TJ. Abnormal bcl-2 and pRb expression are independent correlates of radiation response in muscle-invasive bladder cancer. Clin Cancer Res 1997;3:1823-1829.

316. Rodel C, Grabenbauer GG, Rodel F, Birkenhake S, Kuhn R, Martus P, Zorcher T, Fursich D, Papadopoulos T, Dunst J, Schrott KM, Sauer R. Apoptosis, p53, bcl-2, and Ki-67 in invasive bladder carcinoma: possible predictors for response to radiochemotherapy and successful bladder preservation. Int J Radiat Oncol Biol Phys 2000;46:1213-1221.

317. Stavropoulos NE, Filiadis I, Ioachim E, Hastazeris K, Tsimaris I, Kalogeras D, Stefanaki S, Agnantis NJ. Prognostic significance of p53, bcl-2 and Ki-67 in high risk superficial bladder cancer. Anticancer Res 2002;22:3759-3764.

318. Habuchi T, Kinoshita H, Yamada H, Kakehi Y, Ogawa O, Wu WJ, Takahashi R, Sugiyama T, Yoshida O. Oncogene amplification in urothelial cancers with p53 gene mutation or MDM2 amplification. J Natl Cancer Inst 1994;86:1331-1335.

319. Lianes P, Orlow I, Zhang ZF, Oliva MR, Sarkis AS, Reuter VE, Cordon-Cardo C. Altered patterns of MDM2 and TP53 expression in human bladder cancer. J Natl Cancer Inst 1994;86: 1325-1330.

320. Cappellen D, De Oliveira C, Ricol D, de Medina S, Bourdin J, Sastre-Garau X, Chopin D, Thiery JP, Radvanyi F. Frequent activating mutations of FGFR3 in human bladder and cervix carcinomas. Nat Genet 1999;23:18-20.

321. van Rhijn BW, Lurkin I, Radvanyi F, Kirkels WJ, van der Kwast TH, Zwarthoff EC. The fibroblast growth factor receptor 3 (FGFR3) mutation is a strong indicator of superficial bladder cancer with low recurrence rate. Cancer Res 2001;61:1265-1268.

322. van Rhijn BW, Vis AN, van der Kwast TH, Kirkels WJ, Radvanyi F, Ooms EC, Chopin DK, Boeve ER, Jobsis AC, Zwarthoff EC. Molecular grading of urothelial cell carcinoma with fibroblast growth factor receptor 3 and MIB-1 is superior to pathologic grade for the prediction of clinical outcome. J Clin Oncol 2003;21:1912-1921.

323. Kotake T, Saiki S, Kinouchi T, Shiku H, Nakayama E. Detection of the c-myc gene product in urinary bladder cancer. Jpn J Cancer Res 1990;81:1198-1201.

324. Lipponen PK. Expression of c-myc protein is related to cell proliferation and expression of growth factor receptors in transitional cell bladder cancer. J Pathol 1995;175:203-210.

325. Schmitz-Drager BJ, Schulz WA, Jurgens B, Gerharz CD, van Roeyen CR, Bultel H, Ebert T, Ackermann R. c-myc in bladder cancer. Clinical findings and analysis of mechanism. Urol Res 1997;25 Suppl 1:S45 - S49.

326. Hollstein M, Sidransky D, Vogelstein B, Harris CC. p53 mutations in human cancers. Science 1991;253:49-53.

327. Esrig D, Spruck CH, 3rd, Nichols PW, Chaiwun B, Steven K, Groshen S, Chen SC, Skinner DG, Jones PA, Cote RJ. p53 nuclear protein accumulation correlates with mutations in the p53 gene, tumor grade, and stage in bladder cancer. Am J Pathol 1993;143:1389-1397.

328. Watanabe J, Nishiyama H, Okubo K, Takahashi T, Toda Y, Habuchi T, Kakehi Y, Tada M, Ogawa O. Clinical evaluation of p53 mutations in urothelial carcinoma by IHC and FASAY. Urology 2004 May;63(5):989-993.

329. Esrig D, Elmajian D, Groshen S, Freeman JA, Stein JP, Chen SC, Nichols PW, Skinner DG, Jones PA, Cote RJ. Accumulation of nuclear p53 and tumor progression in bladder cancer. N Engl J Med 1994;331:1259-1264.

330. Fleshner N, Kapusta L, Ezer D, Herschorn S, Klotz L. p53 nuclear accumulation is not associated with decreased disease-free survival in patients with node positive transitional cell carcinoma of the bladder. J Urol 2000;164:1177-1182.

331. Lipponen PK. Over-expression of p53 nuclear oncoprotein in transitional-cell bladder cancer and its prognostic value. Int J Cancer 1993;53:365-370.

332. Lianes P, Charytonowicz E, Cordon-Cardo C, Fradet Y, Grossman HB, Hemstreet GP, Waldman FM, Chew K, Wheeless LL, Faraggi D. Biomarker study of primary nonmetastatic versus metastatic invasive bladder cancer. National Cancer Institute Bladder Tumor Marker Network. Clin Cancer Res 1998;4:1267-1271.

333. Haitel A, Posch B, El-Baz M, Mokhtar AA, Susani M, Ghoneim MA, Marberger M. Bilharzial related, organ confined, muscle invasive bladder cancer: prognostic value of apoptosis markers, proliferation markers, p53, E-cadherin, epidermal growth factor receptor and c-erbB-2. J Urol 2001;165:1481-1487.

334. Schmitz-Drager BJ, Goebell PJ, Ebert T, Fradet Y. p53 immunohistochemistry as a prognostic marker in bladder cancer. Playground for urology scientists? Eur Urol 2000;38:691-699; discussion 700.

335. Llopis J, Alcaraz A, Ribal MJ, Sole M, Ventura PJ, Barranco MA, Rodriguez A, Corral JM, Carretero P. p53 expression predicts progression and poor survival in T1 bladder tumours. Eur Urol 2000;37:644-653.

336. Rodriguez-Alonso A, Pita-Fernandez S, Gonzalez-Carrero J, Nogueira-March JL: p53 and ki67 expression as prognostic factors for cancer-related survival in stage T1 transitional cell bladder carcinoma. Eur Urol 2002;41:182-188; discussion 188-189.

337. Saint F, Le Frere Belda MA, Quintela R, Hoznek A, Patard JJ, Bellot J, Popov Z, Zafrani ES, Abbou CC, Chopin DK, de Medina SG. Pretreatment p53 nuclear overexpression as a prognostic marker in superficial bladder cancer treated with Bacillus Calmette-Guerin (BCG). Eur Urol 2004;45:475-482.

338. Lacombe L, Dalbagni G, Zhang ZF, Cordon-Cardo C, Fair WR, Herr HW, Reuter VE. Overexpression of p53 protein in a high-risk population of patients with superficial bladder cancer before and after bacillus Calmette-Guerin therapy: correlation to clinical outcome. J Clin Oncol 1996;14:2646-2652.

339. Peyromaure M, Weibing S, Sebe P, Verpillat P, Toublanc M, Dauge MC, Boccon-Gibod L, Ravery V. Prognostic value of p53 overexpression in T1G3 bladder tumors treated with bacillus Calmette-Guerin therapy. Urology 2002;59:409-413.

340. Zlotta AR, Noel JC, Fayt I, Drowart A, Van Vooren JP, Huygen K, Simon J, Schulman CC. Correlation and prognostic significance of p53, p21WAF1/CIP1 and Ki-67 expression in patients with superficial bladder tumors treated with bacillus Calmette-Guerin intravesical therapy. J Urol 1999;161:792-798.

341. Wu TT, Chen JH, Lee YH, Huang JK. The role of bcl-2, p53, and

ki-67 index in predicting tumor recurrence for low grade superficial transitional cell bladder carcinoma. J Urol 2000;163:758-760.

342. Gontero P, Casetta G, Zitella A, Ballario R, Pacchioni D, Magnani C, Muir GH, Tizzani A. Evaluation of P53 protein overexpression, Ki67 proliferative activity and mitotic index as markers of tumour recurrence in superficial transitional cell carcinoma of the bladder. Eur Urol 2000;38:287-296.

343. Pfister C, Moore L, Allard P, Larue H, Lacombe L, Tetu B, Meyer F, Fradet Y. Predictive value of cell cycle markers p53, MDM2, p21, and Ki-67 in superficial bladder tumor recurrence. Clin Cancer Res 1999;5:4079-4084.

344. Vatne V, Maartmann-Moe H, Hoestmark J. The prognostic value of p53 in superficially infiltrating transitional cell carcinoma. Scand J Urol Nephrol 1995;29:491-495.

345. Sarkis AS, Bajorin DF, Reuter VE, Herr HW, Netto G, Zhang ZF, Schultz PK, Cordon-Cardo C, Scher HI. Prognostic value of p53 nuclear overexpression in patients with invasive bladder cancer treated with neoadjuvant MVAC. J Clin Oncol 1995;13:1384-1390.

346. Kakehi Y, Ozdemir E, Habuchi T, Yamabe H, Hashimura T, Katsura Y, Yoshida O. Absence of p53 overexpression and favorable response to cisplatin-based neoadjuvant chemotherapy in urothelial carcinomas. Jpn J Cancer Res 1998;89:214-220.

347. Jankevicius F, Goebell P, Kushima M, Schulz WA, Ackermann R, Schmitz-Drager BJ. p21 and p53 Immunostaining and survival following systemic chemotherapy for urothelial cancer. Urol Int 2002;69:174-180.

348. Cote RJ, Esrig D, Groshen S, Jones PA, Skinner DG. p53 and treatment of bladder cancer. Nature 1997;385:123-125.

349. Sengelov L, Horn T, Steven K. p53 nuclear immunoreactivity as a predictor of response and outcome following chemotherapy for metastatic bladder cancer. J Cancer Res Clin Oncol 1997;123:565-570.

350. Ogura K, Habuchi T, Yamada H, Ogawa O, Yoshida O. Immunohistochemical analysis of p53 and proliferating cell nuclear antigen (PCNA) in bladder cancer: positive immunostaining and radiosensitivity. Int J Urol 1995;2:302-308.

351. Osen I, Fossa SD, Majak B, Rotterud R, Berner A. Prognostic factors in muscle-invasive bladder cancer treated with radiotherapy: an immunohistochemical study. Br J Urol 1998;81:862-869.

352. Rotterud R, Berner A, Holm R, Skovlund E, Fossa SD. p53, p21 and mdm2 expression vs the response to radiotherapy in transitional cell carcinoma of the bladder. BJU Int 2001;88:202-208.

353. Cote RJ, Dunn MD, Chatterjee SJ, Stein JP, Shi SR, Tran QC, Hu SX, Xu HJ, Groshen S, Taylor CR, Skinner DG, Benedict WF. Elevated and absent pRb expression is associated with bladder cancer progression and has cooperative effects with p53. Cancer Res 1998;58:1090-1094.

354. Cordon-Cardo C, Zhang ZF, Dalbagni G, Drobnjak M, Charytonowicz E, Hu SX, Xu HJ, Reuter VE, Benedict WF: Cooperative effects of p53 and pRB alterations in primary superficial bladder tumors. Cancer Res 1997;57:1217-1221.

355. Chatterjee SJ, Datar R, Youssefzadeh D, George B, Goebell PJ, Stein JP, Young L, Shi SR, Gee C, Groshen S, Skinner DG, Cote RJ. Combined effects of p53, p21, and pRb expression in the progression of bladder transitional cell carcinoma. J Clin Oncol 2004;22:1007-1013.

356. Shariat SF, Tokunaga H, Zhou J, Kim J, Ayala GE, Benedict WF, Lerner SP. p53, p21, pRB, and p16 expression predict clinical outcome in cystectomy with bladder cancer. J Clin Oncol 2004;22:1014-1024.

357. Cordon-Cardo C, Wartinger D, Petrylak D, Dalbagni G, Fair WR, Fuks Z, Reuter VE. Altered expression of the retinoblastoma gene product: prognostic indicator in bladder cancer. J Natl Cancer Inst 1992;84:1251-1256.

358. Logothetis CJ, Xu HJ, Ro JY, Hu SX, Sahin A, Ordonez N, Benedict WF. Altered expression of retinoblastoma protein and known prognostic variables in locally advanced bladder cancer. J Natl Cancer Inst 1992;84:1256-1261.

359. Grossman HB, Liebert M, Antelo M, Dinney CP, Hu SX, Palmer JL, Benedict WF. p53 and RB expression predict progression in T1 bladder cancer. Clin Cancer Res 1998;4:829-834.

360. Stein JP, Ginsberg DA, Grossfeld GD, Chatterjee SJ, Esrig D, Dickinson MG, Groshen S, Taylor CR, Jones PA, Skinner DG, Cote RJ. Effect of p21WAF1/CIP1 expression on tumor progression in bladder cancer. J Natl Cancer Inst 1998;90:1072-1079.

361. Migaldi M, Sgambato A, Garagnani L, Ardito R, Ferrari P, De Gaetani C, Cittadini A, Trentini GP. Loss of p21Waf1 expression is a strong predictor of reduced survival in primary superficial bladder cancers. Clin Cancer Res 2000;6:3131-3138.

362. Lipponen P, Aaltomaa S, Eskelinen M, Ala-Opas M, Kosma VM. Expression of p21(waf1/cip1) protein in transitional cell bladder tumours and its prognostic value. Eur Urol 1998;34:237-243.

363. Liukkonen T, Lipponen P, Raitanen M, Kaasinen E, Ala-Opas M, Rajala P, Kosma VM. Evaluation of p21WAF1/CIP1 and cyclin D1 expression in the progression of superficial bladder cancer. Finbladder Group. Urol Res 2000;28:285-292.

364. Korkolopoulou P, Christodoulou P, Konstantinidou AE, Thomas-Tsagli E, Kapralos P, Davaris P. Cell cycle regulators in bladder cancer: a multivariate survival study with emphasis on p27Kip1. Hum Pathol 2000;31:751-760.

365. Sgambato A, Migaldi M, Faraglia B, Garagnani L, Romano G, De Gaetani C, Ferrari P, Capelli G, Trentini GP, Cittadini A. Loss of P27Kip1 expression correlates with tumor grade and with reduced disease-free survival in primary superficial bladder cancers. Cancer Res 1999;59:3245-3250.

366. Kamai T, Takagi K, Asami H, Ito Y, Oshima H, Yoshida KI. Decreasing of p27(Kip1) and cyclin E protein levels is associated with progression from superficial into invasive bladder cancer. Br J Cancer 2001;84:1242-1251.

367. Gerdes J, Lemke H, Baisch H, Wacker HH, Schwab U, Stein H. Cell cycle analysis of a cell proliferation-associated human nuclear antigen defined by the monoclonal antibody Ki-67. J Immunol 1984;133:1710-1715.

368. Santos L, Amaro T, Costa C, Pereira S, Bento MJ, Lopes P, Oliveira J, Criado B, Lopes C. Ki-67 index enhances the prognostic accuracy of the urothelial superficial bladder carcinoma risk group classification. Int J Cancer 2003;105:267-272.

369. Liukkonen T, Rajala P, Raitanen M, Rintala E, Kaasinen E, Lipponen P. Prognostic value of MIB-1 score, p53, EGFr, mitotic index and papillary status in primary superficial (Stage pTa/T1) bladder cancer: a prospective comparative study. The Finnbladder Group. Eur Urol 1999;36:393-400.

370. Stavropoulos NE, Filiadis I, Ioachim E, Hastazeris K, Tsimaris I, Kalogeras D, Stefanaki S, Agnantis NJ. Prognostic significance of p53, bcl-2 and Ki-67 in high risk superficial bladder cancer. Anticancer Res 2002;22:3759-3764.

371. Popov Z, Hoznek A, Colombel M, Bastuji-Garin S, Lefrere-Belda MA, Bellot J, Abboh CC, Mazerolles C, Chopin DK. The prognostic value of p53 nuclear overexpression and MIB-1 as a proliferative marker in transitional cell carcinoma of the bladder. Cancer 1997;80:1472-1481.

372. Sgambato A, Migaldi M, Faraglia B, De Aloysio G, Ferrari P, Ardito R, De Gaetani C, Capelli G, Cittadini A, Trentini GP. Cyclin D1 expression in papillary superficial bladder cancer: its association with other cell cycle-associated proteins, cell proliferation and clinical outcome. Int J Cancer 2002;97:671-678.

373. Wagner U, Suess K, Luginbuhl T, Schmid U, Ackermann D, Zellweger T, Maurer R, Alund G, Knonagel H, Rist M, Jordan P, Moch H, Mihatsch MJ, Gasser TC, Sauter G. Cyclin D1 overexpression lacks prognostic significance in superficial urinary bladder cancer. J Pathol 1999;188:44-50.

374. Richter J, Wagner U, Kononen J, Fijan A, Bruderer J, Schmid U, Ackermann D, Maurer R, Alund G, Knonagel H, Rist M, Wilber K, Anabitarte M, Hering F, Hardmeier T, Schonenberger A, Flury R, Jager P, Fehr JL, Schraml P, Moch H, Mihatsch MJ, Gasser T, Kallioniemi OP, Sauter G. High-throughput tissue microarray analysis of cyclin E gene amplification and overexpression in urinary bladder cancer. Am J Pathol 2000;157:787-794.

375. Crew JP, O'Brien T, Bicknell R, Fuggle S, Cranston D, Harris AL. Urinary vascular endothelial growth factor and its correlation with bladder cancer recurrence rates. J Urol 1999;161:799-804.

376. Chow NH, Liu HS, Chan SH, Cheng HL, Tzai TS. Expression of vascular endothelial growth factor in primary superficial bladder cancer. Anticancer Res 1999;19:4593-4597.

377. Inoue K, Slaton JW, Karashima T, Yoshikawa C, Shuin T, Sweeney P, Millikan R, Dinney CP. The prognostic value of angiogenesis factor expression for predicting recurrence and metastasis of bladder cancer after neoadjuvant chemotherapy and radical cystectomy. Clin Cancer Res 2000;6:4866-4873.

378. Grossfeld GD, Ginsberg DA, Stein JP, Bochner BH, Esrig D, Groshen S, Dunn M, Nichols PW, Taylor CR, Skinner DG, Cote RJ. Thrombospondin-1 expression in bladder cancer: association with p53 alterations, tumor angiogenesis, and tumor progression. J Natl Cancer Inst 1997;89:219-227.

379. Shirahama T, Arima J, Akiba S, Sakakura C. Relation between cyclooxygenase-2 expression and tumor invasiveness and patient survival in transitional cell carcinoma of the urinary bladder. Cancer 2001;92:188-193.

380. Shariat SF, Kim JH, Ayala GE, Kho K, Wheeler TM, Lerner SP. Cyclooxygenase-2 is highly expressed in carcinoma in situ and T1 transitional cell carcinoma of the bladder. J Urol 2003;169:938-942.

381. Kim SI, Kwon SM, Kim YS, Hong SJ. Association of cyclooxygenase-2 expression with prognosis of stage T1 grade 3 bladder cancer. Urology 2002;60:816-821.

382. Kanayama H, Yokota K, Kurokawa Y, Murakami Y, Nishitani M, Kagawa S. Prognostic values of matrix metalloproteinase-2 and tissue inhibitor of metalloproteinase-2 expression in bladder cancer. Cancer 1998;82:1359-1366.

383. Gohji K, Fujimoto N, Ohkawa J, Fujii A, Nakajima M. Imbalance between serum matrix metalloproteinase-2 and its inhibitor as a predictor of recurrence of urothelial cancer. Br J Cancer 1998;77:650-655.

384. Bringuier PP, Umbas R, Schaafsma HE, Karthaus HF, Debruyne FM, Schalken JA. Decreased E-cadherin immunoreactivity correlates with poor survival in patients with bladder tumors. Cancer Res 1993;53:3241-3245.

385. Otto T, Birchmeier W, Schmidt U, Hinke A, Schipper J, Rubben H, Raz A. Inverse relation of E-cadherin and autocrine motility factor receptor expression as a prognostic factor in patients with bladder carcinomas. Cancer Res 1994;54:3120-3123.

386. Lipponen PK and Eskelinen MJ. Reduced expression of E-cadherin is related to invasive disease and frequent recurrence in bladder cancer. J Cancer Res Clin Oncol 1995;121:303-308.

387. Ross JS, del Rosario AD, Figge HL, Sheehan C, Fisher HA, Bui HX. E-cadherin expression in papillary transitional cell carcinoma of the urinary bladder. Hum Pathol 1995;26:940-944.

388. Syrigos KN, Harrington K, Waxman J, Krausz T, Pignatelli M. Altered gamma-catenin expression correlates with poor survival in patients with bladder cancer. J Urol 1998;160:1889-1893.

389. Byrne RR, Shariat SF, Brown R, Kattan MW, Morton RJ, Wheeler TM, Lerner SP. E-cadherin immunostaining of bladder transitional cell carcinoma, carcinoma in situ and lymph node metastases with long-term followup. J Urol 2001;165:1473-1479.

390. Matsumura Y, Sugiyama M, Matsumura S, Hayle AJ, Robinson P, Smith JC, Tarin D. Unusual retention of introns in CD44 gene transcripts in bladder cancer provides new diagnostic and clinical oncological opportunities. J Pathol 1995;177:11-20.

391. Miyake H, Eto H, Arakawa S, Kamidono S, Hara I. Over expression of CD44V8-10 in urinary exfoliated cells as an independent prognostic predictor in patients with urothelial cancer. J Urol 2002;167:1282-1287.

392. Hasui Y, Marutsuka K, Asada Y, Osada Y. Prognostic value of urokinase-type plasminogen activator in patients with superficial bladder cancer. Urology 1996;47:34-37.

393. Shariat SF, Monoski MA, Andrews B, Wheeler TM, Lerner SP, Slawin KM. Association of plasma urokinase-type plasminogen activator and its receptor with clinical outcome in patients undergoing radical cystectomy for transitional cell carcinoma of the bladder. Urology 2003;61:1053-1058.

394. Naito S, Sakamoto N, Kotoh S, Goto K, Matsumoto T, Kumazawa J. Correlation between the expression of P-glycoprotein and multidrug-resistant phenotype in transitional cell carcinoma of the urinary tract. Eur Urol 1992;22:158-162.

395. Akdas A, Turkeri LN, Kullu S, Tarcan T, Sakr W, Grignon DJ. Glutathione S-transferase and multidrug-resistant phenotype in transitional cell carcinoma of the bladder. Eur Urol 1996;29:483-486.

396. Pu YS, Tsai TC, Cheng AL, Tsai CY, Tseng NF, Su IJ, Hsieh CY, Lai MK. Expression of MDR-1 gene in transitional cell carcinoma and its correlation with chemotherapy response. J Urol 1996;156:271-275.

397. Tada Y, Wada M, Kuroiwa K, Kinugawa N, Harada T, Nagayama J, Nakagawa M, Naito S, Kuwano M. MDR1 gene overexpression and altered degree of methylation at the promoter region in bladder cancer during chemotherapeutic treatment. Clin Cancer Res 2000;6:4618-4627.

398. Diestra JE, Condom E, Del Muro XG, Scheffer GL, Perez J, Zurita AJ, Munoz-Segui J, Vigues F, Scheper RJ, Capella G, Germa-Lluch JR, Izquierdo MA. Expression of multidrug resistance proteins P-glycoprotein, multidrug resistance protein 1, breast cancer resistance protein and lung resistance related protein in locally advanced bladder cancer treated with neoadjuvant chemotherapy: biological and clinical implications. J Urol 2003;170:1383-1387.

399. Soloway MS. Editorial: Do we have a prostate specific antigen for bladder cancer? J Urol 1999;161:447-448.

Committee 3

Low Grade, Ta (Noninvasive) Urothelial Carcinoma of the Bladder

Chairs

W. Oosterlinck (Belgium)

E. Solsona (Spain)

Members

H. Akaza (Japan)

C. Busch (Sweden)

P. J. Goebell (Germany)

P.-U. Malmström (Sweden)

H. Özen (Turkey)

P. Sved (USA)

CONTENTS

Low Grade, Ta (Noninvasive) Urothelial Carcinoma of the Bladder

W. Oosterlinck, E. Solsona

H. Akaza, C. Busch, P. J. Goebell, P.-U. Malmström, H. Özen, P. Sved

I. INTRODUCTION

The low grade urothelial neoplasms have a clearly different and better outcome than higher grade tumors. While they rarely evolve to a fatal cancer, recurrence of these neoplasms remains a major problem, requiring adjuvant therapies after transurethral resection (TUR) and long-term follow-up. We have moved from using the word *cancer* when describing these tumors, avoiding the psychologic impact of this word on patients. The term *urothelial neoplasms* better describes the matter.

The term *noninvasive* is used here to refer to Ta disease. The term *superficial* is vague, and may include both Ta and T1 tumors. It is used only when referring to studies of both types of tumors.

Noninvasive tumors are the most common presentation of urinary bladder cancer and constitute almost half of all newly-diagnosed patients. In a population-based study from western Sweden, 53% of patients with a first diagnosis of bladder carcinoma had papillary stage Ta disease. Seventy percent of these were low grade carcinomas *(Level 2,* [1]*).* The incidence is low below the age of 50 but thereafter steadily grows in frequency.

1. Definition

The diagnosis of bladder cancer ultimately depends on cystoscopic examination of the bladder and pathologic evaluation of the resected or biopsied lesion. Macroscopically, a lesion is either papillary, solid, flat, or a mixture of these configurations.

Histopathologically, more than 90% of bladder cancer cases are urothelial (transitional cell) carcinoma, approximately 5% are squamous cell carcinoma, and less than 2% are adenocarcinoma. This chapter is devoted to a discussion of urothelial (transitional cell) carcinoma.

Further subclassification is based on two pillars :

1. The TNM classification, which provides a system for staging. *T* refers to the primary tumor and the extent of tumor involvement at the primary site, *N* refers to the lymph node status, and *M* to the presence or absence of distant metastases. Presently, the TNM classification from 2002 is widely accepted [2].

2. The histological grade, which refers to the appearance of the cancer cells under the microscope. In 1998 a new classification of noninvasive urothelial tumors was proposed at the WHO and International Society of Urological Pathology (ISUP) consensus meeting. The new classification system for grading urothelial neoplasms was published by the World Health Organization (WHO) in 2004 (**Table 1**) [3]. The objective with this new version was to avoid the overdiagnosis of cancer and to create better criteria for the different grades. Prior to this classification system, numerous diverse grading schemes for bladder cancer existed. Thus, the same lesion seen by different pathologists would result in very different diagnoses solely based on differences in definitions. Unfortunately, the new system has not been as universally accepted as the recent TNM classification.

In the new WHO 2004 classification, grade 1 tumors were reclassified either as papillary urothelial neoplasms of low malignant potential (PUNLMPs) or true low grade tumors. The grade 2 tumors are reclassified either to low grade or high grade tumors according to specific cytologic and architectural criteria. The terminology used in the new grading system parallels that used in urinary cytology (see Chapter 1: Epidemiology, Staging and Grading, and

Table 1. Nomenclature of Grade Classes (According to WHO 2004) [3]

Papilloma
Papillary urothelial neoplasm of low malignant potential (PUNLMP)
Low grade carcinoma, grade I
High grade carcinoma, grade II
High grade carcinoma, grade III

Diagnosis). A web site illustrating examples of various grades was developed: www. pathology. jhu.edu/bladder. The cells in PUNLMP look very much like normal bladder cells and are slowly growing and unlikely to progress. Nevertheless, PUNLMPs still have a high tendency, although lower than for grade 1 tumors, to recur (Level 3). The differences in recurrence and progression rates justify the distinct classification of PUNLMPs and grade 1 tumors *(Level 3*, [1,4]).

2. Primary Diagnosis

The vast majority of the papillary tumors are detected by the presence of **hematuria**. Sometimes it may be detected on evaluation for a recurrent urinary tract infection or incidentally by ultrasound, which is often performed as an exploration for hematuria. Bladder irritation in the absence of infection may be a symptom of bladder carcinoma but not of a low grade Ta lesion.

Cystoscopy is the method by which most of the papillary tumors are detected.

Urinary **cytology** will be negative in the majority of low grade tumors but is useful at first diagnosis as it predicts the presence of high grade tumors. The role of **urinary markers** is not yet clearly defined (*see Section IX*).

II. ACCURACY OF CYSTOSCOPY IN DEFINING PAPILLARY TUMORS

Outpatient fulguration has become increasingly popular in the management of recurrent, low grade papillary tumors of the bladder. In order to justify this as definitive treatment of such lesions, the urologist must be able to accurately distinguish the cystoscopic features of low grade, noninvasive from high grade, potentially invasive tumors (**Figure 1**).

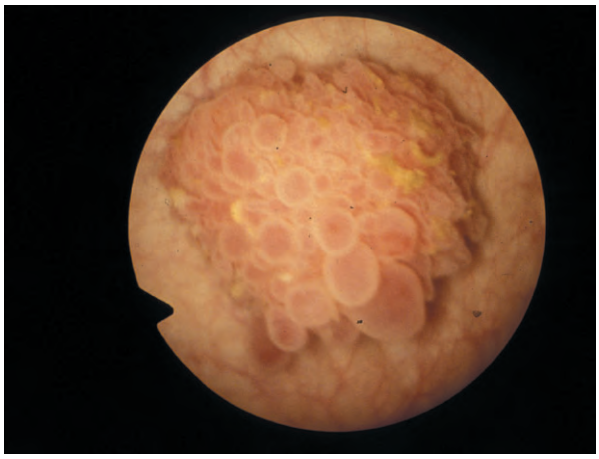


Figure 1. Low Grade Papillary Urothelial Carcinoma

Herr correlated the cystoscopic appearance of recurrent superficial papillary bladder tumors with histology after TUR in 150 consecutive patients (*Level 3*, [5]). Papillary lesions were classified as TaG1, TaG3, or T1G3 based on their cystoscopic appearance. Tumors classified as TaG1 were less than 0.5 cm and had individually discrete papillary fronds of mucosa surrounding a clearly visible fibrovascular core. Tumors with fused or less discrete papillary fronds that occurred in clusters or were greater than 0.5 cm in diameter were usually graded TaG3. Lesions that appeared papillonodular or solid were classified as T1. These latter tumors were all larger than 0.5 cm. Voided urine cytology was also obtained in each case. Of 84 tumors regarded as TaG1 at cystoscopy, 93% (78/84) proved to be low grade papillary tumors histologically. Seventy-two patients had a cystoscopic TaG1 tumor and negative urine cytology. Of these, 98% (71/72) were TaG1 histologically. Of the 84 papillary tumors that appeared to be low grade, 6 of 84 (7%) were high grade and 2 of 84 (2%) were confirmed on biopsy to be invasive. Only 3 of 66 (4.5%) tumors considered to be high grade at cystoscopy proved to be low grade histologically.

In a similar study from the same institution, Herr evaluated the correlation between cystoscopic appearance and histopathology in 125 patients with 144 recurrent papillary tumors (*Level 3*, [6]). Consistent with their previous findings, 90 of 97 tumors (93%) considered TaG1 at cystoscopy were confirmed on biopsy to be low grade papillary lesions. Of the 86 TaG1 tumors associated with negative urine cytology, 85 (99%) proved to be low grade papillary tumors histologically. Only 1 of 97 (1%) tumors deemed TaG1 proved to be invasive by biopsy. Of lesions believed to be high grade or invasive, only 6 of 47 (13%) were overgraded by cystoscopic

appearance. The authors concluded that since the overwhelming majority of tumors which appear to be low grade on cystoscopy prove to be low grade on biopsy, these lesions may be safely managed with fulguration alone, especially in the setting of negative urine cytology.

Oosterlinck et al., in a multi-institutional study, reported that 5.6% of 501 tumors believed to be non-infiltrating at cystoscopy were understaged compared to histopathology (*Level 2*, [7]). Tumors appearing superficial that were less than 3 cm in diameter were correctly staged in 96% of the cases. No data were available regarding the accuracy of cystoscopy in predicting tumor grade. In this EORTC study, the investigators were asked to include patients before histology was available. The number of patients not included because of doubtful interpretation was not reported.

Other authors reported the potential inaccuracies of cystoscopic evaluation of bladder tumors. Cina et al. reported that 7 of 13 (54%) papillary lesions confirmed to be high grade by biopsy were believed to be low grade based on their cystoscopic appearance (*Level 3*, [8]). Of 37 lesions believed to be low grade on cystoscopy, 7 of 37 (19%) proved to be high grade at biopsy. Of 7 invasive lesions, 3 were believed to be noninvasive at cystoscopy. Of 9 lesions considered high grade at cystoscopy, 33% were low grade by histologic examination. One remarkable finding from this study was the excellent accuracy (100%) in differentiating neoplastic from non-neoplastic lesions (such as inflammation or denuded urothelium) by solely using cystoscopic evaluation. The authors concluded that grade and stage of papillary neoplasms could not be accurately predicted by cystoscopic appearance alone.

The contradiction between the two first and the last paper can be explained by a different selection of cases. In Herr's study, only recurrences of Ta or T1 tumors with previous known histology were examined. Oosterlinck's study mainly investigated small, new solitary tumors, while in Cina's study results of TUR specimens without any preselection were studied.

Summary

In summary, these studies show that conflicting data exists regarding the ability of cystoscopic appearance to accurately predict the stage and grade of papillary tumors of the bladder. However, ***in experienced eyes, and in combination with negative urine cytology, low grade papillary neoplasms may be identified accurately in over 90% of cases*** (*Level 3*, [6,7]). Because of the potential for undergrading, ***lesions with the following characteristics should be evaluated further : lesions larger than 0.5 cm in diameter, multiple lesions (>5), those which are papillonodular, and those associated with positive urine cytology.***

III. UPPER URINARY TRACT EXPLORATION IN LOW GRADE Ta BLADDER TUMORS

1. Upper Urinary Tract Exploration at Initial Diagnosis

The need for upper urinary tract imaging when the initial diagnosis of bladder tumors is made is rather questionable [9]. An intravenous urography at initial diagnosis is performed not only for the detection of upper urinary tract tumors, but also for the diagnosis of other asymptomatic diseases such us obstruction or lithiasis.

a) Incidence

In patients with bladder cancer in general, the incidence of upper urinary tract tumors at the time of diagnosis is very low, ranging from 0.3% to 2.3% *(Level 3*, [9,10,12,13]*)*. After analyzing different bladder tumor characteristics, a relationship has been observed between grade and stage of bladder tumor and the incidence of synchronous upper urinary tract tumors: 0 of 78 (0%) for grade 1, 4 of 361 (1.1%) for grade 2, and 5 of 360 (1.3%) for G3, as well as 1.2% for stage Ta to T1, 0% for Ta, and 7% for T1 [10]. In patients with TaG1 or G2 tumors, the incidence of synchronous upper urinary tract tumors is extremely low. Initial intravenous urography also detected 18% of other pathologies, 5.8% unsuspected, but only 1.4% required additional treatment, which did not affect the planned TUR [10]. In other series, only 0.3% of patients needed additional therapy based on intravenous urography findings. Most of the obstructive problems were also documented by ultrasound, routinely carried out as part of the work-up of these patients [9].

b) Reliability of Intravenous Urography

In the diagnosis of upper urinary tract tumors, the reliability of intravenous urography is unsatisfactory,

ranging from 30% to 70% *(Level 3,* [10,14,15]*)*. To define the final diagnosis, additional procedures are necessary in all of the remaining patients.

2. Upper Urinary Tract Exploration During Follow-up

Whether or not to follow patients diagnosed with bladder cancer with intravenous urography is another controversial issue [14-17]. Holmäng et al. observed an incidence of upper tract tumors of 2.9% in patients with bladder cancer: 0.4% for G1, 1.3% for G2, and 0.8% for TaG1 or G2 tumors [11]. Recommendations on how to follow these patients are inconsistent; some authors recommend not following these patients with intravenous urography, while others recommend an investigation of the upper urinary tract every year, every 2 years, every 3 years, or every 5 years *(Level 3,* [11,14,15,17,18]*)*.

a) Incidence

As a whole, the incidence of metachronous upper urinary tract tumor after bladder tumor ranges from 0.7% to 5.9% *(Level 3,* [14,15,19-21]*)*. However, this incidence increases to 13.5% to 19% in high-risk patients and to 21.2% to 29% in patients with associated bladder carcinoma in situ (CIS) *(Level 3,* [16, 22-25]*)*. More specifically, during follow-up the incidence of upper urinary tract tumor for patients with no bladder CIS drops to between 2.3% and 3.1%, 0.9% for low-risk patients, and 2.5% for patients with TaG1 or G2 tumors *(Level 3,* [11, 16, 24, 26]*)*.

A relationship between vesicoureteral reflux after TUR of a bladder tumor and upper tract recurrence has been reported: the incidence increased from 0.4% to 0.9% in those patients without reflux to 6.4% to 19.7% in patients with reflux *(Level 3,* [15, 19,20]*)*. However, the vast majority of patients with reflux and recurrence also had associated high risk factors for upper tract recurrences (bladder CIS, G3 or recurrent tumors). In multivariate analyses, multifocality and the presence of bladder CIS are independent factors for upper urinary tract recurrence in patients with bladder tumors *(Level 3,* [16,27]*)*, but reflux has not been evaluated. In the absence of multivariate analysis including vesicoureteral reflux, its real responsibility in the development of upper urinary tract tumors is not well-established.

b) Interval From Diagnosis of Bladder Tumor and Upper Urinary Tract Recurrence

The reported intervals are extremely wide, with the mean interval ranging from 5.4 months to 6.2 years and even longer for patients at low risk *(Level 3,* [13, 15, 16, 25]*)*. This long interval means that prolonged follow-up for the diagnosis of metachronous upper urinary tract recurrence in patients with TaG1 or G2 tumors would be necessary, requiring a large amount of intravenous urographies. The toxicity of this diagnostic procedure is present, with 0% to 4.6% rates of nephrotoxicity and a 1.6% incidence of anaphylactic reactions. However, with nonionic contrast medium, the toxicity decreases *(Level 3,* [10]*)*.

c) Upper Urinary Tract Cytology

Including routine upper urinary tract cytology in the follow-up of patients with TaG1 or G2 bladder tumors is not justified given the low incidence of upper tract recurrence and the lack of cytology specificity for localizing urothelial carcinoma in patients with bladder cancer *(Level 3,* [28,29]*)*.

3. Prognosis

Whether upper tract tumors detected in asymptomatic patients have a better prognosis than those detected after symptoms develop is unknown. The presence of upper urinary tract tumors initially or after resection of bladder cancer has a negative impact on survival in several series, but this event is usually assessed in high-risk superficial bladder tumors *(Level 3)* [22, 26, 30]. However, the prognosis of patients with upper tract tumors diagnosed after superficial bladder cancer is better than patients with primary upper urinary tract tumors, based on information from the SEER database *(Level 3,* [21]*)*. As a whole, there is no clinical evidence that an early diagnosis improves the prognosis of patients with upper urinary tract disease diagnosed after bladder tumors *(Level 3,* [22, 23]*)*. Also, a relationship between the grade and stage of bladder and grade and stage of upper urinary tract tumors has been reported, with a potential better prognosis for patients with TaG1 or G2 bladder tumors *(Level 3,* [15]*)*. In summary, although there is no clinical evidence, the prognosis of patients with bladder TaG1 or G2 tumors does not seem to be threatened by a delay in diagnosis of upper tract tumors until the presence of positive urinary cytology or development of symptoms.

4. Symptomatic Patients

The assessment of the upper urinary tract in symptomatic patients or those with positive urinary cytology but no bladder tumors is completely justified as part of the diagnostic work-up *(Level 3,* [31]*)*.

Summary

In patients with TaG1 or G2 bladder tumors, the low incidence of upper urinary tract tumors, the need for an extremely prolonged follow-up, the potential minimal prognostic impact of a delay in diagnosis, and the high cost of repeated intravenous urography do not support routine upper urinary tract assessment during follow-up. This was also the conclusion of the guidelines panel of the European Association of Urology (EAU) on upper urinary tract tumors *(Level 3,* [32]*)*.

IV. PRIMARY TREATMENT OF LOW GRADE Ta UROTHELIAL CARCINOMA OF THE BLADDER

The TUR for low grade Ta bladder tumors of course is not different from the TUR for any other superficial bladder cancer (*See Chapter 1)*.

1. Random Biopsies

A low grade superficial bladder tumor is expected when urinary cytology does not show malignant cells, when no suspicious red zones suggest CIS, and when the tumor has a nice papillary structure. In these conditions, **random biopsies** are inappropriate and do not provide any additional information relevant for the treatment and the prognosis of superficial bladder cancer (*Level 2,* [33-35]). The number of abnormalities detected in these cases will be very low *(Level 1,* [36]*)*. Publications emphasizing the need for random biopsies particularly report the detection of CIS *(Level 2,* [37]*)*. This disease will, however, be detected by a positive cytology. Identifying an additional small but invisible Ta or T1 lesion does not alter treatment or prognosis in a substantial way.

Any traumatized bladder mucosa may become an implantation site for floating tumor cells. Although there is no clinical evidence for this phenomenon, there are animal experimental data demonstrating this [38,39]. Among possible explanations for the high rate of early recurrences of superficial bladder cancer is the theory of implantation of cells shed during TUR.

2. Second Resection

In clinical trials controlling for the number of early visible recurrences within 4 weeks of primary resection, the detection of residual tumors with random bladder biopsies is very low [33]. The recurrence rate at 3 months also remains low in this best prognosis group of superficial bladder cancer. As such, it seems unrealistic to expect that the second resection will reveal substantial findings that will change treatment and outcome for the patient in this particular group of superficial bladder cancer. Therefore, a second resection is not indicated if no visible recurrences are present (*Level 2*).

V. ONE EARLY PERIOPERATIVE INSTILLATION OF CHEMOTHERAPY

1. History

The instillation of a chemotherapeutic drug immediately after TUR is an old idea which was initially tested in the 1970s [40, 41]. It was based on the fact that chemotherapy would be able to destroy floating tumor cells and prevent implantation at any traumatized surface of the bladder. This theory was strongly supported by animal experiments [59]. At that time, mainly thiotepa was used. Later, doxorubicin (Adriamycin) and epirubicin (Epodyl) were also evaluated. These first clinical trials suggested a reduction in the rate of tumor recurrence when a perioperative instillation was given [42,43]. After these preliminary results, the need for properly conducted, large scale, randomized controlled studies became evident. The first important study in this regard came from the British Medical Research Council (MRC). Four hundred seventeen patients with newly diagnosed superficial bladder tumors were treated with a complete TUR and then randomized to 1 of 3 groups [44]. Groups 1 and 2 received an instillation of 30 mg of thiotepa at the time of TUR; thereafter, patients in group 2 also received instillations of thiotepa every 3 months for a year. Group 3 was a control group in which no instillation was given. Neither the first publication of the MRC in 1985, nor the second publication of the results with longer follow-up in 1994 showed any differences in the recurrence rates among the 3 groups [44,45]. However, subsequent randomized studies have shown impressive improvements of the recurrence-free rate *(Level 2,* [36,48-53]*)*.

Despite the scientific evidence provided, a single

immediate postoperative instillation has not become routine procedure. The EAU guidelines were the first guidelines advocating for 1 single immediate instillation after TUR in all patients with superficial bladder tumors [53]. As 1 single instillation has been mainly tested in low-risk tumors, there was still doubt regarding the value of 1 immediate instillation in patients with multiple tumors, who are at a higher risk for recurrence. There was also no consensus if all patients with a single, low risk tumor should receive intravesical chemotherapy after the initial TUR. This was mainly the reason to perform a meta-analysis of the published results of randomized clinical trials with 1 single immediate postoperative instillation of chemotherapy in patients with stage Ta or T1 bladder cancer.

2. Meta-analysis of Efficacy

Sylvester et al. included 7 randomized trials with recurrence information on 1476 patients in their meta-analysis (*Level 1,* [54]). Based on a median follow-up of 3.4 years and a maximum of 14.5 years, 267 of 728 patients (36.7%) receiving 1 postoperative instillation of epirubicin, mitomycin C (MMC), thiotepa, or pirarubicin experienced a recurrence as compared to 362 of 748 patients (48.4%) with TUR alone (odds ratio [OR] 0.61, $P < 0.0001$). This meta-analysis has shown that 1 immediate instillation of chemotherapy after TUR decreases the relative risk of recurrence by 39% in patients with Ta or T1 bladder cancer.

Although the majority of the patients included in these randomized trials had a single tumor, it was found that both patients with a single tumor (OR 0.61) and those with multiple tumors (OR 0.44) benefited from a single instillation. However, after 1 instillation, 65.2% of the patients with multiple tumors had a recurrence compared to 35.8% of the patients with a single tumor, showing that one instillation alone is suboptimal treatment in patients with multiple tumors. In a trial excluded from the meta-analysis because some patients received additional instillations before recurrence, Zincke et al. also found that patients with multiple tumors benefited from an immediate instillation of thiotepa or doxorubicin [55]. Defining risk groups according to whether the tumor was single or multiple and the result of the first follow-up cystoscopy, Tolley et al. found that the benefit of MMC in both treatment groups combined was similar in low-, medium-, and high-risk cases [46, 47]. Other subgroup analyses could not be done in the meta-analysis due to the absence of individual patient data, but the 2 other studies in which they were performed suggest that the treatment is beneficial across all categories of patients [36, 52].

3. Working Mechanism

The effect of 1 instillation may be explained either by the chemoresection of tumor left behind after an incomplete TUR or by destroying circulating tumor cells that could implant at the site of resection. Incomplete TUR may be an issue even in patients with solitary tumors as seen by the large variation between institutions in the recurrence rate at the first follow-up cystoscopy after TUR [56]. Oosterlinck et al. found that 10 patients out of 242 had residual tumors 1 month after TUR, only 1 of which was in the instillation arm [36]. Masters et al. found a 44% complete response rate in a marker lesion 3 months after 1 instillation of epirubicin [57]. Thus, 1 instillation can in fact eradicate tumor left behind after TUR.

Supporting the hypothesis of implantation of circulating tumor cells, Whelan et al. found that postoperative irrigation with saline or glycine for 18 hours significantly prolonged the time to first recurrence, with a reduction of 17% in the relative risk of recurrence [38,58]. Several animal experiments also support the hypothesis of tumor implantation at traumatized areas in the bladder [39,59].

4. Duration of the Effect

In those studies in the meta-analysis with the information available, Kaplan-Meier time-to-first-recurrence curves showed that the time point at which the treatment benefit started varied somewhat: in 3 studies there was a reduction in the percent of patients with residual tumors at 1 month or with recurrence already at 3 months and in 1 study the benefit appeared starting at 6 months [36,49,52]. However, in another study the treatment effect appeared only starting at 1 year [36]. As suggested by Solsona et al., the effect of 1 instillation appears to occur early, mainly during the first 2 years, with a possible dilution of the treatment effect with longer follow-up [49]. Investigating the percentage of patients who experience recurrence rather than considering the time to first recurrence may in fact underestimate the size of the treatment effect. However, with long-term follow-up it is clear that 1 immediate instillation prevents, rather than simply delays, recurrences.

5. Timing of the Instillation

In all studies, the instillation was given within 24 hours, generally either immediately after TUR or within 6 hours after. Kaasinen et al. found a doubling in the risk of recurrence if the first of 5 weekly MMC instillations was not given on the same day as the TUR in patients with frequent recurrences [60]. In 2 EORTC trials where patients received 9 instillations of epirubicin or MMC over 6 months, starting treatment on the day of TUR was more effective than starting 7 to 15 days later in patients who did not receive further maintenance after 6 months *(Level* 2, [61]). In another study where patients received 15 instillations of doxorubicin or MMC over 1 year, fewer patients randomized to start treatment within 6 hours recurred as compared to patients randomized to start treatment after 7 to 14 days, especially in the MMC arm *(Level 2,* [62]*)*. There is thus some evidence that the instillation should be given on the same day as the TUR.

6. Intravesical Drugs

With the possible exception of the 1 study with thiotepa in which no difference was found, the meta-analysis suggests that no large differences exist with regard to efficacy between the different chemotherapeutic agents [44,45,54]. However, the study by Burnand et al., which used 90 mg of thiotepa in 100 mL rather than 30 mg in 50 mL (as in the MRC study), found that 1 instillation of thiotepa significantly reduced the percent of patients who recurred, as did Zincke et al. who used 60 mg of thiotepa in 60 mL [40,55]. This suggests that a lower concentration of thiotepa may be responsible for the lack of efficacy. However, results from these 2 additional studies should be interpreted with caution.

7. Cost-effectiveness

Looking at initial recurrences only, 11.7 TURs were saved for every 100 patients treated. Thus, the number needed to treat to prevent 1 recurrence is 1/0.117 = 8.5. Since the cost of a TUR, anesthesia, and hospitalization is probably more than 8.5 times the cost of 1 instillation in most countries, a single instillation should be cost-effective.

8. Toxicity

Despite the fact that no serious adverse effects have been mentioned in the trials published on immediate adjuvant chemotherapy instillations, several reports have appeared on severe and prolonged complications due to extravasation of the drug after an early intravesical instillation. Doherty at al. reported the local effects of an immediate instillation of chemotherapy (mainly epirubicin) in cystectomy specimens [63]. It was associated with a more extensive necrosis of the bladder wall and fat necrosis of extravesical tissue than the usual muscle necrosis seen after TUR alone. An area of thin muscularis propria may undergo necrosis resulting in secondary perforation. None of the 12 patients described by Doherty et al., however, reported local symptoms. In contrast, the effect of extravasation after intravenously administered chemotherapeutic drugs is well-documented. It induces long-lasting necrosis, provoking pain with a low tendency of healing. Recently, several cases of severe and long-lasting complications due to extravasation of MMC have been reported [64]. A distal ureteral stenosis has also been described that was probably due to intravesical MMC [65]. There is certainly an underreporting of these complications as not every urologist who has seen such a complication is eager to report such an event. In any case, urologists should be aware of the potential risk of extravasation of chemotherapeutic drugs and its consequences.

9. Precautions

If there is a possibility of perforation or after an extended TUR, an immediate instillation should not be given. In case of the possibility of intraperitoneal leakage or significant resorption from the extravesical space, it seems advisable not to use a dose which is greater than the dose which is acceptable as 1 single intravenous injection. Indeed, 1 case of myelosuppression has been described when 80 mg of MMC was retained for 2 hours after TUR of a large tumor [66]. Nevertheless, it is clear from the review of the literature that 1 immediate instillation after TUR is an adjuvant treatment that adds hardly any morbidity to the operation itself. Nearly all patients already have a catheter after TUR and, if local regional anesthesia is used, patients will not experience any additional discomfort. The reluctance to use this treatment strategy should be reconsidered since the potential benefits clearly outweigh the possible risks and costs.

VI. FURTHER INTRAVESICAL CHEMOTHERAPY

According to a recent meta-analysis, a single immediate instillation of a chemotherapy agent significantly reduces the recurrence rate in patients included in a low risk group *(Level 1,* [54]*)*. This might be considered as the standard treatment for these patients, but the question is whether this approach is enough for patients at higher risk of recurrence or whether patients need further adjuvant intravesical chemotherapy.

Analyzing the Kaplan-Meier curves of 2 randomized series with long-term follow-up demonstrated that the effect of an immediate single instillation of chemotherapy occurred during the first or second year *(Level 2,* [49,51]*)*. After this period, the curves run parallel and tumor relapses occur in a similar proportion in both the therapeutic and the observation arms. This means that after this period patients are at risk of recurrence according to the natural history of the tumor, regardless of the initial benefit of a single instillation. In a pooled analysis of 5 randomized trials, Hinotsu et al. observed that the effect of intravesical chemotherapy essentially occurred during the early phase of the recurrence (before 500 days), but the effect was no longer observed after this period *(Level 1,* [67]*)*. This trend was also observed in patients with TaG1 or G2 tumors and was particularly remarkable in the TaG2 category according to the higher recurrence rate than TaG1 in short and long-term follow-up. Also, in a series by Tolley et al. including low- and intermediate-risk groups, patients receiving more than 1 single instillation of MMC had a reduction in the recurrence rate compared with patients who only received a single instillation *(Level 2,* [70]*)*. In the meta-analysis from Sylvester et al., patients with multiple tumors had a recurrence rate significantly lower than that of the control group but significantly higher than patients with solitary tumors *(Level 1,* [54]*)* . In consequence, the need of more than one early instillation might be related to prognostic factors for recurrence. In multivariate analysis many prognostic factors have been identified as predictors or recurrence, but in this specific group, multifocality, previous recurrence rate or early recurrence, and size seemed to be the most relevant *(Level 1,* [47, 67]*)* .

As the progression risk is very limited in these patients, one option is to start secondary instillation therapy until the first follow-up cystoscopy. Those patients experiencing a recurrence, especially at multiple sites, at the first follow-up have an increased risk of recurrence and could be selected for this therapy *(Level 1/2,* [47]*)*. Using these prognostic factors, patients at high risk for recurrence can be identified and therapy could be applied as follows: a) one single instillation for patients with good prognostic factors and b) further instillations for patients with prognostic factors associated with a high recurrence rate.

1. Dose and Schedule

In cases where more than a single instillation is needed, the question is what schedule should be recommended ? In the literature, there are no trials designed for this specific group, but there are many defined for low- to intermediate-risk groups, from which one can extrapolate the results. In European series comparing different chemotherapy agents in patients stratified to low- and intermediate-risk groups there is no superiority of any one agent [61,62, *Level 2*; 71-73, *Level 1*].

There is more controversy regarding what is the most suitable schedule for intravesical chemotherapy. Two combined trials from the EORTC defined that administration for longer than 6 months did not improve the recurrence rate when the instillation was administered early *(Level 2,* [61]*)*. This observation was confirmed by Nomata et al., who achieved a recurrence-free rate of 55.1% and 48.5% at 3 years in patients treated with 5 months or 1 year of epirubicin, respectively, with no significant difference between the 2 arms *(Level 2,* [74]*)*. Another randomized trial of 150 patients using early instillation reported a lower recurrence rate after 1 year of treatment with epirubicin (19 instillations) compared to a treatment of only 3 months (9 instillations) *(Level 3,* [75]*)*. Consequently, when early instillation of chemotherapy is administered, a long course of maintenance, more than 1 year, is not necessary, but the suitable duration and number of instillations are not well-defined.

The doses of each chemotherapy agent are not well-established, because they were decided empirically, but in the literature there is a suitable range for each one: doxorubicin 20 to 50 mg, epirubicin 20 to 100 mg, thiotepa 30 to 90 mg, and MMC 20 to 60 mg. MMC 40 mg, epirubicin 50 mg, doxorubicin 50 mg, and thiotepa 60 mg in 50 mL of physiologic solution are most widely used. However, recently the need to adapt the urinary pH for each agent was stressed [77]. A prospective, double-armed, randomized,

multi-institutional phase III trial with the aim to test whether enhancing the drug's concentration in urine would improve its efficacy has been reported *(Level 2,* [77]*)*. Patients in the optimized treatment arm received a 40 mg dose of MMC with pharmacokinetic manipulation to increase drug concentration by decreasing urine volume and urine alkalinization to stabilize the drug. Patients in the standard treatment arm received a 20 mg dose without any additional manipulation. Patients in the optimized arm showed a longer median time to recurrence and a greater recurrence-free fraction at 5 years than patients in the standard treatment arm. This pivotal study proved the feasibility and efficacy of optimizing intravesical chemotherapy.

2. The Role of BCG (Bacille Calmette-Guérin)

Overall, in a systematic literature overview BCG significantly reduces the recurrence rate compared to chemotherapy [79, *Level 2*; 80, *Level 1*]. However, concerning the intermediate- to low-risk group, this evidence is not clear. In 2 recent meta-analyses, BCG was not superior to MMC except for patients previously treated with intravesical chemotherapy *(Level 1,* [81]*)*. However, BCG significantly reduces recurrence and progression in high-risk patents [82, *Level 2*; 83, *Level 1*]. Concerning low- to intermediate-risk groups, in another meta-analysis BCG was not superior to MMC unless maintenance was applied *(Level 1,* [83]*)*. However, all 3 studies with patients at intermediate risk included in this meta-analysis were not randomized trials and did not have homogeneity statistical tests applied. In addition, 1 study was published in abstract form and other methodological problems were observed. In summary, there is no scientific evidence that in the intermediate-risk group BCG is superior to intravesical chemotherapy, even if BCG maintenance is administered. On the other hand, in all series BCG was significantly more toxic than intravesical chemotherapy. In consequence, in patients with TaG1 or G2 tumors at high risk of recurrence, BCG should not be used as first-line treatment but can be used as a second-line therapy.

VII. PROGNOSTIC FACTORS AND FOLLOW-UP

1. Prognostic Factors

Noninvasive low grade Ta bladder tumors account for 25% to 50% of bladder carcinomas. Most of these patients are treated in local hospitals and rarely referred to academic centers. Therefore, there are only a few reports dealing specifically with this group of patients. Within this group of patients, progression is a rare event, but recurrence remains a problem even in the best prognostic groups of patients with TaG1 tumors or PUNLMP.

Holmäng et al. noticed 71% recurrences at 5 years follow-up of TaG1 bladder tumors *(Level 2,* [1]*)*. Haukaas et al. described a single institution experience in 68 patients with TaG1 tumors; 40% of the patients experienced a recurrence within 3 years *(Level 3,* [84]*)* . Holmäng et al. have evaluated recurrence and progression patterns of patients with TaG1 lesions to whom intravesical therapy was rarely administered *(Level 3,* [1]*)*. The recurrence rate was much higher in patients with multiple tumors.

a) Papillary Urothelial Neoplasms of Low Malignant Potential (PUNLMP)

In patients with PUNLMP, there were 35% recurrences at 5 years in 95 cases. More recently, Fujiï et al. evaluated 53 patients with PUNLMP, followed for at least 5 years, and detected a 66% recurrence rate *(Level 3,* [4]*)* . At 2, 5, and 10 years, the recurrence rates were 66%, 52%, and 36%, respectively.

No patients developed higher grade, muscle-invasive tumors or upper urinary tract tumors in the above-mentioned studies. But despite the low malignant potential of these tumors, there is still a high and long-lasting chance for recurrence.

b) Recurrence in Low Grade pTa Tumors

Many studies have examined several clinical factors that predict recurrence.

1. Multiplicity

Multiplicity of the tumor was found to be predominant in prediction of recurrence in all identified studies examining this issue [1,34,68,85,86, *Level 2*; 72,83, *Level 1*; 87,88, *Level 3*]. The recurrence risk is nearly twice as high when more than a single tumor is present.

In the study by Prout et al. of 187 patients with a mean follow-up of 58 months, the recurrence rate was 90% for patients with multiple tumors and 46% for patients with single lesions *(Level 2,* [89]*)*.

2. Recurrence at 3-month Cystoscopy

This was another factor which was studied by several investigators but not specifically in TaG1 tumors [69,86,90,91, *Level 2*; 87, *Level 3*]. All investigators found a strong correlation with later recurrence.

3. Previous Recurrence Rate

A recurrence rate of more than one per year was also found to be a prognostic factor for recurrence [34,68,90 *Level 2*; 72, *Level 1*]. This finding coincides with that of a higher overall recurrence rate when tumor is identified at 3 months.

4. Size of the Tumor

Milan-Rodriguez et al. reported that the risk at recurrence was 1.6 times higher for patients with a tumor greater than 3 cm, as previously reported [72, *Level 1*; 89, *Level 2*; 92].

5. Grade and T Stage

Although of value, these are of less importance in the prediction of recurrence than the above-mentioned factors. Grade and stage have, however, a major impact on the chance of progression.

6. Progression

In the above-mentioned studies, no progression was noticed for the group of patients with PUNLMP, and it has been rarely described in other series *(Level 3,* [93]*).*

2. Follow-up

Patients with TaG1 tumors should be followed, although the expected risk of recurrence as well as the risk of progression to a muscle-invasive disease is very low and early detection of recurrence is not as important as it is for superficial bladder tumors with a higher grade. As elucidated above, the most important factors are multiplicity, recurrence at 3 months, previous recurrence rate, and size of the tumors (greater than 3 cm).

Evolution to a higher grade can occur. Borhan et al. found an evolution to a higher grade in 179 TaG1 tumors in 29 cases (16.3%) ; 5 progressed to grade 2 and 24 to grade 3 *(Level 3,* [94]*).* Only 5 progressed to T1 and 3 to muscle-invasive disease. Holmäng et al. saw a 2.4% progression rate to muscle-invasive disease [1]. Leblanc et al. noted 21 progressions to G2 or G3 and 3 to CIS in a total of 152 TaG1 tumors with a follow-up from 6 to 241 months (mean 76 months) *(Level 3,* [93]*).* Thus, 17% evolved to a higher grade and of them 5 developed muscle-invasive disease (3.3%). Borhan et al. reported a grade progression in 11% of 82 TaG1 and G2 tumors *(Level 3,* [94]*).* Soloway et al. followed 32 patients with low grade tumors for a mean period of 38 months and noted that the tumor growth per month was approximately 1.77 mm [95]. Only 3 patients developed a higher grade or stage.

In conclusion, evolution to higher grade and stage in TaG1 tumors does occur, but in less than 20% of the cases. Evolution to progression is a rare event.

a) Frequency of Cystoscopy

Many authors suggested to diminish the heavy schedules of cystoscopy used in the past and to adapt them to the risk factors mentioned above. However, there are rare data which calculate the risk at any given surveillance schedule. Based on their experience in 120 papillary G1 and G2 tumors, Oge et al. proposed to postpone cystoscopy for another 9 months in those cases where the first cystoscopy at 3 months is negative [96].

Hazard function studies can help the decision on cystoscopy schedules. In an analysis of 1732 patients with all types of superficial bladder tumors, Hinotsu et al. found an earlier peak of recurrence in multiple and recurrent tumors than in single ones when no prophylactic treatment was given *(Level 1,* [67]*).* The early phase recurrence (within 200 days) is decreased by intravesical chemotherapy while late recurrence after 500 days seems not to be influenced.

b) Duration of Follow-up

All studies in which patients were followed over a long period mention recurrence even after several years of follow-up with no disease. A risk of recurrence remains lifelong, but most experts propose to stop cystoscopic surveillance when it remains negative for 5 years.

VIII. OFFICE FULGURATION OF RECURRENT LOW GRADE Ta TUMORS

The majority of patients (75%-80%) with newly-diagnosed bladder cancer present with noninvasive disease. Approximately half of these patients present with low grade lesions, now classified according to the WHO International Society of Urologic Pathology as low grade papillary tumors (TaG1) or papillary urothelial neoplasms of low malignant potential. Such tumors have traditionally been managed with TUR with or without immediate bladder instillation of a chemotherapeutic agent such as MMC. In an attempt to minimize the need for TUR and reduce the cost of hospitalization and anesthesia, several authors have investigated the feasibility and efficacy of outpatient fulguration of cystoscopically-appearing low grade, noninvasive recurrent papillary tumors of the bladder.

1. Feasibility

The feasibility of fulguration or ablation of bladder tumors via flexible cystoscopy has been confirmed in multiple studies. German et al., using topical local anesthetic gel, found that only 2 of 17 (12%) patients described the procedure as painful (*Level 3*) [97]. Dryhurst et al. further refined the anesthetic technique by instilling a 60 mL solution of lidocaine retained in the bladder for 20 min prior to fulguration (*Level 3*) [98]. Syed et al. described the use of the Holmium:Yag laser for tumor ablation via a flexible cystoscope under local anesthesia (*Level 3*) [99]. In that study, 83% of patients scored their pain as 2 or less out of 10 on a visual analog scale.

2. Efficacy

Herr evaluated the efficacy of outpatient fulguration of papillary lesions of the bladder. In this study, patients with a history of both low grade and high grade invasive lesions, some of whom had received BCG, were included (*Level 3*) [100]. All patients were either tumor-free or had a noninvasive recurrence in the 6 months prior to inclusion. A total of 69 patients underwent office fulguration. Of these, 47 (68%) were managed with fulguration alone. Of 22 patients who required TUR, 3 had muscle-invasive disease and 5 had CIS. Of 34 patients who required repeated fulguration, the tumor recurred at the site of prior fulguration in 10 (30%). The procedure was well-tolerated.

In a prospective study, Wedderburn et al. evaluated the efficacy and tolerance of outpatient fulguration in 103 patients with a history of recurrent TaG1 tumors (*Level 3*) [101]. Median follow-up was 21 months. Half of the patients (52/103) had no recurrence following fulguration. In 13 (13%) patients, recurrences occurred either at or close to the site of the original fulguration. Discomfort was mild or negligible for 80% of the patients.

Donat et al. recently presented a prospective analysis of 267 consecutive patients with a history of urothelial carcinoma of the bladder who underwent routine surveillance cystoscopy over a 4-year period (*Level 3*) [102].

These included 238 (89%) with an initial tumor of stage T1 or less and 25 (9%) who presented with a muscle-invasive tumor. All patients had subsequently been tumor-free for 6 months following TUR of their initial tumor. Patients with low grade-appearing and fewer than 5 recurrences, all of which were less than 0.5 cm in diameter, were considered for fulguration. Patients who had positive urine cytology underwent formal biopsy.

Of the 267 patients, 103 underwent office fulguration at least once during the study period, although only 74 of 123 (60%) were managed by fulguration alone. Patients who underwent fulguration were at no greater risk of disease progression or cancer death than those who never underwent fulguration and were managed by TUR of tumor alone.

The authors concluded that office fulguration is appropriate for selected patients with recurrent low grade superficial urothelial carcinoma of the bladder.

Summary

In summary, there is sparse prospective data regarding the efficacy of fulguration alone in the management of recurrent bladder lesions. However, an extensive experience from the Memorial Sloan-Kettering Cancer Center suggests that ***in selected patients with less than 5 small (<0.5 cm) low grade-appearing recurrent tumors and negative urine cytology, office fulguration alone is safe and effective***. All authors concur that office fulguration alone is inappropriate for initial management of a bladder lesion.

IX. URINE CYTOLOGY AND URINE-BASED MARKERS IN LOW GRADE TA UROTHELIAL CARCINOMA OF THE BLADDER

The diagnosis of a papillary superficial bladder cancer (pTa) comprises 2 discrete entities: low grade innocuous lesions and high grade, potentially lethal tumors. These 2 entities vary considerably in appearance, risk and pattern of recurrence, and their biologic propensity to ultimately progress. Although high- and low-risk groups in superficial bladder cancer have been described, clinical or pathological prognostic factors cannot predict progression on an individual basis (*Level 2,* [103]). Therefore, other criteria for identifying patients with a high risk for progression, as well as the identification of “markers” that define tumors that are likely to respond (or not) to specific therapeutic regimens, need to be defined and validated. Only this will provide a basis for patient-specific treatment decisions that better reflect the biology of individual tumors.

Established factors used to identify patients with a higher risk of tumor recurrence or progression include initial tumor stage and grade, number of initial tumors (multifocality), size of initial lesion, presence of associated CIS, early recurrence, stage migration, and response to therapy. Current surveillance schedules are more or less individualized based on these factors. These hallmarks of current risk assessment are the ones against which cytology or urine-based markers need to be compared when evaluating their role and potential.

The role of urine cytology and urine-based markers are discussed here with the focus on low grade papillary tumors. A more comprehensive overview on this topic is provided in Chapters 1 and 2.

1. Initial Tumor Grade

Although the evaluation of urine samples containing tumor cells (urine cytology) has much improved over the recent years, in clinical practice urologists still rely on cystoscopy to detect bladder cancer *(Level 2,* [104]*)*. Due to low cellular yields, atypia, and degenerative changes or alterations of the mucosa caused by therapy, interpretation of cytology can be problematic (*Level 3,* [105]). Various methods are used to obtain shed cells, including voided urine cytology, bladder washings, catheterized urine, and the THINprep method. It is also not common practice to obtain multiple sequential samples for urine cytology prior to any definite judgment. This may have an influence of uncertain magnitude on the reliability of the results. In addition, evidence-based guidelines on the performance of urine cytology are missing in the literature, and although the educational process over the recent years has much improved, the interpretation is still subjective, which makes comparison of results difficult (*Level 3,* [106,107]).

As a recent meta-analysis confirmed, most of the currently available urine-based markers (**Table 2**) are more sensitive (with a median overall sensitivity for all stages ranging from 20%-99%) than urine cytology, which has a low median overall sensitivity of 34% (*Level 2,* [108]). Another meta-analysis showed similar results (**Table 3**) (*Level 2,* [104]). This is especially of clinical interest for the detection of low grade lesions (median overall sensitivity ranging from 2%-97%) and for Ta tumors (median overall sensitivity ranging from 12%-96%) (*Level 2,* [108]). Urine cytology has a lower median overall sensitivity ranging from 4% to 31% for the detection of low grade lesions and from 9% to 25% for the identification of Ta tumors. Thus, urine-based markers may be of interest as a beneficial adjunct to urine cytology. In addition, combining markers may increase their predictive or prognostic value. Comprehensive approaches determining the right combination are awaited and should include the effects on specificity.

In case malignant cells are available, cytology has been shown to have the best specificity, and only a few urine-based markers have been shown to yield comparable results (*Level 2,* [104,108]). Thus, most of the urine-based markers demonstrate higher false positive rates compared to urine cytology (*Level 2,* [104,108], *Level 3* [109]). Besides the fact that in most studies patients had lesions of lower grade or may have already been treated, the presence of microhematuria or concomitant urinary tract infection may have contributed to these results. Although from an economic standpoint many of the current available tests may be superior to cytology, not all can be considered as point-of-care techniques, since some require technical expertise not available in many institutions (*Level 2,* [110,111]). In addition to these disadvantages, some of these tests have exclusion criteria limiting their clinical use and a consensus on cut-off values or test performance has not yet been reached.

Although there is considerable promising data on the advantages of urine-based markers, and despite the obvious disadvantages, especially for the detection of low grade papillary lesions, urine cytology may still remain the standard for bladder cancer screening. However, for the determination of the initial tumor grade, neither cytology alone nor any of the currently available urine-based urinary markers can replace the histopathological evaluation of resected tumor cells.

2. Presence of Associated Carcinoma in Situ

In the case of concurrent CIS or suspected upper urinary tract lesions, cytology may guide further evaluation (33, *Level 1;*37,112, *Level 2*). In addition, urine cytology may identify high grade malignant cells before they are identifiable cystoscopically. Thus, random biopsies become necessary when there is positive urinary cytology or when CIS is suspected. In these instances, the role of urine cytology remains important and urine-based markers may have a higher sensitivity (**Table 2**). However, it should be noted that the total number of patients with CIS was low in all studies (*Level 2,* [108]).

Table 2. Sensitivity of Various Urine-based Markers and Cytology [108]

Sensitivity (95% Confidence Interval)				
	pTa (%)	**G1 (%)**	**CIS (%)**	**Overall (%)**
Urine cytology	15 (9-25)	12 (4-31)	63 (29-87)	34 (20-53)
BTA test	33 (17-53)	32 (14-58)	50 (20-80)	49 (24-74)
BTA-Stat	57 (47-67)	47 (38-56)	73 (54-86)	71 (57-82)
NMP-22	60 (42-76)	61 (35-81)	66 (42-83)	73 (47-87)
BTA-TRAK	57 (31-80)	63 (27-89)	68 (44-85)*	69 (55-80)
FDP	56 (27-81)	42 (7-89)	65 (27-80)	77 (41-93)
Hgb dipstick	25 (12-44)	8 (2-48)	45 (12-83)	52 (27-76)
CYFRA 21-1 (CK 19)	75	86 (40-97)	100	94 (74-99)
UBC (CK 8/18)	62 (41-79)	57 (21-86)	96 (3-99)	66 (50-79)
BCA (CK 8/18)*	58	70	67*	83 (55-95)
CK 20*	96		100*	91 (83-96)
Telomerase	74 (52-88)	61 (30-85)	99 (56-99)	77 (53-91)
HA*	77		87*	89 (67-97)

Modified table according to Lotan and Roehrborn showing the median sensitivity by grade and stage and the overall median sensitivity of urine-based marker tests based on the data of at least 2 independent studies. Asterisk (*) indicates that for these studies the median sensitivity by grade and stage was based on the data of a single study.

Table 3. Sensitivity of Various Urine-based Markers and Cytology [104]

	Overall Sensitivity (95% Confidence Interval) (%)
Urine cytology	55 (48-62)
BTA test	50 (30-65)
BTA-Stat	70 (66-74)
NMP-22	67 (60-73)
BTA-TRAK	66 (62-71)
Telomerase	75 (71-79)

3. Urinary Markers in Follow-up

The aim of these tests is the detection of a recurrent tumor. This leads to 2 different scenarios:

The detection of another consecutive low grade lesion is of questionable value with regard to the determination of disease progression and may have low impact on the clinical management. Urine cytology, with its low sensitivity to detect these lesions, plays only a minor role. Although promising, to date ancillary tests performed to improve the sensitivity of urine cytology have not been shown to be of additive value. In addition, if the low likelihood of recurrence and subsequent progression after a 10-year disease-free follow-up interval leads to the discontinuation of frequent cystoscopies, the need for urine cytology or the use of urine-based markers is debatable.

A progression in tumor grade may help to identify those patients at higher risk for progression (*Level 2*, [4]). It is very unlikely that a high grade lesion is missed by either urine cytology or most of the current available urine-based markers during follow-up since their sensitivity has been proven to be even slightly higher than the sensitivity of urine cytology (*Level 2*, [108]). However, since the specificity of urine cytology remains superior compared to urine-based markers, it may not be replaced in this scenario.

Summary

Urine cytology or urine-based markers need to be evaluated in light of the established factors for risk assessment. Urine cytology contributes to a very limited extent to the determination of these factors, limiting its importance for the management of low grade papillary transitional cell carcinoma. Urine-based markers are needed to improve the predictive and prognostic value of urine cytology in low grade papillary disease, but there is currently no evidence that they are sufficient to replace urine cytology.

In summary, neither urine cytology nor urine-based markers have been demonstrated to be of sufficient value to replace cystoscopy in the diagnosis and follow-up of low grade superficial bladder cancer.

X. LIFESTYLE, DIET, AND FOOD SUPPLEMENTS

As noninvasive bladder cancer is a disease with a long history of development and dietary factors may play a role, it is worthwhile to examine whether advice on lifestyle, diet, or food supplements can be provided to the patient.

1. SMOKING

Smoking is one of the major causes of bladder cancer. Zeegers et al. performed a meta-analysis of 43 published case-control and cohort studies in the literature and analyzed the effect of tobacco use on bladder cancer (*Level 1,* [113]). The adjusted odds ratios (OR) for current cigarette smokers compared to nonsmokers were 3.18 for studies with men, 2.90 for studies with women, and 3.33 for studies of both sexes. Although former smokers have a relatively lower OR than current smokers, it is not significantly different, especially in men (OR 2.90 vs. 3.18). Positive dose-response relationships were found with both the number of cigarettes smoked per day and the number of years smoked.

Zeegers et al. systematically reviewed the effects of smoking on bladder cancer based on previous literature and specifically on the results of the ongoing Netherlands Cohort Study (114, *Level 2*; 116, *Level 3*). They used a rating system to summarize the level of scientific evidence for risk factors as convincing, probable, possible, and no evidence. Based on these criteria, the authors have concluded that cigarette smoking substantially increases the risk of developing bladder cancer. Cigarette smoking duration is the major determinant for bladder cancer development risk independent of differences in tumor invasiveness or morphology. Though cigar and pipe smoking substantially increased the risk of bladder cancer development, these risks disappeared after adjustment for cigarette smoking. It was also found that total smoking duration is much more important than cessation of smoking and age at first exposure (*Level 3,* [115]).

A pooled analysis of 11 case-control studies by Brennan et al. consisted of 2279 cases and 5268 controls from various countries in Europe (*Level 2,* [116]). A dose-response relationship was observed between the numbers of cigarettes smoked per day and bladder cancer. However, this relationship was weaker than that in lung cancer. Furthermore, an immediate and significant decrease in the risk of bladder cancer was also evident for those who quit smoking. This study underscores the fact that, although 1 of every 3 cases of bladder cancer is attributable to past smoking history, another 1 of every 3 cases is due to current smoking. A 40% decrease in risk can be accomplished by smoking cessation. The overall risk of bladder cancer for ever-smokers compared to never-smokers was 3.63 in this study.

Bladder cancer is relatively less frequent in females. Pelucchi et al. investigated smoking habits specifically in females in a case-control study conducted in Italy (*Level 3,* [117]). Compared to never-smokers, ever-smokers and current smokers had odds ratios of 2.47 and 2.87, which were statistically significantly different. Brennan et al. have analyzed the effect of tobacco use on bladder cancer in females using the pooled analysis of 11 European case control studies (*Level 2,* [118]). Similarly to the previous study, the overall risk of bladder cancer among women for ever-smokers compared to never-smokers was found to be 3.1. These studies show that the causal relationship between cigarette smoking and bladder cancer is independent of gender.

Though the causal relationship between cigarette smoking and bladder cancer is well-established, information about the carcinogenic effects of cigar and pipe smoking is far from clear. In a pooled analysis of 6 case-control studies from Europe, this relationship was investigated (*Level 3,* [119]). The relative risk of bladder cancer for smoking any kind of tobacco product was 3.5 compared to nonsmokers. Although cigarette smoking was associated with the highest risk, pipe and cigar smoking had odds ratios of 1.9 and 2.3, respectively. However, a more extensive and recent study has shown that cigar smoking has no effect on the risk of bladder cancer (*Level 3,* [120]). The amount of tobacco consumed and the duration also correlated with the risk of bladder cancer development in cigarette smoking but not in pipe or cigar smoking.

Fleshner et al. showed that although current smoking has an adverse impact on recurrence and progression, there was no difference noted between former smokers and those who quit after diagnosis (*Level 3,*

[121]). This finding contradicts with the aforementioned studies. Although consensus has been reached on the adverse effect of current smoking, extensive studies are needed to clarify whether cessation of smoking at diagnosis is beneficial as well.

2. Fluid Intake

In a prospective study of 47 909 men, a high intake of fluids was associated with reduced risk of bladder cancer after control for potential risk factors (*Level 2/3,* [122]). Study participants in the highest quintile of fluid intake had a 49% lower incidence of bladder cancer than those in the lowest quintile. However, according to one prospective non-randomized study (*Level 3,* [123]*),* a multicenter case-control study (*Level 3,* [124]) and a systematic review (*Level 2,* [114]) of the literature, there was no reduction in risk with high fluid intake.

3. Fruits and Vegetables

A meta-analysis of 7 case-control studies and 3 cohort studies performed by Steinmaus et al. showed that a small elevated bladder cancer risk exists in patients with low fruit consumption versus those with high fruit consumption (relative risk [RR] 1.5) after adjusting for smoking (*Level 2,* [125]). In the same meta-analysis, a less convincing relationship was also reported on the effect of high vegetable consumption (RR 1.2)

The Health Professionals Follow-up Study, which is a prospective cohort study reported by Michaud et al. involving 47 909 men, investigated the effect of total fruit and vegetable intake on bladder cancer development, but failed to show a significant relationship after adjustment for smoking (*Level 2,* [126]). Zeegers et al. also reported an inverse association between bladder cancer and fruit intake comparing the highest and lowest quintile of total fruit consumption (RR 0.7) (*Level 2,* [114]). There was no association between vegetable intake and risk of bladder cancer development in the same study (RR 0.9).

There is possibly no association between total vegetable consumption and bladder cancer development (*Grade B*).

4. Vitamin A

Steinmaus et al. performed a meta-analysis of epidemiological studies linking retinol and carotenoids to bladder cancer (*Level 2,* [125]). The relative risk of low vitamin A intake was 1.10 and thus the authors failed to show a significant impact of dietary Vitamin A. Michaud et al., in the Health Professionals Follow-up Study, also showed that dietary intake of vitamin A was not associated with bladder cancer risk (RR 0.97) (*Level 2,* [126]).

Moreover, neither duration nor dose of vitamin A intake was associated with bladder cancer risk. Zeegers et al., in their systematic review, also reached the conclusion that vitamin A had no association with the risk of bladder cancer (*Level 3,* [115]).

A multicenter, prospective, randomized, double-blind study on the effect of vitamin A analogue on the recurrence rate of patients with superficial bladder cancer recruited 79 eligible patients (*Level 2,* [128]). Although recurrence rates decreased significantly with vitamin A analogue treatment, early withdrawal of a significantly greater number of patients in the placebo arm and side effects in the treatment arm have hampered the validity of the results.

5. Vitamin C

In the Health Professionals Follow-up Study, dietary vitamin C was found to have no association with bladder cancer risk (*Level 2,* [127]). Although vitamin C supplement use for more than 10 years was associated with a significant reduction in bladder cancer risk (RR 0.83), the significance disappeared after adjustment for smoking. The Netherlands Cohort Study reported by Zeegers et al. also confirmed the aforementioned observations, which showed that neither dietary nor supplementary vitamin C had any association with the risk of developing bladder cancer (*Level 2,* [114]).

6. Vitamin E

Vitamin E may have a role in maintaining selenium in its reduced state and inhibiting nitrosamine formation in the gut. The Health Professionals Follow-up Study reported by Michaud et al. found a reduced risk of bladder cancer with a high total intake of vitamin E (*Level 2,* [127]). Subjects who took vitamin E supplements for more than 10 years had a reduction of 30%. In this study, both dietary intake of total vitamin E and vitamin E supplement use decreased the risk of bladder cancer. In multivariate models, current use of vitamin E supplements was inversely associated with bladder cancer risk (RR 0.70). A cohort derived from the Cancer Prevention Study II reported by Jacobs et al. demonstrated the relation-

ship between vitamin E supplements and bladder cancer mortality (*Level 3,* [129]). In this large cohort of US men and women, regular long-term use of vitamin E supplements was associated with a reduced risk of bladder cancer mortality.

However, Zeegers study of the Netherlands cohort failed to show this relationship (*Level 3,* [115]).

7. Vitamin B

Newling et al., in an EORTC study, have reported that pyridoxine administration to patients with Ta and T1 tumors had no effect on recurrence rates when compared to placebo (*Level 1,* [130]). Furthermore, these negative results did not change with adjustment to various prognostic factors.

8. Vitamin Combinations

Lamm et al. studied the effect of a megadose vitamin combination in a double-blind randomized trial (*Level 1,* [131]). A total of 65 patients with biopsy-confirmed urothelial carcinoma of the bladder were randomized to receive the recommended daily allowance of multiple vitamins or a megadose of vitamins A, B6, C, and E plus 90 mg of zinc. There were no significant differences in known risk factors between the groups. However, stratifying the cases according to tumor stage revealed a statistically significant 42% reduction in tumor recurrence for superficial (Ta, T1) and 53% reduction for low grade (G1, G2) urothelial carcinoma in favor of patients receiving megadose vitamins. The high dose vitamins were generally well-tolerated, with mild nausea being the most common side effect. This combination of potentially therapeutic agents was low in toxicity and expense.

9. *Lactobacillus casei* as a Prophylactic Agent for Recurrence of Superficial Bladder Tumors

In a multicenter, prospective, randomized double-blind trial, 139 patients with superficial bladder tumors following TUR were included to evaluate the prophylaxis of recurrence by an oral *Lactobacillus casei* preparation in comparison to placebo (*Level 3,* [132]). Efficacy could be evaluated in 61 patients of the *Lactobacillus casei* group and in 64 in the placebo group. In primary, multiple tumors and recurrent, single tumors, *Lactobacillus casei* showed a better prophylactic effect than placebo. When given in recurrent, multiple tumors, which were at higher risk for recurrence, there was no difference. The differences in favor of *Lactobacillus casei*, however, became only statistically significant when a Cox multivariate analysis was performed (*Level 3,* [132]).

The inhibitory effect of *Lactobacillus casei* on bladder tumors was investigated in an experimental model of nitrosamine-induced rat bladder cancer [133]. Tumor volume was lower in *Lactobacillus casei*-treated rats, and this was more pronounced with a longer duration of treatment. The degree of malignancy of the induced tumors was significantly lower in the treated group.

In an epidemiological study (case-control), a total of 180 cases and 454 population-based controls were selected. The odds ratio for those who had an intake of *Lactobacillus casei* by drinking fermented milk products was 0.46 for 1 to 2 times per week and 0.61 for 3 to 4 or more times per week. This suggest that the habitual intake of *Lactobacillus* bacteria may reduce the risk of superficial bladder tumors [134].

The supposed mechanisms of its action are detoxication of chemical carcinogens and activation of the immune system. Additionally, there is anti-tumor effect demonstrated of intravesical instillation of heat-killed cells of *Lactobacillus casei* on the murine orthotopic bladder tumor MBT-2 [135].

RECOMMENDATIONS

II. ACCURACY OF CYSTOSCOPY IN DEFINING PAPILLARY TUMORS

1. Cystoscopy in experienced hands is accurate in identifying recurrent low grade tumors that are characterized by the absence of the following features *(Grade B).*

2. Lesions with the following characteristics should be evaluated by biopsy *(Grade B):*

   Greater than 0.5 cm in diameter

   Areas of nodularity

   More than 5 lesions present

   Positive urine cytology

   Lesions in patients not yet diagnosed with bladder cancer

III. UPPER URINARY TRACT EXPLORATION IN LOW GRADE TA UROTHELIAL CARCINOMA OF THE BLADDER

1. The diagnostic exploration of the upper urinary tract in patients with Ta G1 or G2 bladder tumors is not recommended at initial diagnosis or during follow-up *(Grade B).*

2. Symptomatic patients or those with positive urinary cytology in the absence of bladder tumors should undergo upper urinary tract exploration *(Grade A).*

IV. PRIMARY TREATMENT OF LOW GRADE TA UROTHELIAL CARCINOMA OF THE BLADDER

1. Urinary cytology is recommended prior to initial TUR for the diagnosis of bladder cancer because, if it is positive, random biopsies have a higher chance to detect CIS of the bladder and a high grade tumor is more likely to be present *(Grade A).*

2. If cytology does not show malignant cells and the lesion has a papillary structure, random biopsies are not indicated. Traumatized bladder mucosa may enhance implantation of tumor cells *(Grade B).*

3. A second resection is not useful in low grade Ta lesions *(Grade B).*

V. ONE EARLY PERIOPERATIVE INSTILLATION OF CHEMOTHERAPY

1. Instillation with MMC (MMC) or epirubicin can reduce the recurrence rate by about 40% in single as well as in multiple superficial bladder tumors and thus is recommended for all types of papillary superficial bladder cancer *(Grade A).*

2. The doses of 40 mg MMC and 50 mg epirubicin in 50 mL are most widely advocated. Higher doses increase the risk for side effects without increasing efficacy *(Grade B).*

3. After extensive resection and in the case of obvious or suspected perforation of the bladder wall, it is prudent not to instill a chemotherapeutic agent as extravasation can provoke annoying and even dangerous complications *(Grade D).*

4. It is advocated to give the instillation the same day of the TUR as it is probably insufficient the day afterwards *(Grade B)* .

5. Further adjuvant intravesical therapy is indicated in multiple tumors as 1 single instillation is an insufficient treatment *(Grade A).*

VI. FURTHER INTRAVESICAL CHEMOTHERAPY

1. Secondary intravesical therapy should be given in patients with low grade Ta tumors when high risk factors for recurrence are associated. Secondary intravesical therapy can be administrated initially in a standard approach or to patients with multiple recurrences at first follow-up cystoscopy *(Grade C).*

2. Intravesical chemotherapy is recommended as a first-line treatment, and the duration of treatment should be less than 6 months *(Grade B).*

3. Intravesical BCG should be reserved for second-line treatment *(Grade A).*

VII. PROGNOSTIC FACTORS AND FOLLOW-UP

1. Although the chance of progression is very low in TaG1 tumors, the number of recurrences remains high and is long-lasting *(Grade B).*

2. Number and size of tumors are the most important prognostic factors in TaG1 tumors *(Grade B).* Recurrence at the first surveillance cystoscopy or a previous recurrence rate of more than 1 per year is also an important prognostic factor *(Grade B).*

3. A cystoscopy is advocated at 3 months. If negative, the next cystoscopy can be postponed for 9 months *(Grade C).*

VIII. OFFICE FULGURATION OF RECURRENT LOW GRADE TA TUMORS

1. Office fulguration alone is not appropriate treatment of an initial bladder tumor *(Grade C).*
2. In selected patients with less than 5 small (<0.5 cm) low grade-appearing recurrent tumors in the setting of negative urine cytology, office fulguration is appropriate *(Grade C).*
3. Whenever there is clinical doubt whether a tumor is low grade, if urine cytology is positive**,** or if there appears to have been a change in the appearance of tumors, formal TUR is necessary *(Grade C).*

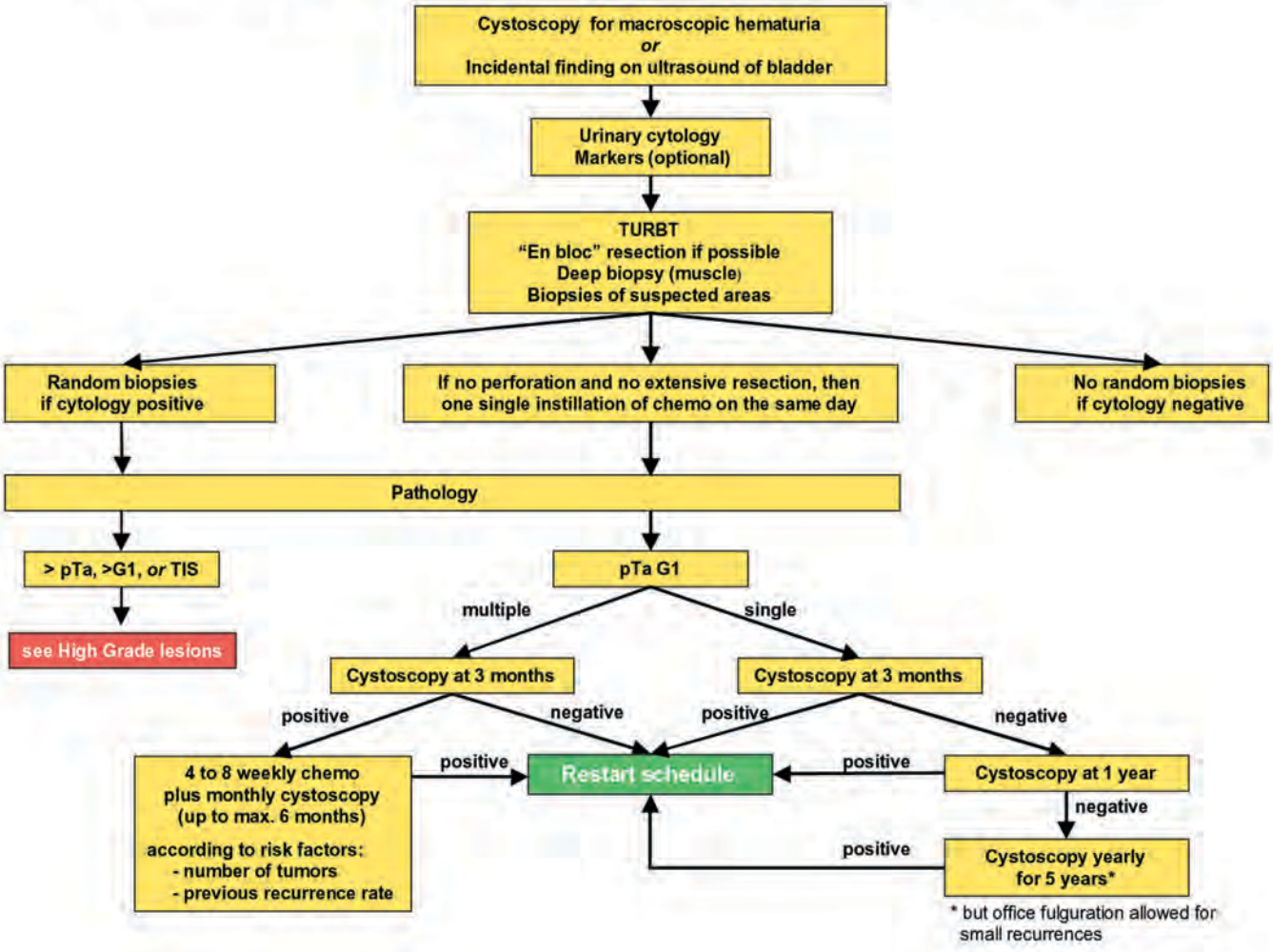
IX. URINE CYTOLOGY AND URINE-BASED MARKERS IN LOW GRADE Ta UROTHELIAL CARCINOMA OF THE BLADDER

1. To define a low grade papillary tumor, neither urine cytology nor urine-based markers are needed *(Grade A).*
2. Urine cytology has its role for the detection of concurrent CIS or high grade malignant cells prior to cystoscopy. Thus, random biopsies become necessary when there is positive urinary cytology or when CIS is suspected *(Grade B).*
3. Urine cytology or the use of urine-based markers should not be used for the follow-up of well-defined low grade lesions with their low liability to progress *(Grade B).*

X. LIFESTYLE, DIET, AND FOOD SUPPLEMENTS

1. Cigarette smoking increases the risk of bladder cancer threefold *(Grade A).*
2. Current smokers have increased adverse outcomes compared to nonsmokers *(Grade B).*
3. The risk increases with the number of cigarettes smoked per day (> 20) and the number of years (> 20) as a smoker *(Grade C).*
4. The favorable effect of quitting smoking after diagnosis of bladder cancer is probable, but not clearly proven *(Grade C).*
5. There is possibly no association between total fluid intake and risk of bladder cancer *(Grade B).*
6. There is a probably a slight inverse relationship between total fruit intake and risk of bladder cancer development *(Grade B).*
7. Vitamins A, B6, and C have no association with the risk of bladder cancer *(Grade B).*
8. A probable moderate inverse relationship between vitamin E supplement use and bladder cancer risk may be present *(Grade C).*
9. *Lactobacillus casei* may have a protective effect on recurrence of superficial bladder tumor *(Grade C).*

Algorithm for the Diagnosis and Follow-up of Papillary Bladder Tumors



XI. REFERENCES

1. Holmäng S, Andius P, Hedelin H, Wester K, Busch C, Johansson SL. Stage progression in Ta papillary urothelial tumors: relationship to grade, immunohistochemical expression of tumor markers, mitotic frequency and DNA ploidy. J Urol 2001;165:1124-1128.
2. Sobin D H, Witteking Ch. Classification of malignant tumors, 6th ed. New York : Wiley-Liss, 2002.
3. World Health Organization (1999) Mostofi FK, Davis CS, Sesterhenn IA. Histological typing of urinary bladder tumors. International histological classification of tumors 2nd ed. World Health Organisation, Geneva, 1999 Bladder tumors. International classification of tumors, no. 10, 2nd ed, Geneva.
4. Fujii Y, Kawakami S, Koga F, Nemoto T, Kihara K: Long-term outcome of bladder papillary urothelial neoplasms of low malignant potential. BJU Int 2003;92:559-562.
5. Herr HW. Does cystoscopy correlate with the histology of recurrent papillary tumors of the bladder? BJU Int 2001;88: 683-685.
6. Herr HW, Donat SM, Dalbagni G. Correlation of cystoscopy with histology of recurrent papillary tumors of the bladder. J Urol 2002;168:978-980.
7. Oosterlinck W, Kurth K, Schroder F, Sylvester R. A plea for cold biopsy, fulguration and immediate bladder instillation with Epirubicin in small superficial bladder tumors. Eur Urol 1993;23:457-459.
8. Cina SJ, Epstein JI, Endrezzi JM, Harmon WJ, Seay TM, Schoenberg MP. Correlation of cystoscopic impression with histologic diagnosis of biopsy specimens of the bladder. Hum Pathol 2001;32:630-637.
9. Goessl C, Knispel HH, Millar K, Klän R. Is routine excretory urography necessary at first diagnosis of bladder cancer? J Urol 1997:157:480-481.
10. Herranz-Amo F, Diaz-Cordero JM, Verdú-Tartajo F, Bueno-Chomón G, Leal-Hernandez F, Bielsa-Carrillo A. Need for intravenous urography in patients with primary transitional carcinoma of the bladder? Eur Urol 1999;36:221-224.
11. Holmäng S, Hedelin H, Anderström C, Holmberg E, Johansson SL. Long-term follow-up of a bladder carcinoma cohort: routine follow up urography is not necessary. J Urol 1998;160:45-48.
12. Arrizabalaga M, Navarro L, Mora M. Carcinomas transicionales del tracto urinario: lesiones sincronicas y metacrónicas. Actas Urol Esp 1994;18:782-796.
13. Yousem DM, Gatewood OM, Goldman SM, Marshall FF. Synchronous and metachronous transitional cell carcinoma of the urinary tract: prevalence, incidence, and radiographic detection. Radiology 1988;167:613-618.
14. Oldbring J, Glifberg I, Mikulowski P, Hellsten S. Carcinoma of the renal pelvis and ureter following bladder carcinoma: frequency, risk factors and clinicopathological findings. J Urol 1989;141:1311-1313.
15. Palou J, Fariña LA, Villavicencio H, Vicente J. Upper tract urothelial tumor after transurethral resection for bladder tumor. Eur Urol 1992; 21:110-114.
16. Solsona E, Iborra I, Ricós JV, Dumont R, Casanova JL, Calabuig C. Upper urinary tract involvement in patients with bladder carcinoma in situ (Tis): Its impact on management. Urology 1997;49:347-352.
17. Walzer Y and Soloway MS. Should followup of patients with bladder cancer include routine excretory urography? J Urol 1983;130:672-673.
18. Smith H, Weaver D, Barjenbruch O, Weinstein S, and Ross G. Routine excretory urography on follow-up in superficial transitional cell carcinoma of bladder. Urology 1989;34:193-196.
19. Amar A and Das S. Upper urinary tract transitional cell carcinoma in patients with bladder carcinoma and associated vesicoureteral reflux. J Urol 1985;133:468-71.
20. De Torres JA, Banús JM, Palou J, Morote J. Vesicorenal reflux and upper urinary tract transitional cell carcinoma after transurethral resection of recurrence superficial bladder carcinoma. J Urol 1987;138:49-51.
21. Rabbani F, Perrotti M, Russo P, Herr HW. Upper-tract tumors after an initial diagnosis of bladder cancer: argument for long-term follow-up. J Clin Oncol 2001;19:94-100.
22. Miller EB, Eure GR, Schellhammer PF. Upper tract transitional cell carcinoma following treatment of superficial bladder cancer with BCG. Urology 1993;42:26-30.
23. Schwalb DA, Herr HW, Sogani PC, Russo P, Sheinfield J, Fair WR. Upper tract disease following intravesical BCG for superficial bladder cancer: five years follow-up (abstract 237). J Urol 1992;147 (suppl):273A.
24. Schwartz CB, Bekirov H, Melman A. Urothealial tumors of upper tract following treatment of primary bladder transitional cell carcinoma. Urology 1992;40:509-511.
25. Herr HW and Whitmore WF Jr. Ureteral carcinoma in situ after successful intravesical therapy for superficial bladder tumors: incidence, possible pathogenesis and management. J Urol 1987;138:292-294.
26. Hurle R, Losa A, Manletti A, Lombo A. Upper urinary tract tumor developing after treatment of superficial bladder cancer. Urology 1999; 53:1144-1148.
27. Millan F, Chechile G, Salvador J, Huguet J, Vicente J. Upper urinary tract tumors after primary superficial bladder tumors: prognostic factors and risk groups. J Urol 2000;164:1183-1187.
28. Gogus C, Baltaci S, Sahinli S, Turkomez K, Beduk Y, Gosu O. Value of selective upper tract cytology for recognition of upper tract tumor after treatment of superficial bladder cancer. Int J Urol 2003;10:243-246.
29. Sadek S, Soloway MS, Hook S, Civantos F. The value of upper tract cytology after transurethral resection of bladder tumor in patients with transitional cell cancer. J Urol 1999;161:77-79.
30. Herr HW, Cookson MS, Soloway SM. Upper tract tumors in patients with primary bladder cancer followed for 15 years. J Urol 1996;156:1286-1287.
31. Solsona E, Iborra I, Ricos JV, Monros JL, Dumont R, Almenar S. Extravesical involvement in patients with bladder carcinoma in situ: biological and therapy implications. J Urol 1996;155:895-900.
32. Oosterlinck W. Solsona E, van der Meijden APM, Sylvester R, Böhle A, Rintala E, Lobel B. EAU Guidelines on Diagnosis and Treatment of Upper Urinary Tract Transitional Cell Carcinoma. Eur Urol 2004;46:147-154.
33. Van der Meijden A, Oosterlinck W, Brausi M, Kurth KH, Sylvester R, de Balincourt C. Significance of bladder biopsies in Ta, T1 bladder tumors: a report from the EORTC Genito-urinary Tract Cancer Cooperative Group. Eur Urol 1999;35:267-271.
34. Witjes J, Kiemeney L, Verbeek A, Heijbroek R, Debruyne F. Random biopsies and the risk of recurrent superficial bladder cancer. A prospective study in 1026 patients. World J Urol 1992;10:231-234.
35. Fernandez Gomez JM, Rodriguez Martinez JJ, Escaf Barmadah S, Perez Garcia J, Garcia J, Casosola Chamorro J. Significance of random biopsies of healthy mucosa in superficial bladder tumor. Arch Esp Urol 2000;53:785-797.
36. Oosterlinck W, Kurth K, Schröder F, Bultinck J, Hammond B, Sylvester R, members of the EORTC-GU Group. A prospective EORTC-GU Group randomized trial comparing transurethral resection followed by a single intravesical instillation of epirubicin or water in single stage Ta, T1 papillary carcinoma of the bladder. J Urol 1993;149:749-752.
37. May F, Treiber U, Hartung R, Schwaibold H. Significance of

random bladder biopsies in superficial bladder cancer. Eur Urol 2003; 44: 47-50.

38. Soloway M and Masters S. Urothelial susceptibility to tumor cell implantation: influence of cauterization. Cancer 1980;46:1158-1163.

39. Pan JS, Slocum HK, Rustum YM, Greco WR, Gaeta JF, Huben RP. Inhibition of implantation of murine bladder tumor by thiotepa in cauterized bladder. J Urol 1989;142(6):1589-1593.

40. Burnand K, Boyd P, Mayo M, Shuttleworth K, Lloyd-Davies R. Single dose intravesical thiotepa as an adjuvant to cystodiathermy in the treatment of transitional cell bladder carcinoma. Br J Urol 1976;48:55-59.

41. Garrett J, Lewis R, Meehan W, Leblanc G. Intravesical thiotepa in the immediate post-operative period in patients with recurrent transitional cell carcinoma of the bladder. J Urol 1978;120:410-411.

42. Abrams P, Choa R, Gaches C, Ashken M, Green N. A controlled trial of single dose intravesical adriamycin in superficial bladder tumors. Br J Urol 1981;53:585-587.

43. Kurth K, Maksimovic P, Hop W, Schroder F, Bakker N. Single dose intravesical epodyl after TUR of Ta TCC bladder carcinoma. World J Urol 1983;1:89-93.

44. MRC Working Party on Urological Cancer. The effect of intravesical thiotepa on the recurrence rate of newly diagnosed superficial bladder cancer. An MRC Study. Br J Urol 1985;57:680-685.

45. Medical Research Council Working Party on Urological Cancer, Subgroup on Superficial Bladder Cancer. The effect of intravesical thiotepa on tumor recurrence after endoscopic treatment of newly diagnosed superficial bladder cancer. A further report with long-term follow up of a Medical Research Council randomized trial. Br J Urol 1994;73:632-638.

46. Tolley DA, Hargreave TB, Smith PH, Williams JL, Grigor KM, Parmar MK, Freedman LS, Uscinska BM. Effect of intravesical mitomycin C on recurrence of newly diagnosed superficial bladder cancer: interim report from the Medical Research Council Subgroup on Superficial Bladder Cancer (Urological Cancer Working Party). Br Med J 1988;296:1759-1761.

47. Tolley DA, Parmar MK, Grigor KM, Lallemand G, Benyon LL, Fellows J, Freedman LS, Grigor KM, Hall RR, Hargreave TB, Munson K, Newling DW, Richards B, Robinson MR, Rose MB, Smith PH, Williams JL, Whelan P. The effect of intravesical mitomycin C on recurrence of newly diagnosed superficial bladder cancer: a further report with 7 years of follow up, J Urol 1996;155:1233-1238.

48. Ali-el-Dein B, Nabeeh A, el-Baz M, Shamaa S, Ashamallah A. Single dose versus multiple instillations of epirubicin as prophylaxis for recurrence after transurethral resection of pTa and pT1 transitional cell bladder tumors: a prospective randomized controlled study. Br J Urol 1997;79:731-735.

49. Solsona E, Iborra I, Ricos J, Monros J, Casanova J, Dumont R. Effectiveness of a single immediate mitomycin C instillation in patients with low risk superficial bladder cancer: short and long-term follow up. J Urol 1999;161:1120-1123.

50. Rajala P, Liukkonen T, Raitanen M, Rintala E, Kaasinen E, Helle M, Lukkarinen O. Transurethral resection with perioperative instillation of interferon-alpha or epirubicin for the prophylaxis of recurrent primary superficial bladder cancer: a prospective randomized multicenter study-FinnBladder III. J Urol 1999;161:1133-1135.

51. Rajala P, Kaasinen E, Raitanen M, Liukkonen T, Rintala E, the Finnbladder Group. Perioperative single dose instillation of epirubicin or interferon-alpha after transurethral resection for the prophylaxis of primary superficial bladder cancer recurrence: a prospective randomized multicenter study—FinnBladder III long-term results. J Urol 2002;168: 981-985.

52. Okamura K, Ono Y, Kinukawa T, Matsuura O, Yamada S, Ando T, Fukatsu T, Ohno Y, Ohshima S; Nagoya University Urological Oncology Group. Randomized study of single early instillation of (2''R)-4'-O-Tetrahydropyranyl-Doxorubicin for a single superficial bladder carcinoma. Cancer 2002;94:2363-2368.

53. Oosterlinck W, Lobel B, Jakse G, Malmstrom P, Stockle M, Sternberg C, The EAU Working Group on Oncological Urology. Guidelines on bladder cancer. Eur Urol 2002;41:105-112.

54. Sylvester R, Oosterlinck W, van der Meijden A. A single immediate postoperative instillation of chemotherapy decreases the risk of recurrence in patients with stage Ta T1 bladder cancer: a meta-analysis of published results of randomized clinical trials. J Urol 2004;171:2181-2185.

55. Zincke H, Utz D, Taylor W, Myers R, Leary F. Influence of thiotepa and doxorubicin instillation at time of transurethral surgical treatment of bladder cancer on tumor recurrence: a prospective, randomized, double-blind, controlled trial. J Urol 1983;129:505-509.

56. Brausi M, Collette L, Kurth K, van der Meijden AP, Oosterlinck W, Witjes JA, Newling D, Bouffioux C, Sylvester RJ; EORTC Genito-Urinary Tract Cancer Collaborative Group. Variability in the recurrence rate at first follow up cystoscopy after TUR in stage Ta T1 transitional cell carcinoma of the bladder: a combined analysis of seven EORTC studies. Eur Urol 2002;41:523-531.

57. Masters J, Popert M, Thompson P, Gibson D, Coptcoat M, Parmar M. Intravesical chemotherapy with epirubicin: a dose response study. J Urol 1999;161:1490-1493.

58. Whelan P, Griffiths G, Stower M, et al. Preliminary results of a MRC randomised controlled trial of post-operative irrigation of superficial bladder cancer. Proceedings of the American Society of Clinical Oncology 2001;20:abstract 708.

59. Weldon T and Soloway M. Susceptibility of urothelium to neoplastic cellular implantation. Urology 1975;5:824-826.

60. Kaasinen E, Rintala E, Hellstrom P, Viitanen J, Juusela H, Rajala P, Korhonen H, Liukkonen T; FinnBladder Group. Factors explaining recurrence in patients undergoing chemoimmunotherapy regimens for frequently recurring superficial bladder carcinoma. Eur Urol 2002;42:167-174.

61. Bouffioux C, Kurth K, Bono A, Oosterlinck W, Kruger CB, De Pauw H, Sylvester R. Intravesical adjuvant chemotherapy for superficial transitional cell bladder carcinoma: results of 2 European Organization for Research and Treatment of Cancer randomized trials with mitomycin C and doxorubicin comparing early versus delayed instillations and short-term versus long-term treatment. J Urol 1995;153:934-941.

62. Iborra I, Ricos J, Monros J, Dumont Martinez R, Casanova Ramon-Borja J, Solsona Narbon E. Resultados de un estudio de quimioprofilaxis intravesical, prospectivo, doble aleatorio, entre dos drogas: la adriamicina y el mitomycin; y dos modos de iniciar las instilaciones: precoz y tardio. Efecto sobre la recidiva y la progression. Arch Esp de Urol 1992;45:1001-1007.

63. Doherty A, Trendell-Smith N, Stirling R, Rogers H, Bellinger J. Perivesical fat necrosis after adjuvant intravesical chemotherapy. BJU Int 1999;83:420-423.

64. Nieuwenhuijzen J, Bex A, Horenblas S. Unusual complication after immediate postoperative intravesical mitomycin C instillation. Eur Urol. 2003;43:711-712.

65. Oehlschlager S, Loessnitzer A, Froehner M, Hakenberg O, Manseck A, Wirth M. Distal ureteral stenosis after early adjuvant intravesical mitomycin C application for superficial bladder cancer. Urol Int 2003;70:74-76.

66. Tawkif A, Neal F, Hong K. Bone marrow suppression after intravesical mitomycin C treatment. J Urol 1986;13:459-460.

67. Hinotsu S, Akaza H, Ohashi Y, Kotake T. Intravesical chemotherapy for maximum prophylaxis of new early phase superficial bladder carcinoma treated by transurethral resection. Cancer 1999;86:1818-1826.

68. Millan F, Chechile J, Salvador J, Palou J, Alagaba F, Vicente J. Primary superficial bladder cancer risk groups according to progression, mortality and recurrence. J Urol 2000;164:680-684.
69. Parmar MK, Freedman LS, Hargreave TB, Tolley DA. Prognostic factors for recurrence and follow-up policies in the treatment of superficial bladder cancer: report from the British Medical Research Council Subgroup on Superficial Bladder Cancer (Urological Cancer Working Party). J Urol 1989;142:284-288.
70. Martinez-Piñeiro JA, Jimenez Leon J, Martinez-Piñeiro L Jr, Fiter L, Mosteiro JA, Navarro J, Garcia Matres MJ, Carcamo P. Bacillus Calmette-Guerin versus doxorubicin versus thiotepa: a randomized prospective study in 202 patients with superficial bladder cancer. J Urol 1990;143;502-506.
71. Schulman CC, Robinson M, Denis L, Smith P, Viggiano G, de Pauw M, Dalesio O, Sylvester R. Prophylactic chemotherapy of superficial bladder transitional cell bladder carcinoma: an EORTC randomised trail comparing thiotepa, an epipodophyllotoxin (VM26) and TUR alone. Eur Urol 1982;8:207-212.
72. Kurth KH, Schroder FH, Tunn U, Ay R, Pavove-Macaluso M, Debruyne F, de Pauw M, Dalesio O, ten Kate F. Adjuvant chemotherapy of superficial transitional cell bladder carcinoma: preliminary results of a European organization for research on treatment of cancer. Randomized trial comparing doxorubicin hydrochloride, ethoglucid and transurethral resection alone. J Urol 1984;132:258-262.
73. Smith JA Jr, Labasky RF, Cockett AT, Fracchia JA, Montie JE, Rowland RG. Bladder cancer clinical guidelines panel summary report on the management of nonmuscle invasive bladder cancer (stages Ta, T1 and TIS). The American Urological Association. J Urol 1999;162:1697-1701.
74. Nomata K, Noguchi M, Kanetake M, Tsuda N, Nayashi M, Yamashita S, Sakuragi T, Kusaba Y, Shindo K, Nagashi Clinical Research Group for bladder cancer. Intravesical adjuvant chemotherapy for superficial transitional bladder cancer: results of a randomised trial with epirubicin comparing short and long-term maintenance treatment. Cancer Chemother Pharmacol 2002;50:266-270.
75. Kogaa K, Kuroiwas K, Yamaguchi A, Osada Y, Tsuneyoshi M, Naito S. A randomised controlled trial of short-term versus long-term prophylactic intravesical instillation chemotherapy for recurrence after transurethral resection of Ta/T1 transitional cell carcinoma of the bladder. J Urol 2004;171:153-157.
76. Harris NM, Duffy PM, Crook TJ, Anderson WR, Sharpe P, Hayes MC, Cooper AJ, Solomon LZ. Intravesical pH: a potentially important variable affecting efficacy and the further development of anthracycline chemotherapy for superficial bladder cancer. BJU Int 2002;90:957-964.
77. Au JL, Badalament RA, Wientjes MG. Methods to improve efficacy of intravesical Mitomycin C: results of a randomised phase III trial. J Natl Cancer Inst 2002;93:597-604.
78. Herr HW, Laudone VP, Whitmore WF. An overview of intravesical therapy for superficial bladder tumors. J Urol 1987;138:1363-1368.
79. Lamm DL. Long-term results of intravesical therapy for superficial bladder cancer. Urol Clin North Amer 1992;19:573-580.
80. Huncharek M and Kupelnick B. Impact of intravesical chemotherapy versus BCG immmunotherapy on recurrence of superficial transitional cell carcinoma of the bladder. Metaanalysis reevaluation. Am J Clin Oncol 2003;26:402-407.
81. Shelley MD, Court JB, Kynaston H, Wilt TJ, Fish RG, Mason M. Intravesical bacillus Calmette-Guerin in Ta and T1 Bladder Cancer (Cochrane review). The Cochrane Library, Issue 4, 2003.
82. Bölhe A, Jocham D, Bock PR. Intravesical bacillus Calmette-Guerin versus mitomycin C for superficial bladder cancer: a formal meta-analysis of comparative studies on recurrence and toxicity. J Urol 2003;169:90-95.
83. Sylvester RJ, van der Meijden A, Lamm DL. Intravesical bacillus Calmette-Guerin reduces the risk of progression in patients with superficial bladder cancer: a meta-analysis of the published results of randomized clinical trials. J Urol 2002;168:1964-1970.
84. Haukaas S, Daehlin L, Maartmann-Moe H, Ulvik NM. The long-term outcome in patients with superficial transitional cell carcinoma of the bladder: a single-institutional experience. BJU Int 1999;83:957-963
85. Zieger K, Wolf H, Olsen PR, H?jgaard K. Long-term follow-up of noninvasive bladder tumors (stage Ta): recurrence and progression. BJU Int 2000;85:824-828.
86. Dalesio O, Schulman CC, Sylvester R, De Pauw M, Robinson M, Denis L, Smith P, Viggiano G, members of EORTC. Prognostic factors in superficial bladder tumors. A study of the European Organization for research on treatment of cancer: genitourinary tract cancer cooperative group. J Urol 1983;129:730-733.
87. Ali-El-Dein B, Sarhan O, Hinev A, Ibrahiem el-HI, Nabeeh A, Ghoneim MA. Superficial bladder tumors: analysis of prognostic factors and construction of a predictive index. BJU Int 2003;92:393-399.
88. Allard P, Bernard B, Fradet Y, Tetu B. The early clinical course of primary Ta and T1 bladder cancer: a proposed prognostic index. BJU Int 1998;81:692-698.
89. Prout GR, Bruce JR, Barton A, Griffin PP, Friedell GH. Treated history of noninvasive grade 1 transitional cell carcinoma. J Urol 1992;148:1413-1419.
90. Larsson P, Wijkström H, Thorstenson A, Adolfsson J, Norming U, Wiklund P, Onelöv E, Steineck G. A population-based study of 538 patients with newly detected urinary bladder neoplasms followed during 5 years. Scand J Urol Nephrol 2003;37:195-201.
91. Fitzpatrick JM, West AB, Butler MR, Lane V, O'Flynn JD. Superficial bladder tumors: the importance of recurrence pattern following initial resection. J Urol 1986;135:920-922.
92. Milan-Rodrigez…
93. Leblanc B, Duclos AJ, Bénard F, Côté J, Valiquette L, Paquin JM, Mauffette F, Faucher R, Perreault JP. Long-term follow-up of initial Ta grade 1 transitional cell carcinoma of the bladder. J Urol 1999;162:1946-1950.
94. Borhan A, Reeder JE, O'Connell MJ, Wright KO, Wheeless LL, di Santagnese PA, McNally ML, Messing EM. Grade progression and regression in recurrent urothelial cancer. J Urol 2003;169:2106-2109.
95. Soloway MS, Bruck DS, Kim SS. Expectant management of small recurrent, non-invasive papillary bladder tumors. J Urol 2003;170:438-441.
96. Oge O, Erdem E, Atsu N, Ahin A, Ozen H. Proposal for changes in cystoscopic follow-up of patients with low-grade pTa bladder tumor. Eur Urol 2000;37:271-274.
97. German K, Hasan ST, Derry C. Cystodiathermy under local anaesthesia using the flexible cystoscope. BJU 1992;69:518-520.
98 Dryhurst DJ and Fowler CG. Flexible cystodiathermy can be rendered painless by using 2% lignocaine solution to provide intravesical anaesthesia. BJU Int 2001;88:437-438.
99. Syed HA, Biyani CS, Bryan N, Brough SJ, Powell CS. Holmium:YAG laser treatment of recurrent superficial bladder carcinoma: Initial clinical experience. J Endourol 2001;15:625-627.
100. Herr HW. Outpatient flexible cystoscopy and fulguration of recurrent superficial bladder tumors. J Urol 1990;144:1365-1366.
101. Wedderburn AW, Ratan P, Birch BR. A prospective trial of flexible cystodiathermy for recurrent transitional cell carcinoma of the bladder. J Urol 1999;161:812-814.
102. Donat SM, North A, Dalbagni G, Herr HW. Efficacy of office fulguration for recurrent low grade papillary bladder tumors less than 0.5 cm. J Urol 2004;171:636-639.

103. Kiemeney LA, Witjes JA, Heijbroek RP, Verbeek AL, Debruyne FM. Predictability of recurrent and progressive disease in individual patients with primary superficial bladder cancer. J Urol 1993;150:60-64.

104. Glas AS, Roos D, Deutekom M, Zwinderman AH, Bossuyt PMM, Kurth KH. Tumor markers in the diagnosis of primary bladder cancer. A systematic review. J Urol. 2003;169:1975-1982.

105. Roy JY, Staerkel GA, Ayala AG. Cytologic and histologic features of superficial bladder cancer. Urol Clin North Am 1992;19:435-453.

106. Sanchez-Carbayo M, Urrutia M, Silva JM, Romani R, Garcia J, Alferez F, Gonzalez deBuitrago JM, Navajo JA. Urinary tissue polypeptide-specific antigen for the diagnosis of bladder cancer. Urology 2000;55:526-532.

107. Sanchez-Carbayo M, Herrero E, Megias J, Mira A, Soria F. Initial evaluation of the new urinary bladder cancer rapid test in the detection of transitional cell carcinoma of the bladder. Urology 1999;54:656-661.

108. Lotan Y and Roehrborn CG. Sensitivity and specificity of commonly available bladder tumor markers versus cytology: results of a comprehensive literature review and meta-analysis. Urology 2003;61:109-118.

109. Friedrich MG, Hellstern A, Toma MI, Hammerer P, Huland H. Are false positive urine tests in the diagnosis of bladder cancer really wrong – or do they predict tumor recurrence ? Eur Urol 2003;43:146-151.

110. Lotan Y and Roehrborn CG. Cost effectiveness of a modified care protocol substituting bladder tumor markers for cystoscopy in the follow-up of patients with transitional cell carcinoma of the bladder: a decision analytical approach. J Urol 2002;167:75-79.

111. Ramakumar S, Bhuiyan J, Besse JA, Roberts SG, Wollan PC, Blute ML, O'Kane DJ. Comparison of screening methods in the detection of bladder cancer. J Urol 1999;161:388-394.

112. Solsona E, Iborra I, Ricos JV, Monros JL, Rubio J, Almenar S. Clinical panurothelial disease in patients with superficial bladder tumors: therapeutic implications. J Urol 2002;167:2007-2011.

113. Zeegers MPA, Tan FES, Dorant E, van den Brandt PA. The impact of characteristics of cigarette smoking on urinary tract cancer risk: a meta analysis of epidemiologic studies. Cancer 2000;89:630-639.

114. Zeegers MPA, Kellen EE, Buntinx EF. The association between smoking, beverage consumption, diet and bladder cancer: a systematic literature review. World J Urol 2004;21:392-401.

115. Zeegers MPA, Goldbohm RA, van den Brandt PA. A prospective study on active and enviromental tobacco smoking and bladder cancer risk (The Netherlands). Cancer Causes and Control 2002;13:83-90.

116. Brennan P, Bogillot O, Cordier S, Greiser E, Schill W, Vineis P, Lopez-Abente G, Tzonou A, Chang-Claude J, Bolm-Audorff U, Jockel KH, Donato F, Serra C, Wahrendorf J, Hours M, T'Mannetje A, Kogevinas M, Boffetta P. Cigarette smoking and bladder cancer in men: a pooled analysis of 11 case-control studies. Int J Cancer 2000;86:289-294.

117. Pelucchi C, La Vecchia C, Negri E, Dal Maso L, Franceschi S. Smoking and other risk factors for bladder cancer in women. Preventive Medicine 2002;35:114-120.

118. Brennan P, Bogillot O, Greiser E, Chang-Claude J, Wahrendorf J, Cordier S, Jockel KH, Lopez-Abente G, Tzonou A, Vineis P, Donato F, Hours M, Serra C, Bolm-Audorff U, Schill W, Kogevinas M, Boffetta P. The contribution of cigarette smoking to bladder cancer in women (Pooled European Data). Cancer Causes and Control 2001;12:411-417.

119. Pitard A, Brennan P, Clavel J, Greiser E, Lopez-Abente G, Chang-Claude J, Wahrendorf J, Serra C, Kogevinas M, Boffetta P. Cigar, pipe, and cigarette smoking and bladder cancer risk in European men. Cancer Causes and Control 2001;12:551-556.

120. Shapiro JA, Jacobs EJ, Thun MJ. Cigar smoking in men and risk of death from tobacco-related cancers. Journal of the National Cancer Institute 2000;9:333-337.

121. Fleshner N, Garland J, Moadel A, Herr H, Ostroff J, Trambert R, O'Sullivan M, Russo P. Influence of smoking status on the disease-related outcomes of patients with tobacco-associated superficial transitional cell carcinoma of the bladder. Cancer 1999;86:2337-2345.

122. Michaud DS, Spiegelman D, Clinton SK, Rimm EB, Curhan GC, Willett WC, Giovannucci EL. Fluid intake and the risk of bladder cancer in men. N Engl J Med 1999;340:1390-1397.

123. Donat SM, Bayuga S, Herr HW, Berwick M. Fluid intake and the risk of tumor recurrence in patients with superficial bladder cancer. J Urol 2003;170:1777-1780.

124. Geoffroy B and Cordier PZS. Fluid consumption and the risk of bladder cancer: results of a multicenter case-contol study. Int J Cancer 2001;93:880-887.

125. Steinmaus CM, Nunez S, Smith AH. Diet and bladder cancer: a meta-analysis of six dietary variables. Am J Epidemiol, 2000;151:693-702.

126. Michaud DS, Spiegelman D, Clinton SK, Rimm EB, Willett WC, Giovannucci EL. Fruit and vegetable intake and incidence of bladder cancer in male prospective cohort. J Natl Cancer Inst 1999;91:605-613.

127. Michaud DS, Spiegelman D, Clinton SK, Rimm EB, Willett WC, Giovannucci EL. Prospective study of dietary supplements, macronutrients, micronutrients and risk of bladder cancer in US men. Am J Epidemiol 2000 152:1145-1153.

128. Studer UE, Jenzer S, Biedermann C, Choller D, Kraft R, von Toggenburg H, Vonbank F. Adjuvant treatment with a vitamin A analogue (Etretinate) after transurethral resection of superficial bladder tumors. Eur Urol 1995;28:284-290.

129. Jacobs EJ, Henion AK, Briggs PJ. Vitamin C and vitamin E supplement use and bladder cancer mortality in a large cohort of US men and women. Am J Epidemiol 2002;156:1002-1010.

130. Newling DWW, Robinson MRG, Smith PH, Byar D, Lockwood R, Stevens I, De Pauw M, Sylvester R. Tryptophan metabolites, pyridoxine and their influence on the recurrence rate of superficial bladder cancer. Eur Urol 1995;27:110-116.

131. Lamm DL, Riggs DR, Shriver JS, vanGilder PF, Rach JF, DeHaven JI. Megadose vitamins in bladder cancer: a double-blind clinical trial. J Urol 1994 ;151:21-26.

132. Aso Y, Akaza H, Kotake T, Tsukamoto T, Imai K, Naito S. Preventive effects of a lactobacillus casei preparation on the recurrence of superficial bladder cancer in a double-blind trial. Eur Urol 1995;27:104-109.

133. Tomita K, Akaza H, Nomoto K, Yokokura T, Matsushima H, Homma Y, Aso Y. Influence of lactobacillus casei on rat bladder carcinogenesis. Jpn J Urol 1994;85:655-663.

134. Ohashi Y, Nakai S, Tsukamoto T, Masumori N, Akaza H, Miyanaga N, Kitamura T, Kawabe K, Kotake T, Kuroda M, Naito S, Koga H, Saito Y, Nomata K, Kitagawa M, Aso Y. Habitual intake of lactic acid bacteria and risk reduction of bladder cancer. Urol Int 2002;68;273-280.

135. Takahashi T, Kushiro A, Nomoto K, Uchida K, Morotomi M, Yokokura T, Akaza H. Antitumor effects of the intravesical instillation of heat killed cells of the Lactobacillus casei strain Shirota on the murine orthotopic bladder tumor MBT-2. J Urol 2001;166:2506-2511.

Committee 4

High Grade Ta Urothelial Carcinoma and Carcinoma in Situ of the Bladder

Chairs

R. Sylvester (Belgium)

A. v.d. Meijden (Netherlands)

Members

J.A. Witjes (Netherlands)

G. Jakse (Germany)

N. Nonomura (Japan)

C. Cheng (Singapore)

A. Torres (Mexico)

R. Watson (Australia)

K.H. Kurth (Netherlands)

CONTENTS

High Grade Ta Urothelial Carcinoma and Carcinoma in Situ of the Bladder

R. Sylvester, A. v.d. Meijden

J. A. Witjes, G. Jakse, N. Nonomura, C. Cheng, A. Torres, R. Watson, K. H. Kurth

I. HIGH GRADE Ta UROTHELIAL CARCINOMA

1. Definition and Characteristics

The most recent TNM Classification of Malignant Tumors, the 6th edition, was published by the International Union Against Cancer in 2002 [1]. Ta tumors are defined here as noninvasive papillary carcinomas, those that do not invade the subepithelial connective tissue (lamina propria).

A number of different tumor grading classification systems have been published, including the 1973 WHO [2], the 1998 WHO/ISUP [3], and the 1999 WHO [4]. Here, high grade refers to grade 3 tumors defined according to the widely used 1973 WHO classification system. There is evidence (*Level 3*) that the high grade group based on the 1998 WHO/ISUP classification is composed of 2 subgroups with different marker profiles and prognoses corresponding to 1973 WHO grades 2 and 3 [5].

2. Incidence

High grade papillary tumors that are confined to the mucosa and do not invade the lamina propria are relatively rare. Based on 12 different series [5-17], **Table 1** shows that the incidence of high grade tumors among Ta tumors varied from 2.9% to 18.0%, with an average of 6.9% (229/3299 patients). The incidence of high grade Ta tumors among all patients with stage Ta or T1 tumors was 4.1% (247/6093 patients) and varied from 1.7% to 9.3%.

Conversely, Herr found that 125 of 148 patients with Ta tumors (84.5%) had high grade tumors [18]. However, this study used the 1998 WHO/ISUP classification system, which does not distinguish between 1973 WHO grades 2 and 3, so the figures are not directly comparable. Also, this was a highly selected group of patients with recurrent disease and 72% had concurrent carcinoma in situ (CIS).

Table 1. Incidence of High Grade Ta Bladder Cancer

Reference	Among Ta Tumors	Among Ta or T1 Tumors
Chen [6]	14/140 (10.0%)	
Haukaas [7]	5/140 (3.6%)	5/231 (2.2%)
Heney [8]	5/175 (2.9%)	5/249 (2.0%)
Holmang [9]	9/77 (11.7%)	9/176 (5.1%)
Holmang [5,10]	13/363 (3.6%)	13/481 (2.7%)
Jakse [11]	16/89 (18.0%)	16/172 (9.3%)
Larsson [12]	15/292 (5.1%)	15/402 (3.7%)
Lebret [13]		32/605 (5.3%)
Lutzeyer [14]	9/270 (3.3%)	9/522 (1.7%)
Millan-Rodriguez [15]	63/546 (11.5%)	63/1527 (4.1%)
Van der Meijden [16]		
Local pathology	53/963 (5.5%)	53/1767 (3.0%)
Review pathology	67/953 (7.0%)	67/1278 (5.2%)
Witjes [17]		
Local pathology	16/246 (6.5%)	16/450 (3.6%)
Review pathology	13/254 (5.1%)	13/450 (2.9%)
Total	229/3299 (6.9%)	247/6093 (4.1%)
Range	2.9% - 18.0%	1.7% - 9.3%

Several papers have highlighted discrepancies between local and review pathology in determining both the tumor stage and grade. Witjes et al. found that only 31% (5 /16) of patients initially classified locally as having high grade Ta tumors were confirmed by review pathology while another 5 of 16 (31%) were reclassified as high grade T1 [17]. In addition, 61.5% (8/13) of the tumors classified as high grade Ta by the review pathologist were not

classified as such by the local pathologist. In the EORTC series [16], the agreement was even worse (**Table 2**). Additional analyses showed that only 21% (11/53) of tumors classified as high grade Ta by the local pathologist were confirmed on pathology review, and nearly 84% (56/67) of the patients classified as having high grade Ta tumors by the review pathologist were not classified as such by the local pathologist. Globally, only 23% of the patients classified as having high grade Ta tumors by the local pathologist were confirmed by review pathology. Thus, inaccuracies in staging and grading can result in the misclassification of a substantial percentage of patients with high grade Ta tumors (*Level 3*).

3. Diagnostic Work-up

Due to the high rate of misclassification in patients originally thought to have high grade Ta tumors, a second-look TUR is indicated in order to reduce the risk of understaging and residual disease (*Level 3, Grade B* [19,20,21]). Bladder mapping biopsies to determine the presence of CIS should be considered due to the high incidence of concurrent CIS - 40% or more - observed in several series (*Level 3, Grade B,* [5,13,18]).

4. Prognosis

Various publications have shown that although tumor multiplicity is the most important prognostic factor for *recurrence*, it is the grade that is the most important prognostic factor for *progression* to muscle-invasive disease [15]. The difference in the progression rate between stages Ta and T1 appears to be less important in high grade tumors [22]. How-ever, across different series, assessment of the risk of progression in patients with high grade Ta tumors is difficult. This is not only due to inaccuracies in staging and grading, but also due to small patient numbers, differences in the grading system used, frequency of concomitant CIS, adjuvant treatment after TURBT, rate of cystectomy, duration of follow-up, and definition of progression (lamina propria or muscle invasion).

Considering the above limitations, **Table 3** presents progression rates for patients with high grade Ta disease in 9 different series of patients with long-term follow-up. It suggests that invasion of the lamina propria occurs in as many as 40% of the patients, and progression to muscle-invasive disease in about 20% to 25% of the patients (*Level 2*).

5. Treatment

Because high grade Ta tumors represent a relatively small subgroup of patients and the histological diagnosis is subject to considerable misclassification, there are no randomized trials comparing the efficacy of different treatment regimens in this patient subgroup. As they have a 20% to 25% chance of progression to muscle-invasive disease, patients with high grade Ta bladder tumors should be treated and followed as high-risk patients (*Grade A,* [23,24]).

Thus, after TURBT, patients with tumors appearing to be high grade Ta should receive 1 immediate instillation of chemotherapy (*Grade A,* [25]). They should undergo a second-look TURBT and bladder mapping biopsies 2 to 4 weeks later (*Grade B*). If residual tumor is found, resect and give 1 immediate instillation of chemotherapy. This is followed, 2 to 3 weeks later, once the diagnosis of high grade Ta has been confirmed, by a 6-week induction course of bacillus Calmette-Guérin (BCG) and 1 to 3 years of maintenance BCG (*Grade A,* [26-28]). The optimal maintenance schedule is unknown.

In case of failure before maintenance BCG has been completed, consider cystectomy if high grade T1 or CIS is present (*Grade B*). For other superficial recurrences, resect and continue maintenance BCG (*Grade B*). If early failure occurs after maintenance BCG has been completed, consider cystectomy (*Grade B*). If later superficial recurrence occurs, consider restarting BCG or other instillations as an alternative to cystectomy (*Grade B*).

These patients require long-term follow-up (*Grade A*), for example every 3 months during the first 2 years, every 4 months during the third year, every 6 months during the fourth and fifth years, and yearly thereafter as long as there is no recurrence (*Grade B,* [28]) (see decision tree at the end chapter).

Table 2. High Grade Ta: Agreement Between Local and Review Pathology

	Van der Meijden [16]	Witjes [17]	Total
Local High Grade Ta Confirmed by Review	11/53 (20.8%)	5/16 (31.3%)	16/69 (23.2%)
Review High Grade Ta Not Identified by Local	56/67 (83.6%)	8/13 (61.5%)	64/80 (80.0%)

Table 3. Progression of High Grade Ta Bladder Cancer

Reference	Treatment After TURBT	Progression	Death Due to Disease	Follow-up
Chen [6]	Chemotherapy	4/14 (28.5%) T1 3/14 (21.4%) T2	NA*	Mean 74 months
Heney [8]	None	1/4 (25.0%) T2	NA	Median 39 months
Herr [18] ISUP	BCG	49/125 (39.2%) T1	32/125 (25.6%)	Min 15 years
Holmang [9]	None Radiotherapy Cystectomy	1/ 9 (11.1%) T2	NA	Min 20 years
Holmang [5]	None Chemotherapy Radiotherapy	6/13 (46.2%) T1b	NA	Min 5 years
Jakse [11]	None	3/16 (18.8%) T1 1/16 (6.3%) T2	1/16 (6.3%)	Median 106 months
Larsson [12]	None Chemotherapy Cystectomy	2/15 (13.3%) T1 1/15 (6.7%) T2	2/10 (20.0%)	Min 5 years
Lebret [13]	BCG	15/32 (46.9%) T1 8/32 (25.0%) T2	4/32 (12.5%)	Median 58 months
Van der Meijden [16]	None Chemotherapy BCG	17/67 (25.4%) T2	NA	Max 14 years

**NA: Data not available*

Summary

High grade Ta tumors defined according to the 1973 WHO grading classification system are relatively rare, accounting for approximately 7% of Ta tumors and 4% of all Ta and T1 tumors. However, inaccuracies in staging and grading can result in the misclassification of 75% or more of patients thought to have high grade Ta tumors.

A second look TUR and bladder mapping biopsies are recommended. Since these patients have a 20% to 25% chance of progression to muscle-invasive disease, they should be treated and followed as high-risk patients. Thus, they should receive 1 immediate instillation of chemotherapy after TUR, a 6-week induction course of BCG, and 1 to 3 years of maintenance BCG.

II. CARCINOMA IN SITU

A number of review papers on carcinoma in situ (CIS) have been published [29-36], some of which are based on previous bladder cancer consensus conferences. This review expands upon these previous papers, taking into account recent publications. However, the problem with many of these publications is that they are based on only a small number of highly-selected patients and on retrospective analyses with different endpoints, evaluation criteria, and durations of follow-up. It is thus difficult to obtain evidence-based results.

1. Definition and Characteristics

CIS is a flat, high grade, noninvasive urothelial carcinoma **(Figure 1)**. Using the 2002 TNM classifica-

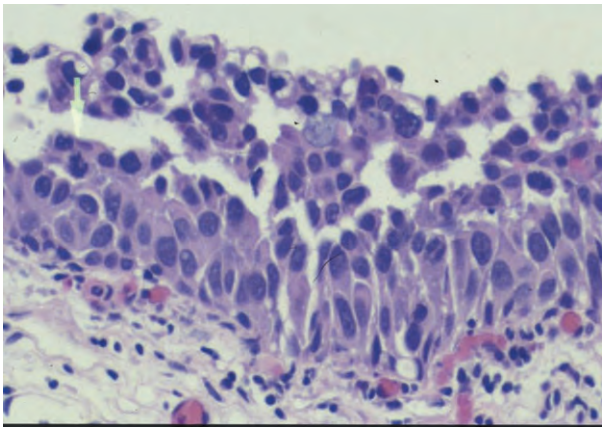


Figure 1. CIS is a flat, high grade, noninvasive urothelial carcinoma

tion, CIS is classified together with Ta and T1 papillary tumors as a superficial bladder cancer [1]. Unlike low grade Ta and T1 tumors, CIS is a highly malignant entity which, when left untreated, has a much higher progression rate than most Ta and T1 tumors (*Level 2,* [29]). The term *carcinoma in situ* might suggest that CIS is a precursor of cancer. While it may be a precursor of *invasive* bladder cancer, the histological and cytological aspects of CIS make this an overtly malignant entity in itself.

Macroscopically, CIS can be missed at cystoscopy or be considered as an inflammatory lesion if not biopsied. It is often multifocal and can occur in the upper urinary tracts and in the prostatic ducts and urethra [34].

In 1998, the WHO/ISUP consensus classification of urothelial neoplasms of the urinary bladder defined CIS as follows [3]:

The lesion is characterized by the presence of cells with large, irregular, hyperchromatic nuclei that may be either present in the entire thickness of the epithelium or only a part of it. Mitotic activity is frequently observed, often in the mid to upper urothelium. CIS encompasses lesions which in the past were designated as severe dysplasia or marked atypia. By definition, all CIS are high grade lesions. CIS should not be subclassified by grade despite the spectrum of pleomorphism seen within this entity.

CIS is classified into 1 of 3 different clinical types [33]:

1. Primary CIS: isolated CIS with no previous or concurrent papillary tumors
2. Secondary CIS: CIS detected during the follow-up of patients with a previous papillary tumor
3. Concurrent CIS: CIS in the presence of papillary tumors

2. Incidence

It has been estimated that 5% to 10% of all patients with superficial bladder cancer have CIS [33, 37, 38]. However, due to differences in patient selection, the lack of a uniform definition and classification system for CIS, and interobserver variability, especially between varying degrees of dysplasia and CIS, the percent of patients with CIS varies from one series to another. For example, Kaasinen found that 5% of patients with superficial bladder cancer had concurrent CIS as compared to 19% reported by Palou [38, 39].

3. Diagnosis of CIS

The diagnosis of CIS is made in most cases by a combination of cystoscopy, urine cytology, and multiple bladder biopsies [31]. Of these, the histology of bladder biopsies is determinant in establishing the diagnosis. In CIS, the coherence and adherence of epithelial cells is decreased and this feature often results in denuded biopsies when taken by cold cup or with the resection loop.

Standard (white-light) cystoscopy might reveal no visible abnormalities at all, although multifocal red, velvet-like patches are often visible **(Figure 2)**. Zaak et al. found that under white-light endoscopy 30% of specimens with grade 2 dysplasia and 53% of specimens with CIS were missed [40].

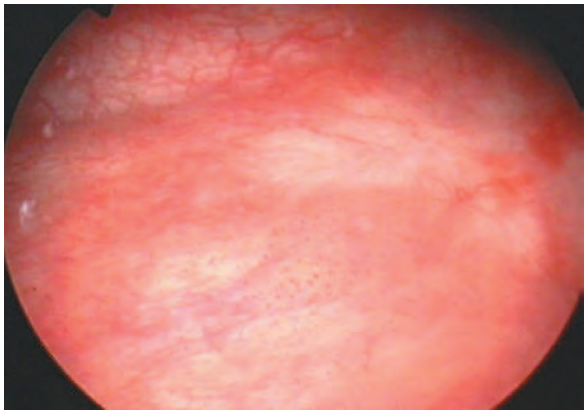


Figure 2 CIS A multifocal red, velvet-like patches are often visible

Fluorescence cystoscopy, which is done with a porphyrin-based photosensitizer, (hex)-aminolevulinic acid (HAL or ALA), will reveal areas in the bladder that are suspicious for CIS and that cannot be seen with white-light cystoscopy. In a group of 83 patients with CIS, HAL cystoscopy detected CIS in 18 patients (22%) that was missed by traditional white-light cystoscopy. [41] Although the use of fluores-

cence cystoscopy improves the detection rate of CIS to more than 95% (*Level 2*), it has not yet been implemented on a regular basis in daily practice [41, 42].

Although CIS is defined as an overt high grade lesion, consensus on the diagnosis does not always exist when the specimen is reviewed by several pathologists. There is both intraobserver and interobserver variability, even between severe dysplasia and CIS. For example, Sharkey found a considerable discrepancy between local and review pathology: 15 of 69 (22%) cases of CIS were downgraded to dysplasia while 8 of 27 (30%) reports of dysplasia were upgraded to CIS [43]. In addition, sampling errors may also lead to an incorrect diagnosis.

Both papillary tumors, and, especially, CIS, shed cells in the urine. Due to a loss of cohesion of cells in the epithelial lining of the bladder in CIS, there is a larger number of floating cells in the urine as well as a high degree of anaplasia. Classic urine cytology will not detect low grade papillary tumors in all cases. However, CIS is a disease that is nearly always detected by urine cytology; both the sensitivity and specificity of urine cytology are over 90%.

During the last decade, many new urine tumor markers have become available such as NMP-22, Immunocyt, BTA stat, and telomerase [44]. In a comprehensive literature review and meta-analysis in 348 patients with CIS, Lotan et al. have shown that some urine-based bladder tumor markers may have a sensitivity which is at least as good as cytology, but the specificity of these tests was not reported and the number of patients included in the various studies was small [45]. Markers such as UroVysion, HA-HAase, and BLCA-4 are promising as they all have a high sensitivity to detect CIS [46]. However, further studies are required before any of these markers can be recommended to replace classic urine cytology (*Level 2, Grade B*).

Controversy exists, however, whether cytology should be derived from voided urine or from a bladder wash (barbotage). It has been stated that more shedded cells are to be expected from rinsing the bladder as compared to voided urine. However, rinsing the bladder requires catheterization, which is a minor but invasive procedure which sometimes leads to urinary tract infection. On the other hand, barbotage fluid can be examined in patients undergoing diagnostic or control cystoscopy.

When high grade cells are found on cytology in the absence of visible tumor on cystoscopy and IVU, and when biopsies from the bladder and prostatic urethra are normal, CIS in the upper urinary tract should be suspected, even though it is rare [47]. It is possible to detect which renal unit is involved by investigating the urine produced by each unit separately. Sampling is done using a ureteral catheter or ureteroscopy. Brushing and biopsies of suspicious areas are also possible, but in many cases neither imaging nor biopsies will confirm the diagnosis. CIS in the upper urinary tract may thus be diagnosed only by repeated cytology.

4. Prognosis

Patients with CIS fall into the high-risk group. Various publications have shown that the presence of CIS is an adverse prognostic factor, especially for progression to muscle-invasive disease and death due to bladder cancer. In a series of more than 1500 patients, CIS was the second most important prognostic factor after grade (*Level 2,* [15]).

Based on the natural history of CIS, approximately 54% of patients with CIS progress to muscle-invasive disease [29]. With BCG, a complete response rate of about 70% to 80% can be achieved [33,48-50]. However, even in complete responders, there is still a high risk of extravesical recurrence (prostatic urethra, ureters, renal pelves), progression within the bladder, and death due to bladder cancer. Jakse found a 5-year disease-free survival rate of 60% in 77 complete responders, 16 of whom (21%) died due to bladder cancer [50]. In a group of 145 patients treated with BCG, at 5 years Kaasinen found an overall 54% disease-free rate, while 14% of patients progressed to T1 or higher and 7% died due to bladder cancer (*Level 2,* [38]).

5. Prognostic Factors in Patients with CIS

Once CIS is diagnosed, there are no completely reliable prognostic factors that can be used to predict the course of the disease, which can be quite variable. The response rate in patients undergoing intravesical treatment as well as the time point of re-sponse may differ substantially from one patient to the next. It would be of great help if prognostic factors could be used to predict which patients will ultimately respond to intravesical treatment and which will not.

Lamm proposed a division of patients into 1 of 3 groups [29,33]:

1. asymptomatic unifocal primary CIS
2. symptomatic multifocal (diffuse) primary CIS
3. CIS associated with prior or concurrent stage Ta or T1 papillary tumors

He hypothesized that the first group is the least aggressive form of CIS, that the second group has a poor prognosis with a high risk of extravesical extension, and that the third group was more heterogeneous.

Orozco defined 4 groups with an increasingly poor prognosis [37]:

1. unifocal primary CIS
2. multifocal primary CIS
3. secondary CIS with noninvasive high grade tumors
4. secondary CIS with high grade tumors that are or become invasive

Hudson and Herr divided patients into 2 risk groups, with good risk patients having unifocal CIS, a single aneuploid line, cell surface receptors, tumor-associated or proliferative antigens, expression of normal urothelial antigens, and a lack of p53 overexpression [30].

These risk groups have never been properly validated, so no conclusions concerning their appropriateness can be drawn. Many prognostic factor publications are based on a retrospective analysis of small patient series from a single institution. We will now review various factors of potential prognostic importance (*Level 3*).

a) Age

Takashi, Cheng, and Griffiths all found that younger patients (less than 60, 65, and 70 years, respectively) had a better prognosis [51-53].

b) Response to BCG

In complete responders, the median duration of response is approximately 5 to 6 years [50,54]. In 77 complete responders not receiving maintenance BCG, after a median follow-up of 7.6 years, 39% recurred in the bladder, 17% had a locoregional extravesical recurrence, 9% developed distant metastases, and 21% died due to bladder cancer [50]. In another series of 55 complete responders receiving maintenance BCG, after a median follow-up of 5.6 years, 33% recurred in the bladder and 11% died due to bladder cancer [54]. Thus, a complete response of CIS after intravesical treatment does not mean that the response will be durable. Even in complete responders, lifelong monitoring of patients with CIS is mandatory.

Nevertheless, various publications have shown that the response to intravesical treatment with BCG or chemotherapy is an important prognostic factor for subsequent progression and death due to disease. Approximately 10% to 20% of complete responders will eventually progress as compared to up to two-thirds or more of nonresponders.

In a group of 111 patients with CIS and 80 patients with high grade T1 urothelial carcinoma, the 3-month response was the most important prognostic factor for subsequent progression: 16 of 150 (11%) complete responders progressed as compared to 27 of 41 (66%) nonresponders [55].

Hudson and Herr [30] reported that 7 of 105 (7%) complete responders progressed at 5 years as compared to 25 of 75 (33%) incomplete responders. In a small series, Van Gils-Gielen found that 6 of 34 (18%) complete responders progressed as compared to 12 of 18 (67%) nonresponders [56]. Two of 34 (6%) responders died due to bladder cancer as compared to 5 of 18 (28%) nonresponders.

Large differences in cystectomy rates between responders and nonresponders have also been reported, approximately 10% in responders as compared to 50% in nonresponders [48,56].

Treatment failure within the first 9 months after 6 weekly BCG instillations is also an alarming signal that requires an immediate reassessment of the patient to exclude muscle-invasive disease or extravesical CIS, either in the upper urinary tract or in the prostatic urethra [57].

Thus, responders have a better prognosis than nonresponders, though early recurrence is also an ominous sign.

c) CIS versus Dysplasia

Assessment of the prognostic importance of CIS relative to dysplasia is difficult since the distinction between CIS and dysplasia is variable from one observer to the next. As mentioned, Sharkey found a considerable discrepancy between local and review pathology [43]. Given this variability and the small number of patients included in many series, contradictions exist in the literature concerning the prognostic importance of dysplasia relative to CIS.

In the 2 largest series, Millan-Rodriguez found CIS but not dysplasia to be of prognostic importance

[15]; however, Kiemeney found that patients with CIS or dysplasia in random biopsies had a higher risk of an increase in tumor stage at 3 years as compared to patients with normal mucosal biopsies, with the difference being the largest for patients with CIS [58].

Cheng found that urothelial dysplasia is a significant risk factor for the development of CIS and invasive carcinoma [59]. In 36 patients with primary untreated urothelial dysplasia, 7 patients (19%) progressed: 4 developed CIS and 3 developed invasive disease.

d) Type of CIS

The frequency of primary CIS relative to secondary and concurrent CIS varies among different publications, ranging from 9% to 69% [60,61]. In 3 recent studies with more than 100 patients each, 17% to 23% of patients with CIS were primary [50,53,54]. In another large series of 304 patients with CIS [38], 30% were primary, 42% secondary, and 28% concurrent. Twenty-eight percent were primary in a retro-spective register of 102 patients with CIS [37]. The risk of secondary CIS increases according to papil-lary tumor grade and stage [62].

There is no difference in the complete response rate to BCG according to type of CIS [50,51,53]. Kaasinen reported that patients with concurrent CIS had the highest progression rate (T1 or higher) and those with primary CIS the lowest [38]. Ovesen found that 1 of 13 (8%) patients with primary CIS progressed as opposed to 26 of 47 (57%) patients with secondary or concurrent CIS [63]. Orozco observed that 8 of 29 (28%) patients with primary CIS increased in stage as compared to 43 of 73 (59%) patients with secondary or concurrent CIS [37]. Two of 29 (7%) patients with primary CIS died of bladder cancer as opposed to 33 of 73 (45%) patients with secondary or concurrent CIS. Losa found a higher risk of progression in CIS associated with T1 papillary tumors as compared to CIS alone on BCG [49]. Likewise, Griffiths also found a higher progression and death rate in patients with concurrent T1 tumors [53].

Thus, overall, patients with primary CIS have the best long-term prognosis while those with concurrent CIS have the worst.

e) Extent of CIS

Multifocal (diffuse) CIS is typically associated with irritative symptoms and may extend to the distal ureter and/or prostatic urethra in up to 30% to 50% of cases [64]. However, the extent of CIS, whether unifocal or multifocal, is defined differently by different authors. Multifocality has been variably defined as the presence of CIS in at least 2, at least 3, or at least 4 different sites.

Some 50% to 70% of patients have at least 2 sites involved [15,49,52,54,65,66], 25% to 45% at least 3 sites [52,56], and about 20% at least 4 sites [50].

Riddle found that 1 of 13 (8%) patients with unifocal disease (one site) progressed compared to 18 of 23 (78%) patients with at least 2 sites involved [65]. Other authors could not show the prognostic importance of the extent of the disease, but the number of patients studied was often small and therefore inadequate [49,51,52,56].

f) Irritative Bladder Symptoms

As many as 25% of patients with CIS are asymptomatic at diagnosis [33]. The percent of patients with irritative bladder symptoms varies between 40% and 75% in different series [51,52,67,68]. Norming found that there was progression (to T1 or higher) in 29 of 45 (64%) patients with irritative bladder symptoms compared to 8 of 18 (44%) patients without irritative bladder symptoms [68]. Neither Cheng nor Takashi could show the prognostic importance of irritative bladder symptoms [51,52].

g) Hematuria

Most patients have at least microscopic hematuria [33] and 40% to 50% have macroscopic hematuria [51,52]. Takashi found that the patients (43/84, 51%) with gross hematuria had a significantly lower complete response rate, 63% versus 85% [51]. Cheng could not show the prognostic importance of macroscopic hematuria, which was present in 54 of 138 (41%) patients, for either progression-free or cancer-specific survival [52].

h) Molecular Markers

Despite some authors having found that DNA ploidy [68] and the loss of E-cadherin expression [69] predict stage progression in CIS patients, the use of molecular markers and cell cycle regulators has not provided a tool that can be used in daily practice to predict their response and prognosis [69].

Anomalies of the p53 tumor suppressor gene have been the most thoroughly investigated. Data suggest that p53 overexpression after BCG treatment may be more important than p53 overexpression prior to the start of treatment. In a small group of 23 patients with CIS, Ick reported that p53 overexpression was present in 21 (90%) patients as compared to 0 of 11

patients with dysplasia. [70] Ick also found that residual CIS with persistent p53 overexpression after BCG treatment was linked to a high rate of progression [70]. Likewise, Ovesen reported that posttreatment p53 overexpression was related to progression (9 of 10 (90%) p53-positive patients progressed as compared to 18 of 49 (37%) p53-negative patients) [63]. Among patients with a complete response, 7 of 34 (21%) patients who were p53-negative after treatment progressed as compared to 3 of 3 (100%) who were p53-positive.

In a group of 33 patients, Sarkis found that pretreatment p53 was related to both stage progression (3 of 18 (17%) progressed to T1 or higher in p53-negative patients compared to 13 of 15 (87%) in p53-positive patients) and death due to bladder cancer [71].

Shariat observed that pretreatment p21 overexpression was related to an increase in stage while patients who were both p21- and p53-positive had the highest risk of stage increase [72].

Assessment of the prognostic importance of p53 across different studies is difficult due to differences in study design, patient selection, choice of the antibody, use of different cutoff values, and small patient numbers [73]. In a review of 138 p53 publications, comprising 3764 patients in 43 trials, no conclusions could be drawn by the authors due to methodological differences in technical aspects, selection of laboratory kits, and especially variations in the cutoff values used to classify a test as being positive or negative [73].

No definitive conclusions on the value of tumor markers can be drawn due to the quality of the available data. Thus, the use of tumor markers to predict response to treatment is not recommended in daily practice (*Grade B*).

i) Extravesical Extension

Patients with CIS are at a high risk of extravesical involvement. Solsona found that 27 of 138 (19.5%) patients with CIS had extravesical involvement at baseline, 6 (4.3%) in the upper tract and 21 (15.2%) in the prostate [47,60]. A total of 34 of 138 (24.6%) patients with CIS had or developed upper urinary tract tumors as compared to 18 of 786 (2.3%) patients with only superficial papillary tumors. When there was upper tract involvement, 23 of 34 (68%) also had prostate involvement (panurothelial disease). Overall, 87 of 138 (63%) patients with CIS developed extravesical involvement.

In 88 patients with CIS who had a complete response with intravesical chemotherapy or BCG, 67% recurred, 12.5% in the bladder and 54.5% in extravesical locations. In 23 nonresponders, 51% develped extravesical disease [60]. Patients with extra-vesical involvement had worse disease-free and cancer-specific survival as compared to CIS patients without extravesical involvement, especially when there was panurothelial disease. In another series, Herr reported upper urinary tract recurrence in 19 of 66 (29%) patients with CIS after a complete response in the bladder with BCG [74]. Intravesical treatment does not affect the prostatic urethra or the upper urinary tract, areas that the instillations do not reach (*Level 3*). Due to the panurothelial nature of CIS, close monitoring of the upper urinary tract and prostate is required.

6. TREATMENT OF CIS

If concurrent CIS is found in association with a muscle-invasive bladder cancer, the therapy for the patient is determined according to the invasive tumor. If concurrent CIS is found in association with a noninvasive tumor (Ta or T1), TUR of the papillary tumors is mandatory for correct staging. No consensus exists thereafter whether conservative (intravesical instillations) or aggressive therapy (cystectomy) should be done, especially when there are concurrent high grade papillary tumors. Randomized trials between instillation therapy and early cystectomy as immediate primary treatment are lacking [36]. Tumor-specific survival rates of early cystectomy series in CIS are excellent, but as many as 40% to 50% of patients may be overtreated. Radiotherapy is not a viable treatment option for CIS.

In his review of 497 patients, Lamm reported that intravesical chemotherapy produced a complete response rate of 48%: 38% in 89 patients treated with thiotepa, 48% in 212 patients treated with doxorubicin, and 53% in 196 patients treated with mitomycin C (MMC) [33]. There was, however, considerable variability with the same drug from one study to the next. In 1496 patients treated with BCG, the com-plete response rate was 72% (*Level 2*). In 2 recent studies of BCG, complete response rates of 83% and 93% were achieved [49,50].

The classic induction course of BCG consists of 6 consecutive weekly intravesical instillations. Some 40% to 60% of patients not responding after this initial induction course respond to a second cycle of 6 weekly instillations (*Level 2*, [49,50,54,57,61,75]).

There are 2 important limitations to drawing conclu-

sions based on an overview of complete re-sponse rates in different studies:

1. There may be important differences between studies with respect to the definition of CIS, patient characteristics, and assessment of response to treatment.

2. An initial complete response is not always durable. As approximately 50% of complete responders may eventually recur with risk of invasion or extravesical recurrence [31,50,75,76], one must take into account the long-term disease-free and progression-free rates.

Treatment recommendations should only be based on the results of randomized clinical trials with long-term follow-up. Unlike papillary tumors, few randomized trials on the treatment of CIS have been published. In addition, there are relatively few randomized trials in patients with CIS alone. Most trials include patients with either papillary tumors or CIS, resulting in only a small number of patients with CIS being entered. Thus, the power to detect treatment differences is low and the reliability of the conclusions is limited.

a) Randomized Trials Comparing Different Chemotherapy Regimens

Eleven randomized trials comparing different chemotherapy regimens were identified; however, 6 of the studies included less than 25 patients with CIS so no conclusions can be drawn from them:

1. Standardized versus optimized MMC [77]

2. MMC plus adriamycin maintenance versus no maintenance after complete response on the combination [78]

3. Thiotepa versus MMC [79]

4. Adriamycin versus thiotepa [80]

5. Adriamycin versus MMC [81]

6. BCG plus epirubicin versus BCG alone [82]

A second study compared adriamycin to MMC in 40 patients with CIS, though separate results were not given by treatment group [83].

Two other underpowered trials with MMC compared:

1. MMC to thiotepa [84]: 7 of 29 (24%) patients with CIS on thiotepa had a complete response compared to 8 of 24 (33%) on MMC

2. Passive to electromotive MMC [85]: At 6 months, 11 of 36 (31%) patients with CIS on passive MMC had a complete response compared to 21 of 36 (58%) patients on electromotive MMC. Based on a median follow-up of 43 months, 9 of 36 (25%) patients on passive MMC were disease-free as compared to 17 of 36 (47%) patients on electromotive MMC.

MMC plus BCG was compared to BCG alone in 2 studies. No results are available in 33 patients with CIS randomized in CUETO trial 93008 [86]. In the only large-scale study, the Nordic trial compared alternating MMC and BCG instillations to BCG alone in 304 patients with CIS [38]. No difference in the complete response rate was seen between the 2 treatment groups: 119 of 159 (75%) patients on the combination had a complete response compared to 120 of 145 (83%) patients on BCG alone. However, based on a median follow-up of 56 months, there was a significantly longer disease-free interval in the BCG monotherapy arm: 80 of 145 (55%) patients were disease-free on BCG alone compared to 72 of 159 (45%) patients on the combination of BCG and MMC.

An alternating schedule of MMC and BCG is not superior to BCG alone (*Level 1*). Due to insufficient data, no other conclusions can be drawn from randomized studies concerning the relative effectiveness of the different chemotherapeutic agents. Electromotive MMC requires further study to assess its merit. Nonrandomized trials suggest that thiotepa may be inferior to adriamycin and MMC (*Level 3*).

b) Randomized Interferon Alpha 2b Trials

High dose intravesical interferon (100 million units) produced a significantly higher complete response rate than low dose interferon (10 million units): 20 of 47 (43%) versus 2 of 38 (5%). At 12 months, the disease-free rates were 21% and 3%, respectively [67]. Intravesical interferon alpha 2b is thus active in the treatment of CIS (*Level 1*).

c) Randomized Trials Comparing BCG to Chemotherapy

For more than 20 years, intravesical BCG, a nonspecific immunotherapy, and intravesical chemotherapy, with drugs such as thiotepa, adriamycin, epirubicin, and mitomycin C, have been used in the treatment of CIS. The relevant clinical question is whether intravesical BCG is more effective than intravesical chemotherapy in the treatment of CIS.

Twelve randomized trials including 845 patients with CIS compared BCG to different chemotherapy regimens:

1. BCG versus MMC (5 trials)

In a Swedish-Norwegian study [87], 83 patients with CIS or dysplasia were randomized to BCG or MMC. With a median follow-up of 64 months, 23 of 41 (56%) patients on BCG remained disease-free as compared to 14 of 42 (33%) on MMC. In just the patients with CIS, the 5-year recurrence-free rates were 55% and 26%, respectively.

A SWOG study reported a complete response rate of 17 of 31 (55%) on BCG and 16 of 35 (46%) on MMC [88].

Based on a median follow-up of 7.2 years, the EORTC/Dutch study found that 11 of 22 (50%) on BCG remained disease-free as compared to 7 of 16 (44%) on MMC [89].

A Dutch study compared 2 different strains of BCG, Tice and RIVM, to MMC: 26 of 38 (68%) on BCG and 8 of 12 (67%) on MMC had a complete response [90].

In an Italian study comparing BCG to MMC [85], 23 of 36 (64%) on BCG and 11 of 36 (31%) on MMC had a complete response at 6 months. However, in a third arm with electromotive MMC, 21 of 36 (58%) had a complete response. Based on a median follow-up of 43 months, 17 of 36 (47%) on BCG, 9 of 36 (25%) on passive MMC, and 17 of 36 (47%) on electromotive MMC remained disease-free.

A sixth trial, Finnbladder 1 [91], which included only 18 patients with CIS, was not properly randomized and thus is not included in this assessment.

2. BCG versus Adriamycin (1 trial)

Lamm reported a significantly higher complete response rate and longer disease-free interval in complete responders on BCG as compared to adriamycin: 45 of 64 (70%) had a complete response versus 23 of 67 (34%); based on a median follow-up of 65 months, 26 of 45 (58%) complete responders on BCG remained disease-free as compared to 8 of 23 (35%) on adriamycin [92]. The estimated 5-year disease-free survival rates were 45% and 18%, respectively.

3. BCG versus Adriamycin versus Thiotepa (1 trial)

Only 17 patients with CIS were randomized to the 3 treatment groups [80]. No conclusions can be drawn due to the small number of patients entered.

4. BCG versus Epirubicin (1 trial)

De Reijke found that 55 of 84 (65%) patients on BCG had a complete response as compared to 47 of 84 (56%) on epirubicin [54]. The duration of complete response was longer on BCG: 18 of 55 (33%) complete responders on BCG recurred as compared to 31 of 47 (66%) on epirubicin.

5. BCG versus Epirubicin versus TUR Alone (1 trial)

Only 9 patients with CIS were entered in this study [93].

6. BCG versus MMC and Adriamycin (1 trial)

In this study [94], 18 of 21 (86%) patients on BCG had a complete response compared to 17 of 21 (81%) on sequential MMC and adriamycin. However, 27 of 42 (64%) patients did not have CIS but rather dysplasia (reported as “grade 2” CIS). Based on a mean follow-up of 47 months, 6 of 21 (29%) on chemotherapy remained disease-free as compared to 16 of 21 (76%) on BCG.

7. BCG and MMC versus MMC Alone (2 trials)

In Finnbladder 2 [66], at 6 months 21 of 28 (75%) patients on MMC and BCG had a complete response compared to 20 of 40 (50%) on MMC alone. Based on a mean follow-up of 33 months, 20 of 28 (71%) patients on MMC and BCG were disease-free compared to 17 of 40 (43%) on MMC alone.

In a Dutch study [95], separate results are not av-ailable for the 65 patients with CIS, 29 of whom were randomized to MMC and BCG and 36 to MMC alone.

8. Summary

The results of the trials comparing BCG to chemotherapy are summarized in **Tables 4** and **5**, both by type of chemotherapy and overall. In over 600 patients, there was a 68% complete response rate on BCG and a 49% complete response rate on chemotherapy (**Table 4**). In the complete responders, 68% of patients treated with BCG remained disease-free as compared to 47% of patients receiving chemo- therapy, based on a median follow-up of 3.75 years. The overall disease-free rates were 51% and 27%, respectively (**Table 5**).

As compared to chemotherapy, treatment with BCG thus increased both the complete response rate and the overall percent of patients remaining disease-free

Table 4. BCG versus Chemotherapy: Complete Response Rate in Patients With CIS

Reference	BCG	Chemotherapy
BCG versus MMC		
Di Stasi [85]	23/36	11/36
Vegt [90]	26/38	8/12
Witjes [89]	NA*/24	NA/16
Lamm [88]	17/31	16/35
Malmstrom [87]	NA/41	NA/42
Total	66/105 (63%)	35/83 (42%)
BCG versus electro MMC		
Di Stasi [85]	23/36 (64%)	21/36 (58%)
BCG versus Adriamycin		
Lamm [92]	45/64	23/67
Martinez-Pineiro [80]	NA/6	NA/6
Total	45/64 (70%)	23/67 (34%)
BCG versus Epirubicin		
De Reijke [54]	55/84	47/84
Melekos [93]	NA/4	NA/3
Total	55/84 (65%)	47/84 (56%)
BCG versus Thiotepa		
Martinez-Pineiro [80]	NA/6	NA/5
BCG versus MMC + ADM		
Sekine [94]	18/21 (86%)	17/21 (81%)
BCG + MMC versus MMC		
Witjes [95]	NA/29	NA/36
Rintala [66]	21/28	20/40
Total	21/28 (75%)	20/40 (50%)
Overall Total	205/302 (68%)	163/331 (49%)

** - NA: Data not available*

(*Level 1*). Treatment with electromotive MMC requires further study before any conclusions can be drawn concerning its long-term efficacy.

d) Randomized Trials Comparing BCG to TURBT Alone

Based on a minimum follow-up of 3 years, 15 of 23 (65%) patients were disease-free on BCG compared to 0 of 26 patients who had TURBT alone [96]. Thus only TURBT or the coagulation of CIS lesions is not by itself sufficient treatment (*Level 1*).

e) Randomized Trials Comparing BCG Maintenance to No Maintenance

In the SWOG trial [75], 233 patients with CIS were randomized at 3 months to no maintenance or to 3 years of maintenance. The complete response rate in the maintenance arm improved from 64 of 117 (55%) at the time of randomization to 97 of 117 (84%) during maintenance, showing the benefit of additional treatment in the initial BCG nonresponders (*Level 1*). CIS complete responders apparently had a longer recurrence-free survival with maintenance.

Seventy-two of 93 patients in the Badalament study had concurrent CIS. Overall, there was no difference in treatment efficacy between 2 years of maintenance BCG and no maintenance [97]. However, separate results were not provided for just the patients with CIS.

Only 11 patients with CIS were randomized in the Hudson trial [98], so no conclusions can be drawn.

f) Randomized Trials Comparing BCG to Bropirimine

Twenty-three of 28 (82%) patients on BCG had a complete response compared to 22 of 27 (81%) on

Table 5. BCG versus Chemotherapy: Disease-free Rate in Patients With CIS

Reference	BCG	Chemotherapy	Median Follow-up (yrs)
BCG versus MMC			
Di Stasi [85]	17/36	9/36	3.6
Vegt [90]	NA*/38	NA/12	3.0
Witjes [89]	11/22	7/16	7.2
Lamm [88]	NA/31	NA/35	2.5
Malmstrom [87]	23/41	14/42	5.3
Total	51/99 (52%)	30/94 (32%)	
BCG versus Electromotive MMC			
Di Stasi [85]	17/36 (47%)	17/36 (47%)	3.6
BCG versus Adriamycin			
Lamm [92]	26/64	8/67	5.4
Martinez-Pineiro [80]	4/6	0/6	3.0
Total	30/70 (43%)	8/73 (11%)	
BCG versus Epirubicin			
De Reijke [54]	37/84	16/84	5.6
Melekos [93]	NA/4	NA/3	
Total	37/84 (44%)	16/84 (19%)	
BCG versus Thiotepa			
Martinez-Pineiro [80]	4/6 (67%)	3/5 (60%)	3.0
BCG versus MMC + ADM			
Sekine [94]	16/21 (76%)	6/21 (29%)	3.9
BCG + MMC versus MMC			
Witjes [95]	NA/29	NA/36	
Rintala [66]	20/28	17/40	2.8
Total	20/28 (71%)	17/40 (43%)	
Overall Total	154/302 (51%)	97/353 (27%)	3.75

**- NA: Data not available*

bropirimine [99]. Based on a maximum follow-up of 3 years, 20 of 23 (87%) complete responders on BCG remained disease-free compared to 14 of 22 (64%) complete responders on bropirimine.

g) Randomized Trials Comparing Full-dose to Reduced-dose BCG

Two trials including patients with CIS have compared different doses of BCG with apparently conflicting results:

1. Thirty-nine patients with CIS were randomized to 27 or 81 mg of Connaught BCG [100]. There was a trend to higher progression and death rates in the reduced-dose arm.

2. In another study, the number of patients with CIS who were randomized to 75 versus 150 mg of Pasteur BCG was not reported [101]. However, among patients with CIS, there was a significantly lower disease-free survival rate on the standard dose, 150 mg: 33% versus 62% at 5 years.

h) BCG Meta-analysis of Progression

In 403 patients with CIS, BCG reduced the risk of progression by 35% as compared to either intravesical chemotherapy or a different immunotherapy (OR = 0.65, 95% CI 0.36 to 1.16, $P = 0.10$). Twenty-five of 212 (12%) patients on BCG progressed as compared to 31 of 191 (16%) patients receiving these other treatments (*Level 1*, [26]).

i) Treatment of Extravesical CIS

The treatment of CIS in the upper urinary tract consists of rinsing the renal unit with BCG or with chemotherapeutic drugs such as mitomycin C or epirubicin. The watery solutions can be introduced

into the upper urinary tract using a ureteral stent or nephrostomy catheter [74,102].

Only anecdotal cases have been reported and experience is therefore limited. Thalmann found that 19 of 22 (86%) patients (25 renal units) with upper urinary tract CIS responded to BCG perfusions [103]. Nine patients (41%) died of their disease after a median follow-up of 50 months (*Level 3*).

Response to the treatment is determined by conversion of cytology in urine derived from the upper urinary tract from high grade to negative. If no response is achieved, a nephroureterectomy should be considered. Before performing a radical cystectomy, the urologist should know whether the prostatic urethra is free of CIS. During cystectomy, the distal ureters should also be investigated for the presence of CIS [31].

If CIS is found in the prostatic urethra, this is an ominous sign [31]. Three different entities might be encountered. CIS may be present only in the epithelial lining of the prostatic urethra. However, CIS might also grow in the prostatic tissue following the prostatic ducts. In the worst case scenario, CIS may be found in the prostatic tissue stroma (T4) and this has the worst prognosis of all. Cystoprostatectomy is advised when CIS is found in the stroma. In the other 2 situations, a TUR of the prostate can be performed followed by intravesical instillations of BCG [31].

For further details concerning the treatment of CIS involving the ureters and prostatic urethra, see Kurth and Lamm [31,33].

j) BCG Toxicity

Because of the more pronounced side effects of BCG as compared to intravesical chemotherapy [54,80, 85,88,90,92], reluctance still exists about its use. However, with increasing experience in applying BCG, serious side effects are now encountered in less than 5% of patients and can be effectively treated in virtually all cases [104].

In a large randomized SWOG study [75], only 16% of patients completed the entire 3-year maintenance schedule, suggesting that maintenance BCG is too toxic (*Level 1*). In a recent EORTC trial including 487 patients treated with BCG [105,106], about one-third of the patients completed the 3 years of maintenance and 99 (20%) stopped due to adverse events. Local BCG side effects did not increase during maintenance and systemic side effects were more frequent during the first 6 months of treatment, after which time they decreased. Two-thirds of all patients who stopped BCG due to side effects did so during the first 6 months of treatment (*Level 1*, [106]).

While BCG-associated cystitis is more frequent than that with mitomycin C, Bohle concluded that it did not differ according to whether BCG maintenance treatment was given or not [27]. Saint and Morgia also concluded that the side effects of BCG were the most prominent during the induction and early maintenance instillations [107,108].

Thus, the assumption that BCG-induced side effects increase with time during maintenance does not appear to be correct (*Level 1*).

k) Treatment of BCG Failures

For BCG-refractory CIS, Kim [35] presented a review of the role of both radical cystectomy and conservative therapy with valrubicin [109-111], interferon alpha 2b [67,112,113], BCG plus interferon alpha 2b [114], bropirimine [115-118], and photodynamic therapy [119-122].

Radical cystectomy is the treatment that is offered to most patients when intravesical treatment has failed [28]. The timing of cystectomy remains a challenge and is still controversial. About 70% of patients treated with an initial BCG induction course of 6 weeks will respond, thus a considerable number of patients will require additional BCG instillations before biopsies and cytology become negative. Approximately 40% to 60% of patients not responding after an initial course of 6 weekly instillations will respond to a second cycle of 6 weekly instillations (*Level 2*, [49,50,54,57,61,75]). Additional complete responses have also been encountered if, after the initial induction course of 6 weeks, maintenance cycles consisting of 3 weekly booster instillations are given (*Level 1*, [75]). On the other hand, the likelihood of progression to muscle-invasive disease or the development of metastases increases with the number of unsuccessful courses. Thus, doubt remains concerning the best time point to abandon conservative treatment and proceed to cystectomy.

In patients for whom cystectomy is not possible, conservative treatment may be considered [123]. In the largest series of BCG-refractory patients with CIS, complete response rates of 19 of 90 (21%) on valrubicin [109], 10 of 22 (45%) on interferon alpha 2b [113], 21 of 65 (32%) on bropirimine [115], and 21 of 36 (58%) and 13 of 27 (48%) on photodynamic therapy [120,121] were observed. In a large phase II study of BCG plus interferon alpha 2b, separate results were not presented for the patients with CIS

who had previously failed BCG [114]. A phase I study of intravesical gemcitabine included 18 BCG-refractory patients, 14 of whom had CIS. Seven of the 18 (39%) patients had a complete response [124].

In summary, BCG plus interferon alpha 2b, photodynamic therapy, and gemcitabine all warrant further evaluation in order to determine their role in the treatment of BCG-refractory patients (*Level 3*).

Summary

CIS is a flat, high grade carcinoma occurring in 5% to 10% of patients with superficial bladder cancer. Diagnosis is made by a combination of cystoscopy, cytology, and multiple bladder biopsies with histology being the determining factor. The marker of choice is cytology. Patients with CIS are at high risk of progression; however, there are no prognostic factors that accurately predict the course of the disease. Immediate cystectomy may be overtreatment in up to 50% of the patients. Evidence-based results of intravesical treatment are limited by the small number of patients treated in randomized trials. A 6 week induction course of BCG and 1 to 3 years of maintenance BCG are recommended since intravesical BCG increases both the complete response rate and long-term disease-free rate as compared to intravesical chemotherapy.

RECOMMENDATIONS

I. TREATMENT AND FOLLOW-UP OF HIGH GRADE Ta UROTHELIAL CARCINOMA

1. As they have a 20% to 25% chance of progression to muscle-invasive disease, patients with high grade Ta bladder tumors should be treated and followed as high-risk patients (*Grade A*, [23,24]).
2. After TURBT, it is thus recommended that patients with tumors appearing to be high grade Ta receive one immediate instillation of chemotherapy (*Grade A*, [25]).
3. These patients should undergo a second-look TURBT and bladder mapping biopsies 2 to 4 weeks later (*Grade B*). If residual tumor is found, resect and give 1 immediate instillation of chemotherapy.
4. This is followed, 2 to 3 weeks later, once the diagnosis of high grade Ta has been confirmed, by a 6-week induction course of bacillus Calmette-Guérin (BCG) and 1 to 3 years of maintenance BCG (*Grade A*, [26-28]). The optimal maintenance schedule is unknown.
5. In case of failure before maintenance BCG has been completed, consider cystectomy if high grade T1 or CIS is present (*Grade B*). For other superficial recurrences, resect and continue maintenance BCG (*Grade B*).
6. If early failure occurs after maintenance BCG has been completed, consider cystectomy (*Grade B*). If later superficial recurrence occurs, consider re-starting BCG or other instillations as an alternative to cystectomy (*Grade B*).
7. These patients require long-term follow-up (*Grade A*), for example every 3 months during the first 2 years, every 4 months during the third year, every 6 months during the fourth and fifth years, and yearly thereafter as long as there is no recurrence (*Grade B*, [28]).

II. CARCINOMA IN SITU OF THE BLADDER

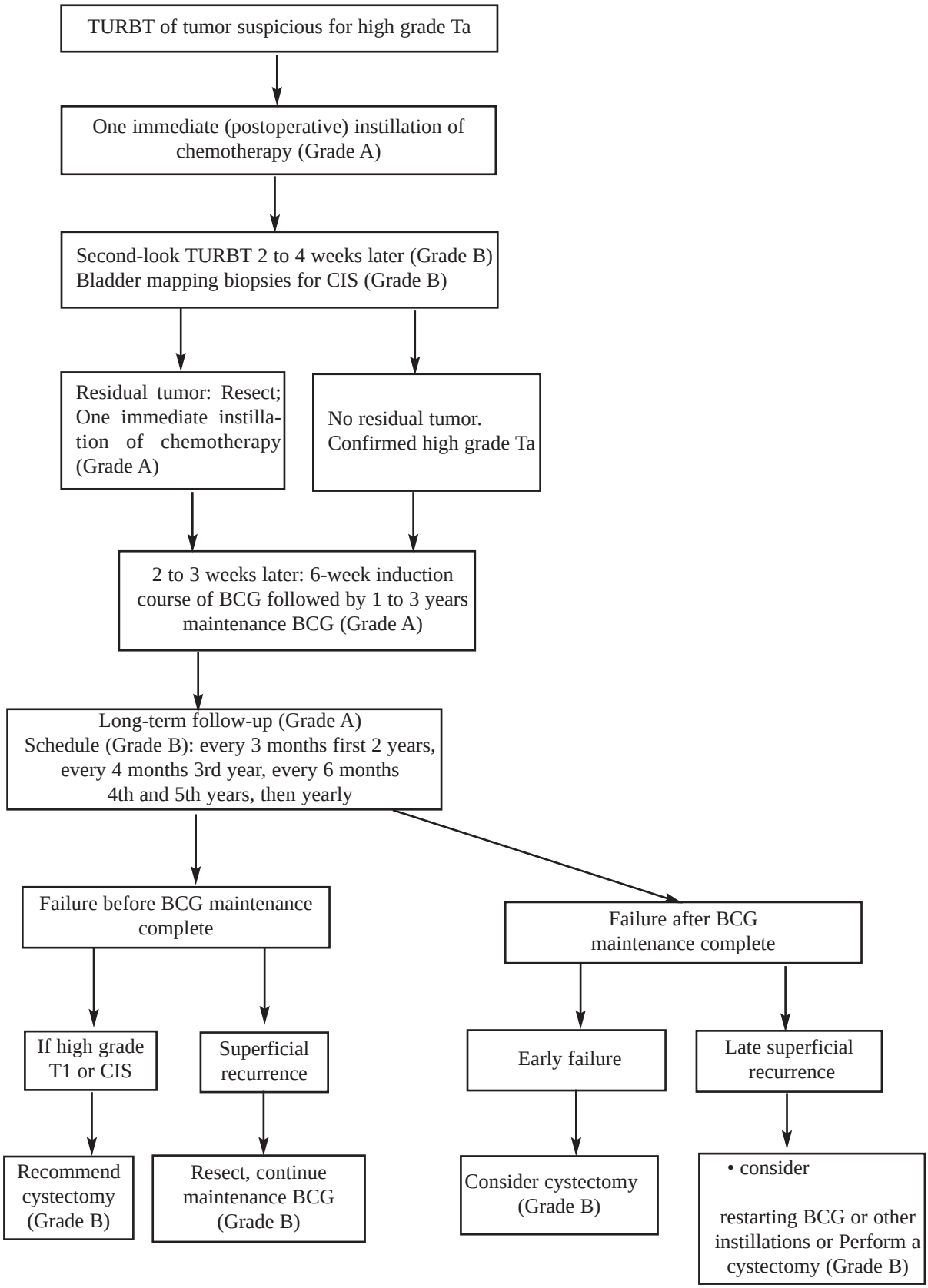
a) Diagnosis of CIS

1. Flourescence cystoscopy should be considered because it has a greater sensitivity than white light cystoscopy (*Grade B*).
2. All suspicious areas in the bladder should be biopsied. In patients with concurrent high grade Ta and in all T1 papillary tumors, a second-look TUR should be done (*Grade B*). In patients with a positive cytology, random biopsies including the prostatic urethra should be taken (*Grade B*). A bladder diagram should be used to identify the exact location where biopsies have been taken. For a proper pathological assessment of the extent of the disease, it is recommended to submit different types of material to the pathologist in separate, properly labeled containers, for example one container with the exophytic part of the tumor, one with the underlying muscle, another with the random mucosal biopsies, and another with biopsies from the prostatic urethra [125].
3. The marker of choice for the detection and follow-up of patients with CIS is cytology (*Grade B*). It is recommended to perform cytology with voided urine unless a bladder wash is done at the time of cystoscopy (*Grade B*).

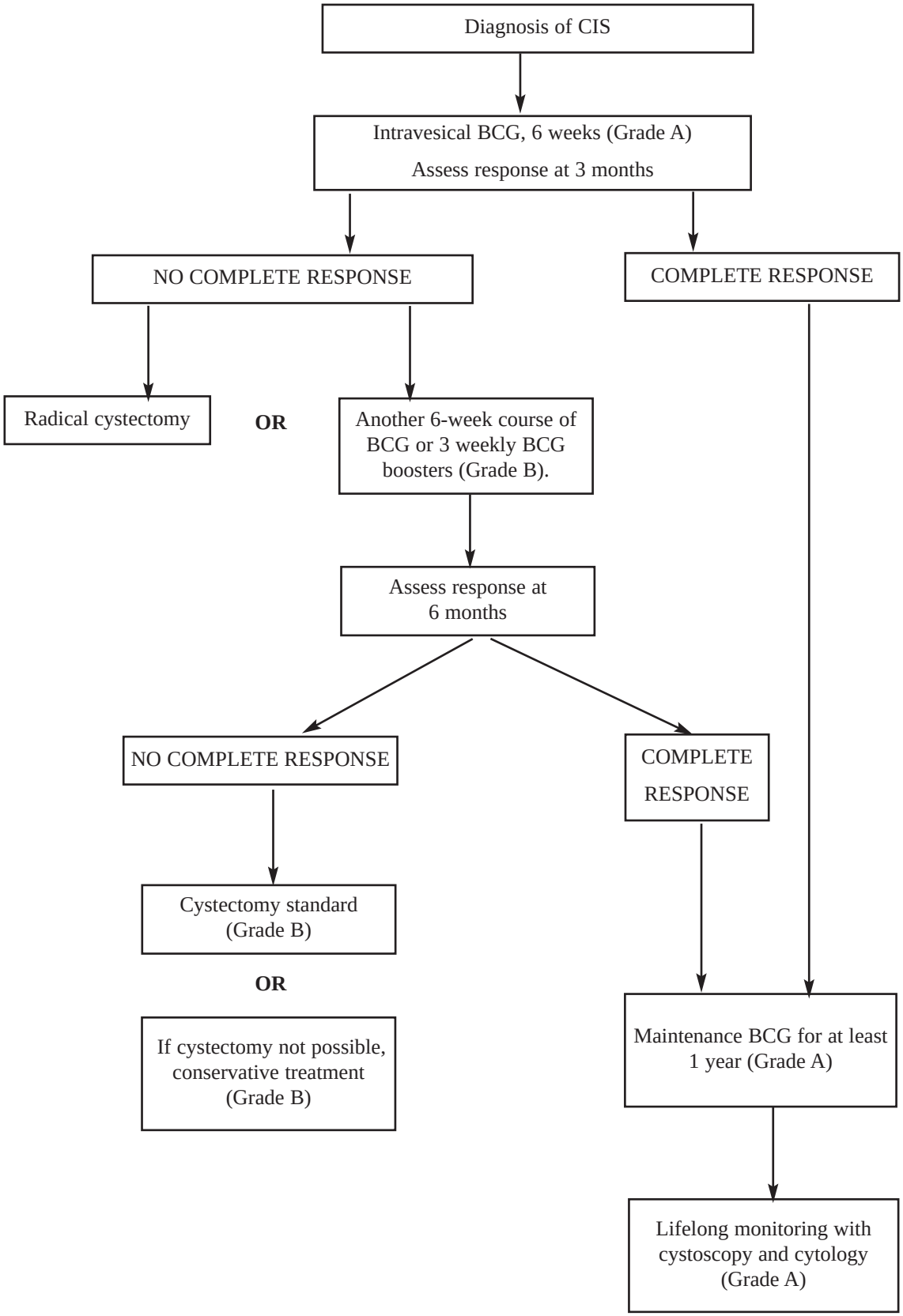
b) Detection, Treatment, and Follow-up of CIS

1. The best marker to diagnose CIS or to assess response to treatment is cytology. None of the other currently available markers have been proven to be superior (*Grade B*).
2. Radical cystectomy at the time of diagnosis of CIS, instead of instillation therapy, provides excellent disease-free survival but is overtreatment in up to 50% of the patients (*Grade A*).
3. The treatment of CIS with intravesical BCG is recommended since it provides the highest rate of complete response as well as the highest long-term disease-free rate among intravesical treatments (*Grade A*).
4. Six weeks only of BCG is suboptimal treatment for CIS. Maintenance BCG treatment is required but the optimal maintenance schedule is un-known. In the absence of treatment failure, at least one year of maintenance BCG is recommended (*Grade A*).
5. The response to intravesical BCG should be assessed 3 months after starting treatment. If no response is seen, one might offer the patient either cystectomy, another 6-week course of BCG, or to continue with 3 weekly boosters (*Grade B*). As approximately 50% of patients will respond to a second course of BCG, cystectomy at 3 months is overtreatment in about 50% of the patients. While failure at 3 months is a poor prognostic factor, the optimal time to abandon conservative treatment and proceed to cystectomy is unknown. Note: response of CIS in the bladder does not influence the course of CIS outside the bladder (upper urinary tract and prostatic urethra).
6. If a complete response has not been achieved at 6 months, the therapy of choice is radical cystectomy (*Grade B*). In patients for whom a cystectomy is not possible, one of the conservative treatments mentioned above may be considered (*Grade B*).
7. Patients with CIS, even complete responders, should be monitored lifelong due to the high risk of recurrence and progression, both within the bladder and extravesically (*Grade A*).

Algorithm 1. Treatment Recommendations for High Grade Ta Urothelial Carcinoma



Algorithm 2. Treatment Recommendations for CIS



REFERENCES

1. Union Internationale Contre le Cancer. TNM Classification of malignant tumors, 6th edition. Eds Sobin L.H. and Wittekind Ch. Wiley-Liss, New York, 2002.
2. Mostofi FK, Sobin LH, and Torlini H. Histological typing of urinary bladder tumors. International Histological Classification of Tumors 10. World Health Organization, Geneva, 1973.
3. Epstein JI, Amin MB, Reuter VR, Mostofi FK and the Bladder Consensus Conference Committee. The World Health Organization/International Society of Urological Pathology consensus classification of urothelial (transitional cell) neoplasms of the urinary bladder. Am J Surg Path 22, 1435 - 1448, 1998.
4. Mostofi FK, Davis CJ, and Sesterhenn IA. Histological typing of urinary bladder tumors. International Histological Classification of Tumors, 2nd ed. World Health Organization, Geneva, 1999.
5. Holmang S, Andius P, Hedelin H, Wester K, Busch C and Johansson SL. Stage progression in Ta papillary urothelial tumors: relationship to grade, immuno-histochemical expression of tumor markers, mitotic frequency and DNA ploidy. J Urol 165, 1124 - 1130, 2001.
6. Chen SS, Chen KK, Lin AT, Chang YH, Wu HH, Hsu TH and Chang LS. The significance of tumor grade in predicting disease progression in stage Ta transitional cell carcinoma of the urinary bladder. Br J Urol 78, 209 - 212, 1996.
7. Haukaas S, Daehlin L, Maartmann-Moe H, Ulvik NM. The long term outcome in patients with superficial transitional cell carcinoma of the bladder: a single institutional experience. BJU Int 83, 957 - 963, 1999.
8. Heney NM, Ahmed S, Flanagan MJ, Frable W, Corder MP, Hafermann MD and Hawkins IR. Superficial bladder cancer: progression and recurrence. J Urol 130, 1083 - 1086, 1983.
9. Holmang S, Hedelin H, Anderstrom C, and Johansson SL. The relationship among multiple recurrences, progression and prognosis of patients with stages Ta and T1 transitional cell cancer of the bladder followed for at least 20 years. J Urol 153, 1823 - 1826, 1995.
10. Holmang S and Johansson SL. Stage Ta-T1 bladder cancer: the relationship between findings at first follow up cystoscopy and subsequent recurrence and progression. J Urol 167, 1634 - 1637, 2002.
11. Jakse G, Loidl W, Seeber G and Hofstadter F. Stage T1, grade 3 transitional cell carcinoma of the bladder: an unfavorable tumor? J Urol 137, 39 - 43, 1987.
12. Larsson P, Wijkstrom H, Thorstenson A, Adolfsson J, Norming U, Wiklund P, Onelov E, Steineck G. A population based study of 538 patients with newly detected urinary bladder neoplasms followed during 5 years. Scand J Urol Nephrol 37, 195 - 201, 2003.
13. Lebret T, Bohin D, Kassardjian Z, Herve JM, Molinie V, Barre P, Lugagne PM, and Botto H. Recurrence, progression and success in stage Ta grade 3 bladder tumors treated with low dose bacillus Calmette-Guerin instillations. J Urol 163, 63 - 67, 2000.
14. Lutzeyer W, Rubben H and Dahm H. Prognostic parameters in superficial bladder cancer: an analysis of 315 cases. J Urol 127, 250 - 252, 1982.
15. Millan-Rodriguez F, Chechile-Toniolo G, Salvador-Bayarri J, Palou J, and Vicente-Rodriquez J. Multivariate analysis of the prognostic factors of primary superficial bladder cancer. J Urol 163, 73-78, 2000.
16. Van der Meijden A, Sylvester R, Collette L, Bono A, and ten Kate F. The role and impact of pathology review on stage and grade assessment of stages Ta and T1 bladder tumors: a combined analysis of 5 EORTC cancer trials. J Urol 164, 1533 - 1537, 2000.
17. Witjes JA, Kiemeney LALM, Schaafsma HE, and Debruyne FMJ. The influence of review pathology on study outcome of a randomized multicentre superficial bladder cancer trial. Br J Urol 73, 172 - 176, 1994.
18. Herr HW. Tumor progression and survival of patients with high grade, non invasive papillary (Ta G3) bladder tumors: 15 year outcome. J Urol 163, 60 - 62, 2003.
19. Donat SM. Evaluation and follow up strategies for superficial bladder cancer. Urol Clin N Am 30, 765 - 776, 2003.
20. Miladi M, Peyromaure M, Zerbib M, Saighi D and Debré B. The value of a second transurethral resection in evaluating patients with bladder tumours. Eur Urol 43, 241 - 245, 2003
21. Jakse G, Algaba F, Malmstrom P-U, and Oosterlinck W. A second-look TUR in T1 transitional cell carcinoma: Why ? Eur Urol 45, 539 - 546, 2004.
22. Norming U, Tribukait B, Nyman CR, Nilsson B and Wang N. Prognostic significance of mucosal aneuploidy in stage Ta/T1 grade 3 carcinoma of the bladder. J Urol 148, 1420 - 1427, 1992.
23. Millan-Rodriguez F, Chechile-Toniolo G, Salvador-Bayarri J, Palou J, Algaba F, and Vicente-Rodriquez J. Primary superficial bladder cancer risk groups according to progression, mortality and recurrence. J Urol 164, 680 - 684, 2000.
24. Droller MJ. Editorial: Urothelial cancer: mucosally confined disease can be aggressive. J Urol 163, 79 - 80, 2000.
25. Sylvester RJ, Oosterlinck W and van der Meijden APM. A single immediate postoperative instillation of chemotherapy decreases the risk of recurrence in patients with stage Ta T1 bladder cancer: a meta-analysis of published results of randomized clinical trials. J Urol 171, 2186 - 2190, 2004.
26. Sylvester RJ, van der Meijden APM, and Lamm DL. Intravesical bacillus Calmette-Guerin reduces the risk of progression in patients with superficial bladder cancer: a meta-analysis of the published results of randomized clinical trials. J Urol 168, 1964 - 1970, 2002.
27. Bohle A, Jocham D and Bock PR. Intravesical bacillus Calmette-Guerin versus mitomycin C for superficial bladder cancer: a formal meta-analysis of comparative studies on recurrence and toxicity. J Urol 169, 90 - 95, 2003.
28. Oosterlinck W, Lobel B, Jakse G, Malmstrom PU, Stockle M, and Sternberg C. The EAU Working Group on Oncological Urology.: Guidelines on bladder cancer. Eur Urol 41, 105 - 112, 2002.
29. Lamm DL. Carcinoma in situ. Urol Clin N Am 19, 499 - 508, 1992.
30. Hudson MA and Herr HW. Carcinoma in situ of the bladder. J Urol 153, 564 - 572, 1995.
31. Kurth KH, Schellhammer PF, Okajima E, Akdas A, Jakse G, Herr HW, Calais da Silva F, Fukushima S, and Nagayama T. Current methods of assessing and treating carcinoma in situ of the bladder with or without involvement of the prostatic urethra. Int J Urol 2 (suppl 2), 8 - 22, 1995.
32. Lamm DL, van der Meijden APM, Akaza H, Brendler CB, Hedlund PO, Mizutani Y, Ratliff TL, Robinson MRG and Shinka T. Intravesical chemotherapy and immunotherapy: how do we assess their effectiveness and what are their limitations and uses? Int J Urol 2 (suppl 2), 23 - 25, 1995.
33. Lamm DL, Herr HW, Jakse G, Kuroda M, Mostofi FK, Okajima E, Sakamoto A, Sesterhenn I, and Calais da Silva F. Updated concepts and treatment of carcinoma in situ. Urol Oncol 4, 130 - 138, 1998.
34. Jakse G. Carcinoma in situ. In: Clinical management of bladder cancer. Ed R.R. Hall, Arnold, London, 1999, pp 149 - 170.

35. Kim JC and Steinberg GD. The limits of bacillus Calmette-Guerin for carcinoma in situ of the bladder. J Urol 165, 745 - 756, 2001.

36. Witjes JA. Bladder carcinoma in situ in 2003: state of the art. Eur Urol 45, 142 - 146, 2004.

37. Orozco RE, Martin AA, and Murphy WM. Carcinoma in situ of the urinary bladder. Clues to host involvement in human carcinogenesis. Cancer 74, 115 - 122, 1994.

38. Kaasinen E, Wijkstrom H, Malmstrom PU, Hellsten S, Duchek M, Mestad O, and Rintala E. Alternating mitomycin C and BCG instillations versus BCG alone in treatment of carcinoma in situ of the urinary bladder: a Nordic study. Eur Urol 43, 637 - 645, 2003.

39. Palou J, Salvador J, Parada R, Chechile G, Millan F, and Vicente J. Carcinoma in situ of the prostatic urethra: the role of intravesical BCG. Urol Integr Invest 6, 165 - 170, 2001.

40. Zaak D, Hungerhuber E, Schneede P, Stepp H, Frimberger D, Corvin S, Schmeller N, Kriegmair M, Hofstetter A, and Knuechel R. Role of 5-aminolevulinic acid in the detection of urothelial premalignant lesions. Cancer 95, 1234 - 1238, 2002.

41. Schmidbauer J, Witjes F, Schmeller N, Donat R, Susani M, and Marberger M. Improved detection of urothelial carcinoma in situ with hexaminolevulinate fluorescence cystoscopy. J Urol 171, 135 - 138, 2004.

42. D'Hallewin MA, Bezdetnaya L and Guillemin F. Fluorescence detection of bladder cancer: a review. Eur Urol 42, 417 - 425, 2002.

43. Sharkey FE and Sarosdy MF. The significance of central pathology review in clinical studies of transitional cell carcinoma in situ. J Urol 157, 68 - 70, 1997.

44. Glas AS, Roos D, Deutekom M, Zwinderman AH, Bossuyt PMM, and Kurth KH. Tumor markers in the diagnosis of primary bladder cancer. A systematic review. J Urol 169, 1975 - 1982, 2003.

45. Lotan Y and Roehrborn CG. Sensitivity and specificity of commonly available bladder tumor markers versus cytology: results of a comprehensive literature review and meta-analysis. Urol 61, 109 - 118, 2003.

46. Lokeshwar VB, Bono AV, Schmitz-Drager B, Droller MJ, Fradet Y, Goebell P, Getzenberg RH, Grossman HB, Habuchi T, Hautmann SH, Hemstreet GP, Marberger M, Messing E, Murphy W, and Schalken JA. Tumor markers beyond cytology. SIU Consensus Conference. Oral presentation, 2005.

47. Solsona E, Iborra I, Ricos JV, Dumont R, Casanova JL and Calabuig C. Upper urinary tract involvement in patients with bladder carcinoma in situ (Tis): its impact on management. Urol 49, 347 - 352, 1997.

48. De Jager R, Guinan P, Lamm D, Khanna O, Brosman S, De Kernion J, Williams R, Richardson C, Muenz L, Reitsma D, Hanna MG. Long-term complete remission in bladder carcinoma in situ with intravesical Tice bacillus Calmette Guerin. Urol 38, 507 - 513, 1991.

49. Losa A, Hurle R and Lembo A. Low dose bacillus Calmette-Guerin for carcinoma in situ of the bladder: long-term results. J Urol 163, 68 - 72, 2000.

50. Jakse G, Hall R, Bono A, Hoeltl W, Carpentier P, Spaander JP, van der Meijden APM, Sylvester R and members of the EORTC GU Group. Intravesical BCG in patients with carcinoma in situ of the urinary bladder: long-term results of EORTC GU Group phase II protocol 30861. Eur Urol 40, 144 - 150, 2001.

51. Takashi M, Katsuno S, Yuba H, Ohshima S, Wakai K, and Ohno Y. Possible factors affecting response to intravesical bacillus Calmette-Guerin (Tokyo 172 strain) therapy for carcinoma in situ of the bladder: a multivariate analysis. Int Urol and Neph 30, 713 - 722, 1998.

52. Cheng L, Cheville JC, Neumann RM, Leibovich BC, Egan KS, Spotts BE, and Bostwick DG. Survival of patients with carcinoma of the urinary bladder. Cancer 85, 2469 - 2474, 1999.

53. Griffiths TRL, Charlton M, Neal DE, and Powell PH. Treatment of carcinoma in situ with intravesical bacillus Calmette-Guerin without maintenance. J Urol 167, 2408 - 2412, 2002.

54. De Reijke TM, Kurth KH, Sylvester RJ, Hall RR, Brausi M, van de Beek K, Landsoght KEJ and Carpentier P. Bacillus Calmette-Guerin versus epirubicin for primary, secondary or concurrent carcinoma in situ of the bladder: Results of a European Organization for the Research and Treatment of Cancer Genito-Urinary Group phase III trial (30906). J Urol 173, 405 - 409, 2005.

55. Solsona E, Iborra I, Dumont R, Rubio-Briones J, Casanova J and Almenar S. The 3-month clinical response to intravesical therapy as a predictive factor for progression in patients with high risk superficial bladder cancer. J Urol 164, 685 - 689, 2000.

56. Van Gils-Gielen RJM, Witjes WPJ, Caris CTM, Debruyne FMJ, Witjes JA and Oosterhof GON. Risk factors in carcinoma in situ of the urinary bladder. Urol 45, 581 - 586, 1995.

57. Merz VW, Marth D, Kraft R, Ackermann DK, Zingg EJ and Studer UE. Analysis of early failures after intravesical instillation therapy with bacillus Calmette-Guerin for carcinoma in situ of the bladder. Br J Urol 75, 180 - 184, 1995.

58. Kiemeney LALM, Witjes JA, Heijbroeck RP, Debruyne FMJ and Verbeek ALM. Dysplasia in normal looking urothelium increases the risk of tumor progression in primary superficial bladder cancer. Eur J Cancer 30A, 1621 - 1625, 1994.

59. Cheng L, Cheville JC, Neumann RM, and Bostwick DG. Natural history of urothelial dysplasia of the bladder. Am J Surg Pathol 23, 443 - 447, 1999.

60. Solsona E, Iborra I, Ricos JV, Monros JL, Dumont R and Almenar S. Extravesical involvement in patients with bladder carcinoma in situ: biological and therapy implications. J Urol 155, 895 - 900, 1996.

61. Coplen DE, Marcus MD, Myers JA, Ratliff TL and Catalona WJ. Long-term followup of patients treated with 1 or 2, 6-week courses of intravesical bacillus Calmette-Guerin: analysis of possible predictors of response free tumor. J Urol 144, 652 - 657, 1990.

62. Algaba F. Superficial bladder cancer and secondary carcinoma in situ. Urol Integr Invest 6, 44 - 47, 2001.

63. Ovesen H, Horn T, and Steven K. Long-term efficacy of intravesical bacillus Calmette-Guerin for carcinoma in situ: relationship of progression to histological response and p53 nuclear accumulation. J Urol 157, 1655 - 1659, 1997.

64. Utz DC and Farrow GM. Carcinoma in situ of the urinary tract. Urol Clin North Am 11, 735-740, 1984.

65. Riddle PR, Chisholm GD, Trott PA, Pugh RC. Flat carcinoma in situ of bladder. Br J Urol 47, 829 - 833, 1975.

66. Rintala, E., Jauhiainen, K., Rajala, P., Ruutu, M., Kaasinen, E., Alfthan, O. and the Finnbladder Group. Alternating mitomycin C and bacillus Calmette-Guerin instillation therapy for carcinoma in situ of the bladder. J Urol 154, 2050 - 2053, 1995.

67. Glashan RW. A randomized controlled study of intravesical a-2b-interferon in carcinoma in situ of the bladder. J Urol 144, 658 - 661, 1990.

68. Norming U, Tribukait B, Gustafson H, Nyman CR, Wang NN, and Wijkstrom H. Deoxyribonucleic acid profile and tumor progression in primary carcinoma in situ of the bladder: a study of 63 patients with grade 3 lesions. J Urol 147, 11 - 15, 1992.

69. Shariat SF, Pahlavan S, Baseman AG, Brown RM, Green AE, Wheeler TM, and Lerner SP. E-cadherin expression predicts clinical outcome in carcinoma in situ of the urinary bladder. Urol 57, 60 - 65, 2001.

70. Ick K, Schultz M, Stout P, and Fan K. Significance of p53 over-

expression in urinary bladder transitional cell carcinoma in situ before and after bacillus Calmette-Guerin treatment. Urol 49, 541 - 547, 1997.

71. Sarkis AS, Dalbagni G, Cordon-Cardo C, Melamed J, Zhang ZF, Sheinfeld J, Fair WR, Herr HW, Reuter VE. Association of p53 nuclear overexpression and tumor progression in carcinoma in situ of the bladder. J Urol 152, 388 - 392, 1994.
72. Shariat SF, Kim J, Raptidis G, Ayala GE and Lerner SP. Association of p53 and p21 expression with clinical outcome in patients with carcinoma in situ of the urinary bladder. Urol 61, 1140 - 1145, 2003.
73. Schmitz-Drager BJ, Goebell PJ, Ebert T and Fradet Y. p53 immunohistochemistry as a prognostic marker in bladder cancer. Playground for urology scientists? Eur Urol 38, 691 - 700, 2000.
74. Herr HW, Whitmore WF. Ureteral carcinoma in situ after successful intravesical therapy for superficial bladder tumors: incidence, possible pathogenesis and management. J Urol 138, 292 - 294, 1987.
75. Lamm, D.L., Blumenstein, B.A., Crissman, J.D., Montie, J.E., Gottesman, J.E., Lowe, B.A., Sarosdy MF, Bohl RD, Grossman HB, Beck TM, Leimert JT and Crawford ED. Maintenance BCG immunotherapy for recurrent Ta, T1 and CIS transitional cell carcinoma of the bladder: a randomized SWOG study. J Urol 163, 1124 - 1129, 2000.
76. Jakse G. BCG for carcinoma in situ. Eur Urol 21 (suppl 2), 30 - 34, 1992.
77. Au JLS, Badalament RA, Wientjes G, Young DC, Warner JA, Venema PL, Pollifrone DL, Harbrecht JD, Chin JL, Lerner SP, and Miles BJ. Methods to improve efficacy of intravesical mitomycin C: results of a randomized phase III trial. J Natl Cancer Inst 93, 597 - 604, 2001.
78. Fukui I, Kihara K, Sekine H, Tachibana Y, Kawai T, Ishiwata D, Oshima H. Intravesical combination chemotherapy with mitomycin C and doxorubicin for superficial bladder cancer: a randomized trial of maintenance versus no maintenance following a complete response. Cancer Chemother Pharmacol 30 (suppl), 37 - 40, 1992.
79. Zincke H, Benson RC, Hilton JF and Taylor WF. Intravesical thiotepa and mitomycin C treatment immediately after transurethral resection and later for superficial (stages Ta and Tis) bladder cancer: a prospective, randomized, stratified study with crossover design. J Urol 134, 1110 - 1114, 1985.
80. Martinez-Pineiro, J.A., Jimenez Leon J., Martinez-Pineiro, L., Fiter, L., Mosteiro, J.A., Navarro J., Garcia Matres MJ and Carcamo P. Bacillus Calmette-Guerin versus doxorubicin versus thiotepa: a randomized prospective study in 202 patients with superficial bladder cancer. J Urol 143, 502 - 506, 1990.
81. Jauhiainen K, Sotarauta M, Permi J and Alfthan O. Effect of mitomycin C and doxorubicin instillation on carcinoma in situ of the urinary bladder: a Finnish Multicenter Study. Eur Urol 12, 32 - 37, 1986.
82. Ali-el-Dein B, Nabeeh A, Ismail EH, and Ghoneim MA. Sequential bacillus Calmette-Guerin and epirubicin versus bacillus Calmette-Guerin alone for superficial bladder tumors: a randomized prospective study. J Urol 162, 339 - 342, 1999.
83. Solsona E, Iborra I, Ricos JV, Monros JL, Dumont R, Casanova J and Calabuig C. Carcinoma in situ associated with superficial bladder tumor. Eur Urol 19, 93 - 96, 1991.
84. Heney NM, Koontz WW, Barton B, Soloway M, Trump DL, Hazra T and Weinstein RS for the National Bladder Cancer Group. Intravesical thiotepa versus mitomycin C in patients with Ta, T1 and TIS transitional cell carcinoma of the bladder: a phase III prospective randomized study. J Urol 140, 1390 - 1393, 1988.
85. Di Stasi SM, Giannantoni A, Stephen RL, Capelli G, Navarra P, Massoud R and Vespani G. Intravesical electromotive mitomycin C versus passive transport mitomycin C for high risk superficial bladder cancer: a prospective randomized study. J Urol 170, 777 - 782, 2003.
86. Solsona E, Gonzalez M, Fernandez JM, Unda M, Bernuy C, and Pertusa C. Random trial comparing intravesical chemo-induction with MMC to BCG vs. intravesical BCG in patients with intermediate-high risk superficial bladder cancer. Efficacy evaluation of CUETO trial No 93008. Eur Urol 1 (suppl 1), 101, 2002, abstract 394.
87. Malmstrom, P.U., Wijkstrom, H., Lundholm, C., Wester, K., Busch, C., Norlen, B.J. et al. 5 year follow up of a randomized prospective study comparing mitomycin C and bacillus Calmette-Guerin in patients with superficial bladder cancer. J Urol 161, 1124 - 1127, 1999.
88. Lamm, D.L, Blumenstein, B.A., Crawford, E.D., Crissman, J.D., Lowe, B.A., Smith, J.A., et al. Randomized intergroup comparison of bacillus Calmette-Guerin immunotherapy and mitomycin C chemotherapy prophylaxis in superficial transitional cell carcinoma of the bladder. A Southwest Oncology Group Study. Urol Oncol 1, 119 - 126, 1995.
89. Witjes, J.A., van der Meijden, A.P.M., Collette, L., Sylvester, R., Debruyne, F.M.J., van Aubel, A., and Witjes WPJ. Long-term follow-up of an EORTC randomized prospective trial comparing intravesical bacille Calmette-Guérin-RIVM and Mitomycin C in superficial bladder cancer. Urol 52, 403 - 410, 1998.
90. Vegt, P.D., Witjes, J.A., Witjes, W.P., Doesburg, W.H., Debruyne, F.M., van der Meijden, A.P. A randomized study of intravesical mitomycin C, bacillus Calmette-Guerin Tice and bacillus Calmette-Guerin RIVM treatment in pTa-pT1 papillary carcinoma and carcinoma in situ of the bladder. J Urol 153, 929 - 933, 1995.
91. Rintala, E., Jauhiainen, K., Alfthan, O., Hansson, E., Juusela, H., Kanerva, K., et al. Intravesical chemotherapy (mitomycin C) versus immunotherapy (bacillus Calmette-Guerin) in superficial bladder cancer. Eur Urol 20, 19 - 25, 1991.
92. Lamm, D.L., Blumenstein, B.A., Crawford, E.D., Montie, J.E., Scardino, P., Grossman, H.B. et al. A randomized trial of intravesical doxorubicin and immunotherapy with BCG for transitional cell carcinoma of the bladder. N Engl J Med 325, 1205 - 1209, 1991.
93. Melekos, M.D., Chionis, H.S., Paranychianakis, G.S., Dauaher, H.H. Intravesical 4'-epi-doxorubin (epirubicin) versus bacillus Calmette-Guerin. A controlled prospective study on the prophylaxis of superficial bladder cancer. Cancer, 72: 1749 - 1755, 1993.
94. Sekine H, Ohya K, Kojima SI, Igarashi K, and Fukui I. Equivalent efficacy of mitomycin C plus doxorubicin instillation to bacillus Calmette-Guerin therapy for carcinoma in situ of the bladder. Int J Urol 8, 483 - 486, 2001.
95. Witjes, J.A., Caris, C.T.M., Mungan, N.A., Debruyne, F.M.J., and Witjes, W.P.J. Results of a randomized phase III trial of sequential intravesical therapy with mitomycin C and bacillus Calmette-Guerin versus mitomycin C alone in patients with superficial bladder cancer. J Urol 160, 1668 - 1672, 1998.
96. Herr HW, Pinsky CM, Whitmore WF, Sogani PC, Oettgen HF and Melamed MR. Long-term effect of intravesical bacillus Calmette-Guerin on flat carcinoma in situ of the bladder. J Urol 135, 265 - 276, 1986.
97. Badalament RA, Herr HW, Wong GY, Gnecco C, Pinsky CM, Whitmore WF, Fair WR, and Oettgen HF. A prospective randomized trial of maintenance versus nonmaintenance intravesical bacillus Calmette-Guerin therapy of superficial bladder cancer. J Clin Oncol 5, 441 - 449, 1987.
98. Hudson MA, Ratliff TL, Gillen DP, Haaff EO, Dresner SM, and Catalona WJ. Single course versus maintenance bacillus Cal-

mette-Guerin therapy for superficial bladder tumors: a prospective randomized trial. J Urol 138, 295 - 298, 1987.

99. Witjes, W.P.J., Konig, M., Boeminghaus, F.P., Hall, R.R., Schulman, C.C., Zurlo, M., Fittipaldo A, Riggi M, and Debruyne FMJ for the European Bropirimine Study Group. Results of a European comparative randomized study comparing oral bropirimine versus intravesical BCG treatment in BCG naïve patients with carcinoma in situ of the urinary bladder. Eur Urol 36, 576 - 581, 1999.

100. Martinez-Pineiro JA, Flores N, Isorna S, Solsona E, Sebastian JL, Pertusa C, Rioja LA, Martinez-Pineiro L, Vela R, Camacho JE, Nogueira JL, Pereira I, Resel L, et al. Long-term follow up of a randomized prospective trial comparing a standard 81 mg dose of intravesical bacilli Calmette-Guerin with a reduced dose of 27 mg in superficial bladder cancer. BJU Int 89, 671 - 680, 2002.

101. Bassi P, Spinadin R, Carando R, Balta G and Pagano F. Modified induction course: a solution to side effects? Eur Urol 37 (suppl 1), 31 - 32, 2000.

102. Nonomura N, Ono Y, Nozawa M, Fukui T, Harada Y, Nishimura K, Takaha N, Takahara S and Okuyama A. Bacillus Calmette-Guerin perfusion therapy for the treatment of transitional cell carcinoma in situ of the upper urinary tract. Eur Urol 38, 701 - 705, 2000.

103. Thalmann GN, Markwalder R, Walter B, and Studer UE. Long-term experience with bacillus Calmette-Guerin therapy of upper urinary tract transitional cell carcinoma in patients not eligible for surgery. J Urol 168, 1381 - 1385, 2002.

104. Lamm DL, van der Meijden APM, Morales A, Brosman SA, Catalona WJ, Herr HW, Soloway MS, Steg A and Debruyne FMJ. Incidence and treatment of complications of bacillus Calmette-Guerin intravesical therapy in superficial bladder cancer. J Urol 147, 596 - 600, 1992.

105. Van der Meijden APM, Brausi M, Zambon V, Kirkels W, de Balincourt C, and Sylvester R. Intravesical instillation of epirubicin, bacillus Calmette-Guerin and bacillus Calmette-Guerin plus isoniazid for intermediate and high risk Ta, T1 papillary carcinoma of the bladder: a European Organization for Research and Treatment of Cancer Genito-Urinary Group randomized phase III trial. J Urol 166, 476 - 481, 2001.

106. Van der Meijden APM, Sylvester RJ, Oosterlinck W, Hoeltl W and Bono AV. Maintenance bacillus Calmette-Guerin for Ta T1 bladder tumors is not associated with increased toxicity: Results from a European Organization for Research and Treatment of Cancer Genito-Urinary Group phase III trial. Eur Urol 44, 429 - 434, 2003.

107. Saint F, Irani J, Patard JJ, Salmon L, Hoznek A, Zammattio S, Debois H, Abbou CC, and Chopin DK. Tolerability of bacille Calmette-Guerin maintenance therapy for superficial bladder cancer. Urol 57, 883 - 888, 2001.

108. Morgia G, Falsaperla M, Madonia M, Vacirca F, La Pira G, De Grande G, Nicololosi D, Raciti G, Capizzi G, Serrao A, and Torrisi B. Use of BCG in immunotherapy of superficial bladder cancer: multicentric investigation on safety and compliance. UroOncol 2, 129 - 135, 2002.

109. Steinberg G, Bahnson R, Brosman S, Middleton R, Wajsman Z, and Wehle M. Efficacy and safety of valrubicin for the treatment of bacillus Calmette-Guerin refractory carcinoma in situ of the bladder. J Urol 163, 761 - 767, 2000.

110. Onrust SV and Lamb HM. Valrubicin. Drugs Aging 15, 69 - 75, 1999.

111. Greenberg RE, Bahnson RR, Wood D, Childs SJ, Bellingham C, Edson M, Bamberger MH, Steinberg GD, Israel M, Sweatman T, Giantonio B, and O'Dwyer PJ. Initial report on intravesical administration of N-trifluoroacetyladriamycin-14-valerate (AD 32) to patients with refractory superficial transitional cell carcinoma of the urinary bladder. Urol 49, 471 - 475, 1997.

112. Torti FM, Shortliffe LD, Williams RD, Pitts WC, Kempson RL, Ross JC, Palmer J, Meyers F, Ferrari M, Hannigan J, et al. Alpha-interferon in superficial bladder cancer: a Northern California Oncology Group Study. J Clin Oncol 6, 476 - 483, 1988.

113. Williams RD, Gleason DM, Smith AY, Zinner NR, Sagalowsky AI, Montie JE, Brosman SA, Marks LS, Brito G, Boxer RJ, Blank BH, Neri R and Rudeen J. Pilot study of intravesical alpha-2b interferon for treatment of bladder carcinoma in situ following BCG failure. J Urol 155 (supplement), 494A, abstract 735, 1996.

114. O'Donnell MA, Lilli K, Leopold C and the National Bacillus Calmette-Guerin/Interferon phase 2 Investigator Group. Interim results from a national multicenter phase II trial of combination bacillus Calmette-Guerin plus interferon alpha-2b for superficial bladder cancer. J Urol 172, 888 - 893, 2004.

115. Sarosdy MF, Manyak MJ, Sagalowsky AI, Belldegrun A, Benson MC, Bihrle W, Carroll PR, Ellis WJ, Hudson MA, Sharkey FE. Oral bropirimine immunotherapy of bladder carcinoma in situ after prior intravesical bacille Calmette-Guerin. Urol 51, 226 - 231, 1998.

116. Sarosdy MF. A review of clinical studies of bropirimine immunotherapy of carcinoma in situ of the bladder and upper urinary tract. Eur Urol 31(Suppl 1), 20-26, 1997.

117. Sarosdy MF, Pisters LL, Carroll PR, Benson MC, Moon TD, Lamm DL, Hudson MA, Lerner SP, Koch MO, and Schellhammer PF. Bropirimine immunotherapy of upper urinary tract carcinoma in situ. Urol 48, 28 - 32, 1996.

118. Sarosdy MF, Lowe BA, Schellhammer PF, Lamm DL, Graham SD Jr, Grossman HB, See WA, Peabody JO, Moon TD, Flanigan RC, Crawford ED, and Morganroth J. Oral bropirimine immunotherapy of carcinoma in situ of the bladder: results of a phase II trial. Urol 48, 21 - 27, 1996.

119. Berger AP, Steiner H, Stenzl A, Akkad T, Bartsch G, and Holtl L. Photodynamic therapy with intravesical instillation of 5-aminolevulinic acid for patients with recurrent superficial bladder cancer: a single-center study. Urol 61, 338 - 341, 2003.

120. Manyak MJ, and Ogan K. Photodynamic therapy for refractory superficial bladder cancer: long-term clinical outcomes of single treatment using intravesical diffusion medium. J Endourol 17, 633 - 639, 2003.

121. Nseyo UO, Shumaker B, Klein EA, and Sutherland K. Photodynamic therapy using porfimer sodium as an alternative to cystectomy in patients with refractory transitional cell carcinoma in situ of the bladder. Bladder Photofrin Study Group. J Urol 160, 39 - 44, 1998.

122. Nseyo UO, DeHaven J, Dougherty TJ, Potter WR, Merrill DL, Lundahl SL, Lamm DL. Photodynamic therapy (PDT) in the treatment of patients with resistant superficial bladder cancer: a long-term experience. J Clin Laser Med Surg 16, 61 - 68, 1998.

123. Joudi FN and O'Donnell MA. Second-line intravesical therapy versus cystectomy for bacilli Calmette-Guerin (BCG) failures. Cur Opin Urol 14, 271 - 275, 2004.

124. Dalbagni G, Russo P, Sheinfeld J, Mazumdar M, Tong W, Rabbani F, Donat MS, Herr HW, Sogani P, dePalma D, and Bajorin D. Phase I trial of intravesical gemcitabine in bacillus Calmette-Guerin refractory transitional cell carcinoma of the bladder. J Clin Oncol 20, 3193 - 3198, 2002.

125. Lopez-Beltran A, Bassi PF, Pavone-Macaluso M, and Montironi R. Handling and pathology reporting of specimens with carcinoma of the urinary bladder, ureter, and renal pelvis. Eur Urol 45,257 - 266, 2004.

Committee 5

T1 Urothelial Carcinoma of the Bladder

Chair

M.A.S. Jewett (Canada)

Members

A.M. Nieder (USA)

M. Brausi (Italy)

D. Lamm (USA)

M. O'Donnell (USA)

K. Tomita (Japan)

H. Woo (Australia)

CONTENTS

T1 Urothelial Carcinoma of the Bladder

M.A.S. Jewett

A.M. Nieder, M. Brausi, D. Lamm, M. O'Donnell, K. Tomita, H. Woo

Most superficial stage T1 urothelial bladder cancers are high grade and appear to grow rapidly with the potential to not only recur but progress to invasion, metastases, and death. In this chapter, we have focused on the elements of treatment success which we define as disease-free survival with a high quality of life, including bladder sparing where possible.

Figure 1 is an algorithm for the management of stage T1 urothelial tumors presenting as new or recurrent tumors after previous management of lower stage tumors. Virtually all are high grade histologically and present a serious risk of progression in stage by invasion or metastases. Timely and aggressive management of these tumors is essential to minimize the risk for the patient. Urologists, in particular, are in a position to make a significant impact on the overall outcome of patients in this category.

The following sections deal with the sequential steps in the assessment, decision-making, and treatment of T1 patients. Urologists, pathologists, and radiologists must work together to not only diagnose new or recurrent tumors but also to accurately assess individual risk of progression and stratify patients for treatment. The technique of resection is important to be complete but also to safely provide sufficient tissue for staging and grading. Random and directed biopsies are frequently indicated. Immediate adjuvant chemotherapy should be used more frequently. In our opinion, re-resection is mandatory, if the surgeon cannot guarantee that a complete TURBT has been performed or when muscle is not present in the pathological specimen. Clinically useful prognostic factors have been defined to stratify patients by risk of progression. Substaging of T1 tumors has been described but remains controversial. Extravesical tumor extension can occur, particularly after BCG (bacille Calmette-Guérin) therapy with an initial complete response, and it should be screened for. The most difficult decision is whether to initiate intravesical therapy or to recommend radical therapy, usually with cystectomy. Initial intravesical therapy should be BCG but careful follow-up is necessary with the intent to recommend cystectomy for persistent or recurrent tumor, although some patients can be managed by salvage intravesical therapy.

I. DIAGNOSIS AND STAGING

1. Technique of Resection

The initial endoscopic evaluation of patients suspected of or documented as having any stage of urothelial bladder cancer should be performed when complete bladder relaxation is assured at the time of transurethral resection of bladder tumor (TURBT), even if cystoscopy was previously performed. The bladder should not be filled to more than one-third capacity and the entire urothelium should be viewed to best appreciate the slightly raised, velvety appearance and the poorly-defined margins of CIS. Bladder distension should be avoided. Instruments for cold-cup biopsy should be available with the set-up. General or peripheral (spinal or epidural) anesthesia is preferable. A bladder diagram (hard copy or electronic) should be completed by the surgeon after a diagnostic cystoscopy in order to describe the location, appearance (papillary, sessile, flat), size, and number of tumors (**Figure 2**). The bladder diagram should be part of the patient record. Endoscopic photography is also an excellent method of documenting bladder abnormalities.

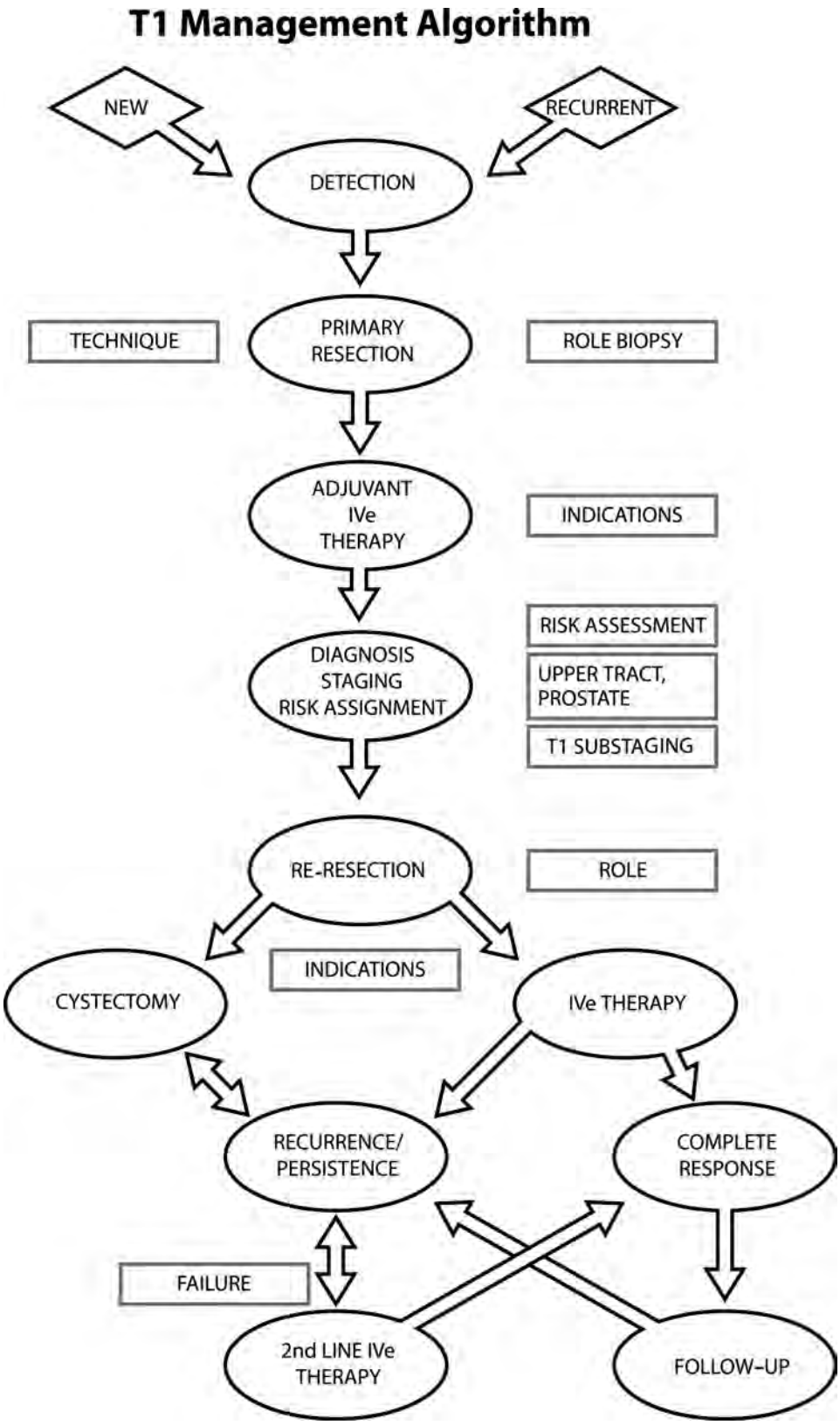


Figure 1. Algorithm of Steps and Issues in the Management of T1 Urothelial Carcinoma of the Bladder
IVe - intravesical

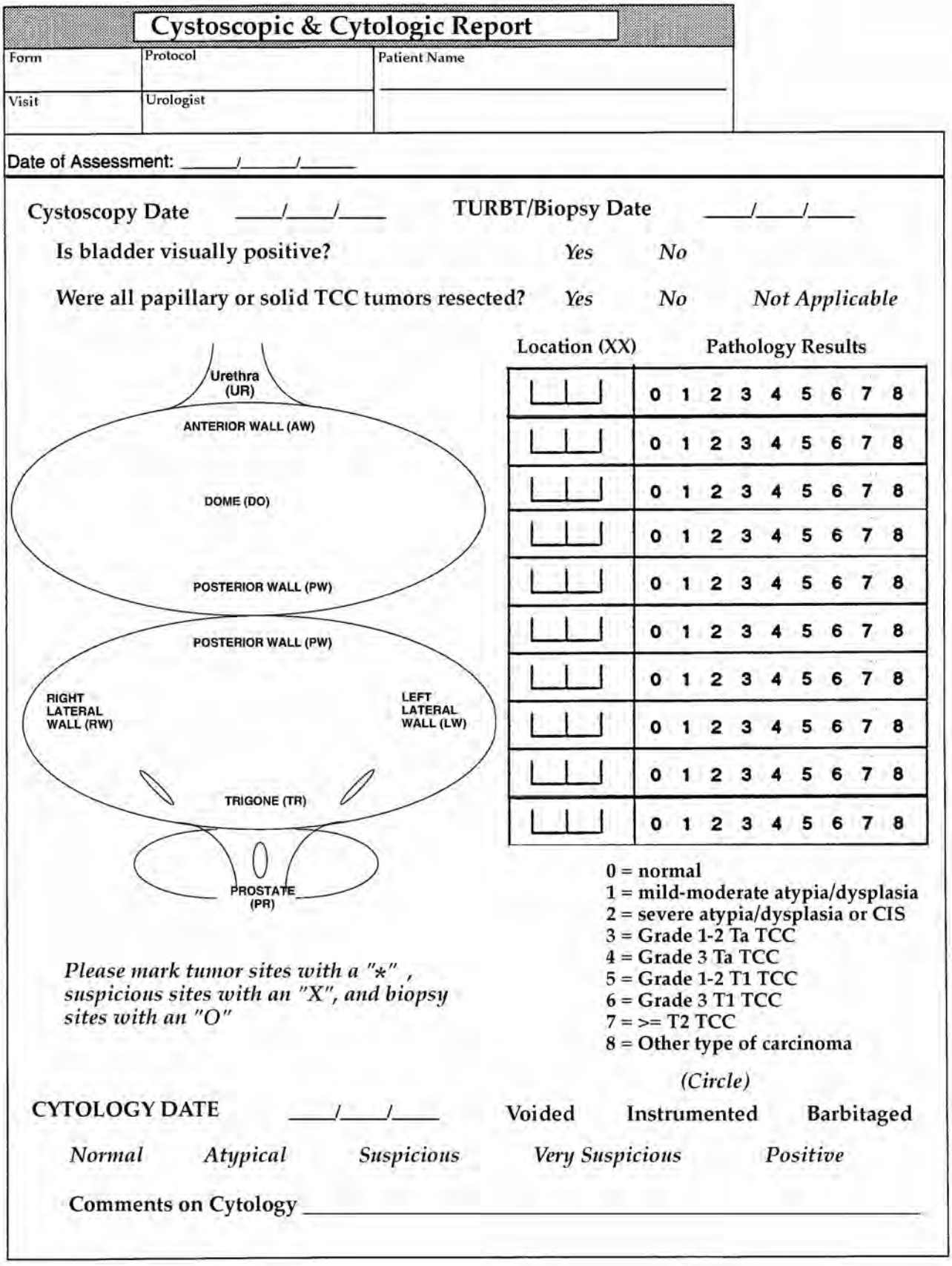


Figure 2. Example of a Bladder Diagram That Could Be Incorporated into a Clinical Record
(courtesy of Dr. Michael O'Donnell)

The initial part of the examination should include a bimanual palpation or examination under anesthesia with the bladder empty, which should be performed before and after TUR, especially if bladder invasion into deep muscle or fat is suspected. The accuracy of bimanual examination to predict pathological stage is not well-established. For superficial bladder tumors, bimanual examination is unlikely to be helpful but its routine practice should be encouraged, although examination before resection may be omitted. In fact, an additional benefit of bimanual palpation in the male is the opportunity to palpate the prostate. Prostatic abnormalities should be duly noted and investigated further as appropriate. The role of MRI is also not well-defined, but may well provide a better assessment of the primary tumor than exam under anesthesia.

Endoscopic resection of bladder tumors may be facilitated with a continuous flow resectoscope. Maintaining the bladder capacity at approximately one-third to one-half of the bladder volume allows excellent visibility and reduces the chance of bladder perforation during resection, especially in women, who may have a thin bladder wall. This is particularly advantageous with tumors located on the posterior wall or dome. Video TUR has become the standard procedure in most institutions. This allows magnification of the field, which is useful for teaching purposes and reducing the surgeon's exposure to body fluids.

Larger tumors should be resected in a systematic fashion by initiating resection at one side and serially removing portions of tumor. Resection sufficient to obtain muscle in the specimen is necessary for staging. A separate biopsy of the tumor base that is free of cautery artifact, such as a cold cup biopsy, can facilitate a correct pathological diagnosis. Histological fragments of the tumor and tumor base should be submitted separately according to depth and surrounding. In general, where possible, all visible tumor(s) should be completely resected with several millimeters of the surrounding urothelium and then fulgurated. A roller electrode can facilitate fulguration. It is essential that the tumor(s) be completely resected. Some have suggested that this may be improved by an independent post-resection inspection by a second surgeon *(Level 3,* [1]*)*. If this cross-control is not performed, a final evaluation of the bladder with a 70° lens is suggested.

Specific situations in the surgical management of superficial bladder tumors include the following:

- Tumor in a diverticulum should be biopsied and, if possible, resected. The appearance of the tumor should dictate the extent of the resection or biopsy. An exophytic papillary tumor can be resected with fulguration of its base.
- Bladder perforation may occur as a result of the obturator nerve reflex and the resulting adductor spasm. Direct local anesthesia of the obturator nerve in the obturator canal can prevent obturator nerve reflex. Local anesthesia with 20 to 30 mL of 2% lidocaine will block the nerve for at least 1 hour.
- Directed (as opposed to random) mucosal biopsies of all suspicious areas of the bladder are mandatory at the time of TURBT, while random biopsies of normal-appearing urothelium should not be part of a routine resection of a low or intermediate grade superficial bladder tumor. (*See Section I.2. Role of Random and Directed Biopsies*.)

2. Role of Random and Directed Biopsies

During the initial endoscopic evaluation, the urologist should make a decision regarding the need for directed (to an area of visible abnormality), selected site, or random mucosal biopsies. Biopsy is of particular importance in cases with positive cytology, especially if no residual tumor is visualized in the bladder.

If selected site biopsies are performed the locations are usually lateral to each ureteral orifice (2), lateral walls (2), posterior wall (1), superior wall (1), and prostate (1). Cold cup biopsies of any erythematous, velvety, or edematous area suspicious for dysplasia or CIS should be performed. The prostatic urethra should be carefully inspected and biopsied in patients with prior positive cytology and no visible tumors or CIS. Prostatic biopsy should include representative tissue from the urethra, ducts, and glands.

Fujimoto et al. prospectively evaluated the usefulness of random bladder biopsies of normal urothelium in patients undergoing TURBT *(Level 2,* [2]*)*. The authors identified cancer in only 8 of 100 biopsies, 5 of which were CIS. They concluded that multiple random biopsies are only indicated in patients with multiple papillary tumors or those with positive cytology. Van der Meijden et al. retrospectively reviewed 2 EORTC studies and evaluated the efficacy of random bladder biopsies *(Level 3,* [3]*)*. Random biopsies of normal-appearing urothelium demonstrated abnormalities in approximately only 10% of patients (only 3.5% CIS), and thus were

thought not to be warranted. Conversely, May et al. found that random bladder biopsies altered therapy in 7% of 1033 consecutive patients *(Level 2,* [4]*)*. In fact, in 14 patients malignancy was identified in only the random biopsy and not in the resection of the primary tumor. Importantly, however, these authors excluded patients with small, primary, solitary bladder tumors. Thus, the committee felt that patients with tumors that appeared to be of low risk in terms of appearance, and with negative cytology, should not undergo random biopsy.

3. Role of Second Resection

The diagnosis and management of superficial bladder cancer are dependent upon an adequate TURBT. The risk of residual tumor being present following initial transurethral resection of T1 tumors has been reported to be as high as 60% (**Table 1**). Most significantly for high grade T1 lesions, it is incumbent on the urologist to ensure that the tumor is actually not muscle-invasive, since this typically changes the treatment options.

Table 1. Understaging in High-risk Non-muscle-invasive Urothelial Carcinoma of the Bladder [5]

Series	Year	Understaged
Pagano	1991	35%
Amling	1994	37%
Soloway	1994	36%
Freeman	1995	34%
Ghoneim	1997	62%
Stein	2000	39%
Cookson	2001	40%

Stein JP. Sem Urol Oncol 2000; 18:289-295. [5]

Herr retrospectively evaluated the concordance of the pathological diagnoses between an initial resection and a second TURBT in 150 patients *(Level 3,* [6]*)*. The results of the second resection changed the treatment in 33% of the patients. He importantly noted the inability to accurately diagnose T1 tumors without muscle in the specimen. Of 23 patients with T1 lesions without muscle in the primary resection, 11 (49%) were upstaged to T2 lesions after review of the second TURBT specimen. However, in this study different urologists performed the first and second TURBTs, different pathologists read the first and second bladder tumor specimens, the time between initial and subsequent resection was variable, and it is not certain that a complete resection was attempted initially. Dutta et al. similarly reported a 64% risk of understaging T1 lesions when muscle was absent compared to only 30% when muscle was present in the TURBT specimens *(Level 3,* [7]*)*.

Other authors have found that a primary resection of a T1 bladder tumor may be inadequate to remove all tumors. Zurkirchen et al. retrospectively reviewed those patients who underwent follow-up TURBTs within 6 weeks of their initial resections *(Level 3,* [8]*)*. Thirty-seven percent of patients with initially diagnosed T1 bladder tumors had persistent tumors on second resection. Grimm et al. similarly retrospectively reviewed 83 patients who underwent repeat TURBT a mean of 7 weeks after initial TURBT *(Level 3,* [9]*)*. Residual tumor was found in 33% of cases, including 53% of those with initially diagnosed T1 bladder tumors. On univariate analysis, both tumor stage and grade were identified as predictive for residual tumor on restaging TURBT. Furthermore, after 5 years there was a significant decrease in disease-free survival between those who underwent a second TURBT and those who did not (63% and 40%, respectively). Brauers et al. evaluated 42 patients with moderate or high grade T1 bladder tumors and reported that 24% of patients were upstaged to T2 or Tis on restaging TURBT *(Level 3,* [6]*)*. Schips et al. prospectively evaluated the findings at first and second TURBT for patients with high grade T1 bladder tumors and also found residual disease in over 50% of patients *(Level 3,* [10]*)*. Both multifocality and tumor grade increased the risk of finding residual tumor on second TURBT. While 76% of patients with a solitary T1 lesion at first TURBT had a negative second TURBT, only 53% of those with multifocal T1 lesions had a negative repeat TURBT. Moreover, 73% of those with papillary-appearing T1 lesions at first resection had a negative repeat TURBT, compared to only 47% of those with solid-appearing T1 lesions.

Early repeat TURBT can be justified for the purposes of identifying understaged T2 tumors that would benefit from prompt treatment with cystectomy. In a series of 189 patients who underwent cystectomy within 3 months of diagnosis of muscle-invasive disease, there was a significantly better 5-year progression-free survival than if cystectomy was performed more than 3 months following diagnosis (55% and 34%, respectively) *(Level 3,* [11]*)*.

Summary

These studies show that ***the risk of upstaging on second TURBT is at least 30% if muscle is present in the specimen and even higher if muscle is not present*** *(Level 3)*. [7,12] Further, ***the risk of residual tumor on second TURBT is also significant***. Even for solitary, papillary-appearing tumors, the risk is 24% to 27% [9, *Level 3*; 10, *Level 2*; 8, *Level 3*] Because of these significant rates, ***it is recommended that a second TURBT be considered for all patients with high grade Ta or any T1 urothelial carcinoma***. This definitive recommendation was difficult for the authors to make, but even experienced surgeons have felt that resection was complete only to find a recurrence, possibly of higher stage, in exactly the same site a short time later. Therefore, we believe that a standard of universal re-resection for high grade or T1 tumors should be recommended in an attempt to prevent understaging and possible progression to metastatic disease. Although no evidence regarding the ***timing of a second TURBT*** is available, the ***consensus opinion*** is that this should be performed ***within 1 to 4 weeks following the initial resection***.

4. Substaging of T1 Pathology

Multiple authors have attempted to substage T1 bladder cancers based on the presence of invasion of the muscularis mucosae. Holmang et al. retrospectively reviewed 121 stage T1 bladder cancers and evaluated whether the tumors invaded above the level of the muscularis mucosae (stage T1a) or invaded into and beyond it (stage T1b) *(Level 3,* [13]*)*. T1a disease was found in 54% of patients and T1b in 40%; only 6% of patients could not be pathologically substaged. Stage T1b tumors were significantly higher grade than T1a tumors; 58% of those with grade 3 T1b tumors ultimately progressed to muscle-invasive disease compared to only 36% with grade 3 T1a tumors. The 5-year overall survivals for T1a and T1b tumors were 54% and 42%, respectively. Hasui et al. similarly reported a worse prognosis for T1 patients with muscularis mucosae invasion *(Level 3,* [14]*)*. With a mean follow-up of 78 months, the progression rates for T1a and T1b cancers were 7% and 54%, respectively. Moreover, the increased risk of progression was seen regardless of the grade, size, or multifocality of the tumor. Angulo et al. also substaged T1 cancers based upon the invasion of the muscularis mucosae *(Level 3,* [15]*)*. Importantly, they reported that they were able to assess the level of invasion and thus substage the T1 tumors in only 58% of 170 cases. The 5-year recurrence-free survivals for those with T1a and T1b tumors were 86% and 52%, respectively. This difference was independent of tumor grade.

Smits et al. further categorized T1 cancers into T1a, T1b, and T1c (up to, in, and beyond the muscularis mucosae, respectively) and retrospectively evaluated the risk of recurrence and progression among the 3 groups *(Level 3,* [16]*)*. There was no difference in the 3-year risk of recurrence among the groups. However, the risks of progression were 6%, 33%, and 55%, respectively. Furthermore, the combination of T1c and CIS increased the risk of progression 27 times that of those without T1c and CIS.

Cheng et al. applied a different method to substage T1 tumors, to obviate the difficulty in identifying the muscularis mucosae level *(Level 3,* [17]*)*. They retrospectively reviewed 55 patients with T1 bladder cancer and compared their TURBT pathology to their pathology at cystectomy, a median 10 days from TURBT. All TURBT specimens were evaluated for depth of stromal invasion—as measured by micrometer from the basement membrane to the deepest tumor cells. There was a significant correlation between the depth of invasion in the TURBT specimen and the final pathological stage at cystectomy. Using a cutoff of 1.5 mm depth of invasion, the sensitivity, specificity, and positive and negative predictive values for predicting advanced stage disease (≥T2) were 81%, 83%, 95%, and 56%, respectively.

Bernardini et al. retrospectively evaluated 94 patients with Ta tumors and compared their substage level with p53 status *(Level 3,* [18]*)*. Overexpression of p53 was identified in 26% of patients with T1a tumors, compared to 53% of patients with T1b tumors ($P < 0.02$). Multivariate analysis demonstrated that patients with T1b tumors and CIS had a 7.5 times greater risk of progression than those with T1a tumors and CIS ($P < 0.001$).

Kondylis et al. retrospectively evaluated whether the response to BCG was different in those with T1a and T1b tumors *(Level 3,* [19]*)*. At a median follow-up of 71 months, the incidence of recurrence was noted in 69% with T1a tumors compared to 65% of T1b tumors ($P = 0.7$). Furthermore, progression was noted in 22% of T1a tumors and 29% of T1b tumors ($P = 0.5$). The authors thus concluded that response to intravesical therapy is not dependent upon T1 substage.

Summary

Though authors have reported on the utility of substaging T1 tumors, ***there is no general consensus among pathologists regarding the presence of the muscularis mucosae***. Furthermore, ***randomized studies have not validated more aggressive treatment for those with deeper T1 lesions***. The consensus is that ***T1 substaging is not yet a validated prognostic factor.***

5. What Are the Important Prognostic Factors?

The most useful predictors of progression in patients with stage T1 urothelial carcinoma are clinical, including histopathology. Traditional factors to predict clinical outcome of T1 urothelial bladder carcinoma following initial TURBT include early recurrence, grade, multiplicity, tumor extent and size, concomitant carcinoma in situ, urothelial carcinoma involving the prostatic mucosa or ducts, and depth of lamina propria invasion *(Level 3,* [17,20,21]*)*. The response to intravesical therapy is a reliable predictor of progression within 9 months *(Level 3,* [22]*)*. Solsona et al. reported that the 80% of patients who did not achieve a complete response by 3 months had progression *(Level 3,* [21]*)*. In addition, this study indicates that high grade tumor, associated carcinoma in situ, or prostatic mucosal/duct involvement represent significant pathological predictors of progression. The relative importance of clinical and pathologic factors varies according to adjuvant therapy. For example, substaging of T1 has not been found to be useful in BCG-treated patients, and recurrence or persistence of disease that is downstaged or downgraded may be evidence of response in an individual patient. Nevertheless, it has been recognized that these prognostic factors are not accurate enough to predict individual clinical behavior of T1 urothelial tumors. Therefore, more reliable indicators of biological aggressiveness are needed.

A number of molecular prognostic markers have been reported for T1 bladder cancer (*see Chapter 2: Tumor Markers Beyond Cytology*). It has been suggested that alterations of cell cycle regulatory proteins involved in the progression from G1 to S phase are among the most promising markers *(Level 3,* [23]*)*. The p53 tumor suppressor gene is commonly altered in human malignancies. Pfister et al. observed mutant p53 in 66% of stage T1 high grade tumors but in no low grade tumors *(Level 3,* [24]*)*. Tumors with mutant p53 inactivate transcription of p21 and the Bax gene *(Level 3,* [25]*)*. Saint et al. reported that pretreatment p53 nuclear overexpression in superficial bladder tumors is associated with a high risk of disease recurrence, progression, and cancer death after BCG therapy *(Level 3,* [26]*)*. Alterations of p53 were associated with BCG failure. Others have not noted that p53 expression before BCG treatment correlated with BCG failure (*Level 3,* [27]). Controversial results have also been reported in regard to p53 expression as an independent predictor of progression. In a case-control study, Llopis et al. showed that p53 expression analyzed at a cutoff of 20% positivity is a significant predictor of progression *(Level 3,* [28]*)*. Steiner et al. did not find p53 status helpful in the selection of candidates for radical therapy (*Level 3,* [29,30]). Lopez-Beltran et al. reported a number of cell cycle regulators that appear to be independent predictors of survival of patients with T1G3 bladder cancer including p27kip1 and the cyclins D1 and D3 *(Level 3,* [31]*)*.

Many other prognostic factors, including genetic alterations, cell adhesion molecules, a family of proteases, growth factors, and other molecular markers, have been studied, but to date do not have enough specificity for clinical use for T1 bladder cancer.

Summary

Useful ***clinical prognostic factors for T1 urothelial bladder cancer include tumor grade, early recurrence, multiplicity, tumor size, concomitant carcinoma in situ, urothelial carcinoma involving the prostatic mucosa or ducts, and depth of lamina propria invasion. The response to intravesical therapy is a very useful clinical marker*** (*Level 3*) [17,20,21]. A great number of molecular and genetic prognostic markers including alterations of p53 have been studied for T1 bladder cancer. However, ***most of these markers have not been validated and are not available for clinical use***.

6. Upper Tract, Prostatic, and Urethral Involvement

The overall risk of upper urinary tract urothelial carcinoma (UUTUC) occurrence in patients with superficial bladder cancer is low, ranging from 2% to 4% (*Level 3,* [32]). However, this risk is higher in patients with high grade and superficially invasive urothelial carcinoma of the bladder, ranging from 13% to 29% (*Level 3,* [33,34]). Herr et al. found a

7% incidence at 5 years after treatment for superficial urothelial carcinoma of the bladder, rising gradually with time to as high as 21% at 15 years *(Level 3,* [32]*)*. Lifelong observation of the upper urinary tracts in such patients is recommended. Hurle et al. reported that patients with UUTUC developing after treatment of superficial bladder cancer could be stratified into 3 groups *(Level 3,* [35]*)*. Those with primary, solitary, low grade (G1-G2) and low stage (Ta-T1) superficial bladder cancer (n = 216) were considered at low risk for disease recurrence or progression and were treated with transurethral resection (TUR) alone. Patients with recurrent or multifocal superficial bladder cancer (n = 182) were considered at intermediate risk and treated with adjuvant intravesical chemotherapy, and 193 patients with CIS, high grade (G3) superficial bladder cancer, or intravesical chemotherapy failure were considered at high risk and treated with BCG. After a median follow-up of 86 months, 2 (0.9%) of 216 patients at low risk, 4 (2.2%) of 182 patients at intermediate risk, and 19 (9.8%) of 193 patients at high risk developed UUTUC. The incidence of UUTUC is significantly higher in patients at high risk compared to those at low risk (P = 0.0004, odds ratio 11.6) and at intermediate risk (P = 0.004, odds ratio 4.8). In addition, 80% of stage pT2-pT3 UUTUC, 90% of multiple UUTUC, and 80% of patients who died from UUTUC were in the high risk group. These data suggest that UUTUC is not only frequent but also of high stage and grade and carries a bad prognosis in patients at high risk. Since UUTUC is often asymptomatic and mortality is high, frequent and lifelong observation of the upper urinary tract is suggested with an annual IVU and urinary cytologic examination and urinalysis every 4 months in patients with superficial bladder cancer at high risk of disease recurrence or progression. Schwartz et al. reported a 3.1% upper tract recurrence rate in patients with superficial bladder cancer and 13% in those with bladder CIS *(Level 3,* [36]*)*. The high upper tract recurrence rate in patients with superficial bladder cancer and CIS has also been confirmed by other authors (range 15.4%-29%) (*Level 3,* [33,37]). Hurle et al. reported that of 51 patients with T1G3 bladder cancer treated with induction plus maintenance BCG courses after TUR and followed up for at least 5 years, 7 (13.7%) had extravesical involvement, 5 (9.8%) had an UUTUC, and 3 (7.9%) of 38 had prostatic involvement (1 of 7 had both) *(Level 3,* [38]*)*.

Vesicoureteral reflux (VUR) after TUR of bladder cancer has been suggested as a mechanism for upper tract recurrence with tumor cell implantation. Amar et al. and De Torres Mateos et al. have reported a higher upper tract recurrence rate in patients with reflux (6.4%-19.7%), compared with those without reflux (0.4%-0.9%) *(Level 3,* [39,40]*)*. However, these studies were retrospective and do not take into account possible transient reflux after TUR when there may be circulating tumor cells or explain unilateral recurrence with bilateral reflux. Solsona et al. reported no significant differences in the upper tract recurrence rates of patients with or without reflux *(Level 3,* [41]*)*. Nevertheless, VUR may be a weak etiologic factor, but multifocality and the presence of CIS seem to be more important etiologic factors. Solsona et al. also reported that solitary upper urinary tract involvement did not have a negative impact on the survival of patients with bladder CIS. However, when associated with prostate involvement, the survival rate was significantly worse compared to those with primary UUTUC.

The incidence of concomitant prostatic urethral involvement with high-risk superficial urothelial carcinoma has been reported to be between 8.7% and 36.0% (*Level 3,* [42]). In these cases, Schellhammer et al. reported that no stromal invasion was found, and 70% of these patients were successfully treated by BCG instillation therapy *(Level 3,* [43]*)*.

Progression to the prostate after BCG instillation therapy was first reported by Catalona et al., who described 4 patients with prostatic involvement after BCG therapy *(Level 3,* [44]*)*. All of these patients had prostatic ductal or prostatic urethral cancer, which can be detected by TUR. Sakamoto et al. recommended TUR biopsy to include prostatic tissue at the 5 and/or 7 o'clock position at the verumontanum *(Level 3,* [45]). Herr et al. reported extravesical recurrence detected by positive urine cytology in patients who had long-term follow-up after TURBT and BCG *(Level 3,* [42]*)*. Among 307 patients, 78 (25%) developed tumors in the upper urinary tract. Among the 251 men, 61 (24%) had tumors detected in the prostatic urethra or ducts (pT4). The median times to detection of an UUTUC or prostatic epithelial tumor were 56 months and 11 months, respectively, and 32% of the UUTUC and 44% of the pT4 relapses were lethal. They concluded that patients with high-risk superficial bladder tumors who are treated successfully by a bladder-sparing strategy are at increased risk for tumor relapse that involves extravesical mucosa.

Herr et al. have also reported prostatic tumor relapse in patients with superficial bladder tumors followed

for 15 years *(Level 3,* [46]*)*. They divided tumor relapses in the prostate into noninvasive (prostatic urethra and ducts) or invasive (stroma) with intraurethral or direct prostatic invasion. Of the 186 patients, 72 (39%) had relapse in the prostate, including 45 (62%) with noninvasive prostatic tumor and 27 (38%) with stromal invasion. The survival rate was 82% in patients with prostatic urethra or duct involvement compared to 48% in those with stromal invasion. Prostatic stromal invasion was an independent prognostic variable of survival *(see Chapter 8: Urothelial Carcinoma of the Prostate).*

During investigation of positive urine cytology, tumors in the upper urinary tract were detected in 25% and in the prostatic urethra or ducts in 24% with multiple recurrent papillary tumors and CIS with long-term follow-up (*Level 3,* [42]). ***Prostatic stromal invasion was an independent prognostic predictor of survival in patients with superficial bladder tumors*** followed for 15 years (*Level 3,* [46]).

Summary

UUTUC is not only frequent but also of high stage and grade, with a bad prognosis in patients in the high-risk group (patients with CIS, high grade (G3) superficial urothelial carcinoma, or intravesical chemotherapy failure) (*Level 3,* [35]). Since UUTUC is often asymptomatic and mortality is high, ***periodic lifelong observation of the upper urinary tract is suggested with appropriate anatomic imaging (retrograde pyelogram/IVU/CT/MRI) and urinary cytologic examination and urinalysis*** in patients with superficial bladder cancer with a high risk of disease recurrence or progression (*Level 3,* [35]). ***The high rate of upper tract and prostate recurrence in superficial bladder cancer patients with CIS has also been confirmed*** by several authors (15.4%-29%) (*Level 3,* [37,38,42]).

II. TREATMENT

1. Role of Immediate Adjuvant Intravesical Therapy

The risk of recurrence of high grade stage T1 urothelial (transitional cell) carcinoma approaches 80%. In the hopes of reducing this risk, many trials have investigated the use of prophylactic or adjuvant intravesical therapy at the time of TURBT. Tolley et al. performed a multicenter, randomized trial of 502 patients with newly diagnosed stage Ta or T1 urothelial carcinoma *(Level 2,* [47]*)*. Those who received intravesical mitomycin C within 24 hours of TURBT had a statistically significant decreased risk of tumor recurrence compared to those who received placebo. No patients reported chemical cystitis; however, 6% of those who received a single dose of mitomycin C reported dysuria and frequency.

Oosterlinck et al. conducted a prospective, multicenter, randomized, placebo-controlled study of 431 patients with superficial urothelial carcinoma comparing a single adjuvant dose of epirubicin (80 mg in 50 mL sterile water) or sterile water (50 mL), within 6 hours after TURBT *(Level 2,* [48]*)*. At a mean follow-up of 2 years, the overall recurrence rates for those who received epirubicin compared to water were 17% and 32%, respectively ($P < 0.0001$). Moreover, when evaluated by subgroups, the recurrence rates for those with stage T1 urothelial carcinoma were 23% and 60%, respectively ($P = 0.065$). The risk of chemical cystitis was 11.7% among those who received epirubicin.

Bouffioux et al. reported the results of 2 EORTC prospective, multicenter, randomized studies comparing the efficacy of either early versus delayed mitomycin C or doxorubicin as adjuvant intravesical therapy *(Level 2,* [49]*)*. In protocol 30831, patients were randomized to receive adjuvant mitomycin C (30 mg in 50 mL saline) either immediately after or 7 to 15 days after TURBT. Instillations were given every week for 4 weeks and then monthly for 5 months for a total of 9 instillations. After completion of 9 doses, patients were randomized again to either maintenance therapy (monthly for 6 months, for a total of 15 instillations) or no maintenance. Protocol 30832 was identical except that it was a study of doxorubicin (50 mg) instead of mitomycin C. A total of 834 patients were eligible for the protocol, 457 in the mitomycin trial and 377 in the doxorubicin trial. The final analyses demonstrated that early intravesical therapy (with or without maintenance) is slightly superior to delayed therapy with maintenance. Furthermore, if early treatment is given, further maintenance therapy is not beneficial. Based on a mean follow-up of 4 years, the progression rate to muscle-invasive disease was 8% to 11% for all patients. Mitomycin C was slightly better tolerated than doxorubicin, with chemical cystitis being reported by 6% and 9%, respectively.

Solsona et al. specifically evaluated the effectiveness of a single dose of mitomycin C in patients with non-

high grade superficial urothelial carcinoma *(Level 2,* [50]*)*. Patients were prospectively randomized to either mitomycin C (30 mg in 50 mL saline) within 6 hours of TURBT or observation (N = 121). Sixty-two of the patients had stage T1 urothelial carcinoma, grade I or II (all high grade tumors or carcinoma in situ were excluded). The risks of recurrence during the first 2 years were 16% and 34%, respectively (P = 0.019); however, the overall risks of recurrence were 40% and 54%, respectively (P = 0.115). Only 2 patients (3.5%) in the mitomycin C group had chemical cystitis.

Krege et al. performed a prospective, randomized, multicenter trial comparing TURBT alone versus TURBT with adjuvant maintenance mitomycin C (20 mg in 50 mL saline every 2 weeks for 1 year and then monthly for an additional year) versus maintenance BCG (120 mg in 50 mL saline weekly for 6 weeks and then monthly for 4 months) *(Level 2,* [51]*)*. Only 25% of the study patients had stage T1 urothelial carcinoma. At a median follow-up of 20 months, there was a statistically significant decrease in risk of recurrence for those who received maintenance adjuvant therapy compared to those who did not. There was no significant difference between those who received mitomycin C or BCG. Mitomycin C was better tolerated than BCG, with cystitis being reported by 16% and 34%, respectively.

Kurth et al. performed a prospective, multicenter, randomized trial comparing TURBT alone to TURBT with adjuvant doxorubicin (50mg in 50 mL saline) or ethoglucid (1.13 gm in 100 mL water) *(Level 2,* [52]*)*. The chemotherapeutic agents were instilled within 1 week of TURBT and were given weekly for 1 month and then monthly for 11 months. The time to first recurrence was significantly greater in those who received either intravesical therapy compared to placebo ($P < 0.001$). These results were noted for both Ta and T1 lesions. However, no differences were noted between doxorubicin and ethoglucid. At 3 years, the recurrence-free survivals for the no therapy group, doxorubicin group, and ethoglucid group were 29%, 48%, and 56%, respectively. The risks of chemical cystitis were similar for those receiving doxorubicin or ethoglucid, 2.8% and 3.6%, respectively.

Sylvester et al. recently performed a meta-analysis regarding the efficacy of a single dose of adjuvant intravesical therapy (*Level 1,* [53]). The authors evaluated 7 previously published trials on a total of over 1400 patients. The authors found conclusive evidence that a single dose of intravesical therapy significantly reduces the risk of recurrence of bladder tumors. They concluded that adjuvant intravesical therapy is the treatment of choice in patients with a single, low grade superficial bladder tumor and should be the initial treatment (prior to subsequent intravesical BCG) in those with higher risk bladder tumors.

Summary

These multicenter, randomized, prospective studies demonstrate that ***the risk of recurrence can be reduced by 50% at 2 years and at least 15% at 5 years with a single dose of adjuvant intravesical chemotherapy*** [47,48,50]. If mitomycin C is given within 24 hours of TURBT, ***maintenance therapy does not significantly reduce the recurrence risk further*** (Level 2, [49]). Because of this significant decrease in recurrence risk, ***it is recommended that a single dose of intravesical chemotherapy be given ideally within 6 hours but no more than 24 hours following TURBT*** unless there has been perforation, extensive/deep resection, or intolerance/allergy to chemotherapy. These recommendations are exclusively for chemotherapy; BCG should never be given immediately postoperatively.

2. Initial Bladder-sparing Approach versus Cystectomy

The goal for treatment of bladder cancer is to minimize the morbidity and mortality of the disease while maximizing the patient's quality of life. This is particularly true of new or recurrent T1 disease. The substantial majority of stage T1 bladder cancers are high grade and therefore at particular risk of progression to incurable metastases. Treatment with TURBT alone without at least adjuvant intravesical therapy has an unacceptable risk of recurrence and progression. Progression in studies of such patients is as high as 35% to 48% within 3 years *(Level 3,* [54-56]*)*. The decision to recommend immediate cystectomy or intravesical therapy with delayed cystectomy for persistent or recurrent tumor is one of the most difficult in the management of all stages of bladder cancer. Quality of life data is interesting in that patients are willing to accept the disabilities incurred with cystectomy to avoid compromising survival if that is the alternative *(Level 3,* [57]*)*.

Selection of the treatment strategy for stage T1 bladder cancer requires consideration of the risks and benefits of cystectomy, repeat transurethral resec-

tion, immediate instillation of chemotherapy, and BCG immunotherapy techniques. As noted above, repeat resection will reveal that residual or recurrent disease and even understaging is frequent. When cystectomy is done for clinical stage T1 disease, as illustrated in **Table 1**, 30% or more of patients will be found to have unsuspected T2 or greater disease. Cystectomy is therefore an option to be considered, and the results of cystectomy should be compared with those of other treatments. In a recent contemporary cystectomy series of 300 patients, the overall 5-year survival for patients undergoing cystectomy for bladder cancer was only 45% [58]. Surprisingly, survival for patients with non-muscle-invasive disease was not significantly better than that for T2 disease, 64% versus 59%. Aggressive surgery should be justified by objective data, but reports of increased mortality in patients who develop muscle-invasion requiring cystectomy while on conservative treatment and observation schedules clearly raise concern about delaying cystectomy.

a) Intravesical Therapy

Prior to the advent of BCG immunotherapy, the incidence of progression in high grade, stage T1 urothelial carcinoma, as illustrated in **Table 2**, ranged from 27% to 65% with follow-up ranging from 36 to 84 months. These poor results and the subsequent confirmation that intravesical chemotherapy fails to reduce disease progression served as justification for cystectomy. These data, however, should not be used to justify cystectomy in the BCG era.

With the advent of BCG, reported results of intravesical therapy in T1 disease, as illustrated in **Table 3**, have dramatically improved. With follow-up ranging from 22 to 78 months, overall progression is in the range of 12%, varying from 0% to 35%. It is quite remarkable that the overall incidence of progression in patients with T1 disease, in the range of 12%, is less than the incidence of occult muscle-invasive disease (up to 30%) in patients who undergo immediate cystectomy [59]. Though patients managed by initial intravesical therapy have a high likelihood of achieving a complete remission, there is some data indicating that the longer-term risks of progression are greater. Cookson et al. reported that after 15 years of follow-up, 53% of patients with initial high-risk superficial bladder cancer progressed to muscle-invasive disease, 36% eventually underwent cystectomy, and 34% were dead of bladder cancer *(Level 3*, [60]*)*. Only 27% were alive with an intact bladder. Similar results have been reported by Shahin et al. with 153 patients managed by either TURBT and

Table 2. Progression in T1G3 Urothelial Carcinoma of the Bladder Without the Use of BCG

Author/Year	N	Progression (%)	Follow-up (mos)
Heney 1983	27	48	36
Rutt 1985	430	31	60
Malmstrom 1987	7	43	60
Jakse 1987	31	33	60
Kaubisch 1991	18	50	36
Mulders 1994	48	27	48
Klan 1995	17	65	72
Holmang 1997	58	48	84
Total	**519**	**33**	

Table 3. History of BCG-Treated T1G3 Urothelial Carcinoma of the Bladder

Author/Year	N	Progression (%)	Follow-up (mos)
Boccon-Gibod 1989	47	21	14-64
Dal Bo 1990	24	25	22
Samodi 1991	62	0	46
Cookson 1992	16	19	59
Eure 1992	30	7	39
Pfister 1995	26	27	54
Hurle 1996	51	14	33
Zhang 1996	23	35	45
Serretta 1996	50	12	52
Vicente 1996	95	11	46
Lebret 1998	35	12	45
Baniel 1998	78	8	56
Klan 1998	109	13	78
Gohji 1999	25	4	63
Brake 2000	44	16	43
Pansadoro 2002	81	15	76
Total	**796**	**12**	

BCG or TURBT alone *(Level 3,* [61]*)*. At a median follow-up of 5.3 years, disease recurred in 70% and 75% of patients treated with BCG and TURBT alone, respectively. Progression was seen in 33% and 36%, respectively. Deferred cystectomy was performed in 29% and 31%, respectively. Overall and disease-specific survival for those receiving BCG compared to TURBT alone was 42% and 77% versus 48% and 79%, respectively. The authors stated that BCG therapy is unlikely to substantially alter the final outcome for patients with high grade T1 urothelial carcinoma.

There are side effects with intravesical therapy. Up to 90% of patients experience irritative lower urinary tract symptoms and a small number of patients have serious, debilitating complications such as sepsis and contracted bladders. Lamm et al. reported that only 16% of patients were able to tolerate a full maintenance course of BCG secondary to adverse effects, albeit in an earlier era *(Level 2,* [62]*)*.

Conservative therapy is an attractive option, given the known response rates to BCG, in many patients with bladder cancer, specifically those with comorbid diseases associated with cigarette smoking and limited life expectancy. Improved BCG treatment strategies, particularly the use of improved maintenance schedules such as the 3-week SWOG schedule, would be expected to provide even better results *(Level 2,* [63]*)*. While young, healthy patients respond equally well to intravesical immunotherapy, even with meticulous follow-up patients remain at long-term risk for recurrence, progression, and death from bladder cancer. Cystectomy removes not only the urothelium at risk in the bladder, but also the prostate and distal ureters, sites where recurrence is difficult to detect and dangerous. These risks, like those of cystectomy itself, should be carefully explained to patients.

Clinical response to intravesical therapy has been shown to be a factor predictive of progression in the case of CIS and mixed groups of T1 and CIS or T1 patients alone; a study of patients treated with intravesical doxorubicin found that 50% of those found to have stage T1 or grade 3 recurrent tumors developed progression *(Level 3,* [64]*)*. The pathological stage of the tumor at recurrence was the only factor predictive of recurrence in this study. Solsona et al. demonstrated a complete clinical response rate to intravesical therapy for T1 disease of 78% in 80 patients *(Level 3,* [21]*)*. However, as in the case of many studies on high risk superficial bladder cancer, T1 tumors in this study were not separated out from CIS in the analysis of risk factors for progression. In this combined group of patients, the 3-month clinical response was a highly predictive factor for the development of progression. A lack of response at the 3-month evaluation was associated with an 82.3% chance of progression.

b) Cystectomy

The disease-specific survival after cystectomy for superficial urothelial carcinoma is higher than that for patients with muscle-invasive disease, but it is not 100%, largely due to understaging. As well, the benefits must be balanced by the morbidity and mortality of the surgery. Amling et al. reported on a large series of 531 patients undergoing cystectomy and found a 2.3% perioperative mortality and a 20.5% rate of complications *(Level 3,* [65]*)*. Similar rates of complications have been reported in other large cystectomy series by Stein et al. and Ghoneim et al. *(Level 3,* [59,66]*)*.

Experience with immediate cystectomy following restaging TURBT for multifocal disease, difficulty of endoscopic access for resection, associated CIS, and visually incomplete resection has been reported. This consensus report is perhaps the only one to attempt to stratify risk as a guide to management with radical cystectomy versus endoscopic resection (**Table 4**). The level of evidence to support these proposed risk categories is at levels 3 and 4.

Table 4. Risk Categories of T1 Tumors

Low-risk T1
Unifocal disease
No associated carcinoma in situ
Tumors in an accessible part of the bladder
Residual disease less than T1 on restaging TURBT
High-risk T1
Multifocal disease
Associated carcinoma in situ
Tumors located in dome and anterior wall of bladder
Residual disease T1 on restaging TURBT

There is significant support for early cystectomy for T1 disease in view of the high late failure rate after initially successful intravesical therapy and the reported good quality of life after cystectomy [67]. However, the proponents of an aggressive initial approach acknowledge that a significant number of

patients will be rendered disease-free with bladder-sparing strategies. Current proposed indications for immediate surgery include younger patients with T1 tumors with at least one additional bad prognostic factor including multifocality, associated CIS, prostatic involvement, and tumor at a site difficult to resect. Bianco et al. performed a multivariate analysis to identify risk factors in patients undergoing cystectomy that influenced cancer-specific survival and found that patients with concomitant CIS and those who had persistent disease after an initial course of BCG therapy were at significant risk *(Level 3,* [68]*)*.

Herr and Sogani retrospectively evaluated 90 patients with high-risk superficial bladder cancer who ultimately underwent cystectomy *(Level 3,* [69]*)*. These authors reported improved 15-year disease-specific survival for those who underwent cystectomy within 2 years after initial BCG treatment. Moreover, those who underwent cystectomy for recurrent superficial disease had an improved outcome over those who underwent surgery for progressive disease. The authors thus concluded that deferring cystectomy until progression to muscle-invasive disease may decrease a patient's overall disease-specific survival. Nevertheless, 217 patients from their original cohort of 307 with high-risk superficial disease never required cystectomy and were thus spared the morbidity of cystectomy.

The presence of metastasis has the most profound impact on survival. A large series of 1054 patients who had undergone radical cystectomy was retrospectively reviewed by Stein et al. *(Level 3,* [59]*)*. The authors identified 401 patients who had pathologically superficial tumors (pT0, pTa, pT1, or pTis). These patients demonstrated improved 5-year recurrence-free survival compared to those with non-organ confined tumors (pT3b, pT4, and those with positive lymph nodes). In fact, no survival differences were observed when comparing superficially noninvasive (pTa, pTis), lamina propria-invasive (pT1), and muscle-invasive tumors (pT2, pT3a), as long as there was no evidence of metastatic disease to the lymph nodes. The overall recurrence-free survivals in those with organ-confined, node-negative disease were 85% and 82% at 5 and 10 years, respectively. A total of 246 patients (24%) had lymph node tumor involvement. The 5- and 10-year recurrence-free survivals for these patients were 35% and 34%, respectively.

c) Patterns of Care

Joudi et al. reported on the practice patterns of urologists in the United States with the management of high grade superficial bladder cancer *(Level 3,* [70]*)*. Of 105 out of 226 urologists responding to a survey, 73% would treat Ta and T1 disease that had already twice failed with BCG with further intravesical therapy. Radical treatment was only selected as an option by 19% of surveyed urologists. In an older study of the practices of British urologists, Bower et al. reported that only 17% would utilize intravesical therapy and 44% would select radical treatment for a typical 60-year-old man with high grade T1 bladder cancer *(Level 3,* [71]*)*. Although presented with different scenarios, the implication is of possible differences in trans-Atlantic approaches to managing high grade superficial disease.

Summary

No prospective, randomized studies have compared immediate cystectomy with conservative therapy of high grade T1 urothelial carcinomas. Patients should be offered both and counseled effectively on the risks and benefits of each, specifically the risks of progression while receiving conservative therapy compared to the morbidity and mortality of cystectomy with a potential survival benefit for those whose pathology is low stage. However, no patient should receive conservative therapy without first undergoing a repeat TURBT to rule-out understaging.

3. Optimal BCG Administration

The original BCG induction therapy regimen was devised by Morales et al. in 1976 [72]. This regimen consisted of 6 weekly doses administered intravesically, as well as a percutaneous dose. Brosman et al. subsequently published their success with BCG without a percutaneous dose in 1982, and that has developed into standard of care treatment [73]. Administration of intravesical BCG before the resection site has begun to reepithelialize may result in systemic absorption and toxicity;induction therapy should be delayed for at least 2 weeks from TURBT [63]. Three months (12 weeks) after the first dose of induction BCG therapy, the patient should be brought back for cystoscopy with possible biopsy (if indicated) and urinary cytology to assess response and then to make a recommendation about the use of maintenance therapy.

The only prospective, randomized study evaluating the efficacy of maintenance BCG was published by Lamm et al. in 2000. Those in the maintenance BCG cohort received BCG once a week for 3 successive

weeks at 3 and 6 months, and then semiannually for up to 3 years *(Level 2,* [63]*)*. With this regimen, recurrence, as well as progression, was significantly reduced. Since only 16% of patients received treatment at each of the 7 scheduled maintenance periods it is anticipated that fewer maintenance treatments are needed. Reduced maintenance schedules, however, have not been adequately evaluated. Current urological practice includes reduction of the dose of BCG to 1/3, 1/10, 1/30, and even 1/100 dose to prevent increasing side effects. Additional studies are evaluating the role of adding interferon. A metanalysis of reports of maintenance therapy also supports its use to not only reduce the risk of recurrence but to reduce the risk of progression [74].

4. BCG FAILURE

a) Scope of the Problem

Although BCG is a highly-effective therapy for bladder cancer, the problem of BCG failure is significant. Indeed, approximately 40% to 50% of patients with T1 disease treated with BCG will either fail to respond or relapse with recurrent disease, usually within the first 5 years (**Table 5**) [38,61,75-96]. The progression rate for these patients during this same time is usually between 15% and 20% but can vary between 7% and 50%, depending on particular circumstances where size, high grade, and concurrent CIS are further adverse prognostic variables and understaging is a recognized problem. Studies employing more intensive BCG retreatment and extended BCG maintenance schedules tend to show better results. The median time to progression generally exceeds 12 months with an estimated progression rate of 5% or less by 6 months [91]. For these patients, radical cystectomy is still the gold standard. However, patients are sometimes reluctant to undergo major surgery for a condition that does not pose an immediate threat to their lives. Furthermore, radical cystectomy is not suitable for a subset of patients with severe comorbidities. A number of alternatives have thus been developed.

b) Defining BCG Failure

In evaluating salvage therapies for use after BCG failure, Herr and Dalbagni aptly noted that comparisons between therapies have been hampered by the lack of standard definitions for BCG failure and BCG-refractory urothelial carcinoma (TCC) [97]. Some series have defined BCG failure after a single induction course of BCG [98,99], others after 2 courses [100]. In addition, the methods of reporting the results have been inconsistent. Most studies have included all patients who received 1 or more courses of BCG [101-103]. Investigators have often combined patients with persistent disease (nonresponders) and patients with recurrent disease after an initial response [98,100], and a few studies have combined patients who were nonresponders to BCG and patients who could not complete BCG therapy because of toxicity (BCG-intolerant) [100,101]. Furthermore, many studies have combined all patients with papillary tumors with and without CIS. Finally, most studies did not indicate the disease-free interval after the last BCG course. These inconsistencies have led to comparisons of outcome in a very heterogeneous population.

In the most general sense, any recurrent disease after initiation of BCG therapy can be referred to as "BCG failure." However, to provide more uniformity in reporting, the following alternative descriptive terms for specific types of BCG failure should be used whenever possible:

BCG-REFRACTORY: Failure to achieve a disease free state by 6 months after initial BCG therapy with either maintenance or re-treatment at 3 months due to either persistent or rapidly recurrent disease [97]. Also includes any progression in stage, grade, or disease extent by 3 months after first cycle of BCG, i.e. *non-improving or worsening disease despite BCG*.

BCG-RESISTANT: Recurrence or persistence of disease at 3 months after induction cycle but of lesser degree, stage, or grade that is no longer present at 6 months from BCG retreatment +/- TUR, i.e. *disease improves then resolves with further BCG*.

BCG-RELAPSING: Recurrence of disease after achieving a disease-free status by 6 months, i.e. *disease resolves after BCG then returns*. Relapse is further defined by time of recurrence as *early* (within 12 months), *intermediate* (12-24 months), or *late* (>24 months). Caution: relapsing disease while on active maintenance (within 3 months) may qualify as BCG-refractory.

BCG-INTOLERANT: Disease recurrence after a less than adequate course of therapy is applied due to a serious adverse event or symptomatic intolerance that mandates discontinuation of further BCG, i.e. *recurrent disease in setting of inadequate BCG treatment due to drug toxicity.*

c) Treatment Options

CYSTECTOMY. There is great variation in practice patterns as to the timing of cystectomy in patients who fail induction BCG therapy. These vary from

immediate surgery after the first follow-up cystoscopy if there is residual disease to delaying until 6 months if a complete response is not achieved. The evidence for this interval is not well-established at the present time. There is general consensus that the prognosis for some patients with aggressive disease can be adversely affected by delayed surgery, but the difficulty is in predicting this risk for the individual. Therefore, alternative bladder-sparing strategies are frequently employed and include the following.

Repeat BCG Treatment. Possibly appropriate for both BCG-resistant and BCG-relapsing disease, the success of a second course of BCG for stage T1 disease has not been extensively reported and only a few published studies have addressed this issue. Cookson et al. reported an initial 69% (59/86) complete response to BCG in patients with any grade T1 disease and then another 70% (19/27) responded to further TUR and BCG including 64% (7/11) with recurrent T1 disease [77]. Similar results were reported by Brake who found a 70% (89/128) enduring response after 1 BCG cycle and 51% (19/37) for the remaining 37 patients (13 of whom had already progressed) [89]. Pansadoro et al. reported that the response rate of 47 patients to TUR plus one cycle of 6 weekly BCG instillations was 53% (25/47) [104]. Of the 22 failures treated with repeat TUR and a second cycle of BCG, 27% (6/22) responded, and, of the remaining 16 patients who received a third cycle of BCG, only 6% (1/16) responded. These results are similar to those reported from BCG studies in non-T1 restricted tumors and illustrate that a second (but not greater) course of BCG may be appropriate in select patients with original stage T1 disease who recur with non-BCG-refractory disease [105]. Unfortunately, there is insufficient data to assess the effectiveness of repeated BCG treatments in refractory patients or those with recurrent T1 disease.

Intravesical Salvage Chemotherapy. Of the various standard intravesical chemotherapeutic agents (thiotepa, doxorubicin, mitomycin C) there is only minimal reported experience with their use in patients failing prior BCG. Malmstrom reported a 19% 3-year disease-free rate among intermediate- and high-risk patients treated with mitomycin C who had failed a prior first induction cycle of BCG [106]. The results for T1 recurrences are unknown. Similarly, there is little data on the newer anthracycline derivative valrubicin. Of 90 valrubicin-treated patients with CIS +/- papillary urothelial carcinoma who had failed at least 2 cycles of prior intravesical therapy, most commonly BCG, only 21% had a complete response at 6 months and 8% by 24 months [107]. Notably, all 5 patients with stage T1 disease (previously resected) plus CIS failed to achieve a complete response. Given these poor results, it appears that current intravesical salvage chemotherapy has little to offer patients failing BCG, especially with stage T1 disease.

Interferon-alpha Immunotherapy. Two observations suggest that IFN–α is unlikely to be of benefit in stage T1 BCG failures. The long-term (> 2 year) success rate of IFN–α monotherapy of BCG failure patients (CIS and/or papillary TCC) is generally under 15% [108]. Furthermore, in a study of IFN–α monotherapy for primary stage T1 disease, IFN–α was found to be no better than placebo at 43 months follow-up [109].

Combination BCG Plus IFN–α. Several single institutional studies have demonstrated that the combination of low-dose BCG plus IFN–α may be useful as a salvage regimen in BCG failures [102, 103,110,111]. With follow-up ranging from 12 to 30 months, disease-free rates were in the range of 50% to 60%, even in patients with recurrent T1 disease. Furthermore, no patient having an expedient cystectomy after BCG plus IFN-α failure had unresectable or metastatic disease. Interim results of an even larger group of 231 BCG failure patients in a multi-institutional study have reported a 42% freedom from disease rate at 24-month median follow-up [112]. The efficacy results for stage T1 patients have not yet been published, but preliminary analysis reveals a similar degree of durable response among an approximate 10% progression rate (M. O'Donnell, personal communication).

Other Alternatives. There is no reliable data published on the use of photodynamic therapy for recurrent stage T1 cancer though it is generally felt to be more effective on surface disease such as CIS [113]. Likewise, although 5-year disease-free survivals of 50% to 60% for radiation therapy for stage T1 disease have been reported, its role as a salvage for BCG failures is not established [114]. Furthermore, for T1 disease alone, local recurrence or progression occurs in approximately 50% [115].

Table 5. Results of TUR and BCG Therapy for Stage T1 Tumors

Author (year)	# of Patients	Tumor Features (n)	Follow-up (months)	% Recur-rence	% Progression	Median Time to Progression (months)	% Cystectomy	Disease-Specific Survival	Comments	Ref
Boccon-Gibod (1989) [75]	47	T1	14-64	36%	21%					75
Eure (1992)	30	T1G3 (24) T1G2 (6)	39	53% 34%	17%				2nd course BCG offered	76
Cookson (1992)	16 44	T1G3 T1G2	59	44% 32%	19% 7%	15 (13-52)			Additional BCG & Maintenance	77
Pfister (1995)	26	T1G3	54	50%	27%		23%	92%		78
Mack (1995)	32	T1G3 (21) T1G2 (11)	57	29%	17%		25%	100%	2nd course BCG + Maintenance no metastasis	79
Pansadoro (1995) Pansadoro (2002)	64 81	T1G3 +/-CIS	42 76	28% 33%	12% 15%	22 (7-58) 16	10% 8%	98% 94%	Novel 4-cycle course BCG 69% Alive with bladder CIS, secondary, Multiple – not significant	80 81
Hurle (1996) Hurle (1999)	51	T1G3 +/-CIS	33 85	45%	14% 18%			86%	+ BCG Maintenance Tumor >3cm; +CIS worse Prognosis 14% extravesical recurrence	82 38
Lebret (1998)	35	T1G3	45	43%	20%		29%	94%	2nd course BCG offered	83
Ayed (1998)	109	T1	48	38%	11%	All < 18mo				84
Baniel (1998)	78	T1G3	56	28%	8%	18 (5-56)				85
Gohji (1999)	45	T1G3	63	36%	4%		9%	100%		86
Geavlete (2000)	247 149	T1G3 T1G2	118	49% 40%					3-year BCG protocol	87
Brake (2000)	44	T1G3	43	27%	16%		9%	89%	2nd course BCG offered 82% Alive with bladder	88
Brake (2000)	74	T1G2	53	26%	13%		3%	94%	2nd course BCG offered 88% Alive with bladder	89
Patard (2001)	50	T1G3	65	52%	22%	~12	30%	86%	2nd course BCG offered	90

Table 5. Results of TUR and BCG Therapy for Stage T1 Tumors (Continued)

Author (year)	# of Patients	Tumor Features (n)	Follow-up (months)	% Recur-rence	% Progression	Median Time to Progression (months)	% Cystectomy	Disease-Specific Survival	Comments	Ref
Pieras (2001)	114	T1G3 1/2 +CIS	6	21%	5%				6-week course BCG All followed with 6 month biopsy	91
Kulkarni (2002)	69	T1G3	?4-5 yr	46%	12%		12%	94%		92
Griffiths (2002)	75	T1G3-CIS	41		49%		29%	59%	6-week course BCG 30% alive with bladder	93
Bogdanovic (2002)	43	T1G3	53	28%	16%	19 (3-43)	12%	95%	2nd course BCG offered	94
Peyromaure (2003)	57	T1G3	53	42%	23%	33.5	14%	88%	2nd course BCG offered SWOG BCG maintenance	95
Shanin (2003)	92	T1G3	64	70%	33%	38	29%	77%	2nd course BCG offered TUR only results similar	61
Cheng (2004)	36	T1G3	24/33/46	44%	25%			86%	Adr & BCG crossover	96

Abbreviations: TUR – transurethral resection; Adr = Adriamycin

Summary

The failure rate of stage T1 disease treated with initial TUR and one cycle of 6 weekly instillations of BCG is significant. The threat of progression remains real but comfortably low enough within the first 6 months of beginning BCG to consider alterna tives to cystectomy for those patients unfit or refusing this standard management option. ***Defining the type of BCG failure may be helpful*** in deciding about conservative treatment strategies where BCG-refractory disease has less of a margin for tolerating treatment-related delays. However, no formal studies studying patterns of BCG failure are yet available for review. The ***current best option for alternative treatment includes re-resection and repeat BCG***, possibly with interferon-alpha as a costimulant. There is no reported evidence of significant efficacy using current intravesical chemotherapy, interferon-alpha monotherapy, photodynamic therapy, or radiation therapy.

5. New Treatment Approaches on the Horizon

a) Technological Advances in Intravesical Chemotherapeutic Drug Delivery

Better delivery of standard intravesical chemotherapeutic agents has the potential to improve outcome in high-risk patients. Currently there are 2 competing technologies undergoing clinical trials that may result in resurgence in the use of intravesical chemotherapy.

Local microwave hyperthermia in conjunction with mitomycin C (20mg/50mL) was compared in a multicenter randomized trial to intravesical mitomycin C alone in 83 patients [116]. Hyperthermia was delivered at a temperature of 42°C for at least 40 minutes. At a minimum follow-up of 24 months, there was a statistically significant reduction in recurrences between the 2 groups (17.1% for chemothermotherapy vs. 57.5% for chemotherapy alone). This modality has also been used in treating patients with high grade superficial bladder cancer (Ta or T1, G3) as a prophylactic (40 mg mitomycin C) or ablative (80 mg mitomycin C) protocol by Gofrit et al. [117] In 24 patients administered the prophylactic protocol, 62.5% were recurrence-free after a mean follow-up of 35.3 months. The ablative protocol was administered to 28 patients with complete ablation of the tumor in 75% and a recurrence free rate of 80.9% at a mean follow-up of 20 months.

Electromotive intravesical mitomycin C (eMMC) has been proposed to improve drug delivery across biological membranes with increased accumulation in bladder tissue. Di Stasi et al. randomized 3 groups of patients with CIS to 40 mg eMMC instillation with 20 mA electric current for 30 minutes, 40 mg passive mitomycin C with a dwell time of 60 minutes or 81 mg BCG with a dwell time of 120 minutes [118]. Patients were scheduled for an initial 6 weekly treatments, a further 6 weekly treatments for non-responders, and a follow-up 10 monthly treatments for responders. There was a statistically significant superior complete response rate at 6 months for eMMC (58%) compared to passive mitomycin C (31%). The response rate of eMMC approached that of BCG (64%). Peak plasma mitomycin C was significantly higher following eMMC than after passive mitomycin C (43 vs. 8 ng/mL), supporting the hypothesis that electromotive MMC increases tissue levels.

b) Sequential Drug Therapy

Alternative approaches have been investigated to improve the efficacy of intravesical therapy. Several investigators have explored the use of BCG combined with chemotherapy. The rationale for giving chemotherapy prior to BCG is to induce sloughing of the urothelium, allowing BCG to better interact with fibronectin and initiating an immune response. However, BCG *immediately* after epirubicin is not well-tolerated. Erol reported that over a third of patients discontinued treatment due to severe cystitis [119].

Rintala et al. reported a novel approach of alternating mitomycin C and BCG for prophylaxis of superficial papillary bladder cancer [120]. After an induction course of mitomycin C, 188 patients with recurring Ta and T1 tumors were randomly assigned to maintenance mitomycin C versus alternating mitomycin C and BCG instillations (Pasteur Strain). The patients were treated for 2 years, and the mean follow-up was 34 months. Alternating mitomycin C and BCG was equal in efficacy to mitomycin C and was clearly superior to transurethral resection alone. For CIS, Rintala et al. reported that alternating BCG with mitomycin C was superior to mitomycin C alone [121]. The superiority of BCG and mitomycin C could, however, be attributed to the presence of BCG in one arm and not the other rather than the alternating mode of delivery. More importantly, no significant side effects developed in the alternating group. A different randomized prospective trial of sequential BCG and eMMC was reported by DiStasi et al. [122]. Compared to 6 weekly BCG instillations fol-

lowed by 1 year of monthly maintenance, a program of BCG, BCG, then eMMC times 3 for weekly induction and eMMC, eMMC, then BCG times 3 for monthly maintenance resulted in a statistically significant decrease in recurrence at 5 to 6 years from 47% to 28%. In contrast, Kaasinen reported that alternating BCG with interferon-alpha after an induction course of mitomycin C was inferior to BCG after mitomycin C [123].

A randomized phase 3 trial of intermediate- and high-risk superficial bladder cancer comparing sequential mitomycin C for 4 weeks followed by weekly BCG versus weekly mitomycin C showed no difference in recurrence or progression [124]. BCG alternating with epirubicin was not superior to BCG alone, but had fewer side effects [125].

BCG monotherapy was superior to an induction course of mitomycin C followed by alternating mitomycin C and BCG instillations in patients with Tis disease [126]. The recurrence-free survival and progression-free survival were also superior in the patients treated with BCG only.

Serrata et al. has reported using adjuvant sequential mitomycin C and epirubicin in 91 of 137 patients with T1G3 bladder cancer after initial TUR [127]. With close to 20 years of follow-up, the overall recurrence rate was 51%, but significantly less in the sequential chemotherapy protocol. The overall progression rate of 9.5% was no different. Only 7% of patients died of bladder cancer, and the cystectomy rate was also 7%.

As yet it is not possible to determine whether mixed chemotherapy or chemoimmunotherapy programs will dependably result in improved outcomes.

c) New Chemotherapeutic Drugs for Intravesical Use

Gemcitabine (2',2'-difluoro-2'-deoxycytidine) is a novel deoxycytidine analog with a broad spectrum of antitumor activity. Gemcitabine has a molecular weight of 299.66 kD, and, after intracellular activation, the active metabolite is incorporated into DNA, resulting in inhibition of further DNA synthesis. Gemcitabine may also inhibit ribonucleotide reductase and cytidine deaminase as part of its cytotoxic activity [128]. Unlike most other chemotherapeutic agents, gemcitabine has no vesicant (tissue-irritating) properties, suggesting it may be better tolerated in the bladder.

Gemcitabine is highly effective (overall response rates ranging from 22.5%-28%) and well tolerated as both first- and second-line, single-agent therapy for the treatment of metastatic urothelial carcinoma [129,130]. Studies have reported a low incidence of systemic side effects. A randomized, multicenter, phase 3 study demonstrated that patients with unresectable or metastatic disease treated with gemcitabine plus cisplatin (GC) had a similar survival to patients treated with MVAC (methotrexate, vinblastine, doxorubicin [Adriamycin], and cisplatin), and GC had a better safety profile and tolerability [131]. Based on its excellent clinical activity, patient tolerability, and chemical characteristics, gemcitabine represents a logical candidate for intravesical therapy.

Dalbagni et al. reported a phase 1 study of intravesical gemcitabine twice a week for 3 weeks, followed by a second cycle after a week of rest, in a heavily pretreated population with BCG-refractory urothelial carcinoma. This study demonstrated that intravesical gemcitabine was well tolerated with minimal bladder irritation and acceptable myelosuppression. Serum levels of gemcitabine were undetectable at concentrations of 5 mg/mL, 10 mg/mL, and 15 mg/mL. However, serum gemcitabine was detected at a concentration of 20 mg/mL. Complete response, as defined by a negative posttreatment cystoscopy including a biopsy of the urothelium and a negative cytology, was achieved in 7 of 18 patients (39%) [101]. This was followed by a phase 2 study of patients with BCG-refractory urothelial carcinoma to determine the efficacy of gemcitabine as an intravesical agent. Twenty-eight patients completed therapy, and 16 achieved a complete response [132].

Laufer et al. reported a phase 1 study of weekly intravesical gemcitabine in 15 patients who received prior intravesical therapy. Serum gemcitabine levels were undetected at concentrations of 5 mg/mL, 10 mg/mL, 15 mg/mL, and 20 mg/mL, while low concentrations were present in all patients receiving 40 mg/mL. However, the metabolite dFdU (2'2'-difluorodeoxyuridine) was detectable in the plasma of patients receiving gemcitabine at concentrations of 15 mg/mL or higher, implying minimal absorption of gemcitabine at lower doses. The authors concluded that intravesical gemcitabine is well-tolerated, with minimal toxicity. Furthermore, no evidence of recurrence at 12 weeks was noted in 9 of 13 evaluable patients [133].

In a recent phase 1 study, De Berardinis reported no systemic detection of gemcitabine at a concentration of 40 mg/mL. However, the inactive metabolite was detected in plasma. They were able to demonstrate

activity of deoxycytidine kinase in tissue samples, an enzyme that produces 2',2'-difluoro-deoxycytidine triphosphate, the active metabolite of gemcitabine [134]. Palou et al. similarly showed excellent tolerability and little absorption with a single dose of gemcitabine immediately post-TUR [135].

The chemoablative activity of intravesical gemcitabine was recently reported in a marker lesion study in patients with papillary Ta or T1 grade 1 or 2 disease [136]. With a sample size of 39 patients, 2000 mg of gemcitabine in 50 mL saline given weekly for 6 weeks resulted in complete ablation of 56% of the marker lesions.

All reports published thus far confirm the low systemic absorption of gemcitabine, the good tolerability with minimal local and systemic toxicity, and, more importantly, its efficacy as an intravesical agent, even in heavily pretreated patients. This agent warrants further investigation in a large cohort of patients, especially to determine the long-term durability.

Another potential chemotherapeutic drug that is still in the intravesical formulation and testing stage is paclitaxel. Its high lipid solubility creates logistic difficulties for efficient intravesical delivery. However, use of dimethyl sulfoxide or bio-adhesive polymer microspheres may circumvent this difficulty [137,138]. In vitro experiments have confirmed that even a brief 2-hour exposure of bladder cancer cells has significant anti-cancer potency [139].

d) New Immunostimulants

While BCG retains its role as the most effective intravesical agent, the liability of a live organism capable of causing a life-threatening septic infection has encouraged a search for equally effective but less toxic alternatives. The most well-developed new immunostimulant on the horizon is Mycobacterial Cell Wall-DNA Extract (MCC). Prepared from *Mycobacterium phlei*, the compound contains a mixture of immunostimulatory mycobacterial DNA attached to antigenic cell wall. In the recently released phase 2 trial results, either a 4 mg or 8 mg weekly dose for 6 weeks was well-tolerated with a complete response rate in patients with CIS +/- T1G3 tumors of between 27% and 38% at 12 months [140]. Further trials are in preparation.

e) The Farther Frontier

Efforts to develop gene therapy approaches remain at the early stages, though proof-of-principle has been established in animal models and limited phase 1 clinical trials [141,142]. Cell-based immunotherapy is also under study with delivery of activated tumoricidal macrophages into the bladder [143]. Studies with agents that target specific growth factor-related signaling pathways are also underway [144].

Summary

There are several developments underway for superficial bladder cancer therapy that are likely to emerge as practical alternatives in the near future. Among the most developed are the new technology machines using microwave or electrical energy to facilitate chemotherapeutic drug transport into the bladder wall. Among new chemotherapeutic drugs, intravesical gemcitabine is showing promising activity while taxane formulations lag a bit behind. The prospect for combined or sequential chemo or chemoimmunotherapy remains enticing but underdeveloped. New immunostimulants will continue to be sought as alternatives to BCG. Further out on the horizon are more novel approaches including gene therapy, active cell-based immune therapy, and signal targeting small molecule drugs.

RECOMMENDATIONS

I. DIAGNOSIS AND STAGING

1. Technique of Resection

1. A thorough endoscopic evaluation of patients with documented or suspected bladder cancer should be performed at the time of TURBT (*Grade C).*

2. A standardized diagram should be used to document individual tumors and biopsy sites as well as findings of the examination under anesthesia *(Grade C).*

3. Resection should result in the presence of muscle in the specimen for adequate staging *(Grade C).*

4. The use of continuous flow resectoscopes should be further evaluated and may provide advantages *(Grade C).*

5. The use of video endoscopy should be further evaluated and may provide advantages *(Grade C).*

6. All visible tumors should be completely resected *(Grade C).*

2. Role of Random and Directed Biopsies

1. Multiple random biopsies of normal-appearing urothelium should not be taken in patients who undergo TUR for low-risk superficial bladder cancer (primary small, single or recurrent single tumors) *(Grade C).*

2. Multiple random biopsies of normal-appearing urothelium are always indicated in high-risk tumors (high grade T1, multiple tumors, recurrent multiple tumors, or CIS) *(Grade C).*

3. The role of multiple random biopsies of normal-appearing urothelium in intermediate-risk tumors remains controversial *(Grade C).*

3. Role of Second Resection

1. A second TURBT should be performed in all patients with a high grade Ta lesion or any T1 lesion *(Grade B).*

2. The suggested optimal timing of repeat TURBT is within 1 to 4 weeks after the first resection *(Grade C).*

4. Substaging of T1 Pathology

• Pathologists are not agreed on the validity and utility of substaging T1 tumors by the depth of invasion in the lamina propria. This stratification of T1 tumors cannot yet be supported *(Grade C).*

5. What Are the Important Prognostic Factors?

1. Though no factor can accurately predict which patients will have recurrence or progression of urothelial carcinoma, the presence of higher grade lesions, multiple and larger lesions, concomitant CIS, and prostatic urothelial carcinoma all may increase the risk *(Grade C).*

2. A number of biological molecular markers may be useful as prognostic factors for T1 bladder cancer *(Grade C).*

6. Upper Tract, Prostatic, and Urethral Involvement

1. Periodic lifelong observation of the upper urinary tract and prostate should be performed in all patients with CIS, high grade (G3) superficial urothelial carcinoma, or intravesical chemotherapy failure *(Grade C).*

2. Examination of the upper urinary tract and prostate is recommended in follow-up of all patients with superficial bladder cancer with persistently positive urine cytology in the absence of a bladder tumor *(Grade C).*

3. Radical therapy at an early stage for patients with relapse in the upper urinary tract or prostate may result in a better prognosis *(Grade C).*

II. TREATMENT

1. Role of Immediate Adjuvant Intravesical Therapy

• A single dose of chemotherapy should be given at the time of TURBT (ideally within 6 hours but no more than 24 hours) whether or not additional therapy is planned, as long as no bladder perforation has occurred *(Grade A).*

2. Initial Bladder-sparing Approach versus Cystectomy

1. Cystectomy and intravesical BCG therapy are both acceptable primary therapies for high grade T1 disease and both options should be discussed. Patients need to be made aware of the lifetime risks of recurrence and progression of their tumors as well as the morbidity, mortality, and expected survival with cystectomy *(Grade C).*

2. Initial bladder conservation for T1 disease with intravesical therapy should not be initiated

without excluding muscle invasion by performing a repeat TURBT *(Grade C).*

3. An ideal candidate for conservative treatment of T1 bladder cancer would be one with solitary or at least completely resectable tumor, a negative upper tract evaluation, and no evidence of invasive disease in the prostatic urethra *(Grade D).* Initial intravesical BCG therapy should be considered for patients with completely resected primary and recurrent T1 tumors based on a negative re-resection who can tolerate BCG and are satisfied with their bladder function *(Grade C).*

4. Patients with recurrent T1 tumors should be considered for cystectomy if they have had 2 prior induction cycles of BCG *(Grade D).*

3. Optimal BCG Administration

1. Primary intravesical therapy should be induction BCG immunotherapy with 6 weekly instillations beginning no sooner than 2 weeks after tumor resection *(Grade B).*

2. Cystoscopy with urinary cytology and possible biopsy should be done at 3 months to confirm the absence of recurrence or progression *(Grade C).*

3. Maintenance therapy should be given. *(Grade A)* While comparison studies have not been done, the SWOG regimen of 3 weekly instillations at 3, 6, and every 6 months for 3 years is recommended *(Grade A)* .

4. BCG Failure

1. Patients failing BCG should ideally be subclassified into definable groups such as BCG-refractory, BCG-resistant, BCG-relapsing, and BCG-intolerant *(Grade D).*

2. Patients failing induction BCG therapy who recur with high grade disease at 6 months should be offered cystectomy *(Grade C).*

3. For patients failing initial induction BCG therapy who are unfit, refuse cystectomy, or have low or intermediate grade disease, an additional course of a BCG-containing intravesical therapy is the preferred option *(Grade C).*

4. Cystectomy is indicated if salvage therapy fails and it should be performed in a timely manner *(Grade C).*

5. New Treatment Approaches on the Horizon

• Further study of therapies for failure of intravesical therapy is to be encouraged *(Grade D).*

REFERENCES

1. Brausi M., Collette L., Kurth KH, van der Meijden AP et al.: Variability in recurrence rate at firts follow-up Cystoscopy after TUR in stage TaT1 TCC of the bladder: a combined analysis of 7 EORTC studies. Eur Urol 2002;41:523-31
2. Fujimoto N., Haradas S., Terado M., Sato H. et al. Multiple biopsies of normal looking urothelium in patients with superficial bladder cancer: are they necessary ? Int. J.Urol 2003;10: 631-5
3. van der Meijden AP, Oostelinck W, Brausi M, Kurth KH et al.. Significance of bladder biopsies in Ta-T1 bladder tumors: a report from EORTC GU Group. Eur.Urol 1999; 35: 267-71
4. May F, Treiber V, Hartung R, Schwaibald H. Significance of random bladder biopsies in superficial bladder cancer Eur Urol 2003; 44: 47-50
5. Stein JP: Indications for early cystectomy. Sem Urol Oncol, 18: 289-95, 2000
6. Brauers A, Buettner R, Jakse G. Second resection and prognosis of primary high risk superficial bladder cancer: is cystectomy often too early? *J Urol.* Mar 2001;165(3):808-810.
7. Dutta SC, Smith JA, Jr., Shappell SB, Coffey CS, Chang SS, Cookson MS. Clinical under staging of high risk nonmuscle invasive urothelial carcinoma treated with radical cystectomy. *J Urol.* Aug 2001;166(2):490-493.
8. Zurkirchen MA, Sulser T, Gaspert A, Hauri D. Second transurethral resection of superficial transitional cell carcinoma of the bladder: a must even for experienced urologists. *Urol Int.* 2004;72(2):99-102.
9. Grimm MO, Steinhoff C, Simon X, Spiegelhalder P, Ackermann R, Vogeli TA. Effect of routine repeat transurethral resection for superficial bladder cancer: a long-term observational study. *J Urol.* Aug 2003;170(2 Pt 1):433-437.
10. Schips L, Augustin H, Zigeuner RE, Galle G, Habermann H, Trummer H, Pummer K, Hubner G. Is repeated transurethral resection justified in patients with newly diagnosed superficial bladder cancer? *Urology*. Feb 2002;59(2):220-223.
11. May M, Nitzke T, Helke C, Vogler H and Hoschke B. Significance of the time between muscle invasion and radical cystectomy with regard to the prognosis of transitional cell carcinoma of the urothelium in the bladder. Scand J Urol Nephrol, 2004;38:231-5.
12. Herr HW. The value of a second transurethral resection in evaluating patients with bladder tumors. *J Urol.* Jul 1999;162(1):74-76.
13. Holmang S, Hedelin H, Anderstrom C, Holmberg E, Johansson SL. The importance of the depth of invasion in stage T1 bladder carcinoma: a prospective cohort study. *J Urol.* Mar 1997;157(3):800-803; discussion 804.
14. Hasui Y, Osada Y, Kitada S, Nishi S. Significance of invasion to the muscularis mucosae on the progression of superficial bladder cancer. *Urology.* Jun 1994;43(6):782-786.
15. Angulo JC, Lopez JI, Grignon DJ, Sanchez-Chapado M. Muscularis mucosa differentiates two populations with different prognosis in stage T1 bladder cancer. *Urology.* Jan 1995;45(1):47-53.
16. Smits G, Schaafsma E, Kiemeney L, Caris C, Debruyne F, Witjes JA. Microstaging of pT1 transitional cell carcinoma of the bladder: identification of subgroups with distinct risks of progression. *Urology.* Dec 1998;52(6):1009-1013; discussion 1013-1004.
17. Cheng L, Weaver AL, Neumann RM, Scherer BG, Bostwick DG. Substaging of T1 bladder carcinoma based on the depth of invasion as measured by micrometer: A new proposal. *Cancer.* Sep 15 1999;86(6):1035-1043.
18. Bernardini S, Billerey C, Martin M, Adessi GL, Wallerand H, Bittard H. The predictive value of muscularis mucosae invasion and p53 over expression on progression of stage T1 bladder carcinoma. *J Urol.* Jan 2001;165(1):42-46; discussion 46.
19. Kondylis FI, Demirci S, Ladaga L, Kolm P, Schellhammer PF. Outcomes after intravesical bacillus Calmette-Guerin are not affected by substaging of high grade T1 transitional cell carcinoma. *J Urol.* Apr 2000;163(4):1120-1123.
20. Millan-Rodriguez F, Chechile-Toniolo G, Salvador-Bayarri J, Palou J and Vicente-Rodriguez J. Multivariate analysis of the prognostic factors of primary superficial bladder cancer. J. Urol**.** 163 **(**2000), 73–78.
21. Solsona E, Iborra I, Dumont R, Rubio-Briones J, Casanova J and Almenar S. The 3-month clinical response to intravesical therapy as a predictive factor for progression in patients with high risk superficial bladder cancer. J. Urol. 164 (2000), 685–689.
22. Herr HW, Badalament RA, Amato DA, Laudone VP, Fair WR and Whitmore WF Jr. Superficial bladder cancer treated with bacillus Calmette-Guerin: a multivariate analysis of factors affecting tumor progression. J Urol. 1989 Jan;141(1):22-9.
23. Sgambato A, Migaldi M, Faraglia B, De Aloysio G, Ferrari P, Ardito R. De Gaetani C, Capelli G, Cittadini A and Trentini GP. Cyclin D1 expression in papillary superficial bladder cancer: its association with other cell cycle-associated proteins. Cell proliferation and clinical outcome. Int. J. Cancer 97 (2002), 671–678
24. Pfister C, Flaman JM, Dunet F, Grise P and Frebourg T. p53 mutations in bladder tumors inactivate the transactivation of the p21 and Bax genes, and have a predictive value for the clinical outcome after bacillus Calmette-Guerin therapy. J Urol. 1999 Jul;162(1):69-73.
25. Lebret T, Becette V, Barbagelatta M, Herve JM, Gaudez F, Barre P, Lugagne PM and Botto H. Correlation between p53 over expression and response to bacillus Calmette-Guerin therapy in a high risk select population of patients with T1G3 bladder cancer. J Urol. 1998 Mar;159(3):788-91.
26. Saint F, Le Frere Belda MA, Quintela R, Hoznek A, Patard JJ, Bellot J, Popov Z, Zafrani ES, Abbou CC, Chopin DK, de Medina SG. Pretreatment p53 nuclear overexpression as a prognostic marker in superficial bladder cancer treated with Bacillus Calmette-Guerin (BCG). Eur Urol. 2004 Apr;45(4):475-82.
27. Lacombe L, Dalbagni G, Zhang ZF, Cordon-Cardo C, Fair WR, Herr HW and Reuter VE.Overexpression of p53 protein in a high-risk population of patients with superficial bladder cancer before and after bacillus Calmette-Guerin therapy: correlation to clinical outcome. J Clin Oncol. 1996 Oct;14(10):2646-52.
28. Llopis J, Alcaraz A, Ribal MJ, Sole M, Ventura PJ, Barranco MA, Rodriguez A, Corral JM and Carretero P. p53 expression predicts progression and poor survival in T1 bladder tumours. Eur Urol. 2000 Jun;37(6):644-53.
29. Steiner G, Bierhoff E, Schmidt D, Leissner J, Wolf HK and Albers P. p53 immunoreactivity in biopsy specimens of T1G3 transitional cell carcinoma of the bladder—a helpful parameter in guiding the decision for or against cystectomy? Eur J Cancer. 2000 Mar;36(5):610-4.
30. Jahnson S and Karlsson MG**.** Predictive value of p53 and pRb immunostaining in locally advanced bladder cancer treated with cystectomy. J Urol. 1998 Oct;160(4):1291-6.
31. Lopez-Beltran A, Luque RJ, Alvarez-Kindelan J, Quintero A, Merlo F, Carrasco JC, Requena MJ and Montironi R. Prognostic Factors in Stage T1 Grade 3 Bladder Cancer Survival: The Role of G1-S Modulators (p53, p21Waf1, p27kip1, Cyclin D1, and Cyclin D3) and Proliferation Index (ki67-MIB1). Eur Urol. 2004 May;45(5):606-12.
32. Herr HW, Cookson MS and Soloway SM. Upper tract tumors in patients with primary bladder cancer followed for 15 years. J Urol. 1996 Oct;156(4):1286-7.

33. Miller EB, Eure GR and Schellhammer PF. Upper tract transitional cell carcinoma following treatment of superficial bladder cancer with BCG. Urology. 1993 Jul;42(1):26-30.

34. Schwalb DM, Herr HW and Fair WR. The management of clinically unconfirmed positive urinary cytology. J Urol. 1993 Dec;150(6):1751-6.

35. Hurle R, Losa A, Manzetti A and Lembo A. Upper urinary tract tumors developing after treatment of superficial bladder cancer: 7-year follow-up of 591 consecutive patients. Urology. 1999 Jun;53(6):1144-8.

36. Schwartz CB, Bekirov H and Melman A**.** Urothelial tumors of upper tract following treatment of primary bladder transitional cell carcinoma.Urology. 1992 Dec;40(6):509-11.

37. Herr HW and Whitmore WF Jr**.** Ureteral carcinoma in situ after successful intravesical therapy for superficial bladder tumors: incidence, possible pathogenesis and management. J Urol. 1987 Aug;138(2):292-4.

38. Hurle R, Losa A, Manzetti A, Lembo A**.** Intravesical bacille Calmette-Guerin in Stage T1 grade 3 bladder cancer therapy: a 7-year follow-up. Urology. 1999 Aug;54(2):258-63.

39. Amar AD and Das S. Upper urinary tract transitional cell carcinoma in patients with bladder carcinoma and associated vesicoureteral reflux. J Urol. 1985 Mar;133(3):468-71.

40. De Torres Mateos JA, Banus Gassol JM, Palou Redorta J and Morote Robles J. Vesicorenal reflux and upper urinary tract transitional cell carcinoma after transurethral resection of recurrent superficial bladder carcinoma. J Urol. 1987 Jul;138(1):49-51

41. Solsona E, Iborra I, Ricos JV, Dumont R, Casanova JL and Calabuig C. Upper urinary tract involvement in patients with bladder carcinoma in situ (Tis): its impact on management. Urology. 1997 Mar;49(3):347-52.

42. Herr HW. Extravesical tumor relapse in patients with superficial bladder tumors. *J. Clin. Oncol.* 1998; 16: 1099-102.

43. Schellhammer PF, Ladaga LE and Moriarty RP. Intravesical bacillus Calmette-Guerin for treatment of superficial transitional cell carcinoma of the prostatic urethra in association with carcinoma of the bladder. J. Urol. 1995; **153**: 53-6.

44. Catalona WJ, Hudson MA, Gillen DP, Andriole GL and Ratliff TL. Risks and benefits of repeated courses of intravesical bacillus Calmette-Guerin therapy for superficial bladder cancer. J. Urol. 1987; 137: 220-24.

45. Sakamoto N, Tsuneyoshi M, Naito S, Kumazawa J. An adequate sampling of the prostate to identify prostatic involvement by urothelial carcinoma in bladder cancer patients. J. Urol. 1993; **149**: 318-21.

46. Herr HW and Donat SM. Prostatic tumor relapse in patients with superficial bladder tumors: 15-year outcome. J Urol. 1999 Jun; 161(6):1854-7.

47. Tolley DA, Parmar MK, Grigor KM, et al. The effect of intravesical mitomycin C on recurrence of newly diagnosed superficial bladder cancer: a further report with 7 years of follow up. *J Urol.* Apr 1996;155(4):1233-1238.

48. Oosterlinck W, Kurth KH, Schroder F, Bultinck J, Hammond B, Sylvester R. A prospective European Organization for Research and Treatment of Cancer Genitourinary Group randomized trial comparing transurethral resection followed by a single intravesical instillation of epirubicin or water in single stage Ta, T1 papillary carcinoma of the bladder. *J Urol.* Apr 1993;149(4):749-752.

49. Bouffioux C, Kurth KH, Bono A, et al. Intravesical adjuvant chemotherapy for superficial transitional cell bladder carcinoma: results of 2 European Organization for Research and Treatment of Cancer randomized trials with mitomycin C and doxorubicin comparing early versus delayed instillations and short-term versus long-term treatment. European Organization for Research and Treatment of Cancer Genitourinary Group. *J Urol.* Mar 1995;153(3 Pt 2):934-941.

50. Solsona E, Iborra I, Ricos JV, Monros JL, Casanova J, Dumont R. Effectiveness of a single immediate mitomycin C instillation in patients with low risk superficial bladder cancer: short and long-term followup. *J Urol.* Apr 1999;161(4):1120-1123.

51. Krege S, Giani G, Meyer R, Otto T, Rubben H. A randomized multicenter trial of adjuvant therapy in superficial bladder cancer: transurethral resection only versus transurethral resection plus mitomycin C versus transurethral resection plus bacillus Calmette-Guerin. Participating Clinics. *J Urol.* Sep 1996; 156 (3):962-966.

52. Kurth K, Tunn U, Ay R, et al. Adjuvant chemotherapy for superficial transitional cell bladder carcinoma: long-term results of a European Organization for Research and Treatment of Cancer randomized trial comparing doxorubicin, ethoglucid and transurethral resection alone. *J Urol.* Aug 1997;158(2):378-384.

53. Sylvester RJ, Oosterlinck W, van der Meijden AP. A single immediate postoperative instillation of chemotherapy decreases the risk of recurrence in patients with stage Ta T1 bladder cancer: a meta-analysis of published results of randomized clinical trials. *J Urol*. 2004 Jun;171(6 Pt 1):2186-90.

54. Heney NM, Ahmed S, Flanagan MJ, Frable W, Corder MP, Hafermann MD and Hawkins IR. Superficial bladder cancer: progression and recurrence. J Urol, 1983;130:1083-6.

55. Pauwels RP, Schapers RF, Smeets AW, Debruyne FM and Geraedts JP. Grading in superficial bladder cancer: (1). Morphological criteria. Br J Urol, 1988;61:129-34

56. Abel PD, Hall RR and Williams G. Should pT1 transitional cell cancers of the bladder be classified as superficial? Br J Urol, 1988;62:235-9.

57. Henningsohn L, Wijkstrom H,Dickan PW,Bergmark K,Steineck G. Distressful symptoms after radical cystectomy with urinary diversion for urinary bladder cancer: A Swedish population-based study. Eur Urol 2001;40:151-162

58. Dalbagni G, Genega E, Hashibe M, Zhang ZF, Russo P, Herr H, Reuter V. Cystectomy for bladder cancer: a contemporary series. J Urol. 2001 Apr;165(4):1111-6.

59. Stein JP, Lieskovsky G, Cote R, Groshen S, Feng AC, Boyd S, Skinner E, Bochner B, Thangathurai D, Mikhail M *et al.*: Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. J Clin Oncol, 2001;19: 666-75.

60. Cookson MS, Herr HW, Zhang ZF, Soloway S, Sogani PC, Fair WR. The treated natural history of high risk superficial bladder cancer: 15-year outcome. J Urol, 1997;158:62-7.

61. Shahin O, Thalmann GN, Rentsch C, Mazzucchelli L, Studer UE. A retrospective analysis of 153 patients treated with or without intravesical bacillus Calmette-Guerin for primary stage T1 grade 3 bladder cancer: recurrence, progression and survival. J Urol, 2003;169:96-100.

62. Lamm DL: Efficacy and safety of bacille Calmette-Guerin immunotherapy in superficial bladder cancer. *Clin Infect Dis*.**31** Suppl 3:S86-90, 2000.

63. Lamm DL, Blumenstein BA, Crissman JD, Montie JE, Gottesman JE, Lowe BA, Sarosdy MF, Bohl RD, Grossman HB, Beck TM, Leimert JT, Crawford ED. Maintenance bacillus Calmette-Guerin immunotherapy for recurrent TA, T1 and carcinoma in situ transitional cell carcinoma of the bladder: a randomized Southwest Oncology Group Study. J Urol, 2000;163:1124-9.

64. Bono AV, Benvenuti C, Damiano G, Lovisolo J. Results of transurethral resection and intravesical doxorubicin prophylaxis in patients with T1G3 bladder cancer. Urology,1994;44:329-34.

65. Amling CL, Thrasher JB, Frazier HA, Dodge RK, Robertson JE and Paulson DF: Radical cystectomy for stages Ta, Tis and T1 transitional cell carcinoma of the bladder. J Urol, 1994;151:31-5.

66. Ghoneim MA, el-Mekresh MM, el-Baz MA, el-Attar IA and Ashamallah A: Radical cystectomy for carcinoma of the bladder: critical evaluation of the results in 1,026 cases. J Urol, 1997;158:393-9.

67. Malavaud B. T1G3 bladder tumours: the case for radical cystectomy. Eur Urol 2004;45:406-10.

68. Bianco FJ Jr, Justa D, Grignon DJ, Sakr WA, Pontes JE and Wood DP Jr. Management of clinical T1 bladder transitional cell carcinoma by radical cystectomy. Urol Oncol 2004;22:290-4.

69. Herr HW and Sogani PC. Does early cystectomy improve the survival of patients with high risk superficial bladder tumors? J Urol, 2001;166:1296-9.

70. Joudi FN, Smith BJ, O'Donnell MA and Konety BR. Contemporary management of superficial bladder cancer in the United States: a pattern of care analysis. Urology, 2003;62:1083-8.

71. Bower M, Ma R, Savage P, Abel P and Waxman J. British urological surgery practice: 2. Renal, bladder and testis cancer. Br J Urol, 1998;81:513-7.

72. Morales A, Eidinger D, Bruce AW. Intracavitary Bacillus Calmette-Guerin in the treatment of superficial bladder tumors. J Urol. 1976 Aug;116(2):180-3.

73. Brosman SA. Experience with bacillus Calmette-Guerin in patients with superficial bladder carcinoma. J Urol. 1982 Jul;128(1):27-30.

74. Sylvester RJ, van der Meijden AP, Lamm DL: Intravesical bacillus Calmette-Guerin reduces the risk of progression in patients with superficial bladder cancer: a meta-analysis of the published results of randomized clinical trials. *J Urol.* **168**(5):1964-70, 2002.

75. Boccon-Gibod L, Leleu C, Herve JM et al. Bladder tumors invading the lamina propria (stage T1): influence of endovesical BCG therapy on recurrence and progression. Prg Clin Biol Res 1989; 310:161-9

76. Eure GR, Cundiff MR, Schellhammer PF. Bacillus Calmette-Guerin therapy for high risk stage T1 superficial bladder cancer. J Urol 1992; 147:376-9.

77. Cookson MS, Sorosdy MF. Management of stage T1 superficial bladder cancer with intravesical bacillus Calmette-Guerin therapy. J Urol 1992; 148:797-801.

78. Pfister C, Lande P, Herve JM, et al. T1G3 bladder tumors: the respective role of BCG and cystectomy. Prog Urol 1995; 5:231-7.

79. Mack D, Frick J. Five-year results of a phase II study with low-dose bacille Calmette-Guerin therapy in high-risk superficial bladder cancer. Urology 1995; 45:958-61.

80. Pansadoro V, Emiliozzi P, Defidio L, et al. Bacillus Calmette-Guerin in the treatment of stage T1 grade 3 transitional cell carcinoma of the bladder: long-term results. J Urol 1995; 154:2054-8.

81. Pansadoro V, Emiliozzi P, De Paula F, et al. Long-term follow-up of G3T1 transitional cell carcinoma of the bladder treated with intravesical bacille Calmette-Guerin: 18-year experience. Urology 2002; 59:227-31.

82. Hurle R, Losa A, Ranieri A, et al. Low dose Pasteur bacillus Calmette-Guerin regimen in stage T1, grade 3 bladder cancer therapy. J Urol 1996; 156:1602-5.

83. Lebret T, Gaudez F, Herve JM, et al. Low-dose BCG instillations in the treatment of stage T1 grade 3 bladder tumours: recurrence, progression and success. Eur Urol 1998; 34:67-72.

84. Ayed M, Ben Hassine L, Ben Slama R, et al. Results of BCG in the treatment of pTa and pT1 bladder tumors. Evaluation of a long protocol using 75 mg of Pasteur strain BCG. Prog Urol 1998; 8:206-10.

85. Baniel J, Grauss D, Engelstein D, Stella A. Intravesical bacillus Calmette-Guerin treatment for stage T1 grade 3 transitional cell carcinoma of the bladder. Urology 1998; 52:785-9.

86. Gohji K, Nomi M, Okamto M, et al. Conservative therapy for stage T1b, grade 3 transitional cell carcinoma of the bladder. Urology 1999; 53:308-13.

87. Geavlete P, Georgescu D, Arabagiu I. Topical immunotherapy with BCG in the adjuvant treatment of superficial bladder tumors-15-year experience. Chirurgia (Bucur) 2000; 95:157-68.

88. Brake M, Loertzer H, Horsch R, Keller H. Recurrence and progression of stage T1, grade 3 transitional cell carcinoma of the bladder following intravesical immunotherapy with bacillus Calmette-Guerin. J Urol 2000; 163:1697-701.

89. Brake M, Loertzer H, Horsch R, Keller H.Long-term results of intravesical bacillus Calmette-Guerin therapy for stage T1 superficial bladder cancer. Urology 2000; 55:673-8.

90. Patard JJ, Moudouni S, Saint F, et al. Tumor progression and survival in patients with T1G3 bladder tumors: multicentric retrospective study comparing 94 patients treated during 17 years. Urology 2001; 58:551-6.

91. Pieras Ayala E, Palau J, Rodriguez-Villamil L, et al. Cystoscopic follow-up of initial G3T1 bladder tumors treated with BCG. Arch Esp Urol 2001; 54:211-7.

92. Kulkarni JN, Gupta R. Recurrence and progression in stage T1G3 bladder tumour with intravesical bacille Calmette-Guerin Danish 1331 strain). BJU Int 2002; 90:554-7.

93. Griffiths TR, Charlton M, Neal DE, Powell PH. Treatment of carcinoma in situ with intravesical bacillus Calmette-Guerin without maintenance. J Urol 2002; 167:2408-12.

94. Bogdanovic J, Marusic G, Djozic J, et al. The management of T1G3 bladder cancer. Urol Int 2002; 69:263-5.

95. Peyromaure M, Guerin F, Amsellem-Ouazana D, et al. Intravesical bacillus Calmette-Guerin therapy for stage T1 grade 3 transitional cell carcinoma of the bladder: recurrence, progression and survival in a study of 57 patients. J Urol 2003; 169:2110-2.

96. Cheng CW, Chan SF, Chan LW, et al. 15-year experience on intravesical therapy of T1G3 urinary bladder cancer: a conservative approach. Jpn J Clin Oncol 2004; 34:202-5.

97. Herr HW, Dalbagni G. Defining bacillus Calmette-Guerin refractory superficial bladder tumors. J Urol 2003; 169:1706-8.

98. Klein EA, Rogatko A, Herr HW. Management of local bacillus Calmette-Guerin failures in superficial bladder cancer. J Urol 1992;147:601-5.

99. Glashan RW. A randomized controlled study of intravesical alpha-2b-interferon in carcinoma in situ of the bladder. J Urol 1990; 144:658-61.

100. Sarosdy MF, Manyak MJ, Sagalowsky AI, et al. Oral bropirimine immunotherapy of bladder carcinoma in situ after prior intravesical bacille Calmette-Guerin. Urology 1998;51:226-31.

101. Dalbagni G, Russo P, Sheinfeld J, et al. Phase I trial of intravesical gemcitabine in bacillus Calmette-Guerin-refractory transitional-cell carcinoma of the bladder. J Clin Oncology 2002; 20:3193-8.

102. O'Donnell MA, Krohn J, DeWolf WC. Salvage intravesical therapy with interferon-alpha 2b plus low dose bacillus Calmette-Guerin is effective in patients with superficial bladder cancer in whom bacillus Calmette-Guerin alone previously failed. J Urol 2001; 166:1300-4.

103. Luciani LG, Neulander E, Murphy WM, et al. Risk of continued intravesical therapy and delayed cystectomy in BCG-refractory superficial bladder cancer: an investigational approach. Urology 2001;58:376-9.

104. Pansadoro V, De Paula F. Intravesical bacillus Calmette-Guerin in the treatment of superficial transitional cell carcinoma of the bladder. J Urol 1987; 138:299-301.

105. Coplen DE, Marcus MD, Myers JA, et al. Long-term followup of patients treated with 1 or 2, 6-week courses of intravesical bacillus Calmette-Guerin: analysis of possible predictors of response free of tumor. J Urol 1990; 144:652-7.

106. Malmstrom PU, Wijkstrom H, Lundholm C, et al. 5-year followup of a randomized prospective study comparing mitomycin C and bacillus Calmette-Guerin in patients with superficial bladder carcinoma. Swedish-Norwegian Bladder Cancer Study Group. J Urol 1999; 161:1124-7.

107. Steinberg G, Bahnson R, Brosman S, et al. Efficacy and safety of valrubicin for the treatment of bacillus Calmette-Guerin refractory carcinoma in situ of the bladder. J Urol 2000; 163:761-7.

108. Belldegrun AS, Franklin JR, O'Donnell MA, et al. Superficial bladder cancer: the role of interferon-alpha. J Urol 1998; 159:1793-801.

109. Portillo J, Martin B, Hernandez R, et al. Results at 43 months' follow-up of a double-blind, randomized, prospective clinical trial using intravesical interferon alpha-2b in the prophylaxis of stage pT1 transitional cell carcinoma of the bladder. Urology 1997: 49:187-90.

110. Punnen SP, Chin JL, Jewett MA. Management of bacillus Calmette-Guerin (BCG) refractory superficial bladder cancer: results with intravesical BCG and Interferon combination therapy. Can J Urol 2003; 10:1790-5.

111. Lam JS, Benson MC, O'Donnell MA, et al. Bacillus Calmette-Guerin plus interferon-alpha2B intravesical therapy maintains an extended treatment plan for superficial bladder cancer with minimal toxicity. Urol Oncol 2003; 21:354-60.

112. O'Donnell MA, Lilli K, Leopold C. Interim results from a national multicenter phase II trial of combination bacillus Calmette-Guerin plus interferon alfa-2B for superficial bladder cancer. J Urol 2004; 176:888-92.

113. Berger AP, Steiner H, Stenzl A, et al. Photodynamic therapy with intravesical instillation of 5-aminolevulinic acid for patients with recurrent superficial bladder cancer: a single center study. Urology 2003; 61:338-41.

114. Dunst J, Sauer R, Schrott KM, et al. Organ-sparing treatment of advanced bladder cancer: a 10-year experience. Int J Radiat Oncol Biol Phys. 1994; 30:261-6.

115. Rodel C, Dunst J, Grabenbauer GG, et al. Radiotherapy is an effective treatment for high-risk T1-bladder cancer. Strahlenther Onkol 2001; 177:82-8.

116. Colombo R, Da Pozzo LF, Salonia A, et al. Multicentric study comparing intravesical chemotherapy alone and with local microwave hyperthermia for prophylaxis of recurrence of superficial transitional cell carcinoma. Journal of Clinical Oncology 2003;21:4270-4276.

117. Gofrit ON, Shapiro A, Pode D et. al. Combined local bladder hyperthermia and intravesical chemotherapy for the treatment of high-grade superficial bladder cancer. Urology 2004; 63: 466-471.

118. Di Stasi SM , Giannantoni A , Stephen RL et. al. Intravesical electromotive mitomycin C versus passive transport mitomycin C for high risk superficial bladder cancer: a prospective randomized study. Journal of Urology 2003;170:777-782.

119. Erol A, Ozgur S, Basar M, et al. Trial with bacillus Calmette-Guerin and epirubicin combination in the prophylaxis of superficial bladder cancer. Urologia Internationalis 1994;52:69-72.

120. Rintala E, Jauhiainen K, Kaasinen E, et al. Alternating mitomycin C and bacillus Calmette-Guerin instillation prophylaxis for recurrent papillary (stages Ta to T1) superficial bladder cancer. Finnbladder Group [see comments]. Journal of Urology 1996;156:56-59; discussion 59-60.

121. Rintala E, Jauhiainen K, Rajala P, et al. Alternating mitomycin C and bacillus Calmette-Guerin instillation therapy for carcinoma in situ of the bladder. The Finnbladder Group. Journal of Urology 1995;154:2050-2053

122. Di Stasi SM, Giannantoni A, Stephen RL, et al. Sequential intravesical bacillus Calmette-Guerin and electromotive mitomycin-C for high risk superficial bladder cancer: A prospective controlled study. Journal of Urology 2004; 171:74.

123. Kaasinen E, Rintala E, Pere AK, et al. Weekly mitomycin C followed by monthly bacillus Calmette-Guerin or alternating monthly interferon-alpha2B and bacillus Calmette-Guerin for prophylaxis of recurrent papillary superficial bladder carcinoma. Journal of Urology 2000;164:47-52.

124. Witjes JA, Caris CT, Mungan NA, et al. Results of a randomized phase III trial of sequential intravesical therapy with mitomycin C and bacillus Calmette-Guerin versus mitomycin C alone in patients with superficial bladder cancer. [see comment]. Journal of Urology 1998;160:1668-1671.

125. Ali-El-Dein B, Nabeeh A, Ismail EH, et al. Sequential bacillus Calmette-Guerin and epirubicin versus bacillus Calmette-Guerin alone for superficial bladder tumors: a randomized prospective study. Journal of Urology 1999;162:339-342.

126. Kaasinen E, Wijkstrom H, Malmstrom PU, et al. Alternating mitomycin C and BCG instillations versus BCG alone in treatment of carcinoma in situ of the urinary bladder: a nordic study. European Urology 2003;43:637-645.

127. Serretta V, Pavone C, Ingargiola GB, et al. TUR and adjuvant inravesical chemotherapy in T1G3 bladder tumors: recurrence, progression and survival in 137 selected patients followed up to 20 years. Eur Urol 2004; 45:730-5.

128. Burris HA, 3rd, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial [see comments]. Journal of Clinical Oncology 1997;15:2403-2413.

129. Stadler WM, Kuzel T, Roth B, et al. Phase II study of single-agent gemcitabine in previously untreated patients with metastatic urothelial cancer. J Clin Oncol 1997;15:3394-3398.

130. Lorusso V, Pollera CF, Antimi M, et al. A phase II study of gemcitabine in patients with transitional cell carcinoma of the urinary tract previously treated with platinum. Italian Co-operative Group on Bladder Cancer. Eur J Cancer 1998;34:1208-1212.

131. von der Maase H, Hansen SW, Roberts JT, et al. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. J Clin Oncol. 2000; 18:3068-77.

132. Dalbagni G, Mazumdar M, Russo P, et al. Phase II trial of intravesical gemcitabine in BCG-refractory transitional cell carcinoma of the bladder. Journal of urology 2004;171:Abstract 274.

133. Laufer M, Ramalingam S, Schoenberg MP, et al. Intravesical gemcitabine therapy for superficial transitional cell carcinoma of the bladder: a phase I and pharmacokinetic study. Journal of Clinical Oncology 2003;21:697-703.

134. De Berardinis E, Antonini G, Peters GJ, et al. Intravesical administration of gemcitabine in superficial bladder cancer: a phase I study with pharmacodynamic evaluation. BJU International 2004;93:491-494.

135. Palou J, Carcas A, Segarra J, et al. Phase I pharmacokinetic study of a single intravesical instillation of gemcitabine administered immediately after transurethral resection plus multiple random biopsies in pateients with superficial bladder cancer. J Urol 2004; 172:485-8.

136. Gontero P, Casetta G, Maso G, et al. Phase II study to investigate the ablative efficacy of intravesical administration of gemcitabine in intermediate-risk superficial bladder cancer (SBC). Eur Urol 2004; 46:339-43.

137. Chen D, Song D, Wientjes MG, Au JL. Effect of dimethyl sulfoxide on bladder tissue penetration of inravesical paclitaxel. Clin Cancer Res 2003; 9:363-9.

138. Le Visage C, Rioux-Leclercq N, Haller M, at al. Efficacy of paclitaxel released from bio-adhesive polymer microspheres on model superficial bladder cancer. J Urol 2004; 171:1324-9.

139. Au JL, Kalns J, Gan Y, Wientjes MG. Pharmacologic effects of paclitaxel in human bladder tumors. Cancer Chemother Pharmacol 1997; 41:69-74.

140. Morales A, Voccia I, Steinhoff G, et al. Mycobacterium phlei cell wall extract for the treatment of superficial bladder cancer: final results of a phase 2 trial. J Urol suppl 2004; 171: 74.

141. Gomella LG, Mastrangelo MJ, McCue PA, et al. Phase I study of intravesical vaccinia virus as a vector for gene therapy of bladder cancer..J Urol 2001; 166:1291-5.

142. Yamashita M, Rosser CJ, Zhou JH, et al. Syn3 provides high levels of intravesical adenoviral-mediated gene transfer for gene therapy of genetically altered urothelium and superficial bladder cancer. Cancer Gene Ther. 2002; 9:687-91.

143. Thiounn N, Pages F, Mejean A, Descotes JL, et al. Adoptive immunotherapy for superficial bladder cancer with autologous macrophage activated killer cells. J Urol. 2002;168:2373-6.

144. Doll RJ, Kirschmeier P, Bishop WR. Farnesyltransferase inhibitors as anticancer agents: critical crossroads. Curr Opin Drug Discov Devel 2004; 7:478-86.

Committee 6

Muscle-invasive Urothelial Carcinoma of the Bladder

Chair

S. B. Malkowicz (USA)

Members

H. van Poppel (Belgium)

G. Mickisch (Germany)

V. Pansadoro (Italy)

J. Thüroff (Germany)

M. Soloway (USA)

S. Chang (USA)

M. Benson (USA)

I. Fukui (Japan)

CONTENTS

Muscle-invasive Urothelial Carcinoma of the Bladder

S. B. Malkowicz

H. van Poppel, G. Mickisch, V. Pansadoro, J. Thüroff, M. Soloway, S. Chang, M. Benson, I. Fukui

Urothelial (transitional cell) carcinoma of the bladder is a significant neoplasm with over 55,000 new cases and 12,000 cancer-related deaths per year in the United States. It is the 5th most common cancer in the USA and the 4th leading cause of cancer deaths. The majority of these deaths are due to the effects of muscle-invasive disease, which account for approximately one-third of the de novo cases and are derived from about 10% to 15% of preexisting cases of superficial disease. The disease occurs predominantly in men yet is increasing in incidence in women in a manner that cannot be entirely explained by increased tobacco use [1].

The principal clinical findings of muscle-invasive disease are gross or microscopic hematuria, and, to a much lesser extent, voiding dysfunction or pelvic pain. The diagnosis is made by transurethral resection of the lesion with the intent to obtain deep biopsies with representative samples of detrusor muscle.

Preoperative staging has classically been very inaccurate and has not improved appreciably in the past several years. This is of particular concern when deciding on less aggressive forms of therapy for muscle-invasive disease. In an evaluation of SEER (Surveillance, Epidemiology and End Results) registries, 154 patients diagnosed in 1995 were reviewed with regard to treatment choices [2]. Patients were most commonly treated with transurethral resection only (49.1%) or cystectomy only (31%). In an evaluation of SEER data from 1988 to 1999, the treatment choice in octogenarians was full or partial cystectomy in 12% of cases while TUR alone was used in 79% of patients, despite the fact that cystectomy is associated with the greatest risk reduction in cancer death or death from other causes [3].

I. INITIAL CONSIDERATIONS

1. Preoperative Staging

Preoperative evaluation is based on the natural history of bladder cancer metastases and the operational characteristics of the tests employed. Generally an evaluation of the chest (chest x-ray or chest CT) is performed as well as abdominal and pelvic cross-sectional imaging. Both modalities suffer from errors of understaging and overstaging in approximately 30% of patients. In one series of 105 patients, the false negative rate with regard to positive nodes was 68% while the false positive rate was 16% [4]. MR imaging is considered somewhat more accurate yet still ranges from 50% to 90%. Cross-sectional imaging also provides information on urinary tract obstruction that is clinically useful [5]. MR upstaging from T2 to T3 disease also provides independent clinically useful information in the outcome of patients treated by radiotherapy [6]. Bone scans may be useful for those with signs or symptoms of bone involvement but add little to the overall management of patients [7]. Positron emission tomography has had a limited role in bladder cancer staging and diagnosis due to the excretion of tracer into the bladder. Lymph node staging has an accuracy of 80%, which equals or exceeds other modalities [8]. In addition, FDG and ^{11}C-methionine PET have been studied in the bladder.

2. Timing of Cystectomy

The appropriate timing of cystectomy after diagnosis has only recently been investigated. In several retrospective reviews, very similar conclusions have been drawn. A cohort of 167 patients, 50 of whom received no adjuvant therapy, were evaluated with

respect to treatment from time of diagnosis [9]. Those treated within 3 months demonstrated superior recurrence-free, cause-specific, and overall survival to those who were treated later. Final pathology in each group was similar, though a greater degree of vascular involvement was noted in the late group. In a series of 247 patients with a mean age of 66, overall 3-year survival was 59.1%, with a lower survival (35%) in those with a treatment delay of 12 weeks or more compared to those treated earlier (62.1%) [10]. Similarly, extravesical or node-positive disease was greater in those patients treated later (84% vs. 42%). When adjusted for nodal status and pathologic stages, the interval to treatment was still statistically significant (HR 1.93, 95% CI [0.99 to 3.76], $P = 0.05$). Patient delay (second opinions) and medical optimization were the most common reasons for delay. In a similar series of 153 cystectomy patients, a significant increase in pT3 pathologic stage was noted (81% vs. 52%) in the patients treated 90 days beyond diagnosis [11].

3. Preoperative Assessment and Clinical Care Pathways

The intense surgical aspects of radical cystectomy suggest concern for the routine use of this procedure in elderly patients. Several clinical series, however, demonstrate the ability to successfully perform this procedure with good outcomes in older patients (defined as 75 years old or older) with significant comorbidity. The surgical mortality of such series ranges from 0% to 4.5%, with the majority less than 2% [12-16]. The patients have been classified according to the American Society of Anesthesiologists rating. Even those series with patients scoring 3 or higher have demonstrated 0% mortality [13]. Less data is available with regard to long-term follow-up in elderly patients. In a recent report on 38 elder patients (mean age 79) with 22 months of follow-up, 29% of patients were alive. In the 17 patients in whom the cause of death could be established, 14 were due to bladder cancer [17]. In another series of 96 elderly surgery patients, the perioperative mortality was 3.1% and all-cause mortality at 3 months was 8.3% [18].

The impact of comorbid disease on patients undergoing cystectomy in general was evaluated in a cohort of 106 patients (mean age 65) using the Charlston Index. This index score of comorbidity was associated with overall survival, disease-specific survival, and risk of extravesical disease depending on the specific outcome model tested [19]. In this series, the index was evaluated in a general cystectomy population and was not age-specific.

Once the decision has been made to proceed with surgery, the patient must be optimized mentally, physically, and socially. Due to internal and external pressures, collaborative clinical care pathways have been increasingly used to aid in this process. Pooling the expertise of surgeon and ancillary staff, these guidelines attempt to safely streamline care while heeding to increasing financial pressures. This has been supported by studies examining radical prostatectomy [20-22]. For more complex operations, such as radical cystectomy, more variability in the duration of hospitalization can be anticipated, but recent studies have verified the efficacy of such guidelines [23]. There is a financial value of a clinical care pathway model that shortens hospitalization. Importantly, however, pathways only provide a framework and must continue to evolve to improve patient care.

An example of a successful pathway used at Vanderbilt University is outlined: extensive preoperative teaching as well as counseling and optimal stoma site marking by an enterostomal nurse; early morning hospital admission following a preoperative clear liquid diet and bowel preparation completed at home; limited laboratory analysis; short term or no nasogastric tube decompression; early ambulation; continued perioperative teaching; and post-hospitalization nursing care. These guidelines outline routine care but, depending upon the clinical situation, deviations from the pathway can and must occur at any time for individual patients [23].

This pathway is safe and effective. The overall minor complication rate was approximately 30% with a major complication rate of 5% and mortality rate of 1%. Of these minor complications, postoperative paralytic ileus was the most common (57%). The median duration of hospital stay was 7 days [23]. Other series have had similar results [14].

Despite streamlining and decreasing hospitalization, the clinical outcomes do not differ greatly from past series. The overall complication rate from the Duke University cohort was 32% and operative mortality was 2.5% [24]. Figueroa et al. reported an early complication rate of 25% in patients less than 70 years of age and 32% in patients 70 years of age or older [14]. Montie and Wood reviewed complications over an 8-year period in the 1980's and reported an operative mortality rate of 0.4%. Their "technical complication" rate was 2% but minor complications were not specifically discussed [25]. The vast majority of

patients (85%) underwent ileal conduit diversion. This was also the case in a recent series from Great Britain where 93% of patients underwent an ileal loop diversion. The overall "adverse event" rate was 22% with sepsis being the most common, followed by thromboembolic complications including deep venous thromboses and pulmonary emboli. Their overall mortality rate was 1.9% [26].

A clinical pathway can be used safely with different types of diversion. No significant difference in hospital stay among orthotopic neobladder patients compared to those patients that undergo ileal conduit has been demonstrated [27]. Many factors influence the choice of diversion and how patients recover, but diversion type did not correlate with hospitalization. Benson et al. reported on outcomes comparison in 73 patients who underwent radical cystectomy and either conduit or continent diversions and also found no significant difference in either complication rate or length of hospitalization between urinary diversion types [28].

4. Molecular Markers

The ability to provide stratifying criteria beyond tumor stage and lymph node status to the clinical characterization of muscle-invasive tumors would be extremely useful. Preoperative markers may predict the greater probability of lymph node involvement or tumor recurrence, and tissue markers might further direct the application of adjuvant therapy or alter the intensity of postoperative follow-up. Furthermore, there is the possibility of optimally identifying patients best suited for a particular initial therapy. Currently several fairly large retrospective studies of archival material have demonstrated the potential utility of several classic markers, and many smaller studies are suggesting the utility of other identified candidate biomarkers.

A retrospective review of 243 cystectomy specimens has identified abnormal p53 expression as an independent marker for disease progression (60%-80% vs. 7%-11%) and disease-specific mortality in organ-confined muscle-invasive disease [29]. A further evaluation of p21 $^{waf1/cip1}$, a cyclin dependent kinase inhibitor, and p53 in 242 cystectomy specimens demonstrated the independent predictive ability of p21 status with respect to tumor progression and patient survival. It was also evident that preservation of p21 function had a positive impact on p53-positive tumors, with poorest outcomes demonstrated in those cases with aberrant expression for both markers [30].

A retrospective evaluation of the retinoblastoma gene product pRb demonstrated worse clinical outcomes such as 5-year survival (33% vs. 66%) in those patients with absent or elevated expression of protein. Further stratification was obtained when a model evaluating p53 and pRb was evaluated (79% vs. 16% 5-year survival) [31]. The evaluation of angiogenesis-related predictors such as thrombospondin has the ability to predict patient outcomes yet are not independent of p53 [32].

The exploration of several putative markers in moderate size cohorts of cystectomy patients has yielded a group of candidate markers with independent predictive ability for lymph node involvement and clinical progression in patients with muscle-invasive disease [33-40]. The majority of these, such as transforming growth factor-beta, soluble E-cadherin, and uroplasminogen/uroplasminogen receptor can be measured in the serum. If confirmed prospectively, these markers, alone or in combination, may provide further guidance for performing more extensive lymph node dissections or considering the use of adjuvant therapies beyond surgery. In one multifactorial evaluation of several cell cycle markers (p53, p21, pRb, and p16) altered expression was noted in each marker, yet p53 demonstrated the most robust predictive power, followed by p21 [41].

Less data on markers exists for those patients treated with bladder-sparing protocols. In 1 evaluation of 82 patients, p53 and p21 status had independent predictive power in determining outcomes and survival in those patients treated with combined modality approaches. pRb offered little information [42]. However, in another study of 108 patients, loss of pRb staining provided the strongest predictor of a complete response to therapy and relapse-free survival [43].

Currently, 2 large prospective randomized trials are ongoing to evaluate the ability of p53 status to guide therapeutic decisions. The multi-institutional p53 trial is investigating the role of p53 status as it pertains to adjuvant chemotherapy in organ-confined disease. Those patients who are p53-positive will be randomized to observation or 3 courses of adjuvant MVAC. The study is designed to detect a 20% difference in survival. In another study at Memorial Sloan Kettering Cancer Center, patients with clinically organ-confined disease and wild-type p53 staining will undergo complete TUR and neoadjuvant MVAC followed with conservative management. In addition to feasibility, the study will evaluate how many patients can be appropriately treated with bladder-sparing therapy.

II. RADICAL CYSTECTOMY

1. General outcomes

Intermediate and long-term results from radical cystectomy are available from several series and provide a benchmark for alternative forms of treatment. In the USC series of 1054 patients, median follow-up was 10.2 years with a range of 0 to 28 years for patients with a median age of 66 (22-93) [44] . Overall recurrence-free survival was 68% and 66% at 5 and 10 years. In patients with superficial (pT0-pT1), node-negative disease, 5- and 10-year survival was clustered at 92% to 83% and 86% to 78%. For muscle-invasive, organ-confined disease, 5- and 10-year findings were in the 89% to 76% range, while extravesical, node-negative tumors demonstrated a 62% 5- and 10-year survival with pT4 tumors exhibiting a 50% to 45% survival over this time period. Those patients with positive lymph nodes (24%) demonstrated 5- and 10-year survivals of 35% and 34%, respectively. Thirty percent of patients demonstrated recurrences at a median time of 12 months, with a local recurrence rate of 7%.

In a recent evaluation of 300 patients from Memorial Sloan Kettering Cancer Center with a median follow-up of 65 months, the disease-specific survival was 67% and there was clearly a dichotomy between organ-contained and non-organ-contained disease (60%-63% for pT2a-pT2b and 31% for pT3-pT4) [45]. In this regard, the distinctions between pT3a and pT3b disease have been evaluated in one series demonstrating no difference in the survival rate, lymph node status, or recurrence rate among these patients [46].

In a pooled series of 518 patients with a median follow-up of 4.4 years, the overall survival rate was 58% and the 5-year node-negative survivals for T1 to T4 disease were 81%, 74%, 47%, and 38% respectively [47]. Node-positive patients demonstrated a 5-year survival of 30%.

A contemporary series of 507 patients (median age 66) demonstrates a 5-year disease-free and overall survival of 73% and 62% in patients with organ-confined, node-negative disease and 56% and 49% for extravesical, node-negative cases [48]. Positive lymph nodes were found in 24% of patients. Local recurrence ranged from 3% to 11% depending on tumor stage. Distant metastases were noted in 25% of patients with localized disease and 51% of patients with positive lymph nodes.

In a series of 1026 cases from Mansoura, overall 5-year survival was 48% [49]. This series is notable for the difference in pathologic case mix since 59% were squamous cell carcinoma and only 22% urothelial (transitional cell) carcinoma. Positive lymph nodes were found in 18.3% of cases and demonstrated a 23.4% 5-year survival. Five-year survival was approximately 60% for pT2 disease, 45% for pT3, and 16% for pT4.

Surgical mortality rates in most series range from 1% to 3%. Significant preoperative cardiovascular morbidity, the intensity of the surgery, and potential septic complications associated with cystectomy and urinary diversion contribute to this. Contemporary series also demonstrate that 25% to 30% of patients will experience morbidity associated with the surgery within the first 4 months, attesting to the intensity of the surgery. Blood loss during cystectomy can range from 600 to 1800 mL with some significant outliers. Newer stapling and cautery devices may help decrease this particular morbidity. In a prospective trial of 70 patients, an articulating linear staple cutter was compared to traditional techniques and demonstrated significantly lower blood loss and less need for transfusion (5.7% vs. 34.3%) (*Level 2*, [50]). These devices may be particularly useful in women, in whom an association with greater blood loss and transfusion requirement has been documented in some series [51].

Classically, the outcomes for salvage cystectomy have been significantly worse than those encountered in nonirradiated patients. In a small series of patients (18), it was demonstrated that this surgery is feasible even with continent diversion [52]. Average blood loss was 840 mL but continence rates were 67% during the daytime and 56% at night. In another series of salvage cystectomies in patients originally treated for prostate cancer, an average blood loss of 1175 mL was noted with an early complication rate of 55% [53]. No rectal injuries or perioperative deaths occurred, and extravesical disease was more common (60% vs. 30%) in those patients who underwent prior radiation therapy. In expert hands, surgery even in the presence of gross nodal disease can be warranted. In a series of 84 patients, a 24% 10-year survival was noted [54].

Surgery also can play a role in the resection of local or distant metastases in carefully selected patients [55-57]. With preoperative chemotherapy, 40% to 50% of locoregional resected lesions will demonstrate no tumor, while distant sites may be positive in up to 80% of cases. Overall median 5-year survival is approximately 33% to 46%.

2. Procedural Standardization

Further efforts have been made to standardize the basic aspects of cystectomy to provide uniformity in outcomes. In an evaluation of 637 patients from a single institution, it was demonstrated that improved overall survival rate and a reduced local recurrence rate were associated with negative surgical margins and a greater number of lymph nodes removed [58]. Survival was improved if 13 or more nodes were sampled, and there was a greater correlation with negative soft tissue margins in node-negative and node-positive patients if 13 nodes were sampled. This concept was further evaluated in a cooperative group effort in which 1091 cystectomies from 4 institutions (16 surgeons) were evaluated [59]. Surgical margins were correlated with patient age, prior therapy, tumor stage, and the extent of the lymph node dissection. General recommendations included an effort to examine 10 to 14 nodes per case and strive for a positive margin rate of less than 10% in nonbulky tumors, less than 15% in pT3 to pT4 lesions, and 20% in salvage situations. Reasons for limiting the lymph node dissection included age greater than 75 (in 35% of cases) and significant prior treatment (50%). Higher volume surgeons tended to operate on more elderly, sicker, and pretreated patients. In another evaluation of patients participating in a cooperative group trial for neoadjuvant chemotherapy, it was noted that the overall quality of pathological examination was high, but in 10% of specimens no mention of the soft tissue margins was made, nor were lymph nodes described in 18% of cases [60]. In a secondary analysis of this patient group (SWOG 8710), a multivariable model looking at 5-year survival and local recurrence (overall 54% and 15%) in this group of 268 patients demonstrated that negative surgical margins (hazard ratio [HR] 0.37, $P = 0.0007$) and the effect of 10 or greater nodes removed (HR 0.51, $P = 0.0001$) had an impact independent of MVAC therapy, node status, or pathologic stage [61]. These data strongly suggest the impact of surgical factors on the outcome in cystectomy patients and the value of suggesting general standards for the procedure.

3. Lymph Node Status and the Role of Lymphadenectomy

Clinical staging of lymph node status in patients with muscle-invasive disease remains inaccurate. The finding of clinically occult disease can range from 15% to 27% with cross-sectional imaging using MRI and computed tomography. New ferromagnetic contrast agents demonstrating improved staging in prostate cancer patients may prove valuable in further discrimination of lymph node status in patients with bladder cancer [62]. Current positron emission tomography techniques are not useful, with a reported false negative rate of approximately 30%.

Sentinel lymph node evaluation has become standard in certain malignancies and is being evaluated in muscle-invasive bladder cancer. This is somewhat complicated in the case of muscle-invasive bladder cancer since the lymphatic drainage of the bladder is variable and there is minimal data correlating tumor position in the bladder with positive lymph node location. Additionally, there is inferential data suggesting the phenomenon of skip metastases to higher echelon nodes as well as crossing lymphatic drainage [63-65]. Current studies employing endoscopic tracer instillation prior to cystectomy demonstrate the absence of a sentinel node at the time of cystectomy in up to 20% of cases, and the localization of sentinel nodes, when detected, beyond the obturator node region in a third of the cases. This is clearly an area for further study that may provide clinically useful information.

a) Clinical Practice

The value of a lymph node dissection in conjunction with radical cystectomy with regard to obtaining more accurate pathologic assessment and potentially improved survival has been advocated by several academic groups for many years. Recent clinical data can provide a better assessment of the validity of these claims with regard to survival and optimal stratification of patients undergoing surgical treatment for muscle-invasive disease. Both clinical stage and lymph node status independently contribute to predicting prognosis, but the correlation of nodal metastasis and increased clinical stage is clear.

Current general practice suggests that less than half of American patients undergoing cystectomy do not undergo pelvic lymph node dissection or have 4 or less nodes removed. In those patients with lower stage clinical disease, 1 percent or less underwent a lymph node dissection in conjunction with their surgery [66]. Therefore, a disparity exists between general practice and professional recommendations for this procedure in patients undergoing cystectomy.

The standard pelvic lymph node dissection includes the obturator packets and extends laterally to the external iliac vein. The cephalad extent of the dissection terminates at the bifurcation of the common iliac vessels. An extended version of the procedure

demarcates the inferior mesenteric artery as the cephalad boundary and includes paracaval, intra-aortocaval, para-aortic, presacral, common iliac, and external iliac nodes as part of the dissection.

b) Impact on Survival

Since 15% to 25% of patients with clinically node-negative disease may harbor micrometastases, some patients will definitely benefit from a lymph node dissection. Classically, lymph node involvement was almost uniformly fatal, yet the incorporation of lymph node dissection in patients with gross adenopathy, microscopic disease, and no pathologic lymph node disease provides a survival advantage. In 84 patients with cystectomy and lymph node dissection alone in the setting of evident positive disease, the 10-year survival rate was 24% [54]. In general, 5-year survival is 25% to 35% in patients with positive nodes. This figure is even higher (44%) in those patients with node-positive organ-confined disease. In comparing node-negative patients with a standard or extensive dissection, a slight survival advantage has been described in those patients undergoing the extended dissection [67].

Recent studies have been evaluating the factors which predict for survival advantage with a lymph node dissection. There are data for and against the predictive value of the classic TNM system [68,69]. Newer reports suggest the value of the total number of nodes harvested in a dissection [70-73]. Recently, there is no agreed upon optimal number required to confer a survival advantage. More recently, it has been suggested that normalization of the lymph involvement by creating a ratio of the positive nodes to the number of dissected nodes may provide superior clinical information. A cutpoint of less than or greater than 20% node positivity was first suggested as a discriminator of survival in such patients and similar findings have been noted in other series [68]. A recent multicenter retrospective evaluation demonstrated the independent prognostic value of node density and the total number of positive nodes in predicting progression and survival (AUA 2004). It has also been recently demonstrated that more nodes are demonstrated on final pathology when the material is sent in distinct anatomic packets rather than as an en bloc specimen [74].

Further data from the SEER database demonstrate the impact of the extent of surgery on survival [75].

Summary

The value of extended lymph node dissection as noted by recent findings in the literature is not yet reflected in general urologic practice. This gap needs to be bridged as there appears to be some curative value in the lymph node dissection alone and potential greater value in identifying high-risk patients with low-volume disease with the greatest potential for cure with adjuvant therapy. Lymphatic anatomy of the urinary bladder requires further investigation with respect to sentinel node status, skip lesions, and crossover drainage. Additionally, the value of lymph node density as a predictive index needs further validation. The development of molecular markers for the prediction of nodal status and prediction of clinical prognosis in node-positive patients will further expand our ability to stratify and optimally treat this patient population.

4. Ureteral Margins at Cystectomy: Do Frozen Sections Matter?

The role of frozen section pathology of the ureteral margins at the time of cystectomy has been controversial. Although a common practice, little evidence has been presented either way for the impact on outcomes with this practice. The persistence of tumor on successive biopsies could result in excessive ureteral shortening and the need to modify the urinary diversion. Furthermore, the concern for local recurrence or an increase in ureteral anastomotic strictures has persisted. The available data on the impact of ureteral margins [76-80] suggest a 2% to 8% chance of detecting carcinoma in situ on frozen section during cystectomy. Some form of ureteral abnormality in the form of atypia or dysplasia may exist at twice that rate. In 4 clinical series with a median follow-up of 50 months, 1 of 51 patients with persistent abnormal findings on repeat frozen sections developed an anastomotic recurrence and 4 other patients developed upper tract recurrence over a mean follow-up of 42 months [76,79]. In one series, all 4 patients with CIS at the margin eventually died of their disease, yet none had an upper tract recurrence [77].

5. Nerve- and Seminal-sparing Cystectomy

While the John Hopkins group pioneered potency-sparing cystoprostatectomy, potency cannot be achieved in a large percent of patients. Even when the operation is performed by skilled and experi-

enced surgeons, the preservation of normal sexual function does not exceed 40% to 60% of cases and urinary incontinence, mainly during the night, persists in a significant number (*Level 3,* [81]). Thus, modified cystectomy has been tried, with preservation of vas deferens, prostatic capsule (hypertrophied transition zone is removed with bladder), or prostate and seminal vesicles in males, and all internal genitalia in females. An ileal bladder substitution is anastomosed to the margins of the prostate in males and urethra in females. Selection of patients should be limited to lower clinical stage patients since prostatic involvement is associated with significant clinical progression and seminal vesicle involvement, while rare (less than 1% of most large cystectomy series), is associated with a less than 10% 3- and 5-year survival [82,83].

Muto and Moroni started this modified cystectomy, which they call "seminal-sparing cystectomy," with orthotopic bladder replacement in the treatment of superficial bladder cancer refractory to conservative management in a cohort of patients with normal sexual activity who wished to preserve it and no tumor involvement in the prostatic urethra [84]. Subsequent to their preliminary report on 42 patients in 1998, Muto et al. reported long-term follow-up (median of 68 months) results in 61 evaluable male patients (mean age 49) including 5 with invasive (T2G3) bladder cancer, all of whom preoperatively had a normal serum PSA level (0.8-3.4) and transrectal ultrasound of the prostate (*Level 3,* [85]). Normal erectile function without pharmacologic help was preserved in 95% of the patients. Complete daytime continence was reached in 95% and nighttime continence was reached in 31% of the patients. The early postoperative and delayed complication rate was 18% and 26%, respectively. Although prostate cancer and high grade prostatic intraepithelial neoplasia were noted in 1 and 3 patients, respectively, these patients had undetectable (<0.2 ng/mL) PSA levels without adjuvant therapy at a median follow-up of 19 months. Fifty-five patients are alive and 6 patients are dead, 5 of cancer progression.

Horenblas et al. (*Level 3,* [86]) applied this procedure in 10 males and 3 females with bladder cancer clinically staged T1 to T3 (mean age 55). All patients with tumor growth in the bladder neck, males with tumor in the prostatic urethra, and females with invasive tumor in the trigone were excluded from the surgery. Further requirements are patient motivation for the preservation of sexual function, no prostate cancer in males, and no cervical or uterine abnormalities in females. After the operation, erections were normal in 7 men, with antegrade ejaculation in 5, and vaginal lubrication was reported to be normal in all women. Daytime continence was achieved in 9 men and 2 women, while nighttime continence was achieved in 7 and 2, respectively. One woman and 3 men perform intermittent catheterization because of postvoid residual urine. At a mean follow-up of 3.5 years, 2 patients have died of distant metastasis without local recurrence and 1 developed prostate cancer 5 years after cystectomy.

Vallancien et al. (*Level 3,* [87]) reported treatment results of seminal-sparing cystectomy performed in 100 male patients (mean age 64) including 40 pT2, 23 pT3, and 13 N+ patients. All patients had a normal digital rectal examination, PSA less than 4 ng/mL, and no hypoechoic areas of the prostate. In the vast majority of the patients, cystectomy was carried out just after TURP. The 5-year cancer-specific survival was 90% in pT0 to pT1, 73% in pT2, 63% in pT3, and 8% in N+. Prostate cancer was diagnosed in 3 patients. At 1 year follow-up, 86 of 88 patients are fully continent during the day and 84 (95%) void 1 to 2 times a night to stay dry. Of 61 patients with previously adequate sexual function, 50 (82%) maintained potency with retrograde ejaculation secondary to TURP, 6 have partial potency, and 5 are impotent.

A small series of men by Fang-Jian et al. [88] demonstrated preservation of sexual function in 75% of men who were intact preoperatively, while a series of 25 men reported by Saidi et al. [89] with a median follow-up of 46 months (ages 47-75) did demonstrate one case of prostate cancer after 36 months, which was successfully treated with radiation therapy.

Colombo et al. (*Level 3,* [90]) studied 27 male patients (mean age 52) with superficial high-risk (22 patients) or muscle-invasive T2 bladder cancer (5 patients) who underwent nerve- and seminal-sparing cystectomy with construction of neobladder following sextant prostatic biopsy and transurethral resection of the prostate. Fully normal postoperative erectile function was documented in all patients and a retrograde ejaculation with reliable sperm retrieval from urine was also documented. Further, diurnal and nocturnal urinary continence was achieved immediately after indwelling catheter removal in 18 (67%), while the remaining 9 patients obtained complete urinary continence within 15 days after catheter removal. No patients needed to wear any pads. At a mean follow-up of 32 months, no patient had local recurrence or prostatic carcinoma. One patient with positive lymph nodes died of disseminated disease.

Summary

Seminal-sparing cystectomy (preservation of seminal vesicles, vas deferens, and prostate or prostatic capsule) in relatively young and sexually active patients with organ-confined bladder tumors without high risk of subsequent urethral recurrence is effective in preservation of not only sexual activities but also urinary continence. The effect on therapeutic efficacy associated with this surgical approach will require longer follow-up studies in larger patient populations.

6. Radical Cystectomy in Females

In women, radical cystectomy for muscle-invasive bladder cancer has historically been the equivalent of an anterior exenteration. This includes removal of the uterus, fallopian tubes, ovaries, bladder, urethra, and a segment of anterior vaginal wall. This remains the gold standard. However, early detection combined with a desire to improve the functional outcomes including sexual abilities and urinary control have led surgeons to modify their techniques in select patients where preservation of disease-free urethra is possible.

Although the majority of women still undergo ileal conduit urinary diversion or continent cutaneous diversion, orthotopic urinary diversion has become increasingly viable as an option. Stein et al. and others subsequently have demonstrated the oncologic safety of orthotopic reconstruction in properly selected female patients [91-93]. Exclusion criteria for orthotopic neobladder reconstruction include tumor involving the bladder neck, diffuse carcinoma in situ, and a positive bladder neck margin at the time of radical cystectomy [91]. In addition, females with large, palpable tumors along the anterior vaginal wall are not appropriate candidates. In properly selected patients, local recurrence rates have been extremely low and functional outcomes have been comparable to those reported among male patients [94-98].

The technique and outcomes of orthotopic diversion in females have been well-described [95,96]. These technical refinements include avoidance of overlapping suture lines, the interposition of a vascularized omental pedicle, and preservation of the anterior vaginal wall [94]. In patients with nonpalpable tumors, the plane between the posterior bladder wall and the anterior vaginal wall can be developed while ligating the posterior-lateral pedicles. The plane is developed to the level of the bladder neck, and the anterior and posterior dissections are connected with preservation of the bladder neck.

It was recently reported that there is a very low incidence of secondary malignancies discovered incidentally or urothelial involvement of adjacent organs found at the time of cystectomy [99]. In this series, only a single gynecologic malignancy was found and involvement of the uterus by direct extension of bladder cancer was discovered in only 2 patients, both of whom had clinical suspicion based on bimanual examination or preoperative imaging. Thus, in most women the risk of gynecologic involvement of urologic malignancy is small and can usually be determined either preoperatively or at the time of surgery. This was also the case in another larger series by Ali-el-Dein et al. [100]. In an evaluation of 609 female cystectomy specimens, 64% of which were squamous cell carcinoma, gynecologic organ involvement by the bladder cancer was seen in 2.6% of cases. The involvement of gynecologic organs was most commonly noted in posterior wall tumors. The potential for improved functional outcomes and quality of life through preservation of gynecological organs, particularly among young women with invasive bladder cancer, is an area of ongoing research. These younger women are more likely to be concerned about preservation of fertility and continuation of normal hormonal status [101].

In properly selected patients, functional outcomes have been comparable to those reported among male patients [92-98]. Daytime continence rates range from between 70% to 95%, with high rates of overall satisfaction. There may be a higher rate of urinary retention regarding intermittent catheterization, and all patients undergoing diversion should receive preoperative counseling regarding this as well as other possible complications. The newest techniques in male patients can be used in the female patient. In fact, robotic cystectomy and orthotopic diversion in females has recently been described [93].

7. Postoperative Follow-up: What is the appropriate follow-up for patients treated for muscle-invasive bladder cancer?

The majority of patients with muscle-invasive bladder cancer are treated with cystectomy and some form of urinary diversion. After recovery they are at risk for local and distant recurrence as well as metabolic deterioration of their renal and gastroin-

testinal systems. Patients can also experience disease recurrence in the urethra or upper urinary tract. Those individuals treated with bladder-sparing therapies also require continued monitoring of their intact bladder. An appropriate schema for disease monitoring should be based on natural timing of recurrence in patients with invasive disease and the probability of disease recurrence or functional deterioration at particular sites. Contemporary cystectomy series demonstrate a 5% to 15% chance of local disease recurrence that is associated with nodal status (25%-50%) at the time of surgery and clinical stage of disease (15%-50%). The majority of recurrences are manifest in the first 24 months and many are concentrated within 6 to 18 months after surgery. Fifty percent to 70% of these local recurrences are noted without concomitant distant disease.

Distant recurrence is noted in approximately 50% of cystectomy patients and the majority (80%-90%) of these is noted within 24 months. Some progression is demonstrated from year 2 to 5 and even beyond 5 years. Again, nodal status and pathologic tumor stage strongly influence the probability of recurrence. The most common sites of recurrence are the lung, liver, and bones.

Metabolic alterations of renal and GI function can occur frequently in patients who have undergone a cystectomy and urinary diversion. Vitamin B12 reabsorption and bile acid metabolism are affected by significant resection of the distal ileum. Long-term evaluation of patients demonstrates that 35% of patients may require B12 supplementation after 3 to 5 years [102]. Hyperlipidemia has also been associated with long-term urinary diversion. Mild metabolic acidosis (hypochloremic, hypokalemic) is noted in approximately 15% of patients and may require metabolic supplementation. In some instances this can be due to poor emptying, requiring an evaluation for reservoir deterioration.

Urethral recurrence is a major concern and may occur in 5% to 15% of patients. The relative risk of recurrence is increased with prostate pathology and is highest in those patients with stromal invasion of urothelial carcinoma (20%-60%). The risk of distal urethral recurrence is not amplified with carcinoma in situ or tumor multifocality. It appears that the risk of urethral recurrence is lower in those individuals who have undergone an orthotopic diversion (2%-4%) compared to those individuals with cutaneous diversions (4%-8%) [103]. Whether this is due to patient selection or the effect of urine in contact with the urethra is not totally clear. Urethral recurrence occurs in 3% to 15% of women and is associated with tumor at the bladder neck.

Upper tract recurrence is uncommon (2%-4%) in cystectomy series and generally occurs 24 to 40 months after surgery. Those patients with carcinoma in situ, urethral involvement, and ureteral involvement are at higher risk of recurrence. Ureteric obstruction occurs in 1% to 15% of cases and is managed by open reoperation or endoscopic techniques. Renal deterioration can occur in up to 30% of patients over time with or without obstruction.

Appropriate follow-up of the cystectomy patient would include frequent early monitoring of the chest, abdomen, and pelvis for local and distant recurrence as well as a standard metabolic evaluation. Monitoring of the upper tracts and urethra is also important. A reasonable schema based on the available data for site of recurrence and the time frame for recurrent disease is offered by Bochner et al. [104].

III. OTHER THERAPIES FOR MUSCLE-INVASIVE BLADDER CANCER

1. The Role of Partial Cystectomy

Partial cystectomy is an alternate form of therapy for muscle-invasive disease in a select cohort of patients. The available data is derived from retrospective reports and much of the information must be distinguished from primary urachal lesions or metastatic deposits to the bladder [105-108]. Approximately 5% (range 5%-15%) of any patient group presenting with muscle-invasive disease might be considered for partial cystectomy. The principle limiting factor is the location of the tumor. In the majority of cases these represent lesions of the bladder dome. In a recent clinical series, 81% of tumors were clinical stage T2 or T3, while approximately 40% demonstrated similar stages pathologically [109]. In general, there was a stage shift downward. Overall 5-year survival was 69%, with 74% of these patients maintaining an intact bladder. On univariate analysis, carcinoma in situ and multifocal lesions were a risk factor for superficial recurrence (80%), while positive surgical margins and lymph node involvement were factors for advanced recurrence (80% of patients). Median follow-up was 33 months.

Contemporarily, it should be possible to perform such surgery without compromise of bladder function and with an overall low complication rate. More

recent series demonstrate no instances of wound implantation. Patient selection is a key component of success (mean tumor size of the most recent series was 3.3 cm). Those lesions in the lateral wall and trigone are the most difficult to treat in this manner and other techniques should be considered.

One indication for partial cystectomy in a site other than the dome is for a tumor associated with a bladder diverticulum. Data for outcome assessment is very scanty. A recent series of 39 patients treated patients a variety of ways, including with partial cystectomy, for tumor in a diverticulum [110]. Thirteen demonstrated T2 or greater disease and had 45% 5-year survival. Those patients with Ta and T1 disease performed better (83% and 72%).

The small number of patients in these series precludes meaningful comparison to cystectomy. There are no prospective trials of this technique compared to cystectomy or TURBT. Overall 5-year survival tends to be somewhat lower stage per stage than contemporary cystectomy series, yet such a comparison involves multiple biases.

Additionally, this technique has been incorporated into bladder-sparing protocols after initial chemotherapy in small numbers of patients (n = 13) [111]. Those patients consolidated to a T0 status after partial cystectomy have a 5-year survival of approximately 60% [111,112].

2. Radical TUR - Indications and Results

Classic data suggest the potential for long-term disease-free survival in select patients treated with transurethral resection (TUR) alone of their bladder tumor [113,114]. Advantages of this form of therapy are decreased morbidity and greater applicability to populations with significant comorbidity. Disadvantages include the significant potential for pathologic misstaging and undertreatment of significant disease.

In efforts to obtain a “complete” TUR prior to cystectomy in a series of 90 patients, 29.4% with initial muscle-invasive disease demonstrated pT2 tumor on the cystectomy specimen [115]. In another series of 80 patients with a precystectomy complete TUR, 75% of the cases demonstrated residual disease, and the T2 patients demonstrated pT2 or higher pathology in almost all cases [116].

In unselected classic retrospective series determined primarily by patient preference, not physician selection, 5-year survival rates were 30% to 37% [113,117]. Other studies demonstrate 5-year survival rates ranging from 40% to 60% in T2a and T2b disease, which includes therapeutic consolidation with cystectomy [114,118]. The treatment of T2 and greater tumors with complete TUR and chemotherapy has yielded 60% 5-year survival with bladder preservation [119].

Two major prospective reviews provide significant information with regard to application and outcomes of this approach. Herr reported a 10-year experience on 99 patients treated with complete TUR and Solsona described a series of 133 patients with invasive cancer treated in the same fashion. In both cases, these cohorts represented approximately 21% of the patients evaluated with muscle-invasive disease during this time period [120,121]. The 10-year disease-specific survival in both groups was approximately 75%. In Herr’s series, those patients with residual T1 disease fared less well with a 57% survival rate. Additionally 34% of patients experienced a muscle-invasive relapse requiring therapeutic consolidation with cystectomy. The Solsona series demonstrated relapse with muscle invasion in 36% of patients, a third of whom could be salvaged with radical surgery.

The Herr series did not evaluate tumor size and morphology yet it is intimated that careful selection of tumors was performed. A univariate and multivariate analysis was performed with the Solsona data which yielded only carcinoma in situ as a variable for disease progression. Large lesions were predominantly papillary with few sessile lesions greater than 3 centimeters.

The available data suggests that transurethral resection alone is an option in a limited number (approximately 20%) of patients presenting with muscle-invasive disease. Very careful consideration to the clinical characteristics of the tumors is essential in selecting patients for such therapy. Close follow-up of these patients is mandatory, with the understanding that approximately a third of these patients will experience muscle-invasive relapse and may require consolidation of therapy with radical cystectomy. No data is available with regard to molecular markers and how they may better discriminate outcome.

3. Laparoscopic and Robotic Surgery

Minimally-invasive techniques have had an impact on all aspects of urology, and with their maturation, case series reports are now regularly reported on their application to invasive bladder cancer, which has traditionally been associated with the most

aggressive forms of open surgery in urology. A combination of techniques have been employed to perform a cystectomy and some form of urinary diversion including pure laparoscopic cystectomy and extracorporeal ileal loop or continent pouch, complete intracorporeal cystectomy and diversion (ileal loop and continent diversion), and hand-assisted laparoscopic radical cystoprostatectomy and extracorporeal urinary diversion. Use of robotic assistance for radical cystectomy has also been reported. Approximately 150 to 200 cases have been described in the literature.

The common denominator in these reports is previous extensive experience with laparoscopic techniques and a significant operative time (8 to 12 hours) for the initial cases. Blood loss appears generally less than that encountered with open surgery (300 to 600 mL) while hospitalization times vary with respect to regional and national practice. In several American series the postoperative period ranges from 5 to 8 days.

Complications include major vascular injury and hypercarbia necessitating open conversion. In many series few early complications are reported. Contrasting this to early outcomes with open surgery at centers of excellence, this suggests very careful patient selection in these small series, a higher threshold for defining complications, or a decrease in overall early complications that will be sustained with larger numbers. Currently follow-up on most patients is quite short.

4. Bladder-sparing Therapy

Combined modality therapy for the treatment of muscle-invasive bladder cancer has been evaluated in multiple single center studies and in some intergroup trials as well [122,123]. It arose as an option for those wishing to undergo organ-sparing surgery as well as an approach for those patients who are poor candidates for surgery. There have been no direct comparative trials between radical cystectomy and organ-sparing approaches. The majority of treatment plans have been similar to those originally proposed by the MGH group which consists of complete transurethral resection of the tumor, induction chemotherapy, and possible radiation, which is followed by a clinical re-evaluation. Those with a complete response are consolidated with further chemotherapy and radiation.

The overall 5-year survival rate for patients so treated is 45%-55% with disease-specific survival in the 55%-65% range. Disease-specific survival with an intact bladder is slightly decreased in the 43%-55% range [122-125]. Smaller series of highly selected clinical T2 patients have demonstrated higher overall and disease-specific outcomes (70%-80%) [126]. On the average, 25% to 30% of patients require cystectomy as a component of treatment consolidation.

Clinical and molecular characteristics of patients may aid in selecting appropriate candidates for therapy. Early series demonstrated the poor outcome of patients with an initial presentation of hydronephrosis [122] and other investigators have shown the negative impact of initial carcinoma in situ [127]. In 1 series of 111 patients, 60 demonstrated a complete response to initial chemotherapy. These were stratified by p53 expression status. All patients with T2 p53-negative tumors survived 10 years, while those patients with T2 disease who were p53-positive demonstrated a 47% 10-year survival [128]. The impact of p53 status on higher clinical stage disease was minimal (67% vs. 63%). Recent data in patients receiving gemcitabine and radiotherapy as part of a bladder preservation protocol suggest that overall quality of life is not significantly impaired for overall parameters and is slightly lower in bladder-specific measurements (FACT-BL) for those patients receiving higher doses of therapy. This reflects the tolerability of such regimens [129].

Summary

Multimodality organ-preserving therapy for invasive bladder cancer is feasible and provides reasonable results for those individuals unfit or unwilling to undergo radical cystectomy. There are no direct comparisons of organ-sparing protocols to radical cystectomy. Those patients with resectable clinical T2 disease will attain the best clinical outcomes. p53 status has been suggested as a potential prognostic factor in determining favorable outcomes with this mode of therapy, and quality of life is not severely impaired by such treatment. Multimodal organ-sparing therapy should be discussed with patients as an option to treat lower volume invasive disease, and offered as an alternative for those patients with muscle-invasive disease who refuse cystectomy or are precluded for consideration of cystectomy due to severe comorbidities.

RECOMMENDATIONS

I. INITIAL CONSIDERATIONS

1. Retrospective analysis of cystectomy series suggests that time to definitive treatment may have an independent impact on pathology and survival outcomes. An effort to treat patients within 12 weeks of diagnosis is suggested to optimize outcomes, with the realization that medical optimization of the high-risk patient takes precedence *(Level 3, Grade B)*.

2. Older patients with significant comorbidity can demonstrate surgical outcomes similar to younger patients at surgical centers of high volume. Patients should not be rejected as surgery candidates only on the basis of chronological age. More involved measures of comorbidity may provide a better measure of clinical outcomes than classic anesthesia evaluations. Clinical pathways may streamline care and provide cost-effective measures for providing service. It remains to be seen if they improve outcomes *(Level 3, Grade B)*.

3. At the current time there are no prospective data regarding tumor markers in muscle-invasive bladder cancer to guide therapeutic decision making. Routine tissue staining for biomarkers for purely clinical decisions is not recommended. This is due to the lack of standardization regarding the interpretation of staining as well as the lack of prospective data. Prospective trials incorporating marker data should be supported and encouraged. Newer, putative markers for muscle-invasive disease (both tissue and serum) are emerging and warrant prospective validation *(Level 3, Grade B)*.

II. RADICAL CYSTECTOMY

1. Radical cystectomy and bilateral pelvic lymph node dissection is the standard of care for muscle-invasive bladder cancer. The overall disease-specific survival for organ-confined disease is in the 70% to 85% range over 5 years and does not show significant deterioration over a period of 10 years. Similarly, extravesical disease and node-positive disease demonstrate 5-year survival in the 50% to 60% range and 30% range, respectively, with sustained responses over a decade. These findings are not matched or exceeded by other modalities.

   Patients should be counseled about the significant proportion of minor (30%) and major (3%-5%) complications associated with surgery as well as the 1% to 3% surgical mortality rate. Blood loss may be lessened with new stapling and cautery techniques.

   Cystectomy can be applied in the salvage setting and in the case of evident adenopathy with reasonable results and higher complication rates. Metastasis resection can be considered in select cases *(Level 3, Grade B)*.

2. Surgical factors such as the reduction in positive soft tissue margins and extent of lymph node dissection can have an influence on 5-year survival and local recurrence. All efforts to obtain negative margins should be made at the time of surgery as well as an effort to remove 10 or more nodes during the procedure. Heavily pretreated patients, those with significant comorbidity demanding expedient surgery, and those patients with anatomically sparse nodes may not meet these surgical criteria *(Levels 2 and 3, Grade A/B)*.

3. At this time the preponderance of data suggest that a well-performed pelvic lymph node dissection contributes little in the way of surgical morbidity and clearly aids in surgical staging. It is possible that it adds to the overall therapeutic effect of the surgery, especially in lower volume nodal disease. The value of higher level dissection (above the common iliac vessels) remains to be determined.

4. Frozen section pathology at the time of cystectomy can identify those patients of higher risk of subsequent upper tract disease and potential poor outcomes, yet does not affect anastomotic integrity or anastomotic recurrence in the overwhelming majority of cases. It is a simple adjunct to the general procedure that should not be discouraged *(Level 3, Grade B)*.

5. In relatively young and sexually active patients with organ-confined bladder cancer, nerve- and seminal-sparing cystectomy can be done with satisfactory preservation of function, yet the potential for clinical outcome for cancer control remains to be determined. It should currently be performed in very select cases *(Level 3, Grade B)*.

6. In the absence of bulky disease or the suspected involvement of gynecologic organs, the preservation of gynecologic organs in younger female cystectomy patients is advised *(Level 3, Grade B)*.

7. Patients should be followed at short intervals over the first 2 years beyond their surgery. Monitoring should include biochemical monitoring, imaging of the chest, abdomen, and pelvis, and monitoring of the retained urethra *(Level 3, Grade B)*.

III. OTHER THERAPIES FOR MUSCLE-INVASIVE BLADDER CANCER

1. Partial cystectomy remains an appropriate option for treatment of muscle-invasive bladder cancer on initial presentation in a small group (3%-5%) of patients. It is particularly applicable to small lesions in the dome of the bladder, and has a role in the consolidation of neoadjuvant chemotherapy in a small proportion of patients. Overall 5-year survival is approximately 60%-70% and is difficult to compare to radical cystectomy series. Patient selection is a critical factor to clinical success *(Level 3, Grade B)*.

2. Radical transurethral resection of muscle-invasive bladder tumors is an acceptable alternative to cystectomy in a select proportion of patients demonstrating muscle-invasive disease. Repeat TUR with downstaging to pT0 is important to assure a reasonable long-term outcome. Aggressive early and continued surveillance is mandatory *(Level 3, Grade B)*. Studies correlating molecular markers and outcomes would be useful *(Level 3, Grade B)*.

3. Minimally-invasive techniques for the treatment of muscle-invasive bladder cancer are feasible and should continue to be explored by groups with a high overall level of expertise in laparoscopic and robotic surgery. Besides improvements in blood loss, the ability to identify true advantages of these techniques in treating this disease will require meticulous longer-term follow-up of larger cohorts of patients *(Levels 3 and 4, Grade B/C)*.

4. Multimodal organ-sparing therapy should be discussed with patients as an option to treat lower volume invasive disease, and offered as an alternative for those patients with muscle-invasive disease who refuse cystectomy or are precluded for consideration of cystectomy due to severe comorbidities *(Level 3, Grade B)*.

REFERENCES

1. Hayne D, Arya M, Quinn MJ, Babb PJ, Beacock CJ, Patel HR. Current trends in bladder cancer in England and Wales.J Urol. 2004 Sep;172(3):1051-5.
2. Snyder C, Harlan L, Knopf K, Potosky A, Kaplan R. Patterns of care for the treatment of bladder cancer.J Urol. 2003 May;169(5):1697-701.
3. Hollenbeck B K, Miller D C, Taub D, Dunn R L, et al: Aggressive treatment for bladder cancer is associated with improved overall survival among patients 80 years old and older. Urology Aug 64(2);292-7, 2004.
4. Herr HW: Routine CT scan in cystectomy patients: does it change management? Urology May;47(5):785, 1996.
5. Haleblian GE, Skinner EC, Dickinson MG, Lieskovsky G, Boyd SD, Skinner DG. Hydronephrosis as a prognostic indicator in bladder cancer patients.J Urol. 1998 Dec;160(6 Pt 1):2011-4.
6. Robinson P, Collins CD, Ryder WD, Carrington BM, et al: Relationship of MRI and clinical staging to outcome in invasive bladder cancer treated by radiotherapy. Clin Radiol Apr;55(4):301-6, 2000.
7. Braendengen M, Winderen M, Fossa SD: Clinical significance of routine pre-cystectomy bone scans in patients with muscle-invasive bladder cancer. Br J Urol Jan;77(1)L36-40, 1996.
8. Bachor R, Korzerke J, Reske S N, et al: Lymph node staging of bladder neck carcinoma with positron emission tomography in patients with bladder cancer. Eur J Num Med 24;615-20, 1997.
9. Hara I, Miyake H, Hara S, Gotoh A, et al: Optimal timing of radical cystectomy for patients with invasive transitional cell carcinoma of the bladder. Jap J of Clin Oncol 32;14-18, 2002.
10. Sanchez-Ortiz R F, Huang W C, Mick R, Van Arsdalen K, et al: An interval longer than 12 weeks between the diagnosis of muscle invasion and cystectomy is associated with worse outcome in bladder carcinoma. J of Urol Jan 169(1);110-115, 2003.
11. Chang S S, Hassan J M, Cokson M S, Wells N, et al: Delaying radical cystectomy for muscle invasive bladder cancer results in worse pathological stage. J Urol Oct 170(4 Pt 1);1085-7, 2003.
12. Stroumbakis N, Herr H W, Cookson M S, Fair W R: Radical cystectomy in the octogenarian. J of Urol Dec 158;2113-2117, 1997.
13. Chang S S, Alberts G, Cookson M S, Smith J A Jr.: Radical cystectomy is safe in elderly patients at high risk. J Urol Sept 166(3); 938-41, 2001.
14. Figueroa, A. J., Stein, J. P., Dickinson, M. et al.: Radical cystectomy for elderly patients with bladder carcinoma: an updated experience with 404 patients. Cancer, 83: 141, 1998.
15. Soulie M, Straub M, Game X, Seguin P, et al: A multicenter study of the morbidity of radical cystectomy in select elderly patients with bladder cancer. J Urol Mar 167(3);1325-8, 2002.
16. Lance RS, Dinney CP, Swanson D, Babaian RJ, Pisters LL, Palmer LJ, Grossman HB.Radical cystectomy for invasive bladder cancer in the octogenarian.Oncol Rep. 2001 Jul-Aug;8(4):723-6.
17. Farnham S B, Cookson M S, Alberts G, Smith Jr, J A, et al: Benefit of radical cystectomy in the elderly patient with significant co-morbidities. Uro Oncol 22;178-181, 2004.
18. Chahal R, Sundaram SK, Iddenden R, Forman DF, Weston PM, Harrison SC. A study of the morbidity, mortality and long-term survival following radical cystectomy and radical radiotherapy in the treatment of invasive bladder cancer in Yorkshire. Eur Urol. 2003 Mar;43(3):246-57.
19. Miller DC, Taub DA, Dunn RL, Montie JE, et al: The impact of co-morbid disease on cancer control and survival following radical cystectomy. J Urol Jan;169(1):105-9, 2003.
20. Gheiler, E. L., Lovisolo, J. A., Tiguert, R. et al.: Results of a clinical care pathway for radical prostatectomy patients in an open hospital - multiphysician system. European Urology, 35: 210, 1999.
21. Klein, E. A., Grass, J. A., Calabrese, D. A. et al.: Maintaining quality of care and patient satisfaction with radical prostatectomy in the era of cost containment. Urology, 48: 269, 1996.
22. Koch, M. O., Smith, J. A., Jr., Hodge, E. M. et al.: Prospective development of a cost-efficient program for radical retropubic prostatectomy. Urology, 44: 311, 1994.
23. Baumgartner, R. G., Wells, N., Chang, S. S. et al.: Causes of increased length of stay following radical cystectomy. Urol Nurs, 22: 319, 2002.
24. Frazier, H. A., Robertson, J. E., Paulson, D. F.: Complications of radical cystectomy and urinary diversion: a retrospective review of 675 cases in 2 decades. Journal of Urology, 148: 1401, 1992.
25. Montie, J. E., Wood, D. P., Jr.: The risk of radical cystectomy. British Journal of Urology, 63: 483, 1989.
26. Rosario, D. J., Becker, M., Anderson, J. B.: The changing pattern of mortality and morbidity from radical cystectomy. BJU International, 85: 427, 2000.
27. Parekh, D. J., Gilbert, W. B., Koch, M. O. et al.: Continent urinary reconstruction versus ileal conduit: a contemporary single-institution comparison of perioperative morbidity and mortality. Urology, 55: 852, 2000.
28. Benson, M. C., Slawin, K. M., Wechsler, M. H. et al.: Analysis of continent versus standard urinary diversion. British Journal of Urology, 69: 156, 1992.
29. Esrig D, Elmajian D, Groshen S, Freeman JA, Stein JP, Chen SC, Nichols PW, Skinner DG, Jones PA, Cote RJ. Accumulation of nuclear p53 and tumor progression in bladder cancer. N Engl J Med. 1994 Nov 10;331(19):1259-64.
30. Stein JP, Ginsberg DA, Grossfeld GD, Chatterjee SJ, Esrig D, Dickinson MG, Groshen S, Taylor CR, Jones PA, Skinner DG, Cote RJ. Effect of p21WAF1/CIP1 expression on tumor progression in bladder cancer. J Natl Cancer Inst. 1998 Jul 15;90(14):1072-9.
31. Cote RJ, Dunn MD, Chatterjee SJ, Stein JP, Shi SR, Tran QC, Hu SX, Xu HJ, Groshen S, Taylor CR, Skinner DG, Benedict WF. Elevated and absent pRb expression is associated with bladder cancer progression and has cooperative effects with p53. Cancer Res. 1998 Mar 15;58(6):1090-4.
32. Grossfeld GD, Ginsberg DA, Stein JP, Bochner BH, Esrig D, Groshen S, Dunn M, Nichols PW, Taylor CR, Skinner DG, Cote RJ.Thrombospondin-1 expression in bladder cancer: association with p53 alterations, tumor angiogenesis, and tumor progression. J Natl Cancer Inst. 1997 Feb 5;89(3):219-27.
33. Byrne RR, Shariat SF, Brown R, Kattan MV, et al: E-cadherin immunostaining of bladder transitional cell carcinoma, carcinoma in situ and lymph node metastases with long-term followup. J Urol May;165(5):1473-9, 2001.
34. Matsumoto K. Shariat SF, Casella R, Wheeler TM, et al: Preoperative plasma soluble E-cadherin predicts metastases to lymph nodes and prognosis in patients undergoing radical cystectomy. J Urol Dec;170(6 Pt 1):2248-52, 2003.
35. Shariat SF, Monoski MA, Andrews B, Wheeler TM, et al: Association of plasma urokinase-type plasminogen activator and its receptor with clinical outcome in patients undergoing radical cystectomy for transitional cell carcinoma of the bladder. Urology May;61(5):1053-8, 2003.
36. Del Pizzo JJ, Borkowski A, Jacobs SC, Kyprianou N: Loss of cell cycle regulators p27(Kip1) and cyclin E in transitional cell carcinoma of the bladder correlates with tumor grade and patient survival. Am J Pathol Oct;155(4):1129-36, 1999.

37. Shariat SF, Kim J, Nguyen C, Wheeler TM, et al: Correlation of preoperative levels of IGF-I and IGFBP-3 with pathologic parameters and clinical outcome in patients with bladder cancer. Urology Feb;61(2):359-64, 2003.

38. Shariat SF, Kim JH, Ayala GE, Kho K, et al: Cyclooxygenase-2 is highly expressed in carcinoma in situ and T1 transitional cell carcinoma of the bladder. J Urol Mar;169(3):938-42, 2003.

39. Zhao H, Grossman HB, Spitz MR, Lerner SP, et al: Plasma levels of insulin-like growth factor-1 and binding protein-3, and their association with bladder cancer risk. J Urol Feb;169(2):714-7, 2003.

40. Andrews B, Shariat SF, Kim JH, Wheeler TM, et al: Preoperative plasma levels of interleukin-6 and its soluble receptor predict disease recurrence and survival of patients with bladder cancer. J Urol Mar;167(3):1475-81, 2002.

41. Malmstrom PU, Ren ZP, Sherif A, de la Torre M, et al: Early metastatic progression of bladder carcinoma: molecular profile of primary tumor and sentinel lymph node. J Urol Nov;168(5):2240-4, 2002.

42. Garcia del Muro X, Condom E, Vigues F, Castellsague X, Figueras A, Munoz J, Sola J, Soler T, Capella G, Germa JR. p53 and p21 Expression levels predict organ preservation and survival in invasive bladder carcinoma treated with a combined-modality approach. Cancer. 2004 May 1;100(9):1859-67.

43. Agerbaek M, Alsner J, Marcussen N, Lundbeck F, von der Maase H.Retinoblastoma protein expression is an independent predictor of both radiation response and survival in muscle-invasive bladder cancer. Br J Cancer. 2003 Jul 21;89(2):298-304.

44. Stein JP, Lieskovsky G, Cote R, Groshen S, et al: Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. J Clin Oncol Feb;1;19(3)l666-75, 2001.

45. Dalbagni G, Genega E, Hashibe M, Zhang ZF: Cystectomy for bladder cancer: a contemporary series. J Urol Apr;165(4):1111-6, 2001.

46. Quek ML, Stein JP, Clark PE, Daneshmand S, et al: Natural history of surgically treated bladder carcinoma with extravesical tumor extension. Cancer Sep 1;98(5):955-61, 2003.

47. Takahashi A, Tsukamoto T, Tobisu K, Shinohara N, et al: Radical cystectomy for invasive bladder cancer: results of multi-institutional pooled analysis. Jpn J Clin Oncol Jan;34(1):14-9, 2004.

48. Madersbacher S, Hochreiter W, Burkhard, F, Thalmann G N, et al: Radical cystectomy for bladder cancer today – A homogeneous series without neoadjuvant therapy. J of Clin Oncol Feb 21(4);690-696, 2003.

49. Ghoneim MA, el-Mekresh MM, el-Baz MA, el-Attar et al: Radical cystectomy for carcinoma of the bladder: critical evaluation of the results in 1.026 cases. J Urol Aug;158(2):393-9, 1997.

50. Chang S S, Smith Jr. J A, Cookson M S: Decreasing blood loss in patients treated with radical cystectomy: a prospective randomized trial using a new stapling device. J of Urol Mar 169;951-954, 2002.

51. Lee K L, Freiha F, Presti J C Jr, Harcharan S Gill: Gender difference in radical cystectomy: complications and blood loss. Adult Urology 63(6); 1095-99, 2004.

52. Bochner BH, Figueroa AJ, Skinner EC, Lieskovsky G, et al: Salvage radical cystoprostatectomy and orthotopic urinary diversion following radiation failure. J Urol Jul;160(1):29-33. 1998.

53. Schuster TG, Marcovich R, Sheffield J, Montie JE, Lee CT. Radical cystectomy for bladder cancer after definitive prostate cancer treatment. Urology. 2003 Feb;61(2):342-7; discussion 347.

54. Herr HW, Donat SM: Outcome of patients with grossly node positive bladder cancer after pelvic lymph node dissection and radical cystectomy. J Urol Jan;165(1):62-4: discussion 64, 2001.

55. Miller RS, Freiha FS, Reese JH, Ozen H, Torti FM. Cisplatin, methotrexate and vinblastine plus surgical restaging for patients with advanced transitional cell carcinoma of the urothelium. J Urol. 1993 Jul;150(1):65-9.

56. Dodd PM, McCaffrey JA, Herr H, Mazumdar M, Bacik J, Higgins G, Boyle MG, Scher HI, Bajorin DF. Outcome of postchemotherapy surgery after treatment with methotrexate, vinblastine, doxorubicin, and cisplatin in patients with unresectable or metastatic transitional cell carcinoma. J Clin Oncol. 1999 Aug;17(8):2546-52.

57. Siefker-Radtke AO, Walsh GL, Pisters LL, Shen Y, Swanson DA, Logothetis CJ, Millikan RE. Is there a role for surgery in the management of metastatic urothelial cancer? The M. D. Anderson experience. J Urol. 2004 Jan;171(1):145-8.

58. Herr HW: Extent of surgery and pathology evaluation has an impact on bladder cancer outcomes after radical cystectomy. Urology Jan;61(1):105-8, 2003.

59. Herr H, Lee C, Chang S, Lerner S: Standardization of radical cystectomy and pelvic lymph node dissection for bladder cancer: A collaborative group report. J of Urol May 171;1823-1828, 2004.

60. Herr HW, Faulkner JR, Grossman HB, Crawford ED: Pathologic evaluation of radical cystectomy specimens: a cooperative group report. Cancer June1;100(11):2470-5, 2004.

61. Herr HW, Faulkner JR, Grossman HB, Natale RB, et al: Surgical factors influence bladder cancer outcomes: a cooperative group report. J Clin Oncol Jul 15;22(14):2781-9, 2004. Epub June 15, 2004.

62. Harisinghani MG, Dixon WT, Saksena MA, Brachtel E, Blezek DJ, Dhawale PJ, Torabi M, Hahn PF. MR lymphangiography: imaging strategies to optimize the imaging of lymph nodes with ferumoxtran-10. Radiographics. 2004 May-Jun;24(3):867-78.

63. Leissner J, Hohenfellner R, Thuroff JW, Wolf HK: Lymphadenectomy in patients with transitional cell carcinoma of the urinary bladder; significance for staging and prognosis. BJU Int May;85(7):817-23, 2000.

64. Mills RD, Turner WH, Fleischmann A, Markwalder R, Thalmann GN, Studer UE. Pelvic lymph node metastases from bladder cancer: outcome in 83 patients after radical cystectomy and pelvic lymphadenectomy. J Urol. 2001 Jul;166(1):19-23.

65. Liedberg F, Chebil G, Davidsson T, Malmstrom PU, Sherif A, Thorn M, De La Torre M, Mansson W. Bladder cancer and the sentinel node concept. Aktuelle Urol. 2003 Mar;34(2):115-8.

66. Konety B R, Joslyn S A: Factors influencing aggressive therapy for bladder cancer: an analysis of data from the SEER program. J Urol Nov 170(5);1765-71, 2003.

67. Poulsen A, Horn T, Steven K: Radical cystectomy: extending the limits of pelvic lymph node dissection improves survival for patients with bladder cancer confined to the bladder wall. J Urol 160;2015-9, 1998.

68. Herr HW: Superiority of ratio based lymph node staging for bladder cancer. J Urol Mar;169(3):943-5, 2003.

69. Vieweg J, Gschwend J E. Herr H W, et al: The impact of primary stage on survival in patients with lymph node positive bladder cancer. J Urol 161;72-6, 1999.

70. Vieweg J, Gschwend J E, Herr H, et al: Pelvic lymph nodes dissection can be curative in patients with lymph node positive disease. J Urol 161;449-54, 1999.

71. Leissner J, Ghoneim H, Abol-Enein J, et al: Extended radical lymphadenectomy in patients with urothelial bladder cancer; results of a prospective multicenter study. J Urol 171;139-44, 2004.

72. Lerner S P, Skinner D G, Lieskovsky G, et al: The rationale for en bloc PLND for bladder cancer patients with nodal metastases: long-term results. J Urol 149;758-64, 1993.

73. Herr H W: Surgical factors in bladder cancer: more (nodes) + more (pathology) = less (mortality). BJU 92;187-8, 2003.

74. Bochner BH, Herr HW, Reuter VE: Impact of separate versus en bloc pelvic lymph node dissection on the number of lymph nodes retrieved in cystectomy specimens. J Urol Dec;166 (6):2295-6, 2001.

75. Konety B R, Joslyn S A, O'Donnell M: Extent of pelvic lymphadenectomy and its impact on outcome in patients diagnoses with bladder cancer: Analysis of data from the surveillance, epidemiology and end results program data base. J of Urol Mar 169;946-950, 2003.

76. Silver DA , Stoumbakis n, Russo P Fair WR, Herr HW. Ureteral carcinoma in situ at radical csytectomy:does the margin matter? J. Urol. 158:768-71, 1997.

77. Schoenberg M P, Carter H B, Epstein J I: Ureteral frozen section analysis during cystectomy: a reassessment. J Urol Apr 155(4);1218-20, 1996.

78. Johnson D E, Wishnow K I, Tenney D: Are frozen-section examinations of ureteral margins required for all patients undergoing radical cystectomy for bladder cancer? Urology Jun 33(6);451-4, 1989.

79. Kenworthy P, Tanguay S, Dinney CP. The risk of upper tract recurrence following cystectomy in patients with transitional cell carcinoma involving the distal ureter. J. Urol.155:504-5, 1996.

80. Huang W, Sanchez-Ortiz RF, Genega EM, Malkowicz SB. The significance of frozen section ureteral abnormalities at the time of cystectomy. J. Urol 171:67, 2004. Abstract.

81. Schlegel PN, Walsh PC: Neuroanatomical approach to radical cystoprostatectomy with preservation of sexual function. J Urol 38-1402, 1987.

82. Daneshmand S, Stein JP, Lessner Tj, Quek ML, Nichols PW, Miranda G, Cai J, Groshen S, Skinner EC, Skinner DG. Prognosis of seminal vesicle involvement by transitional cell carcinoma of the bladder. J.Urol (2004) 172:81-84

83. Volkmer BG, Kufer R, Maier S, Bartsch G Jr., Bach D, Hautmann, RE, Gschwend JE. Outcome in patients with seminal vesicle invasion after radical csytectomy. J. Urol 2003, 169:1299-1302.

84. Muto G, Moroni M: Seminal-sparing cystectomy and ileocapsuloplasty. Acta Urol Ital 12-47, 1998.

85. Muto G, Bardari F, D'urso L, Giona C: Seminal sparing cystectomy and ileocapsuloplasty: long-term follow-up results. J Urol 172;76-80, 2004.

86. Horenblas S, Meinhardt W, Ijzerman W, Moonen LF: Sexuality preserving cystectomy and neobladder: initial results. J Urol Sep;166(3):837-40, 2001.

87. Vallancien G, Fettouh HAE, Cathelineau X, Baumert H, Fromont G, Guillonneau B. Cystectomy with prostate sparing for bladder cancer in 100 patients: 10-year experience. J Urol 2002; 168:2413-7

88. Fang-Jian Z, Zi-Ke Q, Hui H, Zhou-Wei, L, Zhi-Gang W. Radical cystectomy with sparing partial prostate for invasive bladder cancer. Chin. J. Cancer 22:1066-1069, 2004.

89. Saidi A, Nahon O, Daniel L, Lay F, Lechevallier E, Coulange C. Prostate-sparing cystectomy: long term functional and oncological results. Prog. Urol 14:172-77, 2004.

90. Colombo R, Bertini R, Salonia A, Naspro R, Ghezzi, M, Mazzoccoli, B, Deho, F, Montorsi, F, Rigatti, P: Overall clinical outcomes after nerve and seminal sparing radical cystectomy for the treatment of organ confined bladder cancer. J Urol 2004; 171: 1819-1822.

91. Stein, J. P., Esrig, D., Freeman, J. A. et al.: Prospective pathologic analysis of female cystectomy specimens: risk factors for orthotopic diversion in women. Urology, 51: 951, 1998.

92. Ghoneim, M. A.: Surgical atlas: Orthotopic bladder substitution in women after cystectomy for bladder cancer. BJU Int, 93: 891, 2004

93. Ali-el-Dein, B., Abdel-Latif, M., Ashamallah, A. et al.: Local urethral recurrence after radical cystectomy and orthotopic bladder substitution in women: a prospective study. J Urol, 171: 275, 2004

94. Chang, S. S., Cole, E., Cookson, M. S. et al.: Preservation of the anterior vaginal wall during female radical cystectomy with orthotopic urinary diversion: technique and results. J Urol, 168: 1442, 2002

95. Ali-el-Dein, B., el-Sobky, E., Hohenfellner, M. et al.: Orthotopic bladder substitution in women: functional evaluation. J Urol, 161: 1875, 1999

96. Blute, M. L., Gburek, B. M.: Continent orthotopic urinary diversion in female patients: early Mayo Clinic experience. Mayo Clin Proc, 73: 501, 1998

97. Mills, R. D., Studer, U. E.: Female orthotopic bladder substitution: a good operation in the right circumstances]. J Urol, 163: 1501, 2000

98. Ghoneim, M. A.: Orthotopic bladder substitution in women following cystectomy for bladder cancer. Urol Clin North Am, 24: 225, 1997

99. Chang, S. S., Cole, E., Smith, J. A., Jr. et al.: Pathological findings of gynecologic organs obtained at female radical cystectomy. J Urol, 168: 147, 2002

100. Ali-El-Dein B, Abdel-Latif M, Mosbah A, Eraky I, Shaaban AA, Taha NM, Ghoneim MA.Secondary malignant involvement of gynecologic organs in radical cystectomy specimens in women: is it mandatory to remove these organs routinely? J Urol. 2004 Sep;172(3):885-7.

101. Stenzl, A., Draxl, H., Posch, B. et al.: The risk of urethral tumors in female bladder cancer: can the urethra be used for orthotopic reconstruction of the lower urinary tract? J Urol, 153: 950, 199

102. Akerlund S, Delin K, Kock NG, Lycke G, Philipson BM, Volkmann R Renal function and upper urinary tract configuration following urinary diversion to a continent ileal reservoir (Kock pouch): a prospective 5 to 11-year followup after reservoir construction. .J Urol. 1989 Oct;142(4):964-8.

103. Stein JP, Clark P, Miranda G, Cai J, Groshen S, Skinner DG. Urethral tumor recurrence following cystectomy and urinary diversion: clinical and pathological characteristics in 768 male patients. J Urol. 2005 Apr;173(4):1163-8.

104. Bochner BH, Montie JE, Lee CT. Follow-up strategies and management of recurrence in urologic oncology bladder cancer: invasive bladder cancer. Urol Clin North Am. 2003 Nov;30(4):777-89.

105. Cummings KB, Mason, JT, Correa RJJr. And Gibbons RP. Segmental resection in the management of bladder carcinoma. J. Urol. 119:56-62, 1978

106. Novick AC and Stewart BH. Partial cystectomyin the treatment of primary and secondary carcinoma of the bladder. J. Urol 116:570-75, 1976

107. Sweeney P, Kursh ED, and Resnick MI. Partial cystectomy. Urol. Clin North Am. 19:701-11, 1992

108. Kaneti J. Partial cystectomy in the management of blader carcinoma. Eur. Urol. 12:249-57, 1986

109. Holzbeierlein, JM, Lopez-Corona E, Bochner BH, Herr HW, Donat SM, Russo P, Dalbagni G, Sogani PC. Partial cystectomy:A contemporary review of the MSKCC experience and recommendations for patient selection. J.Urol 172:878-881, 2004.

110. Golijanin D. Yossepowitch O, Beck SD, Sogani P, Dalbagni G. Carcinoma in a bladder diverticulum: presentation and treatment outcome. J. Urol. 170:1761-64, 2003.

111. Sternberg CN, Pansadoro V, Calabro F, Schnetzer S, Giannarelli D, Emiliozzi P, De Pauala F, Scarpone P, DeCarli P, Pizzo M, Plantania A, Amini M. Can patient selection for bladder preservation be based on response to chemotherapy? Cancer 97:1644-52, 2003.

112. Herr HW, Bajorin DF, and Scher HI. Neoadjuvant chemotherapy and bladder –sparing surgery for invasive bladder cancer: ten-year outcome. J.Clin Oncol. 16:1298-301, 1998.

113. Barnes RW, Dick AL, Hadley HL, Johnston OL. Survival following transurethral resection of bladder carcinoma. Cancer Res. 1977 Aug;37(8 Pt 2):2895-7.

114. Henry K, Miller J, Mori M, Loening S, Fallon B. Comparison of transurethral resection to radical therapies for stage B bladder tumors. J Urol. 1988 Nov;140(5):964-7.

115. Lee SE, Jeong IG, Ku JH, Kwak C, Lee E, Jeong JS. Impact of transurethral resection of bladder tumor: analysis of cystectomy specimens to evaluate for residual tumor. Urology. 2004 May;63(5):873-7; discussion 877.

116. Bayraktar Z, Gurbuz G, Tasci AI, Sevin G. Staging error in the bladder tumor: the correlation between stage of TUR and cystectomy. Int Urol Nephrol. 2001;33(4):627-9.

117. Roosen JU, Geertsen U, Jahn H, Weinreich J, Nissen HM. Invasive, high grade transitional cell carcinoma of the bladder treated with transurethral resection. A survival analysis focusing on TUR as monotherapy. Scand J Urol Nephrol. 1997 Feb;31(1):39-42.

118. O'Flynn JD, Smith JM, Hanson JS. Transurethral resection for the assessment and treatment of vesical neoplasms: a review of 840 consecutive cases. Eur Urol. 1975;1(1):38-40.

119. Thomas DJ, Roberts JT, Hall RR, Reading J. Radical transurethral resection and chemotherapy in the treatment of muscle-invasive bladder cancer: a long-term follow-up. BJU Int. 1999 Mar;83(4):432-7.

120. Herr HW. Transurethral resection of muscle-invasive bladder cancer: 10-year outcome. J Clin Oncol. 2001 Jan 1;19(1):89-93.

121. Solsona E, Iborra I, Ricos JV, Monros JL, Casanova J, Calabuig C. Feasibility of transurethral resection for muscle infiltrating carcinoma of the bladder: long-term followup of a prospective study. J Urol. 1998 Jan;159(1):95-8; discussion 98-9.

122. Kaufman DS, Shipley WS, Friffin PP, Henery NM, Althausen AF, Efird JT. Selective preservation by combination treatment of invasive bladder cancer N.Enngl.J. Med. 1993 329:1377-1382, 1993.

123. Tester W, Capplan R, Heaney J, Venner P, Whittington R, Byhard R, True L, Shipley W. Neoaduvant combined modality program with selective organ preservation for invasive bladder cancer: Results of RTOG Phase II Trial 8802. J. Clin. Oncol. 14:119-126, 1996.

124. Shipley WU, Kaufman DS, Zehr E, Heney NM, et al: Selective bladder preservation by combined modality protocol treatment: long-term outcomes of 190 patients with invasive bladder cancer. Urology Jul;60(1):62-7L duscyssuib 67-8, 2002.

125. Cervek J, Cufer T, Zakotnik B, Kragelj, Bosrstnar S, Matos T, and Sumer-Pregelj, M. Int. J. Rad. Oncol. Biol. Phys. 41:273-278, 1998.

126. Zapatero A, Vidales C, Marin A, Cerezo L. Arellano R, Rabadan M and Perez-Torrubia A. Invasive Baldder Cancer: A single institution experience with bladder sparing approach. Int. J. Cancer 90:287-294, 2000

127. Peyromaure M, Slama J, Beuzeboc P, Ponvert D, Bebre B, and Zerbib M. Concurrent chemoradiotherapy for clinical stage T2 bladder cancer: report of a single institution. Urology 63:73-77, 2004.

128. Herr HW, Bajorin DF, Scher HI, Cordon-Cardo C. and Reuter VE. Can p53 help select patients with invasive bladder cancer for bladder preservation? J.Urol. 161:20-23, 1999.

129. Herman JM. Smith DC, Montie J, Hayman JA, Sullivan MA, Kent, E Griffin, KA, Esper P, and Sandler HM Prospective quality of life assessment in patients receiving concurrent gemcitabine and radiotherapy as a bladder preservation strategy. Urology 64:69-73, 2004.

Committee 7

Urinary Diversion

Chair

R. E. Hautmann (Germany)

Members

H. Abol-Enein (Egypt)

K. Hafez (USA)

I. Hara (Japan)

W. Mansson (Sweden)

R. D. Mills (UK)

J. D. Montie (USA)

A. I. Sagalowsky (USA)

J. P. Stein (USA)

A. Stenzl (Germany)

U. E. Studer (Switzerland)

B. G. Volkmer (Germany)

CONTENTS

Urinary Diversion

R. E. Hautmann

H. Abol-Enein, K. Hafez, I. Hara, W. Mansson, R. D. Mills, J. D. Montie, A. I. Sagalowsky, J. P. Stein, A. Stenzl, U. E. Studer, B. G. Volkmer

The goals of urinary diversion following cystectomy have evolved from simple diversion and protection of the upper tracts to functional and anatomical restoration as close as possible to the natural preoperative state. This evolution of urinary diversion has developed along the 3 distinct paths of incontinent cutaneous diversion (conduit); continent, cutaneous diversion (pouch); and, most recently, continent urinary diversion to the intact native urethra (neobladder, orthotopic reconstruction). During the last 15 years, orthotopic reconstruction has evolved from "experimental surgery" to "standard of care at larger medical centers" to the "preferred method of urinary diversion" in both sexes. The ileal conduit was described in 1950 by Bricker and has remained a standard urinary diversion against which others are judged. During the last decade, the time-honored conduit has given way to the increasingly frequent use of orthotopic reconstruction.

The International Consultation on Urological Diseases (ICUD) consultations have looked at published evidence and produced recommendations at various levels. For proper assignment to levels of evidence, one has to consider study design (prospective, retrospective), number of patients enrolled, if the study cohort consists of all patients available or not, type of assessment tool and its psychometric properties (validity/reliability), and response rate. Unfortunately, not a single randomized controlled study within the field of urinary diversion exists. Consequently, almost all studies used in this report are of Level 3 evidence (incorporates Oxford 3a, 3b, and 4) - good quality retrospective studies or case series - or Level 4 evidence (incorporates Oxford 4) including expert opinion based on "first principles" research. Therefore, the grades of recommendations given are mostly of Grade C. Grade C recommendation is given when expert opinion is delivered without a formal analytical process, such as by Delphi. In order to check the validity of the consensus reached by the diversion group the chairman has asked the committee members after the final consensus meeting to disclose experience, surgical volume, and types of diversions used at their home institutions. The result is presented in **Table 1** and is in full harmony with the recommendations the panel has made.

I. GENERAL ASPECTS OF URINARY DIVERSION

1. Indications, Contraindications, and Patient Selection

a) Substantial Change in Paradigm

The goal of patient counseling about urinary diversion should be to determine the method that is the safest for cancer control, has the fewest complications in both the short- and long-term, and provides the easiest adjustment for the patients' lifestyle, supporting the best quality of life. The paradigm for choosing a urinary diversion has changed substantially. Now all cystectomy patients are candidates for a neobladder, and we should identify patients in whom orthotopic reconstruction may be less ideal.

The proportion of cystectomy patients receiving a neobladder has increased at medical centers to 50% to 90% [1-4].

b) Patient Selection Criteria: Absolute and Relative Contraindications

An absolute contraindication to continent diversion of any type is compromised renal function as a result

Table 1. Urinary Diversions Performed by the Authors

	# of cystec-tomies	Period	Neo-bladder	Continent cutaneous pouch	Conduit	UC/TUUC	Anal	Others
Ann Arbor	643	02/95-09/04	45.1 %	1.4 %	53.5 %	0.0 %	0.0 %	0.0 %
Bern	327	01/99-09/04	54.0 %	3.0 %	37.0 %	0.0 %	3.0 %	NA
Dallas	228	01/99-09/04	30.0 %	6.0 %	64.0 %	0.0 %	0.0 %	0.0 %
Kobe	87	02/89-09/04	46.0 %	2.3 %	10.3 %	41.4 %	0.0 %	0.0 %
Los Angeles	1359	08/71-12/01	51.6 %	25.8 %	22.3 %	0.0 %	0.0 %	0.3 %
Lund	119	01/00-09/04	28.6 %	31.1 %	40.3 %	0.0 %	0.0 %	0.0 %
Mansoura	3157	01/80-01/04	39.1 %	3.5 %	34.4 %	0.0 %	23.1 %	0.0 %
Ulm	1209	01/86-09/04	66.2 %	0.5 %	22.6 %	8.9 %	1.5 %	0.4 %
Total	7129		46.9 %	7.6 %	32.7 %	2.0 %	10.6 %	0.1 %

NA - not available; UC/TUUC - cutaneous ureterostomy/transureteroureterostomy

of long-standing obstruction or chronic renal failure, with serum creatinine above 150 to 200 µmol/L. Severe hepatic dysfunction is also a contraindication to continent diversion. Patients with compromised intestinal function, particularly inflammatory bowel disease, may be better served by an incontinent bowel conduit. Orthotopic reconstruction is also absolutely contraindicated in all patients in whom simultaneous urethrectomy is indicated based on their primary tumor [5,6]. The role of relative contraindications and comorbidities is steadily decreasing. However, some of them, such as mental impairment, external sphincter dysfunction, or recurrent urethral strictures, deserve serious consideration.

Paramount to success of anal sphincter-controlled bladder substitutes is an adequate anal sphincter mechanism. Inability of the patient to retain 400 to 500 mL in the upright position for 1 hour is a contraindication [7]. Patients with neurogenic bladder are not suitable candidates either, as there may be associated anal sphincter dysfunction [8].

Urologists should first consider permanent urinary diversion for patients who undergo total cystectomy due to invasive bladder cancer. In fact, less attention has been directed to palliative urinary diversions in the treatment of bladder cancer. However, mainly in 2 situations, this type of urinary diversion has significant meaning for patients with bladder cancer. First, patients who cannot have total cystectomy because of advanced stage or poor general condition sometimes require urinary diversion due to uncontrollable symptoms (such as hematuria or pain) or uremia. Second, patients undergoing total cystectomy but not urinary diversion using intestinal segment are candidates for palliative urinary diversion. Patients with severe bowel adhesion or disease or patients who need short and less invasive surgery due to medical conditions need palliative urinary diversion.

2. Intestinal Tissues as Substitutes for the Bladder – the Phenomenon of Maturation

a) Intestinal Tissues as a Substitute for the Bladder

It would be ideal if the transposed gut segment over time lost its own organization and intrinsic control, and the smooth muscle changed properties to become more like normal detrusor and was reinervated through the sacral parasympathetic micturition pathway, so that it could contribute to bladder emptying. Potentially the greatest difference between conduit and neobladder is that the conduit functions as a somewhat longer ureter, whereas a neobladder is a substitute for the detrusor. Understanding orthotopic bladder replacement in full requires understanding the phenomenon of maturation. Unlike a conduit, the motor and pharmacologic responses of a neobladder change dramatically towards that of the original bladder [9]. Maturation of a neobladder takes anywhere from a few weeks or several months to up to 8 years [9]. Approximately 4 to 6 weeks after surgery, patients with conduits are usually into a well-established routine.

b) Gut Muscle as a Substitute for the Detrusor

1. Structural Changes

Interstitial cells of Cajal (ICC), so named for their identification with the interstitial cells observed by Cajal in the mammalian small intestine [10], possess a morphology and location specific for each of the specialized regions of the gastrointestinal tract [11]. ICC are considered of primary importance for gastrointestinal motility and are accepted as the intestinal pacemaker cells. In the small intestines of humans, ICC are located in 2 different muscular layers [12]. One population (the ICC-MP) is located between the longitudinal and circular muscle layers and has a relationship to the myenteric plexus (MP). The presence of this cell type has been correlated with slow-wave activity and found to be of fundamental importance for the occurrence of normal peristalsis [13]. The second ICC population (the ICC-DMP) is specific to the small intestine. It is located between the innermost inner circular muscle layer and outermost subdivisions of the circular muscle layer, in association with the deep muscular plexus (DMP), and its role might be related to motility specific to this gut area. Faussone-Pellegrini and coworkers have studied motor patterns, intraluminal pressures, volume capacity, and histoanatomic characteristics in full-thickness specimens from orthotopic ileal bladders removed during corrective surgery [14]. In the detubularized segments 1 to 6 years after reconstruction, the ICC-MP were scarce, and intact ICC-DMP cells and DMP nerve fibers were not seen. Furthermore, the innermost circular muscle layer could not be identified. This loss of structural organization was associated with a better functional outcome. In contrast, in the tubular segments the ICC-MP, ICC-DMP, and circular muscle layer retrained normal features for up to 3 years. After this, ICC-DMP were lost, DMP nerve fibers were scant, and the circular muscle layer appeared degenerate, but the ICC-MP remained intact. It was apparent that those reservoirs maintaining a normal ICC-MP population developed pressure waves and those segments with intact ICC-DMP had a contractile response to distention. Whether these physiological changes are a result of the ileal segment chronically functioning as a reservoir or the product of the surgical interruption of myoneural networks and the ICC syncytium is unclear **(Table 2)**.

2. Pharmacologic Changes

In experimental animals, it has been possible to follow the changes in function of implanted segments after their incorporation into the bladder, to see if they do indeed become more like detrusor in their function. Batra et al. have looked in detail at the changes in the pharmacologic properties of muscle strips taken from the ileal segment of augmentation cystoplasty in rabbit models [15]. The contractile response of the ileal segment changed from the response typical of normal ileum to a phasic response more characteristic of detrusor. Furthermore, the normal ileal relaxation reverses to a contractile response similar to that seen in the detrusor, after incorporation into the cystoplasty. The number of muscarinic receptors in the ileal segment decreased after incorporation. Further experiments comparing strip responses from tubular and detubularized segments showed that these changes were more profound in detubular cystoplasties, compati-

Table 2. Distribution of Interstitial Cells of Cajal (ICC) in Ileal Reservoirs (Humans) and Motor Response Characteristics

	Tubular		Detubularized
	Early (< 3 years)	Late (3-8 years)	Early + Late
ICC - muscular plexus	Retained	Retained	Scarce
ICC - deep muscular plexus	Retained	Lost	Lost
Deep muscular plexus nerve fibers	Retained	Scant	Disappeared
Inner circular muscle layer	Retained	Scant	Disappeared
Pressure	High	High	Low
Peristaltic activity	Normal	Normal	Absent
Contractile activity			
- Low filling	Present		
- Increased filling		Present	
Capacity	Low	Increased	High

ble with the concept that the surgical interruption of myoneural networks is the primary signal for the transformation from ileal-type to detrusor-type responses, as opposed to exposure to urine or chronic functioning as a reservoir.

c) Gut Mucosa as a Substitute for the Urothelium

Most research on transposed gut segments has focused on the potential for malignancy arising in the reconstructed bladder substitute. This will not be discussed here.

- Structural and Ultrastructural Changes in Neobladder Mucosa

Systematic follow-up of the effects of the ileal mucosa in patients with continent reservoirs reveals constant and homogeneous changes. They seem to be directly related to the time since surgery and can be subdivided into early and late. From these observations and those published previously, it seems evident that when the ileum is removed from its absorptive function and must respond to a chronic irritative stimulus, the result is biphasic; the first inflammatory phase is followed by a second regressive phase in which the epithelium tends to assume a morphology similar to the urothelium, more adapted for coating and protective functions than for absorption. Therefore, it is not surprising that it should be the structures responsible for absorption (brush border and villi) that suffer the most damage. Considering that in a normal ileum the villi increase the absorptive surface eightfold in comparison to a flat surface, their atrophy greatly reduces the area of absorption and, consequently, the risk of metabolic alterations. Paneth's cells (which produce digestive enzymes) and goblet cells seem more tolerant to the prolonged contact with urine and the regressive phenomena appear significantly later. Because the villi and crypta are markedly shorter, the ileal mucosa tends to become linear **(Table 3)**. This also explains the alternation of areas in which cells with few microvilli (corresponding to the primitive surface epithelium) are predominant with others in which goblet cells (corresponding to the primitive glandular epithelium) are predominant. After four years of follow-up, the areas of villous atrophy predominate, Paneth's and goblet cells are scanty, and only few residual glands are visible. The resulting epithelium has lost its absorptive and secretory functions to acquire the function of a urinary reservoir. Electron microscopy and enzyme histochemistry also showed that in the epithelial cells there was a reduction in the number of cell organelles and a decreased metabolic activity

Table 3. Structural and Ultrastructural Changes in Ileal Neobladder Mucosa

Early (< 1 year) Inflammatory	**Late (1-4 years) Regressive**
Infiltration of lamina propria	Villous atrophy
Rarefaction of terminal web	Shortening crypts
Goblet cell hyperplasia	Goblet cells decreased (> 4 years)
Reduction of microvilli - toxic effect of urine	Flat mucosa
- low pH	Stratified epithelium
- ischemia	
- lack of contact with intestinal content	

[16]. Progressive mucosal atrophy has been observed in continent colonic reservoirs. They show similar, although much less severe, changes of the microvilli [16,17]. Follow-up studies in patients with ileal conduits also showed atrophic changes with reduction of the villous height, although there are wide variations between different authors and individual patients [18].

The final result of the process of maturation can be summarized as follows:

- Structure and pharmacologic response of the implanted ileum (not colon) changes to detrusor-type responses.
- Structural and ultrastructural changes in ileal (not colonic) mucosa lead to a primitive surface and glandular epithelium similar to urothelium.
- The transformation of the ileal mucosa minimizes the risk of metabolic complications. Consequently, Mother Nature has engineered a new bladder almost as good as the one given initially [19].

3. Detubularization

Although it would be ideal if the bowel segment could contribute to voluntary voiding, in reality this does not seem to happen, thus, a highly compliant neobladder is the desired outcome [20]. Detubularized bowel segments provide greater capacity at lower pressure and require a shorter length of intestine than do intact segments. Four factors account for their superiority: their configuration takes advantage of the geometric fact that volume increases by the

square of the radius so that a pouch has a larger diameter than a tube; they accommodate to filling more readily because, as La Place´s law states, the container with the greater radius and, thus, the greater mural tension, will hold larger volumes at lower pressure; compliance is superior to that of the tubular bowel; and contractile ability is blunted by the failure of contractions to encompass the entire circumference [21].

These theoretical considerations are consistent with clinical observations showing that detubularization increases reservoir capacity substantially, and delays the onset and reduces the amplitude of the pressure rise produced by contractions. These findings account for the markedly improved nocturnal continence (80% vs. 17% at 2 years), the longer voiding intervals (4 vs. 2.5 hours at 1 year), and the predisposition to urinary retention (25% vs 0% at 1 year) with detubularized versus tubularized bladder substitution. Altering the shape of a reservoir from spherical to ellipsoid is calculated to have only a slight effect on its mechanical characteristics. Consequently, the essence of detubularization is to create a reservoir with high capacity, while shape is of secondary importance [22].

4. Which Gut Segment Should Be Used

a) Biological Consequences of Exposing Gut Mucosa to Urine

Intestinal segments vary in handling of solutes. Length of bowel segment, surface area, duration of urinary exposure, solute concentration, pH, renal function and urine osmolality all play a role. The reservoir surface is exceedingly difficult to estimate. There is no difference between ileal and colonic mucosa in regard to sodium absorbing capacity. However, in the colon, chloride absorption and bicarbonate excretion are more pronounced, and there is increasing evidence to suggest that inherent chloride absorption is maintained when in contact with urine [16,23-27]. Therefore, it may be preferable to use ileum rather than colon for bladder reconstruction to reduce the risk of hyperchloremic acidosis, particularly in the presence of renal impairment. There are clear differences between ileum and colon in regard to metabolic consequences (*see Section I.2.c: Gut Mucosa as a Substitute for the Urothelium*), but this is only one consideration when planning orthotopic reconstruction. However, due to the reduced absorption of electrolytes in ileal urinary reservoirs, it seems that ileum is preferable to large bowel for storing urine, at least in patients with decreased kidney function and increased risk for metabolic disorders [28,29]. An obvious advantage of the sigmoid reservoir is its ease of accessibility. However, there is the substantial disadvantage of high reservoir pressures as compared to cecum or ileum that is confirmed by most urodynamic studies [30-32]. We recommend using a sigmoid reservoir only in cases in which ileum or right colon are not available [2]. An advantage of the ileocolonic reservoir is its greatest initial volume as a reservoir. However, it requires mobilization of the entire right colon and is potentially the most tedious procedure to perform [33]. The greatest disadvantage of the procedure is the loss of the ileocecal valve. There is also a greater risk of vitamin B12 deficiency secondary to resection of the terminal ileum.

Most investigators have reported on one single type of diversion. Santucci et al. performed 6 different continent urinary reservoir operations and revealed remarkably different continence rates and urodynamic data. Their experience suggests that neobladders composed of stomach or sigmoid should be used only under unusual circumstances because of the high rates of incontinence [32]. Of course, other patient and surgeon issues might supersede these guidelines. Surgeon preference, length of surgery, ease of construction, potential need for revision, differences in body image, and other patient characteristics are among the many factors that must be considered when choosing which type of orthotopic reconstruction to provide each individual patient.

b) Capacity and Pressure Characteristics of Reservoirs (Table 4)

Berglund et al. have studied the volume capacity and the pressure characteristics of 3 types of intestinal reservoirs - the continent ileostomy, the continent ileal urostomy, and the continent cecostomy - at varying intervals after surgical construction of the reservoirs [34]. The volume increases of the ileostomy and the urostomy reservoirs were almost identical but were significantly greater than that of the cecal reservoir. The basal pressure was low in all types of reservoirs, although somewhat higher in the cecal reservoir at greater filling volumes. In the ileal reservoirs, motor activity appeared at a filling volume of about 40% of the maximal capacity, whereas in the cecal reservoir motor activity was recorded at all filling levels. The motor activity increased with greater volumes. The amplitude of the highest pressure wave in the cecal reservoir was twice as high as that of the ileal reservoirs. The motor activity of the cecal reservoir, calculated in 2 different ways, was 10 to 20 times greater than in the ileal reservoirs.

Table 4. Capacity and Pressure Characteristics of Reservoirs

	Ileum	*Colon*
Volume increase		
- Initially		Advantage
- Late	Advantage	
Capacity		
- First contraction	Advantage	
- Maximum contraction	Advantage	
Involuntary contractions		
- Maximum amplitude	Advantage	
Motor activity (calculated)		10 – 20x higher
Distensibility		Advantage
Ileum (ICL) > Colon (CCL) > Ileum (ILL) > Colon (CLL)		
Compliance	Advantage	

CCL - colonic circular layer; CLL - colonic longitudinal layer; ICL - ileal circular layer; ILL - ileal longitudinal layer

An interesting comparison of the properties of different gut smooth muscles was made by Hohenfeller et al., who examined the ileal and cecal segments incorporated into a canine model of the Mainz bladder substitution. Sonomicrometry transducers were implanted in the circular and longitudinal muscular layers to allow measurements of their properties. It was found that the circular ileal layer was most distensible, followed by the colonic circular and the longitudinal ileal layers. The longitudinal layer of the colonic segment was relatively indistensible [35]. Clinically significant cystoplasty contractions are arbitrarily defined as those 40 cm H_2O in amplitude or higher that begin to occur at low volumes (less than 200 mL). The incidence of such contractions was 70% for tubular ileocystoplasties, 36% for tubular right colon, 10% for detubularized colon, and none in the patients with detubularized ileocystoplasties [36]. The detubularized ileal reservoir for either continent stomal diversion or bladder replacement would seem to constitute the ideal low pressure reservoir.

5. Metabolic Consequences

a) Hyperchloremic Metabolic Acidosis

In 1950, Ferris and Odel were the first to describe the unusual electrolyte pattern characterized by hypokalemia, hyperchloremic acidosis, and absorption of ammonia in patients with ureterosigmoid diversion [37]. The use of colon for urinary reservoirs may lead to serum hyperosmolarity and subsequent decreased aldosterone release with increased antidiuretic hormone release. This metabolic disturbance results in highly concentrated urine from which the colonic mucosa will absorb more sodium and chloride. Classically, these patients become acidotic and with close scrutiny all have at least a mild degree of metabolic acidosis following continent diversion using colonic segments [38]. The principal mechanism leading to the production of acidosis is thought to be ammonium reabsorption. Ammonia, ionized ammonium, and chloride are reabsorbed when ileum or colon is exposed to urine [38,39]. The acid load comes mainly from the reabsorption of ammonium chloride. Quantitatively, hydrogen reabsorption is minimal and bicarbonate secretion is exceeded many times by ammonium reabsorption. Ammonia may diffuse freely across the bowel mucosa, and, as urinary pH increases, absorption will increase. However, there is evidence that reabsorption of ionized ammonium occurs, which can be seen at luminal pH 5 when ionized ammonia is present in only small amounts. Also, in brush border membrane studies, ammonium transport can be demonstrated against an ammonia concentration gradient [40]. If the sodium concentration in a urinary reservoir is increased, ammonium absorption is decreased. Recent evidence has suggested that ammonium absorption may occur through substitution for sodium in the sodium-hydrogen antiport with the ammonium ion acting as a competitive inhibitor of sodium uptake [41]. There is also evidence of ionized ammonium absorption through potassium channels, although this is not thought to contribute significantly to acidosis [40]. Current treatment of

hyperchloremic metabolic acidosis involves alkalizing agents and/or blockers of chloride transport. Oral sodium bicarbonate is effective in restoring normal acid base status, but intestinal gas formation can be a problem, and the dose is not easily predictable. Alternatively, sodium citrate may be given but the taste is unpleasant. Sodium supplements may increase blood pressure or cause fluid retention and pulmonary edema in patients at risk. If excessive sodium loads are undesirable, chlorpromazine or nicotinic acid may be used, although they are also not without significant side effects. They act through inhibition of cyclic adenosine monophosphate, thereby impeding chloride transport, and alone will not correct acidosis but will alleviate the situation, allowing a reduced dose of alkalizing agent [40].

The key to successful management is proper diagnosis by exclusion of urinary infection and sepsis, and awareness of the salt-losing syndrome. Proper treatment includes catheter reinsertion to ensure good drainage and to minimize further chemical reabsorption, rehydration with intravenous normal saline, and correction of acidosis with sodium bicarbonate. Patients with incomplete emptying and those with reduced renal function are most vulnerable to these metabolic problems [43,44].

b) Hypokalemia and Other Electrolyte Abnormalities

Hypokalemia and total body depletion of potassium may be seen with ileal and colonic urinary intestinal diversion, although more frequently with the latter as ileal segments absorb more potassium. In one study, patients with ureterocolonic diversion had a 30% decrease in total body potassium and those with an ileal conduit had up to a 14% decrease [45].

The potassium depletion is probably due to renal potassium wasting as a consequence of renal damage, osmotic diuresis, and gut loss through intestinal secretion. The latter probably has a relatively minor role quantitatively. It has been shown that ileal segments, when exposed to high concentrations of potassium in the urine, reabsorb some of the potassium, whereas colon is less likely to do so [26]. Therefore, treatment with potassium citrate is often most appropriate for patients with colonic reservoirs.

Acid base balance should be monitored regularly in patients with continent diversion, particularly in the early postoperative period. One should have a high index of suspicion if patients with urinary diversion have nonspecific illness. Acidosis and electrolyte disturbance should be excluded early. Normal serum pH and bicarbonate do not exclude a severely compensated metabolic acidosis, and blood gas analysis and body weight measurements are required. If possible, these patients should not be given hydrogen antagonists or proton pump inhibitors as they will contribute to systemic acidosis by preventing hydrogen excretion with subsequent bicarbonate preservation on the cellular side [29].

Hypocalcemia and/or hypomagnesemia severe enough to cause symptoms do occur, but they are infrequent complications of urinary intestinal diversion. Hypocalcemia is a consequence of depleted body calcium stores and excessive renal wasting. The chronic acidosis is buffered by carbonate in the bone with subsequent release of calcium in the circulation. The kidneys clear the released calcium resulting in a gradual decrease in body calcium stores. There is also an inhibition of renal tubular absorption of calcium directly by sulfate and enhanced by acidosis. Treatment consists of calcium therapy [46].

Magnesium deficiency is usually due to nutritional depletion but it may be a result of renal wasting. The altered calcium metabolism, acidosis, and sulfate metabolism all interfere with renal tubular magnesium reabsorption [46].

c) Altered Sensorium

Altered cerebration may occur as a consequence of magnesium deficiency, drug intoxication, or abnormalities in ammonium metabolism. Symptoms due to magnesium deficiency are usually observed when magnesium concentration is less than 1 mEq/L. The symptoms are due to neuromuscular dysfunction and consist of personality changes that may lead to delirium and psychosis, muscular weakness, tremors, and, rarely, tetany. Seizures and death may occur if the deficiency persists. The most common cause of an altered sensorium is the consequence of altered ammonia metabolism [42].

d) Disorders of Hepatic Metabolism

When intestine is interposed in the urinary tract, there is a marked increase in the absorption of ammonia into the portal circulation due to the increased load of ammonia from the urine. The liver clears the increased ammonia load resulting in imperceptible alterations in its serum concentrations. Ammonia is incorporated into the ornithine cycle to create urea. It has been shown that the liver rapidly adapts by increasing its capacity for ureagenesis [47]. This hepatic reserve for ammonia clearance is

great, and it is unlikely that acute changes in ammonia loads result in significant alterations in serum ammonia levels when hepatic function is normal. However, small amounts of endotoxin can significantly affect hepatic metabolism and transport [48]. Hyperammonemic encephalopathy has been reported most commonly in patients with ureterosigmoidostomy [49]. The patients who suffer ammoniogenic coma with clinical normal liver function generally have a significant infection with a urease-producing bacterium. Often the infection is associated with obstruction of the urinary tract. The direct access of bacteria and endotoxin to the liver via the portal circulation results in altered hepatic metabolism without significant alterations in hepatic enzyme concentrations [42].

e) Abnormal Drug Metabolism

Drugs secreted unchanged in the urine and absorbed by the intestinal tract are most likely to lead to problems. Of particular interest are chemotherapeutic agents used in the treatment of bladder cancer. Methotrexate toxicity in patients with ileal conduits is well recognized [50,51]. Patients with continent diversion receiving chemotherapy should be monitored closely, stay well-hydrated, and have the reservoir drained during treatment. Other drugs reported to be absorbed from intestinal segments in the urinary tract include phenytoin, theophylline, and antibiotics [25,52]. Diabetics appear to have an enhanced ability to absorb glucose from intestinal reservoirs and, therefore, screening with urine tests may be inaccurate, and so surveillance of known diabetics should rely on blood tests [53].

f) Vitamin B12 Deficiency

Vitamin B12 absorption occurs primarily in the terminal ileum. Thus, use of ileum, and, to a lesser degree, the ileocecal segment, for orthotopic neobladder construction may lead to chronic vitamin B12 deficiency in some patients. Chronic vitamin B12 deficiency is insidious and may result in irreversible neurologic and hematologic sequelae. The absolute prevalence and clinical significance of this entity in neobladder patients is undetermined. Vitamin B12 absorption decreases with age and with declining renal function. From baseline levels, depletion of body stores of vitamin B12 requires 3 to 5 years. All of these variables account for the wide range of vitamin B12 deficiency reported (0%-33%) in various series [42,54-59]. Neobladders consisting entirely of colon segments have been reported not to affect vitamin B12 levels [54,59]. One group reported that monitoring levels of vitamin B12 alone underestimates the true incidence of tissue cobalamin deficiency [56]. Abnormal levels of vitamin B12, methylmalonic acid, or homocysteine were observed in 14%, 29%, and 43% of 12 patients with ileal neobladders at a mean follow-up of 4.6 years (range 0-10 years). Other investigators report that holotranscobalamin levels are more accurate and specific indicators of tissue cobalamin deficiency and are decreased in one-third of patients in long-term follow-up [58]. Still other investigators report that routine administration of vitamin B12 every 6 months prevents vitamin B12 deficiency in all patients at 10 year follow-up [57]. The merits of monitoring vitamin B12 levels versus routine chronic supplementation may be debated from a cost and practical standpoint. However, as survival after treatment for bladder cancer steadily improves and the number of patients with continent urinary diversions increases, this issue may assume increasing importance.

g) Decreased Linear Growth

There is considerable evidence to suggest that urinary intestinal diversion has a detrimental effect on growth and development. Long-term follow-up for rats with unilateral ureterosigmoidostomy demonstrated significantly decreased femoral bone length compared to non-diverted controls [60]. Numerous clinical studies have demonstrated decrease in linear growth in children after ileal bladder augmentation [61,62].

h) Bone Demineralization

A worrying potential long-term effect of urinary intestinal diversion is bone demineralization, which has been most clearly demonstrated in children with rickets and adults with osteomalacia after ureterosigmoidostomy [63,64]. In these conditions, bone mineral loss is replaced by osteoid, resulting in decreased bone strength. The etiology is complex but long-term changes in acid base balance are likely the major contributory factor. Chronic acidosis may affect the skeleton in 3 ways:

a) Bone minerals, including calcium, carbonate and sodium, act as buffers in exchange for hydrogen ions, thus decreasing the skeletal calcium content [65,66].

b) Acidosis impairs 1-hydroxylation of 25-hydroxycholecalciferol in the kidney and activated vitamin D deficiency results in bone mineralization defects [67].

c) Acidosis activates osteoclasts, resulting in bone resorption [68]. In addition, there may be poor intestinal absorption of calcium and vitamin D following ileal resection.

Patients with preexisting renal disease will be more prone to acidosis and also may have impaired activated vitamin D production secondary to tubular cell damage, and so they are at particular risk. Changes in acid base balance may be subtle, and, as experiments in animals with urinary diversion have demonstrated, oral supplementation with bicarbonate can prevent demineralization in the absence of significant systemic acidosis [66]. Some institutions now recommend oral sodium bicarbonate when base deficit is more than 2.5 mmol/L [69]. Patients may be asymptomatic, complain of pain in weight-bearing joints, or present with fractures. Long-term follow-up of patients with myelomeningocele with intestine in the urinary tract has revealed an increased number of fractures and intervention rate for spinal curvature with increased incidence of non-union and delayed healing compared to controls treated with intermittent catheterization [61]. This finding suggests that, although severe defects in bone demineralization are not often seen, it is likely that many patients have subtle alterations in bone mineral density with prolonged follow-up after urinary intestinal diversion. Women, who are susceptible to postmenopausal osteoporosis, and young patients, who are growing and may live with urinary diversion for many years, seem to be at greatest risk. Laboratory tests may be normal despite symptoms, although in general there is reduced serum calcium and phosphate with elevated alkaline phosphatase [66,70]. Parathormone levels are usually not elevated and serum levels of activated vitamin D may be normal. Radiological appearances are usually also normal. Bone densitometry is useful but may not detect subtle changes without repeat testing. Bone biopsy may be the only way to confirm diagnosis. Therefore, follow-up is difficult, especially as the process takes many years. With normal renal function, severe bone defects are not common after continent diversion with ileal or colonic reservoirs. The risk may be slightly higher with colonic reservoirs as calcium re-uptake is less efficient from colonic than ileal segments [70]. Follow-up studies have revealed contrasting findings. Normal bone mineral density has been reported in patients with orthotopic ileal reservoirs up to 17 years following urinary diversion [71,72]. Also, bone mineralization was not affected in patients with continent cecal reservoirs followed more than 5 years [73]. A recent study demonstrated significantly decreased bone mineral density and increased urinary pyridinium cross-links associated with metabolic acidosis after Indiana and Kock pouch formation [74]. Also, urinary diversion with the ileal Kock reservoir reduced bone mineral density of the spine and total skeleton compared to normal age matched controls [75]. Additional prospective studies with longer follow-up are required before the risks of bone demineralization and subsequent fracture rate associated with continent diversion are known. The contradictory reports on bone mineral density following urinary intestinal diversion might be related to different bone densitometers and lack of pediatric normal data in first generation densitometers. Patients who present with osteomalacia should have acid base abnormalities corrected first, which may relieve symptoms and lead to remineralization [63,76]. If remineralization does not occur, further treatment should be given with activated vitamin D and calcium supplements [64].

i) Mucus Production

Bowel mucosa secretes mucus made up of a glycoprotein core of long sequence amino acids with a molecular weight of 2 to 20 million Daltons with side chains of monosaccharides wrapped around the protein core [77,78]. The glycoprotein core is made by the rough endoplasmic reticulum of goblet cells. In solution, the glycoprotein becomes hydrated and viscous. Continent urinary diversions produce around 35 grams of mucus per day [79]. In the early postoperative period, the indwelling catheters must be carefully irrigated to prevent initial mucus buildup within the diversion [80,81]. Patients with good spontaneous voiding and complete emptying usually pass the mucus spontaneously in the urine. In contrast, patients with incomplete emptying or those performing CIC may need to irrigate to remove retained mucus. Mucus accumulation may occur in some neobladder patients with apparently normal voiding. Some investigators report that an increase in mucus production may be an early sign of urinary infection and irritation in the diversion [82]. Early or late mucus retention has been reported in 0.58% to 2% and in 3% of patients, respectively [1,83]. N-acetylcysteine and urea are effective mucolytic agents [77,84,86]. N-acetylcysteine is a water-soluble thiol that reduces the disulfide bonds in the mucus. In contrast, carbocysteine causes mucus precipitation rather than dissolution. Successful dissolution of a mucus plug in an ileal ureter has been reported after initial instillation of 300 mL of 1% N-

acetylcysteine through a nephrostomy tube followed by oral N-acetylcysteine 700 mg 4 times daily [87]. Irrigation of urinary diversions with N-acetylcysteine at smaller volumes and higher concentrations (30 mL, 20%) also has been found to be effective [77,79]. Urea appears to break the hydrogen bonds within mucus and is faster and more potent than N-acetylcysteine [77,79,85]. In vitro, 12 grams urea per 100 grams mucus produced 90% and 100% dissolution of mucus within 5 minutes and 30 minutes, respectively. Once a large mucus plug occurs, none of the drugs may be effective, and manual evacuation through a large resectoscope sheath is most effective [88]. Oral therapy with ranitidine has been reported to decrease mucus production in patients with urinary diversions [78]. However, in another prospective, randomized study of patients with urinary diversions, neither taking ranitidine nor aspirin produced any change in mucus production [89]. Whether chronic adaptation of bowel mucosa incorporated into urinary diversions leading to decreased mucus production occurs is controversial. Some investigators report decreased mucus over time [90], while others do not (*Level 3,* [91]). Ileal mucosa appears to atrophy over time when exposed to urine [92-94], while colonic mucosa is preserved and retains its mucus and immunoglobulin secretory capacities [95]. The minority of patients with recurrent mucus retention must be made aware of the importance of this problem, should be instructed in periodic catheter irrigation and mucus evacuation, and should be offered a trial of medical therapy with N-acetylcysteine or urea.

6. Postoperative Rehabilitation (First 30 Days)

There are 2 major goals in the early postoperative period: to minimize postoperative complications and to return the patient to the usual state of health.

a) Initial Postoperative Course

Early postoperative care in the post-cystectomy patient is driven by the goals of minimizing complications, educating patients, and providing cost-effective care. The use of clinical pathways has been shown to facilitate attainment of all of the above goals. The pathways provide guidelines for patient care, but the clinician should not hesitate to diverge from the pathway based on clinical event. Routine postoperative ICU monitoring is not necessary. Chang et al. reported on 304 patients after radical cystectomy, 94% of whom were admitted to the general care floor and managed with clinical pathways [96]. Those patients admitted to the ICU had greater resource utilization and longer hospital stays, but tended to be sicker overall than the floor patients (as measured by ASA score). The authors concluded that initial postoperative cystectomy care could be safely conducted on a general care floor, with ICU admission reserved for the sickest and most labor-intensive patients. Postoperative medications should reflect the need for prophylaxis, pain control, and management of a given patient's comorbidities. Adequate pain control enables early ambulation and deep breathing, thus reducing the risks of deep venous thrombosis and pulmonary complications. Epidural catheters or patient-controlled analgesia are effective means of individualizing delivery of pain medications [97]. Histamine blockers or proton pump inhibitors should be used for prophylaxis against ulcers, and either compression devices or low molecular weight heparin should be utilized for DVT prophylaxis. Incentive spirometry, coughing, and deep-breathing exercises help to minimize postoperative respiratory complications. The routine use of nasogastric decompression is unnecessary. Cheatham et al. compared patients with routine postoperative nasogastric decompression with those in whom nasogastric decompression was performed for clinical indications only; patients who did not receive a routine nasogastric tube fared better in terms of complications such as fever, atelectasis, and pneumonia, and advanced more quickly to a regular diet [98]. In another study, patients who were given metoclopramide in association with early removal of the nasogastric tube (within the first 24 hours after surgery) had fewer episodes of atelectasis, more rapid return of bowel function, and earlier ability to tolerate a regular diet [99]. Inman et al. retrospectively analyzed 430 patients after cystectomy and urinary diversion, and found that prolonged gastric decompression was associated with delayed return of bowel function and prolonged hospitalization [100]. Mohler and Flanigan showed that malnourished patients had poorer outcomes compared with nutritionally optimized patients [101]. The authors found that the need for nutritional support postoperatively was associated with increased morbidity and mortality. Their results suggest that preoperative optimization of nutrition status is crucial.

b) Urinary Catheters

Decompression of the detubularized bowel segment used for the neobladder is critical to ensuring good healing of the suture lines and prompt emptying of

the neobladder. The urinary catheter should be irrigated frequently to clear the bladder of mucus, beginning on the first postoperative day [102]. It is important that the patient be adept in catheter irrigation in order to avoid postoperative mucus retention and possible compromise of the neobladder. The duration of catheter drainage is individualized, but typically is 2 to 3 weeks. Ankem et al.'s recent study demonstrated that routine pouchograms before catheter removal were not necessary [103].

c) Postoperative Visit

The first postoperative visit is typically 2 to 3 weeks after surgery, at which time the Foley catheter is removed. After Foley removal, the patient is instructed to empty the neobladder regularly (every 2-4 hours). Patients are taught to intermittently self-catheterize if necessary to accomplish this goal; hypercontinence is more common in women than in men. Patients should be told that the normal sensation of bladder fullness will be absent, although most patients report an awareness of pelvic sensation that they will recognize as filling of the neobladder [104]. Patients also need to be taught how to void with a neobladder. Pelvic floor muscle exercises, as well as increasing intraabdominal pressure (using the Valsalva or Crede maneuvers), allows controlled voiding and continence between voids [105,106]. Adequate fluid intake should be encouraged to facilitate voiding and minimize the likelihood of obstruction by mucus [107].

Summary

Postoperative care of patients after neobladder construction is focused on minimizing complications as well as providing patient education. Prophylactic measures should be employed to reduce the occurrence of predictable complications. Early involvement of the patient and family in care of the neobladder is invaluable in establishing realistic expectations for recovery, improving communication with members of the health care team, and promoting well-being.

7. Long-term Follow-up

Follow-up after radical cystectomy and neobladder formation should address the following aspects: local and distant cancer control, long-term renal function, long-term metabolic abnormalities, and long-term functional outcome of the neobladder. The last 3 aspects are covered in other sections. Cancer recurrence remains a major concern for the patient and the physician. Tumor can recur either locally or distantly. Local recurrence may occur in the remaining urothelium which includes the urethra, the ureter, and the renal pelvis, or may present as local recurrence in the pelvis. Distant recurrence may manifest as lymphatic or remote organ spread. In order to detect these recurrences at the earliest time, follow-up protocols were established based on history, physical examination, laboratory studies, and imaging.

a) History and Physical Exam

Patients are evaluated postoperatively at regular intervals. The majority of patients who recur do so in the first 2 years after surgery. Thus, most authorities recommend close observation during the first 24 months [80,108]. Patients are usually evaluated and examined at months 1, 3, 6, 12, 18, and 24 postoperatively, then annually thereafter for at least 5 years. A careful interval history and physical examination (including pelvic or rectal examinations) should be performed as these elicit symptoms of tumor recurrence or metabolic derangement. Complaints such as weight loss, progressive weakness, or extremity numbness may raise suspicion for malnutrition or vitamin B12 deficiency. Hematuria or persistent pelvic, perineal, or bone pain may be manifestations of local tumor recurrence or distant metastases.

b) Imaging

Postoperative imaging should focus on morphologic changes in the upper tracts as well as detection of de novo urothelial tumors and surveillance for possible pelvic recurrence and distant metastatic disease. Imaging is also useful for diagnosis and management of postoperative complications [109]. The choice of imaging modality is based on patient characteristics as well as clinical indications. Computed tomography and ultrasonography are useful in searching for extrinsic mass lesions such as urinoma, abscess, hematoma, lymphocele, or recurrent tumor. Surveillance for upper tract recurrence may be performed by intravenous urography, or, more recently, CT urography. Ultrasonography and magnetic resonance urography are useful in patients with renal insufficiency or contrast allergy [110]. Bone scans are only indicated in patients with bone pain suspicious for metastases or in patients with advanced disease (≥ T3 and pN+) [111].

c) Urine Cytology and Urethral Wash

The choice of urinary diversion may alter the cyto-

morphologic features of urothelial cells [112]. Our literature search found no studies evaluating voided cytology following neobladder diversion; however, we believe that urine cytology does have a role in surveillance, especially in high-volume centers with experienced cytopathologists. More commonly, urethral wash cytology is used [111,113]. Cytology from urethral washings is both sensitive (90%) and specific (100%) [113,114], and permits early diagnosis of local urethral recurrence, hopefully improving survival [115-117]. However, a recent retrospective analysis from Memorial Sloan Kettering Cancer Center found no difference in survival between patients with symptomatic urethral recurrences and those who were diagnosed by urethral wash cytology [118].

d) Laboratory Studies

At each patient visit, a complete blood count and comprehensive metabolic panel should be performed. In patients with ileal neobladders, vitamin B12 and folic acid levels are measured 2 years after surgery. Urinalysis and urine culture are not routine but may be helpful in symptomatic patients. It is important to remember that urine cultures from neobladders (unlike conduit diversions) are typically sterile. However, about half of neobladder patients who void normally will have a positive urine culture. More than half of these patients will develop uncomplicated urinary tract infection and 18% will develop urosepsis over a 5-year period [119].

Summary

Long-term follow-up of patients after neobladder diversion is centered on surveillance for local and distant metastatic disease, functional outcome of the neobladder, preservation of renal upper tracts, and early detection and treatment of metabolic abnormalities. Using a scheduled follow-up protocol enables both the clinician and the patient to easily identify the laboratories and imaging to be performed at each interval.

8. Quality of Life After Radical Cystectomy

At present, the optimal form of urinary diversion after cystectomy for muscle-invasive bladder cancer remains a controversial issue. It has been suggested that orthotopic bladder substitution allows a life similar to that in individuals with a native lower urinary tract. In fact, Henningsohn et al. found similar well-being and subjective quality of life (QoL) in recurrence-free Danish patients as in a frequency-matched control population (*Level 3,* [120]). Is this result merely an expression of the well-known “response shift” or is orthotopic substitution a true restitutio ad integrum in most aspects of life? A major obstacle for all researchers in the field is the lack of a universal definition of the term “quality of life.” Thus, it may differ between cultures, countries, and, consequently, study groups. It is doubtful if the introduction of “health-related quality of life” has enhanced our ability to determine what to include or to leave out, as it is unlikely that one can divide quality of life into its health- and non-health related components. The conceptual vagueness is impressively reflected by the whole host of measuring modalities (open or structured face-to-face interview, telephone interview, proxy rating, and self-report), and the multitude of generic and disease-specific questionnaires available. Ad hoc questionnaires have often been used until recently. Especially in postal questionnaire surveys, missing data and low response rates remain major problems. The use of a neutral third party for carrying out studies may be of importance (*Level 2,* [121]). Today, it is agreed that instruments used should be tested for validity and reliability. Well-known generic instruments include SF-36, SIP, NHP, and EQ. The instruments HADS, POMS, PAIS, and BDI measure mental and psychological distress. The most commonly used cancer-specific instruments are QLQ-C30 from the EORTC, FLIC, FACT-G, and CARES-SF. There are a few bladder cancer specific instruments available (QLQ-BLM30 and QLQ-BLS 24 from EORTC, FACT-BL, and recently FACT-VCI). A relevant question is when adaptation after cystectomy is optimal. Kulaksizoglu et al. studied patients prospectively and found that the time frame for adaptation is about 1 year (*Level 2,* [122]). In the study by Hardt, mental quality of life showed a slight increase and physical quality of life a slight decrease from preoperative assessment to follow-up at 1 year (*Level 2,* [123]). Speculated reasons for the change in mental quality of life were that fear and worry from initial diagnosis and upcoming surgery disappears after surgery or the influence of response shift (a shift in patients judgment of quality of life). For physical quality of life, diversion of urine and abdominal scar were speculated explanations. Coping strategies were studied, and a buffering effect of a continent diversion for depressive coping on mental quality of life was noted.

a) Conduit Diversion versus Continent Cutaneous Diversion

There is only 1 prospective study, first reported by Hardt et al. (*Level 2,* [123]). They found that perceived global satisfaction was high with both methods and that the majority of patients would choose the same method again. An extension was recently published [124]. Mental quality of life showed a slight increase and physical quality of life a slight decrease from preoperative measurement to follow-up at 1 year after surgery. This report focused on coping strategies.

Similar results, without differences between the groups, were obtained in 5 retrospective studies, which all used ad hoc instruments (*Level 3*, [125-129]). These studies all note that stomal problems are more frequent among conduit patients.

b) Conduit Diversion versus Orthotopic Bladder Substitution

Since 1995, 8 studies, all retrospective, have been published (*Level 3*, [130-137]). All except 3 used established validated instruments [130-132]. One of the studies included only 6 conduit patients. Apart from that study, only the study by Hobisch shows superiority for orthotopic bladder substitution [133]. QLQ-C30 was used and patients with neobladders scored significantly better than patients with conduits in all functional domains (physical, role, emotional, cognitive, and social). While only 36% of patients with conduits would recommend the operation to a friend, 97% of the patients with neobladders would.

The other studies failed to show a difference [134-137]. Both Fujisawa et al. and Salinas et al., using SF-36, found general health and emotional functioning below a US control population.

c) Conduit Diversion versus Continent Cutaneous Diversion versus Orthotopic Bladder Substitution

This form of comparison was carried out in 6 studies, 2 of which are prospective and consecutive (*Level 2,* [138,139]). Most patients reported practical or emotional problems with no differences between the groups.

Similar results were obtained in the retrospective studies by Hart et al. and by Kitamura et al., apart from conduit patients reporting more problems with bathing habits (*Level 3,* [140,141]). The study by McGuire et al. found a difference in only 1 single item in SF-36 (*Level 3,* [142]). Thus, patients with continent reconstruction did not differ from the normal population in degree of mental distress, while this was common in conduit patients. However, only 54% of the patients returned the questionnaire.

Henningsohn et al. studied sources of symptom-induced distress and found sexual dysfunction to be the most distressing after cystectomy in all 3 types of reconstruction (*Level 3,* [143]).

d) Continent Cutaneous Diversion versus Orthotopic Bladder Substitution

The literature contains 3 retrospective studies (*Level 3,* [144-146]). In none of them were there any differences with regard to mode of diversion.

e) Conduit Diversion versus Anal Diversion

There is only 1 study published. Satoh et al. found no differences in overall quality of life, but rectal reservoir patients scored in some items (*Level 3,* [147]).

Summary

The published literature on quality of life after radical cystectomy is rather extensive. However, the scientific quality is rather low, and flaws in patient selection and methodology are common. There is no randomized controlled study. Such a study is desirable, but probably difficult to conduct. Published evidence does not support an advantage of one type of reconstruction over the others with regard to quality of life. An important reason is probably that patients are subjected to method-to-patient matching preoperatively and thus prepared for disadvantages and advantages with the different methods.

9. Renal Function After Urinary Diversion

An important requirement for reconstruction of the lower urinary tract is that it should not jeopardize the integrity of the upper urinary tract. Development of partial or complete obstruction of the urine flow, reflux of infected urine, and formation of stones are all factors that may adversely affect the renal function. A very large number of techniques for ureterointestinal anastomosis have been described, and so far no single method has proved superior to the others.

Most clinical reports published on renal function after urinary diversion are retrospective. Comparison between studies is therefore difficult due to differences in patient age, underlying disorder, the use of radiotherapy, preoperative and postoperative routines, and the duration of the follow-up. Type of

suture material and the use and duration of stenting are other factors that might be of importance. The functional status of the upper urinary tract prior to the urinary diversion is most valuable information but is often lacking in clinical reports. Another problem relates to the methods of measuring renal function after urinary diversion. Many reports rely on serum creatinine and urography, but both are imprecise for the purpose. More accurate methods of estimating renal function take into account the excretion and the plasma level of a substance freely filtered trough the glomeruli, such as ^{51}Cr-EDTA and iohexol.

Refluxing anastomoses are most often direct end-to-side, commonly used for ileal conduit diversion. The most commonly used techniques for implantation into an ileal segment are antirefluxing anastomoses - the afferent loop as in the Studer pouch, the intussuscepted ileal nipple valve as in the Kock pouch, the Le Duc technique, the split-cuff ureteric nipple, and the serous-lined extramural tunnel, and, for implantation into a colonic segment, the submucous tunnel.

a) Randomized Studies

The literature contains only 3 randomized studies, all of moderate methodological quality. Kristjansson et al. compared conduit diversion to continent cutaneous diversion, antirefluxing ureterointestinal anastomosis to refluxing anastomosis for conduit diversion, and ileal conduit versus colonic conduit (*Level 2,* [148,149]). No statistically significant differences were found with regard to symptomatic urinary tract infection, number of ureterointestinal anastomotic strictures, and incidence of GFR deterioration. With a mean follow-up of 10 years, the mean GFR fell from 88 to 71 mL/min in patients with ileal conduits and from 88 mL/min to 65 mL/min in patients with colonic conduits. Corresponding figures for patients with continent diversions were 100 mL/min and 85 mL/min, respectively. Scarring was more common in refluxing than in antirefluxing units ($P = 0.06$).

Studer et al. compared antirefluxing anastomoses (ileal nipple valve or split-cuff ureteric nipple) in a short afferent segment with refluxing ureterointestinal anastomosis to an 18 to 20 cm afferent segment in patients with ileal neobladders and found the former to be associated with a statistically significant higher incidence of upper tract dilatation, but this was based on a low number of patients and a wide confidence interval (*Level 2,* [150]).

Osman et al. compared the ileal W neobladder with the serous-lined extramural tunnel technique to the ileal urethral Kock pouch with an afferent nipple valve (*Level 2,* [151]). The incidences of ureteric stricture and reflux were similar.

b) Conduit Diversion - Case Series

In a large series by Madersbacher et al., patients had been followed for a minimum of 5 years after ileal conduit diversion (*Level 3,* [152]). Ten percent of the patients developed stenosis of the ureterointestinal anastomosis, 20% developed upper tract stones, increasing to 38% after 10 years. Morphological and functional deterioration developed in 27%, most often in the form of hydronephrosis or shrunken kidney. Renal pathology was present in 40% after 5 years, increasing to 80% after 10 years. Iborra et al. reported impaired renal function in 14% of patients followed for more than 10 years (*Level 3,* [153]). A similar figure was noted by Fontaine et al., who found a nonsignificant decrease in creatinine clearance in 22 patients followed for more than 5 years after jejunal conduit diversion (*Level 3,* [154]). Of these, 2 had a decrease in creatinine clearance of more than 20% due to ureterojejunal obstruction.

c) Continent Reconstruction – Case Series With Information on GFR

Apart from the study by Kristjansson, there are 2 studies which provide information on GFR. In patients with orthotopic Kock ileal neobladders, Steven et al. reported a median clearance of 98 mL/min preoperatively, which decreased to 93 mL/min at 3 years and 90 mL/min at 5 years (*Level 3,* [44]). Ureteral obstruction occurred in 3%, 2.4% being due to afferent nipple stenosis and only 0.6% due to stricture of the ureterointestinal anastomosis. Reflux was noted in 9% to 13% and was not associated with loss in GFR. Jonsson et al. studied patients who had undergone continent cutaneous diversion using a Kock reservoir and found a significant reduction in GFR in patients with long-term follow-up (*Level 3,* [155]). However, this decrease was of the same magnitude as would be expected in a control population with increasing age. Reoperations due to afferent nipple dysfunction or stricture of the ureteroileal anastomosis were necessary in 15% of the patients.

d) Continent Reconstruction – Other Case Series of Well-known Techniques

Thoeny et al. evaluated the upper urinary tracts in patients with Studer neobladders followed for 5 years or more (*Level 3,* [156]). De novo shrinkage of the parenchyma was observed in only 1% of preoperatively normal renal units. Stricture of ureteroin-

testinal anastomosis occurred in 3% of 148 units. In 9%, dilated upper tracts were noted, but without obstruction, confirming that dilation does not always result from obstruction. Mean serum creatinine was 98 µmol/L preoperatively, 103 µmol/L at 5 years, and 83 µmol/L at 10 years postoperatively. Hautmann et al. reported on 363 patients with ileal W neobladders (*Level 3*, [1]). Ureteric implantation was by the Le Duc technique or a chimney. Reoperation for ureterointestinal stricture was done in 9% of the patients, and renal deterioration occurred in 1%. With the latter technique, a stricture rate of 1% was recently reported [19]. Elmajian et al. reported on the Kock ileal neobladder and found afferent nipple stenosis, reflux, and ureterointestinal anastomotic stricture in 2.4%, 2.0%, and 1.4% of the patients, respectively, after median follow-up of 3.6 years (*Level 3*, [157]). In the study by Abol-Enein et al. on the W-shaped ileal neobladder with serous-lined extramural ureteral implantation, anastomotic stricture occurred in 4% of implanted ureters and reflux was noted in 3% (*Level 3*, [83]). In the 2 latter reports, information on renal function is not given. In patients with right colon bladder substitutions or continent cutaneous diversions, Månsson et al. reported a stricture rate of 2% in patients with Le Duc ureteric implantation (*Level 3*, [81]). The serum creatinine levels of 11 of 162 patients rose over 120 µmol/L, and 3 of these rose to over 165 µmol/L after mean follow-up of 5 years. Using an ileocecal pouch for bladder substitution (Mainz pouch), stricture of the ureterointestinal anastomosis (submucous tunnel) was reported in 7% of renal units, but data on renal function was not given (*Level 3*, [158]). In a study of patients with Mainz pouch I followed for 5 to 16 years, median serum creatinine was 1.0 mg/dL (88.4 µmol/L) with 25th and 75th percentiles of 0.9 and 1.2 mg/dL (79.6 and 106.1 µmol/L) (*Level 3*, [58]). Recent publications suggest that an antirefluxing anastomosis is unnecessary in patients with low pressure pouches, giving low figure rates for strictures after short follow-up [19,159-161].

e) Continent Anal Diversion

In a medium-term follow-up study, Bissada et al. reported stable renal function in 92% of patients after classic ureterosigmoidostomy (*Level 3*, [162]). Radiographic deterioration was present in 23% of the renal units, and was severe in 7%. Bastian et al. also found stable renal function after Mainz pouch II diversion (*Level 3*, [163]). Pyelonephritis occurred in 14% of the patients.

Summary

While there is a rich literature on urinary diversion, few publications give data on renal function. The majority of reports are case series with a low level of evidence. The literature does not support benefits of one type of ureteric implantation over another. Prospective randomized studies are needed to clarify this issue. Renal function decreases at long-term follow-up, but this is at least partly due to normal aging. There is no evidence to suggest that patients with continent reconstruction do less well than conduit patients with regard to renal function.

10. Urinary Tract Infection

Normal urothelium has several defense mechanisms against bacteria. Voiding function is a physical action to wash out bacteria, which is most primitive but effective. Urothelium has inhibitory action against bacterial adherence. One of the reasons why bacteriuria frequently occurs when bowel is used as urinary diversion is that bowel epithelium lacks an inhibitory action against bacterial adherence. Acidic or high osmolar urine itself also has some anti-bacterial actions. Specific and non-specific immune system components such as polymorphonuclear leukocytes (PMN) or secreting immunoglobulins also play roles. In patients with urinary diversions, some of these mechanisms are impaired and susceptible to bacterial infection. There are several types of urinary diversions and the characteristics of urinary tract infections vary according to each type of urinary diversion. Since there is a big difference between intubated and tubeless urinary diversions, these will be discussed separately.

a) Intubated Cutaneous Ureterostomy

Although catheterless urinary diversion should be considered permanent, intubated cutaneous ureterostomy or percutaneous nephrostomy is applied to selected patients with high-risk conditions. In these patients, UTI is inevitable and bacteria in these patients are very similar to those detected in usual complicated UTIs. Frequently identified bacteria are *Proteus* species, *Escherichia coli*, *Enterococcus* species, and *Klebsiella* species. Although bacteriuria is inevitable in these patients, pyelonephritis occurs especially when urine passage is impaired. Thus, the only way to prevent serious UTI in these patients is to change the catheter periodically with appropriate administration of antibiotics when needed.

b) Tubeless Cutaneous Ureterostomy

It has been thought that tubeless cutaneous ureterostomy is feasible only when the ureter is dilated [164]. In fact, ureteral ischemia with stricture formation and stomal stenosis are the most common complications of ureterostomy. The rate of stenosis varies from 15% to 67%, according to various reports. In these patients, subsequent pyelonephritis due to urine obstruction is a crucial problem. Matsuda et al. reported that 22 (56%) of 39 patients with tubeless cutaneous ureterostomies showed bacteria in urine collected from the renal pelvis with a double lumen catheter [165]. However, pyuria was observed only in 6 (15%) patients. Thus, most of the bacteria is clinically insignificant in these patients. Urine passage seems to be the most important factor for UTI in patients with tubeless cutaneous ureterostomies - insignificant bacteriuria will become significant when urine passage is impaired.

c) Ileal Conduit

As previously mentioned, an increased incidence of bacteriuria, bacteremia, and septic episodes occurs in patient with bowel interruption. Bruce et al. intensively studied UTI in patients with ileal conduits [166]. According to his report, the incidence of bacteriuria was 84%, and 14% had clinical evidence of pyelonephritis. This incidence of bacteriuria is similar to other reports [167]. *Proteus* species, *Klebsiella* species, *E. coli*, *Pseudomonas* species, *Enterococcus* species, and yeast are frequently-detected pathogens. Electron microscopy examination of cup biopsy specimens from the conduit shows virtually no bacteria adhering to the columnar cells of the conduit, although Gram positive cocci were seen adhering to the keratinized cells from the mucocutaneous junction [166]. They also found that a number of the bacterial isolates from the conduits were found to attach to human urothelial cells in vitro, indicating these pathogens can cause retrograde infection. Recently, Madersbacher et al. reported on long-term outcomes after ileal conduit diversion [152]. They demonstrated a high rate of conduit-related complications including urolithiasis; infection; and metabolic, conduit, bowel, stoma, and renal dysfunction. Clinically evident UTI was observed in 30 (23%) of 131 patients with ileal conduits who were followed for more than 5 years. Urosepsis occurred in 5 patients (3.8%). Minton et al. studied the relationship between UTI and urodynamics of conduits [168]. They showed that the longer a patient survives following diversion, the greater the chances for subsequent urinary infection. Manometric studies of the conduit indicated that urinary infection was most prevalent in conduits having irregular, weak, peristaltic contractions.

Summary

In summary, we have to pay much attention to UTI in patients with ileal conduits. This complication is observed early and late. Urodynamic evaluation is recommended in patients with ileal conduits who have recurrent UTIs.

d) Cutaneous Continent Diversion

Patients with continent diversions also have a significant incidence of bacteriuria. Indeed, the rate of positive urine culture was reported to be 67% with ileal reservoirs [169], 67% with cecal reservoirs [170], 71% with Kock pouches, and 56% with Indiana pouches [171]. Bacterial species in urine are *E. coli*, *Pseudomonas* species, *Klebsiella* species, *Proteus* species, and *Enterococcus* species, which are very similar to usual complicated UTI. The microbial flora of stoma and peristomal skin are different from that of a continent urinary reservoir [170]. The reasons for the increased incidence of bacteriuria are unclear, but it is likely that the intestine is incapable of inhibiting bacterial proliferation in contrast to the urothelium. Comparing to cutaneous ureterostomy or ileal conduit, clinically significant UTI is less common and asymptomatic bacteriuria in patients with continent ileal reservoir should not be treated with antibiotics [169]. An antireflux technique of ureterointestinal anastomosis, such as the Le Duc technique, contributes to a low incidence of UTI [172].

e) Orthotopic Neobladder

There are few studies concerning UTI in patients with orthotopic neobladders [119,173]. Wullt et al. reported that 67% of the specimens from patients with neobladders were culture-positive, and half of them contained uropathogenic species, such as *E. coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Enterococcus faecalis*, which are similar to those found in other types of urinary diversion [173]. Bacterial colonization was strongly correlated with residual urine. However, all the patients in this study were asymptomatic. Thus, the necessity of antibiotic treatment and clinical significance of bacteriuria in these patients are controversial. Wood et al. reported that 67% of the patients with orthotopic neobladder

had a positive urinalysis, and 51% of these patients had a positive urine culture [119]. The overall rate of UTI was 39%, and 12% had urosepsis. In fact, more studies seem to be needed to make conclusions concerning UTI in patients with orthotopic neobladders. In an animal experiment of a rat bladder augmentation model using ileum, Nakano et al. reported that the type I pilus of *E. coli* is one of the main causes of asymptomatic bacteriuria after urinary reconstruction using ileum [174].

Summary

Bacteriuria is inevitable in intubated cutaneous ureterostomy and significant UTI occurs frequently. Although bacteriuria is also observed in more than half of patients with tubeless cutaneous ureterostomy, clinical UTI occurs less provided urine passage is not obstructed. About two-thirds of patients with urinary diversions using intestinal segments show bacteriuria. UTI is a rather crucial problem for patients with ileal conduits even after long follow-up. In patients with continent urinary reservoirs and orthotopic neobladders, UTI is not a serious complication, as long as urine is voided smoothly.

II. ORTHOTOPIC RECONSTRUCTIONI

Ileal reservoirs are the most common form of neobladders used worldwide. There are 3 major categories:

1. The Hemi Kock, originally developed by Kock and popularized by Skinner and associates [175,176]. The most recent modification is technically complex, time consuming, and has yet to be widely adopted [2].
2. The second type of ileal reservoir initially described by Studer, which has the advantage of an afferent limb that facilitates ureteroileal anastomosis without valve formation [177].
3. The third type of ileal reservoir is the ileal neobladder, a W-shaped reservoir as described by Hautmann and coworkers [178-180]. Its obvious advantages are the best early continence rates as a consequence of having the greatest volume of all reservoirs.

Both incorporation of an afferent or efferent limb for ureteral anastomosis and orthotopic anastomosis of the ureters directly into the reservoir, with or without an antireflux technique, are feasible [2,179,181,182].

1. Patient Selection

a) Patient Factors: For

The primary patient factor is the "patient's desire for a neobladder." The patient needs a certain motivation to tolerate the initial and sometimes lasting inconveniences of nocturnal incontinence associated with a neobladder. Most patients readily accept some degree of nocturnal incontinence for the benefit of avoiding an external stoma and pouch, but not all patients do, and realistic expectations of the functional outcome are essential for both the surgeon and the patient [9].

The psychologically-damaging stigma to the patient who enters surgery expecting a neobladder but awakens with a stoma plays an increasing role. It should always be remembered that in many parts of the world, a bag may either be socially unacceptable or economically unrealistic as a long-term solution. These pressures drive the urologist toward some form of continent urinary diversion, and, although rectal pouches have been used widely as alternatives to conduits, continent catheterizable reservoirs or orthotopic bladder substitutes in particular represent attractive options [19].

b) Patient Factors: Against

There are still patients who are better served with a conduit. Patient factors against a neobladder are:

1. If the patient's main motivation is to "get out of the hospital as soon as possible" and resume normal, rather sedentary activities. Many frail patients undergoing cystectomy will have less disruption of normal activities with a well-functioning conduit than an orthotopic reservoir associated with less than ideal continence.
2. The "little old lady" living in social isolation.
3. No concern about body image. Most older patients do not have the same cosmetic concerns that a younger patient might have, and their main goal is returning to their previous lifestyle, which is often quite sedentary [183].

c) Patient Selection Criteria: Oncologic Factors

Following cystectomy, the rhabdosphincter must remain intact. Nevertheless, the cancer operation must not be compromised. This concern applies to 2 aspects of selection: urethral tumor recurrence in

men and the use of orthotopic replacement in women.

1. One of the initial deterrents to orthotopic diversion is the risk for urethral recurrence of cancer. See below.
2. Orthotopic bladder substitution for women with invasive bladder cancer has been popularized recently [184-186]. For oncologic justification see below.

Increasing experience with orthotopic reconstruction has fostered less restrictions for patient selection based on tumor stage. Should extensive pelvic disease, a palpable mass, or positive but resectable lymph nodes preclude a neobladder because of the high propensity for a pelvic recurrence or distant relapse? There is no convincing evidence that a patient with an orthotopic diversion tolerates adjuvant chemotherapy less well or that a pelvic recurrence is any more difficult to manage with a neobladder than after an ileal conduit. Patients can anticipate normal neobladder function until the time of death [187].

However, adjuvant chemotherapy may substantially weaken the patient and prolong the time for neobladder maturation. Nevertheless, our philosophy respects the patient's desire for a neobladder; if the patient is strongly motivated, he or she gets a neobladder. Even though the patient has a poor prognosis and relapse is likely to occur, we still try to construct the diversion they want. Previous radiation therapy, especially with an advanced cancer, usually mitigates against an orthotopic diversion but does not absolutely preclude it. However, all patients should be informed that diversion to the skin either by a continent reservoir or ileal conduit may be necessary due to unexpected tumor extent, and an appropriate stoma site should be marked on the abdominal wall beforehand.

d) Current Practice

Despite the fact that orthotopic bladder replacement provides the ideal method of urinary diversion after cystectomy, many patients treated outside of centers that are dedicated to neobladder reconstruction receive an ileal conduit. Why? These patients often have adverse clinical factors such as increased age, more comorbidities, and more previous cancer therapy, including patients with previously deemed unresectable cancers undergoing desperation cystectomy or after failed combined radiation therapy and chemotherapy regimens [183]. Thus, despite a strong desire to offer orthotopic diversion whenever possible, some patients do not qualify on the basis of current clinical judgment. An ileal conduit remains an expedient, safe, and appropriate method of diversion in these patients. Many factors go into the decision to perform a urinary diversion and must be kept paramount in discussing the pros and cons of each method with the patient and his or her family.

2. Is Reflux Prevention Necessary?

High pressure reflux with or without infection may lead to renal damage (*Level 3*, [188]). Antireflux procedures were therefore developed in order to reduce this risk following urinary diversion. Some of these techniques were developed prior to the introduction of orthotopic reconstruction, and their continued use with orthotopic reconstruction has been rather random and unscientific. Many surgeons with expertise in the field of reconstruction have abandoned any form of antireflux procedure with orthotopic reconstruction (*Level 4*, [19]). The need for reflux prevention with a low pressure detubularized orthotopic reconstruction is not the same as with a conduit, continent cutaneous diversion, or ureterosigmoidostomy. There are many potential causes for deterioration in renal function after urinary tract reconstruction. Randomized controlled trial evidence is therefore important in order to draw valid conclusions about the need for antireflux procedures. Unfortunately, few studies have been carried out in humans. The main problem with antireflux procedures is increased surgical complexity, which results in a higher complication rate. In fact, the particular problem of renal deterioration that one is trying to avoid may be seen more frequently as a result of obstruction at the ureteroileal junction.

Studer and colleagues prospectively randomized 70 patients undergoing orthotopic reconstruction to have either a freely refluxing end-to-side ureteroileal anastomosis into an afferent isoperistaltic ileal limb or an antirefluxing nipple valve (*Level 2*, [150]). Ureteroileal stenosis resulting in severe upper tract dilation was seen in 13.5% of those ureterorenal units with antirefluxing nipple valves compared with only 3% of those with an afferent tubular segment. Although follow-up in this study was only medium-term, most patients were followed until death and the trial was abandoned as there were significantly more complications with intussuscepted nipple valves. Perhaps this form of antireflux mechanism has a particularly high complication rate, but others groups have reported high rates of stenosis using other

forms of antireflux techniques as discussed below. Subsequent longer-term follow-up of 76 patients at a mean of 84 months after afferent ileal limb bladder substitution showed only 1% of ureterorenal units to have lost cortical thickness on ultrasound, which was associated with ureteroileal stenosis (*Level 3*, [156]).

An afferent ileal limb does not prevent reflux altogether, but under normal voiding conditions, without an overfilled reservoir, reflux is minimal as the afferent tubular segment acts as a dynamic antireflux system. Videourodynamics do not show reflux of contrast medium during the Valsalva maneuver as pressure rises simultaneously in the bladder substitute and the upper tract (*Level 2*, [150]). Although measurement of renal cortical thickness and serum creatinine will not detect more minor degrees of renal deterioration that would be picked up with radioisotope measurement or glomerular filtration rate, it seems that the afferent ileal limb is safe in terms of renal function at 7 to 15 years.

As a result, others have now developed variations on this theme such as the 3 to 5 cm chimney reported by Hautmann and Simon, who found a reduction in the ureteroileal stenosis rate of 9.5% in 363 consecutive patients with the Le Duc antireflux procedure to 1% in 195 subsequent patients with freely-refluxing anastomosis (*Level 3*, [187]).

In a nonrandomized study of refluxing and nonrefluxing ureteroileal anastomoses in both Indiana pouch and ileal orthotopic bladder substitutes, Pantuck and colleagues also found a statistically significantly higher rate of benign ureteroileal stenosis with nonrefluxing anastomoses (13%) compared to a simple end-to-side anastomosis (1.7%) at a mean follow-up of 41 months (*Level 3*, [159]). They found no difference in the rates of hydronephrosis, pyelonephritis, upper tract stone formation, or serum creatinine between those with refluxing or nonrefluxing anastomoses. In contrast, Kristjansson and colleagues, in a randomized study of refluxing versus nonrefluxing ureteroenteric anastomoses with either an ileal or colonic conduit, found the ureteroileal stricture rate to be unrelated to the mode of implantation (*Level 2*, [148]). The overall stricture rate was however higher than one might expect at 13.2% at a mean follow-up of 10 years. (Since this report they have modified antireflux techniques to a simpler submucosal tunnel.) They found no difference in reduction of GFR between kidneys with and without reflux protection. If in a chronically infected conduit system no difference in GFR is detected with refluxing and nonrefluxing techniques, then it is unlikely that a difference would be seen with an orthotopic bladder substitute in which urine is usually sterile. One should also remember that antireflux valves will not spare the upper tract from the effects of sustained high pressure in a bladder substitute. High pressure will close the valve, and, as urine production continues, pressure in the upper tract will increase until the bladder pressure reduces (*Level 2*, [150]).

Summary

In conclusion, we believe that a simple end-to-side freely refluxing anastomosis into an afferent limb of a low pressure orthotopic reconstruction, in combination with regular voiding and close follow-up, is the procedure with the lowest overall complication rate. Continued peristalsis in the afferent ileal limb reduces but does not eliminate reflux. The potential benefits of "conventional" antireflux procedures in combination with orthotopic reconstruction seem outweighed by the higher complication and associated reoperation rates.

3. Upper Tract Safety (Long-term)

Long-term safety of the upper tracts is an essential requirement for successful lower urinary tract reconstruction. There are many potential reasons for deterioration in renal function including transmission of high bladder pressure to the upper urinary tract (reflux or functional obstruction), stone formation, infection, and physical obstruction at any site (ureteroileal being the most common). The pathological changes seen with varying etiologies are the same, and, thus, the cause at the time of detection may not be obvious. In addition to a natural age-related decline, there may be many nonurologic causes for declining renal function such as hypertension, diabetes, drugs, and so on. A number of retrospective studies have reported renal functional and morphological deterioration ranging from 13% to 41% after ileal conduit diversion (*Levels 2 and 3*, [152,189,190]). Following continent cutaneous diversion, Kristjansson and colleagues reported a decrease in renal function in 28% of patients 11 years after cecal reservoir creation (*Level 2*, [148]). Akerlund and colleagues reported upper tract dilation at a mean of 6.6 years after Kock pouch formation (continent ileal reservoir) in 5 of 17 patients (29%), which was associated with scarring in 2 (*Level 2*, [191]). Only 1 patient (6%), however, had an abnormal creatinine at the last follow-up, though 4 had a

low age-adjusted glomerular filtration rate (GFR) (3 of these had a low GFR preoperatively).

There are few long-term reports of renal function following orthotopic reconstruction. In addition, reported methods of measuring renal function usually rely on serum creatinine or radiological studies, both of which have limitations. Serum creatinine only begins to rise after a significant reduction in glomerular filtration, and the presence of upper tract dilation does not necessarily equate to a reduction in renal function. Many studies are also retrospective with incomplete preoperative data. Measurement of preoperative and postoperative renal function using radioisotope studies would provide the best information on the safety of orthotopic reconstruction with regard to the upper tracts.

Thoeny and colleagues reported a prospective analysis of renal morphology and function in 76 patients with a median follow-up of 84 months (range 60-155 months) after a low pressure ileal afferent limb bladder substitute (*Level 2*, [156]). Serum creatinine and IVU were performed preoperatively and at regular intervals postoperatively. Of 148 ureterorenal units, 141 (95%) showed no significant change in size or parenchymal thickness. In 6 (4%), renal size and parenchymal thickness decreased, and in 1 parenchymal thickness alone reduced. However, the majority (5) of these ureterorenal units had preoperative renal pathology such as dilation, obstruction, or scarring. Loss of parenchyma from kidneys that were normal preoperatively was seen in only 2 ureterorenal units (1%) and was associated with ureteroileal stenosis. Preoperative mean serum creatinine ± SD was 98 ± 19 μmol/L and at 10 years thereafter was 83 ± 27 μmol/L. Twelve of 76 patients (16%) had increased serum creatinine, 5 of whom had preoperative dilation or obstruction. In this prospective study, renal deterioration was seen only in the presence of preexisting renal pathology or postoperative obstruction. Nevertheless, more precise assessment of GFR is missing.

Summary

In conclusion, renal deterioration following an orthotopic reconstruction with an afferent ileal limb is minimal at 10-year follow-up. Close follow-up is required in order to identify correctable causes early, particularly ureteroileal stenosis. Those with pre-existing renal pathology prior to surgery seem to be at greatest risk of postoperative renal deterioration.

4. CONTINENCE

Continence following orthotopic urinary diversion is dependent on an intact urethral sphincter mechanism and pelvic floor, which are able to maintain a resistance pressure across the urethral continence zone that exceeds the pressure generated within the diversion [19,192,193]. This latter pressure is influenced by the size and configuration of the intestinal segment utilized for the diversion in accordance with the law of La Place, pressure = tension/volume. Additional factors influencing continence include urethral length and sensitivity, patient age and mental status, intact pelvic nerve supply to the rhabdosphincter, completeness of voiding, and presence or absence of bacteriuria. The innervation to the pelvic rhabdosphincter includes the pudendal nerve and intrapelvic somatic afferent sensory and efferent motor fibers supplying the intrinsic urethral sphincter (*Level 2 and 3*, [194,195]). Multiple choices of intestinal segment (ileal, ileocecal, folded right colon or with ileal patch, or sigmoid) reconfigured in many ways (see below) can each achieve large capacity (more than 300 mL) and overall high levels of continence provided the principles of detubularization and creation of a low pressure chamber are adhered to as described earlier in this chapter. Continence improves over time during the initial 6 to 12 months postoperatively as the compliance of the diversion increases, allowing storage of greater volume at lower pressure [19,80]. Patients learn to void by performing a Valsalva maneuver in coordination with relaxation of the pelvic floor, resulting in spontaneous voiding to empty the diversion. Objective quantification of continence in various series utilizing specific techniques of orthotopic reconstruction is hampered by a wide range of reporting methodology, including subjective and objective, arbitrary definitions of degree of continence determined at various time points postoperatively. Thuroff et al. and Hautmann et al. provide a framework for reporting continence in urinary diversions that conforms to the recommendations of the International Continence Society as reflected in **Appendix 1**, adapted from Hautmann et al. [1,196]. Continence results must be separated into day and night control and evaluated among men and women separately.

a) Day Continence

Daytime continence is achieved earlier postoperatively than nighttime continence [4]. The overall rate of daytime continence that is “good or excellent” as variously defined as either totally dry or with use of 1 pad per day 1 year following orthotopic diversion

is approximately 85% to 90% as shown in **Table 5** (*Level 3*, [1,44,54,55,83,157,176,193,195,197-209]). Nesrallah et al. found that elongated ileal neobladders had lower daytime continence than more spherical neobladders at 36 months postoperatively (41% vs. 69%) but that the results were the same by 1 year (89% vs. 87%) (*Level 3*, [208]). However, they noted that by 1 year the spherical neobladders tended to enlarge to greater capacity (820 mL vs. 460 mL), to have a higher prevalence of postvoid residual urine volume over 100 mL (52% vs. 14%, $P < 0.05$), and a greater need for clean intermittent catheterization (CIC) (19% vs. 0%, respectively). Hautmann reported that decreased functional urethral length after surgery is associated with frequent or continuous leakage when the patient is walking, more so than during transient increases in stress-related rises in abdominal pressure during activities such as sneezing or coughing [19]. Hugonnet et al. reported that decreased urethral sensitivity at but not distal to the membranous urethra in men with neobladders was associated with higher rates of incontinence [210,211]. Daytime continence rates may decrease 4 to 5 years postoperatively due in part to decreased tone of the urethral sphincter with advanced age [212]. Thus, patient age at the time of cystectomy and urinary diversion is a relative factor in the decision for or against orthotopic reconstruction. Persistent severe incontinence following orthotopic urinary diversion may be treated by periurethral collagen injection or definitive placement of a urethral sling or artificial urinary sphincter. The benefits of collagen injections in this patient group have been modest in degree and duration [213].

b) Night Continence

Urinary control at night also requires a 6 to 12 month interval postoperatively to reach maximum levels as the capacity and compliance of the diversion increase. Patients are instructed initially to limit fluid intake after the evening meal, to void before going to sleep, and to set an alarm clock to awaken and void once or twice during the night. Many patients wear a pad at night. The reported rates of enuresis vary widely from 0% to 67% (*Levels 2 and 3*, [19,157,193,199,214,215]). Such a large range reflects differences in the stringency of the definition of night continence in various series. Suffice it to say that some degree of night leakage is common in all types of orthotopic diversion. The majority of series report a prevalence of nighttime leakage of 20% to 30% (**Table 6**) [1,44,54,55,83,157,176,199, 200,203, 207,209]. Ghoneim et al. and El Bahnasawy et al. found similar rates of enuresis varying from 27% to 50% at increasing follow-up intervals beyond 12 months in male patients with either hemi-Kock or Hautmann ileal neobladders (*Level 3*, [200,203]). Patients with enuresis had higher pressures, maximal volumes, postvoid residual urine volumes, and rates of positive urine cultures, and lower maximal urethral pressures, flow rates, and compliance compared to those without enuresis by univariate analysis as shown in **Table 7**. However, in multivariate analysis only the amplitude of uninhibited contractions and increased postvoid residual volume remained associated with enuresis. Also, the effect on enuresis of treating bacteriuria was not reported. Higher amplitude and frequency of uninhibited contractions and increased postvoid residual volumes also were found in female neobladder patients [209]. In some series [44], increased age was associated with a higher rate of enuresis, while in other reports [203] age did not correlate. Use of imipramine hydrochloride 25 mg at bedtime is reported to decrease nighttime leakage in up to 25% of patients (*Level 3*, [200,203]). Rates of complete nighttime continence without any pads are reported as 45% to 65% of patients [55,176]. Factors involved in nocturnal leakage in neobladders are summarized in **Appendix 2**, adapted from Hautmann [19].

c) Voiding Dysfunction and CIC

Neobladder patients learn to void by simultaneous relaxation of the pelvic floor musculature and raising of intraabdominal pressure by performing a Valsalva maneuver [19,80]. Voiding dysfunction requires CIC in 4% to 33% of men with neobladders (*Levels 2 and 3*, [4,44,173,193,216,217]). Stricture must always be excluded as a cause of incomplete voiding. Incomplete emptying and so-called *hypercontinence* require CIC in 0% to 53% of females with neobladders [184,218]. The factors leading to the higher rate of voiding dysfunction in women than in men remain somewhat unclear. The majority of investigators feel the primary cause of hypercontinence in female neobladder patients is formation of a “pouchocele” from lack of posterior support of the neobladder leading to angulation and obstruction of the neobladder-urethral junction [80,178,184,195,198,216,218-220]. Techniques to prevent pouchocele formation include urethral suspension, placement of omentum into the space posterior to the pouch, and suspension of the vaginal fornices to Cooper’s ligament [202,221]. Other investigators report that preservation of the autonomic nerve supply to the upper vagina and periurethral area is important to prevent

Table 5. Daytime Continence Following Orthotopic Urinary Diversion

Series	Configuration	#, Sex	Continence, %			Follow-up, mos	CIC, %
			T	G	P		
Alcini, 1993 [54]	Cecoileal	30, M	100			21.2±14.8	n/a
Gburek, 1998 [197]	Ileal, Studer	62, M; 4, F	88			n/a	21
Abol-Enein, 2001 [83]	Ileal, Hautmann	353, M; 97, F	93.3	6.7		n/a	Rare
							9.3
Elmajian, 1996 [157]	Hemi-Kock	295, M	87		2	n/a	5
Stein, 1997 [195]	Hemi-Kock	34, F	85	12	3	n/a	15
Stein, 1998 [176]	Ileal, T pouch	40	75	20	5	n/a	n/a
Lee, 2003 [55]	Ileal,	101, M; 29, F	67	20	13	n/a	9
Arai,1999 [198]	Ileal	12, F	58	33	8	n/a	8-25
Hautmann, 1999 [1]	Ileal	n/a	95			n/a	n/a
Steven, 2000 [44]	Ileal	166, M	97			n/a	n/a
Studer, 1996 [199]	Ileal	n/a	92			n/a	n/a
Ghoneim, 1992 [200]	Ileal	n/a	92			n/a	n/a
Kurzrock, 1995 [201]	Ileal	M	92			n/a	n/a
Stenzl, 1996 [202]	n/a	F	88			n/a	n/a
El Bahnasawy, 2000 [203]	Ileal	100, M	50			n/a	n/a
Lin, 2000 [204]	Gastric	8, M	47	63		n/a	n/a
Mills, 2000 [205]	Ileal, Studer	15, F	79			6	n/a
			83			12	
			100			24	
Steers, 2000 [193]		2238	86			26±18	n/a
Constantinides, 2001 [206]		50	91		9	30 (8-59)	4
Beduk, 2003 [207]	Cecoileal	19			5.3	36 (12-69)	n/a
	Ileal	36			5.5		
Nesrallah, 2004 [208]	Ileal	59	88			n/a	n/a
Shaaban, 2003 [209]	Hemi-Kock	338, M; 15, F	93.7		4.4	88	0.98

T – total; G – good; P – poor; n/a – data not available

Table 6. Nighttime Continence Following Orthotopic Urinary Diversion

Series	Configuration	#, Sex	Satisfactory Continence, %	Follow-up, mos
Ghoneim, 1992 [200]	Hemi-Kock	n/a	73	n/a
Hautmann, 1999 [1]	Ileal	n/a	66-93	n/a
Studer, 1995 [199]	Ileal	n/a	80	n/a
Elmajian, 1996 [157]	Hemi-Kock	n/a	n/a	n/a
El Bahnasawy, 2000 [203]	Ileal-Hautmann Hemi-Kock	100, M	50-73	12
Shaaban, 2003 [209]	Ileal	338-M; 15-F	73	88
Steven, 2000 [44]	Ileal	166-M	75 85	12 36
Beduk, 2003 [207]	Ileocecal Ileal	19 36	79 90	36 36
Lee, 2003 [55]	Ileal, Hautmann Ileal, Studer	37 93	85 85	n/a
Stein, 1998 [176]	Ileal, T pouch	40	85	n/a
Abol Enein, 2001 [83]	n/a	n/a	80	n/a
Alcini, 1993 [54]	Ileocecal	30, M	89	36

n/a – not available

Table 7. Urodynamic and Urine Culture Results in Neobladder Patients With or Without Enuresis

Parameter	Enuresis	No Enuresis	P value
Maximal uninhibited contraction, cmH_2O	49	33	0.0001
Duration uninhibited contraction, sec	39.6	27.4	0.0001
Compliance, mL/cmH_2O	28.3	39.9	0.0005
Postvoid residual, mL	75.6	18.8	0.004
Positive urine culture, %	72	20	0.001

hypercontinence (*Levels 2 and 3*, [194,205,222,223]. However, the fact that continence, effective voiding, and rates of hypercontinence are equivalent in centers that perform complete pelvic sympathectomy during female cystectomy to those that do not suggests that preservation of the vaginal and periurethral innervation is not an essential feature [195,218,224]. Accumulating experience suggests that avoidance of excess pouch size by selection of an approximately 40 cm length of bowel rather than 60 cm leads to improved voiding function with adequate functional storage capacity as well as less risk of metabolic complications (see below). Factors associated with failure of voiding in neobladders are summarized in **Appendix 3**, adapted from Hautmann [19].

5. Oncologic Safety

Oncologic safety only plays a role in urinary diversion if the margin of resection is altered for an orthotopic bladder substitution or for functional aspects such as continence and potency. These aspects are all incorporated in the following 3 aspects: urethral recurrence, nerve-sparing cystectomy, and pelvic recurrence.

a) Urethral Recurrence Rate

1. Male Urethra

In the older literature, urethrectomy in conjunction with radical cystectomy for bladder cancer was suggested or strongly recommended. However, in recent years orthotopic reconstruction of the lower urinary tract has gained popularity, both by patients and doctors, which precludes a simultaneous prophylactic urethrectomy at the time of cystectomy (*Level 3*, [1,225]). In general, the incidence of urethral tumors of patients with primary and recurrent bladder tumors of all stages is around 6% if the primary tumor is treated by TURBT only (*Level 3*, [226]).

Metachronous urethral recurrence after cystectomy seems to be dependent on the type of urinary diversion and the time interval (**Table 8**) [44,227-231]. Freeman et al. demonstrated that patients with heterotopic urinary diversions have the highest incidence of secondary urethral tumors (10%) followed by patients with orthotopic urinary diversions (4%) in a more recent series (*Level 3*, [230]). Furthermore, the depth of prostatic urethral or ductal urothelial (transitional cell) carcinoma and prostatic continuity of the primary bladder cancer does alter the prognosis regarding urethral recurrence (*Level 3*, [232, 233]). Carcinoma in situ and tumor multifocality are correlated with a higher incidence of concurrent prostatic urethral involvement, but do not seem to have an increased risk of urethral recurrence [230,234].

2. Female Urethra

In the older literature concentrating on urethral tumor involvement, female cases are only rarely discussed. There has recently been focused interest, however, in data concerning the risk of secondary urothelial tumors in female bladder cancer patients undergoing urethra-sparing surgery. In a more recent study, urethral tumor involvement was confirmed as being 2% in female patients with biopsy-proven bladder cancer of all grades and stages and a mean follow-up of 5.5 years [186]. Most recent reports describe a close relationship between tumor involvement of the bladder neck and secondary urethral tumors. In these studies, there was no urethral tumor occurrence unless the bladder cancer involved the bladder neck (*Levels 3 and 4*, [235-237]). In some studies, vaginal involvement was an additional [238], or the only [239], preoperative risk factor for urethral tumor.

From these data, one may conclude that female patients without tumor either at the bladder neck or at frozen section of the proximal urethra at the time of cystectomy can probably be spared a portion of the urethra to enable lower urinary reconstruction to the urethra without running a greater risk of developing recurrent urethral tumors than their selected male counterparts.

b) Nerve-sparing Cystectomy: Risks and Advantages in Both Sexes

1. Male

Nerve-sparing radical cystectomy in male patients can apparently be done in a selected subgroup with good oncological and functional results. Schoenberg et al. demonstrated a disease-specific 10-year survival rate of 69% and a 10-year survival rate free of local recurrence of 94% [240]. Recovery of sexual function was achieved in 62% of men aged 40 to 49 years and gradually diminished in each decade to a rate of 20% in 70 to 79 year-old men *(Level 3)*.

Turner et al. found an additional beneficial effect on postoperative urinary continence due to preservation of the autonomic pelvic plexus [241]. Continence was seen in 94% of male patients with nerve preservation versus 83% of patients without nerve preservation *(Level 3)*.

The anatomic locations of autonomic nerves in both male and female patients with regard to pelvic organs and their function have been studied in human cadavers by dissection as well as experimental studies [242-244]. This data seems to confirm experimentally a clinical observation that decreased sensitivity in the membranous urethra adjacent to the

Table 8. Incidence of Urethral Tumor Recurrence and Time Interval After Cystoprostatectomy for Bladder Cancer*

Author	Number of patients	Number of urethral tumor recurrences (%)	Interval to recurrence
Steven 2000 [44]	166	2 (1.2)	n.g.
Slaton 1999 [227]	210	4 (1.9)	Median 15 months
Lebret 1998 [228]	106	0 (0)	
Robert 1996 [229]	185	8 (4.3)	6-36 months
Freeman 1996 [230]	436	34 (7.7)	
	174 (Neo)	5 (2.9)	Median 2.3 years
	262 (HUD)	29 (11.1)	Median 1.6 years
Freeman 1994 [231] (Review of 18 studies)	2062	208 (10.1)	Mostly in the first 5 years

Neo - Kock ileal neobladder; HUD - heterotopic urinary diversion; n.g.- no data were given
* - cystoprostatectomies with negative urethral margins on frozen sections

intestinourethral anastomosis correlates with postoperative continence. There are indications that this sensitivity is related to autonomic nerve preservation [211].

2. Female

The course of the autonomic nerves in correlation to the female pelvic viscera has been outlined in cadaver studies [245].

Their role in female patients undergoing radical cystectomy and orthotopic bladder substitution is controversial. Several authors have presented data that would strongly favor the role of autonomic nerves for continence and micturition, although a urinary retention rate of 11% is still observed (*Levels 3 and 4,* [205,222,246]). Stein et al. and Ali-el-Dein et al. did not see any benefit of nerve preservation. The urinary retention rates were 15% and 16%, respectively (*Levels 3 and 4,* [195,236]).

c) Pelvic Recurrence After Cystectomy and Orthotopic Bladder Substitution

Freeman et al. found an overall local recurrence rate of 11% in a study of predominantly male patients, which was the same as in a smaller French series of male patients receiving an orthotopic neobladder despite positive (N1 or N2) lymph nodes at cystectomy (*Levels 3 and 4,* [230,247]). A similar pelvic recurrence rate of 14% (all of them concurrent with distant metastases) was seen in another study looking at patients with unfavorable histology [248]. In these studies, one-half to two-thirds of patients with pelvic recurrence retained adequate neobladder function until death or the last follow-up. The type of urinary diversion did not change the risk of complications, response to salvage treatment, or overall survival in one study of patients with pelvic recurrence [249]. Hautmann compared 210 patients with immediate cystectomy to 88 patients with delayed cystectomy due to neoadjuvant chemotherapy, radiation, or adjuvant treatment of T1 disease and found a significantly higher pelvic recurrence in the delayed cystectomy group (26% vs. 12%) [250]. In women, pelvic recurrence after anterior exenteration was 3% in 2 studies after a median follow-up of 30 and 24 months, but in both series these recurrences were in patients without urothelial carcinoma [195,246]. The pelvic recurrence rate was 12% in a larger study with a large portion of squamous cell carcinoma [251]. When preserving the anterior vaginal wall, and thus the entire vagina, for functional reasons, a local recurrence was seen in 5% of the patients with neobladders [252].

6. Sexuality-preserving Orthotopic Reconstruction

Radical cystectomy remains a standard therapy for patients with high grade muscle-invasive bladder cancer [225]. Classic radical cystectomy includes lymphadenectomy and the removal of the prostate, seminal vesicles, and part of the vas deferens in men, and the removal of the uterus, cervix, fallopian tubes, ovaries, anterior vaginal wall, and urethra in women. To provide a more natural voiding pattern and improve the quality of life of patients requiring cystectomy, orthotopic diversion has become the ideal form of reconstruction in both men and women. Sexuality-preserving techniques have been proposed to further improve the quality of life of these patients without compromising the oncologic outcomes. These techniques and concepts must be examined separately in men and women.

a) Preservation of Sexual Function in Men Undergoing Orthotopic Reconstruction

Nerve-sparing techniques have been advocated in properly selected patients in order to maintain sexual potency following radical cystoprostatectomy. In carefully selected men, nerve-sparing cystoprostatectomy does not appear to increase the local recurrence rate [240]. However, even under the best of circumstances, functional potency following nerve-sparing cystoprostatectomy is generally less than 60% [241].

Subsequently, it has been suggested that in order to minimize the risk of incontinence and impotence without compromising the oncologic outcomes, prostate- and seminal vesicle-sparing cystectomy may be performed in patients with urothelial carcinoma of the bladder [253-255]. In these prostate-sparing cystectomies, a transurethral resection (TUR) of the prostate is generally performed first, leaving the prostatic capsule intact. If no evidence of prostate cancer or urothelial carcinoma of the prostate is found (usually on frozen section analysis) patients then undergo preservation of the vas deferens, seminal vesicles, and neurovascular bundles, with urinary reconstruction to the prostatic capsule. With short-term follow-up, functional results have been good with day and nighttime continence of 97% and 95%, respectively, and potency rates of 82% in one series [253].

Several major oncologic issues with prostate-sparing cystectomy must be addressed. It is well known that in patients undergoing cystoprostatectomy for bladder cancer, over 40% demonstrate histologic evi-

dence of prostate cancer [256-258] and nearly 30% to 40% will demonstrate prostate involvement (urethra, prostatic ducts, or stroma) with urothelial carcinoma [256,259]. Furthermore, the ability to accurately detect prostate cancer or urothelial carcinoma on frozen section of the prostate TUR specimen is unknown. These oncologic concerns, and the fact that there is little long-term follow-up in patients treated with prostate-sparing techniques, should caution the routine application of this procedure in patients with urothelial carcinoma of the bladder. A large review of cystectomy and orthotopic diversion reported good day and nighttime continence in 87% and 72% of 2,238 patients, respectively, which compares favorably to prostate-sparing techniques [193].

In highly-selected men with nonurothelial tumors, sexuality-preserving cystectomy has been reported with excellent results [260]. These patients are usually younger patients (median age 26 years) with nonurothelial carcinoma who strongly desire to maintain fertility, sexuality, and voiding per urethra. In one series, the neobladder was anastomosed to the apex of the prostate with preservation of the sexual organs.

b) Preservation of Sexual Function in Women Undergoing Orthotopic Reconstruction

Pathologic studies of female cystectomy specimens have demonstrated that the female urethra can be preserved in carefully selected women with bladder cancer and have identified pathologic risk factors to select appropriate female candidates for orthotopic substitution [186,235,238,239,261].

The 2 most important risk factors for urethral tumor involvement in women are bladder neck and anterior vaginal wall involvement with tumor. However, although tumor involvement of the bladder neck or anterior vaginal wall is a significant risk factor for urethral tumor in women, approximately 50% of female patients with these factors have an uninvolved urethra and may be appropriate candidates for orthotopic reconstruction. Intraoperative frozen section analysis of the distal surgical margin (proximal urethra) in women provides an accurate assessment of the urethra and may appropriately determine candidacy for orthotopic diversion. Current indications for urethrectomy (contraindications to orthotopic diversion) in female patients include carcinoma at the urethral margin detected on intraoperative frozen section analysis.

Tumor involvement of the anterior vaginal wall is seen in approximately 5% of women and can generally be detected clinically on pelvic examination. This suggests that the vast majority of women may have the anterior vaginal wall preserved at the time of cystectomy without compromising the oncologic procedure [238,239,261]. It is thought that preservation of the anterior vaginal wall should allow for improved sexual function, decrease the risk of neobladder-vaginal fistulae, and provide better clinical outcomes in women undergoing orthotopic diversion [236,252,262].

Chronic urinary retention or hypercontinence has been observed in 20% to 40% of women undergoing orthotopic reconstruction and is thought to be primarily related to mechanical factors resulting in the lack of proper back support of the neobladder with prolapse of the unsupported vaginal stump and ultimate neobladder pelvic descent [236]. Preservation of the anterior vaginal wall and omental interposition between the neobladder and anterior vaginal wall should also enhance the support of the neobladder and prevent the prolapse and angulation of the pouch-urethral anastomosis with resulting hypercontinence. Importantly, this maneuver may also help prevent suture line fistulae. In properly selected patients, preservation of the anterior vaginal wall does not appear to increase pelvic recurrence and has contributed to improved functional outcomes in women with improved sexual function and overall quality of life.

Summary

In conclusion, prostate-sparing cystectomy should not routinely be performed due to the oncologic risks of prostate cancer and bladder cancer involving the prostate in men with urothelial carcinoma of the bladder. Excellent continence results are seen with radical cystectomy and orthotopic reconstruction to the urethra. Nerve-sparing radical cystectomy is a safer option, but a significant number of patients may require adjuvant treatment for erectile dysfunction. Sexuality-preserving cystectomy may be performed in highly selected young men with good functional results for nonurothelial malignancies.

There is good data and evidence to suggest that preservation of sexuality with anterior vaginal wall-sparing radical cystectomy in women is appropriate from an oncologic perspective in most women undergoing cystectomy for bladder cancer. In addition, preserving the anterior vaginal wall may improve functional voiding and decrease the risk of pouch-vaginal fistulae.

7. Specific Complications

a) General

Complications of neobladder formation may be divided into early or late complications related to the initial surgical procedure, and as directly or not related to the neobladder itself. The various complications of continent urinary diversion have been reported extensively (*Level 3*, [1,19,44,55,83,151, 157,159,176,195,197,206,207,209,263-274]). **Tables 9 and 10** show the prevalence of the most commonly reported early and late complications from numerous series [1, 44, 55, 83, 157, 176, 195, 197, 206,207,209,272,273]. One must acknowledge the limitations in comparing results across series which include variations in sample size, duration of follow-up, stringency in identification of complications, and various neobladder reconfigurations and surgical techniques. Nevertheless, they provide a framework for assessing the risk of specific and overall complications. In general, the overall and specific complications for the various forms of orthotopic urinary diversion are similar in type and frequency to those for ileal conduit diversion (*Level 3*, [19,263,274,275]). In addition, it appears that complication rates are comparable for different types of neobladders. Lee et al. compared 37 Hautmann and 93 Studer ileal neobladders and found no difference in complications [55]. Parekh et al. [273] reported that overall complication rates and reoperation rates were 12% versus 22% and 3.4% versus 8.6% among patients who received a continent diversion versus an ileal conduit, respectively. The results likely were influenced in part by a selection bias favoring continent diversion in healthier patients. In another uncontrolled retrospective study, the same investigators reported that perioperative complication rates following neobladder construction in patients with American Society of Anesthesia risk group 3 were not higher than those in lower risk groups [272]. Beduk et al. found similar complication rates and equivalent functional outcomes in ileocecal (Mainz pouch) and ileal (Abol-Enein) neobladders [207]. Gburek et al. reported equivalent complication rates among 66 patients with Studer ileal neobladders and 66 with ileal conduits [197].

Several complications are unique to orthotopic urinary diversion compared to conduits. The rate of ventral incisional hernia is distinctly higher, as shown in **Table 10**. Chronic abdominal straining with a Valsalva maneuver to promote voiding is believed to be the explanation. Neobladder-enteric fistula and neobladder-cutaneous fistula are infrequent occurrences. The risk of fistula between the neobladder and other pelvic organs (rectum, vagina, ileum) is increased, but still low (under 10%), following pelvic radiation therapy [205]. The overall rates of reoperation for complications following continent cutaneous and orthotopic urinary diversion have been reported extensively [1, 19, 197, 263, 274, 275]. The early and late reoperation rates are 3% to 7% and 13% to 30%, respectively, in multiple series with variable durations of follow-up *(Level 3)*. The majority of the direct urinary tract complications (for example, pouch calculi, ureteroenteric anastomotic strictures, intestinourethral anastomosis strictures, anterior urethral strictures, mucus retention, and renal calculi) are corrected by endoscopic means. The exception is the high rate of open ureteral revision of ureteroenteric strictures. In contrast, the majority of wound-related (such as hernia and dehiscence) and bowel complications (such as obstruction and pouch-enteric fistula) require open surgical repair.

b) Ureteroenteric Stricture

Further discussion of complication rates of specific techniques of ureteroenteric anastomosis in continent urinary diversion is warranted. The considerations and outcomes for or against direct versus antireflux anastomosis were presented earlier in this text *(see Section II. 2. Is Reflux Prevention Necessary?)*. A low rate of anastomotic obstruction is paramount [156]. The technical ease and applicability of a given technique for ureters of various lengths and calibers are secondary. In a literature review and report of personal experience with over 2,000 direct end-to-side ureteroileal anastomoses into various forms of diversion, Skinner noted a 3% rate of late anastomotic obstruction (*Level 3*, [276]). There is extensive literature on the Le Duc technique of placing the ureter into an incised ileal mucosal trough of 2 to 3 cm length with or without a mucosal covering over the ureter and with or without spatulation of the end of the ureter [264-267,270,277,278]. The technique is quite easy to perform. The rates of obstruction and reflux for the various types of Le Duc reimplant are 2% to 31.6% and 0% to 15%, respectively. Split-cuff nipple ureteral reimplantation has a low rate of obstruction (3.1%-7%) and reflux (3.2%-10%) [268,279]. However, the technique is difficult and is not widely employed. Extensive long-term experience with a stapled intussuscepted ileal nipple valve distal to the direct ureteroileal anastomosis to prevent reflux has been reported in hemi-Kock

Table 9. Early Complications After Orthotopic Urinary Diversion (%)

Complication	Constantinides, 2001 [206]	Lee, 2003 [55]	Stein, 1997 [195]	Stein, 1998 [176]	Parekh, 2000, 2002 [272, 273]	Shaaban, 2003 [209]
Neobladder-related						
Ureteroenteric leak	4	0.8				2.4
Ureteroenteric stricture	2					
Urethral-enteric leak	2					7.7
Urethral-enteric stricture						
Neobladder leak			2.9			
Neobladder bleed						
Neobladder infarct						
Neobladder-vaginal fistula					1.6	
Retained stent, drain		0.8	2.9		1.2	
General						
Prolonged ileus	10	4.6	2.9	2.5	2.6	1.2
Acute pyelonephritis	2	0.8			7.1	
Sepsis					2.4	
Wound infection		3			3.6	0.6
Dehiscence				2.5		
Pelvic abscess	2				1.2	
Bowel leak		0.8				
Small bowel obstruction		1.6			0.8	
Lymphocele						3
Deep vein thrombosis	2				0.8-2.4	1.2
Pulmonary embolism	2		2.9		1.2	
Myocardial infarction						
Arrhythmia					3.6	
Pneumonia	4			2.5	0.8	
Gastrointestinal bleed	2					2.1
Postop bleed						
Cholecystitis						
Pancreatitis						
Death				2.5	0-1.1	0.9
Overall			11	12.5	12	19

Table 9. Early Complications After Orthotopic Urinary Diversion (%) (continued)

Complication	Steven, 2000 [44]	Gburek, 1998 [197]	Abol-Enein, 2001 [83]	Hautmann, 1996 [1]
Neobladder-related				
Ureteroenteric leak	7.2			1.1
Ureteroenteric stricture		2		
Urethral-enteric leak	0.6			6.6
Urethral-enteric stricture		3		3
Neobladder leak	2.4	2	2.4	0.3
Neobladder bleed				0.3
Neobladder infarct	0.6			
Neobladder-vaginal fistula			3.1	
Retained stent, drain				
General				
Prolonged ileus	1.2	6	1.3	10.7
Acute pyelonephritis		3		
Sepsis				
Wound infection		5	2	5.8
Dehiscence	9.6			
Pelvic abscess				
Bowel leak				1.1
Small bowel obstruction	1.2	2		
Lymphocele	1.8		2.2	3.5
Deep vein thrombosis			1.3	3
Pulmonary embolism		2		1.1
Myocardial infarction				0.3
Arrhythmia				3.8
Pneumonia				4.6
Gastrointestinal bleed			0.4	1.6
Postop bleed				1.9
Cholecystitis				0.3
Pancreatitis				0.3
Death	0	2	0.9	3.8
Overall	23.5		9	39.1

Table 10. Late Complications After Orthotopic Urinary Diversion (%)

Complication	Constan-tinides, 2001 [206]	Lee, 2003 [55]	Parekh, 2002 [272]	Beduk, 2003 [207]	Steven, 2000 [44]	Shaaban, 2003 [209]
Neobladder-related						
Ureteroenteric stricture	2	2.3			3	3.1
Ureteral reflux	8			4.2-7.9		
Pyelonephritis	2	3.9		13.8-15.8		
Urethral-enteric stricture	2	9.2			3.6	1.9
Neobladder-enteric fistula	2	0.8				
Neobladder-cutaneous fistula						
Neobladder calculi	2	0.8			16.3	16
Hematuria		0.8				
Chronic bacteriuria					24	33
Renal calculus						
Upper tract deterioration						
General						
Small bowel obstruction		3.8			1.2	2.8
Incisional hernia	4	4.6			10.2	
Lymphocele					3.6	
Pulmonary embolism					0.6	
Chronic diarrhea			1.2			
Renal failure						
Acidosis	4	0.8			1.8	
Vitamin B12 deficiency		1.6			6-33	
Biliary tract						
Enteritis						
Bowel perforatiom						

Table 10. Late Complications After Orthotopic Urinary Diversion (%) (continued)

Complication	Gburek, 1998 [197]	Abol-Enein, 2001 [83]	Elmaj-ian, 1996 [157]	Hautmann, 1996 [1]	Stein, 1997 [195]
Neobladder-related					
Ureteroenteric stricture	2			9.3	
Ureteral reflux		3		3.3	
Pyelonephritis	3			6.3	
Urethral-enteric stricture		2		2.2	
Neobladder-enteric fistula				1.5	
Neobladder-cutaneous fistula				0.3	
Neobladder calculi		2.9	4.1	0.5	2.9
Hematuria					
Chronic bacteriuria		50			
Renal calculus	2			2.2	
Upper tract deterioration		3.8		1.1	
General					
Small bowel obstruction	11	0.8		2.7	5.8
Incisional hernia				3.8	
Lymphocele	2				
Pulmonary embolism					
Chronic diarrhea					
Renal failure				0.8	
Acidosis					
Vitamin B12 deficiency					
Biliary tract				1	
Enteritis				0.6	
Bowel perforatiom				0.5	

neobladders as well as in cutaneous reservoirs as discussed elsewhere in this chapter [44,151,267,269]. Other techniques are preferred due to the high rates of reoperation (10%-16%) for stone formation on exposed metal staples or nipple slippage, ischemia, and necrosis.

The extraluminal serosal trough ureteral reimplant creates an antireflux flap valve which is easy to perform and is applicable to both normal caliber and dilated ureters [1,83,151,271,280]. The reported rates of initial leak, stricture, reflux, and upper tract deterioration for this technique of ureteral reimplantation are 0% to 7.7%, 3.8% to 9.3%, 1.0% to 3.3%, and 1.1% to 4.8%, respectively *(Level 3)*. The same concept of an extraluminal serosal trough flap valve to prevent reflux is employed in the ileal T-pouch with direct ureteral implantation onto a limb of ileum tunneled into the neobladder wall [281]. The great majority of ureteroenteric anastomotic strictures occur within the first 1 to 2 years postoperatively regardless of the type of reimplant [19, 159, 263, 265, 270]. However, the risk is cumulative over time and ureteroenteric strictures have been reported as long as 6 years postoperatively [159].

Ureteral ischemia is the most common cause of ureteroenteric stricture. Limited mobilization of the ureter and discarding of the distal pelvic portion is recommended to minimize the risk of stricture. The left ureter in particular is at risk for obstruction due to angulation as the ureter is brought under or through the left colonic mesentery to reach the neobladder. The left limb of a neobladder sits anteriorly, unlike the posterior presacral position of the base of an ileal conduit. The left ureter must not make a hairpin turn to reach the neobladder, or obstruction may occur. If placement of the left ureter under the free edge of the left colonic mesentery causes angulation against the inferior mesenteric artery, the ureter may be brought through a higher avascular window within the colonic mesentery. A potential role of chronic bacteriuria as a cause of periureteral inflammation leading to stricture is controversial. Ureteroenteric obstruction in neobladders often is clinically silent and is detected by increased serum creatinine or on follow-up imaging studies.

Assessment of the effectiveness of various forms of therapy for ureteroenteric stricture in neobladders is limited by the relatively small number of reported cases and the variable length of follow-up. Either retrograde or antegrade endoscopic and percutaneous attempts at correction are attempted first. Reported success rates for dilation and stenting alone versus dilation, incision, and stenting are 20.0% to 50.0% versus 44.4% to 63.0%, respectively [83, 148, 149, 151, 270,279]. There is a high rate of recurrent stricture after initial success with dilation alone. Open surgical repair is a more invasive procedure but has a success rate of over 90% (*Level 3,* [83,279]). The open approach to a right-sided ureteral stricture is easier than on the left and may be performed without reentering the peritoneum in most cases.

c) Metabolic

Potential metabolic complications following continent urinary diversion are important and may have serious consequences for patients if they are not recognized and corrected. The long-term metabolic safety of orthotopic diversion has been considered earlier and only a few points are reemphasized here. Incorporation of shorter (40-50 cm rather than 60 cm) intestinal segments is preferable from both a metabolic and a functional urodynamic standpoint.

• Acidosis

In the early postoperative period when oral intake is resumed and the catheter is removed from the neobladder, patients may experience a salt-losing syndrome [19,29,80]. If uncorrected, this may lead to weakness, lethargy, nausea, vomiting, and weight loss, which in turn produce dehydration with hypochloremic, hyperkalemic metabolic acidosis. The key to successful management is proper diagnosis by exclusion of urinary infection and sepsis, and awareness of the salt-losing syndrome. Proper treatment includes catheter reinsertion to ensure good drainage and to minimize further chemical reabsorption, rehydration with intravenous normal saline, and correction of acidosis with sodium bicarbonate. Patients with incomplete emptying and those with reduced renal function are most vulnerable to these metabolic problems (*Level 3,* [43,44]). Occasional patients with colonic neobladders may develop hypokalemia due to secretion of potassium into the urine from the colon [42,43]. Patients also may develop acidosis from reabsorption of ionized ammonium present in urine infected with urease-splitting bacteria [42,80].

There is a wide range in the reported prevalence of acidosis among neobladder patients and the need for early or chronic sodium bicarbonate therapy. The prevalence of the overt clinical salt-losing syndrome described above is low, provided patients empty the pouch efficiently. However, some investigators find that with careful study nearly all neobladder patients demonstrate metabolic acidosis in the early postop-

erative period and should receive sodium bicarbonate 2 to 6 grams daily for 3 to 6 weeks [80]. One group of investigators reported mild hyperchloremia without acidosis in 4% of patients with ileal neobladders [206].

Several groups have compared the rates of metabolic acidosis in ileocecal, cecal-right colon, and ileal neobladders. Alcini et al. found no evidence of metabolic acidosis in 30 patients with ileocecal neobladders who were followed for an average of 21.2 ± 14.8 months as shown in **Table 11** [54]. In a later study, the same investigators compared metabolic parameters in 18 patients with ileal neobladders and 45 with ileocecal neobladders at a mean follow-up of 51 months [43]. The incidence of acidosis with or without hyperchloremia was 5.5% versus 8.9% versus 7.9% and 5.5% versus 13.3% versus 11.1% for ileal versus ileocecal versus all neobladders, respectively. There were no differences between serum pH, pCO2, pO2, bicarbonate, chloride, or potassium between the 2 groups.

Table 11. Acid-base and Electrolyte Parameters in Patients with Ileocecal Neobladders [54]

Arterial blood gas:	
Mean pH (range)	7.372±0.027 (7.299-7.410)
Average HCO3 (range)	21.9±2.3 mmol/L (15.9-24.9, normal 21-26)
Average base excess (range)	-2.3±2.4 mmol/L (-8.7 - 0.8, normal –2.5 - 2.5)
Average Chloride (range)	104.5±3.4 mEq/l (range 98-110, normal 98-108)
Na and K normal	

d) Chronic Bacteriuria

The reported prevalence of chronic bacteriuria in patients with neobladders is variable from less than 12% to 79% (*Level 3,* [44,80,83,119,173,209]).

The prevalence of bacteriuria is fairly steady over time as demonstrated by the findings of Steven and Poulsen that the rate of bacteriuria at 1 year, 3 years, and 5 years in patients with ileal neobladders was 26.0%, 34.3%, and 24.2%, respectively [44].

Wood et al. reported positive urine cultures in only 50% of patients despite bacteriuria in 78% [119]. The same authors reported the incidences of clinical urinary tract infection or urosepsis of only 39% and 12%, respectively. This supports the view that bacteriuria in most neobladder patients is asymptomatic and represents a colonization rather than a clinical infection, provided there is good emptying.

Wullt et al. provided a detailed study of bacteriuria and positive culture rates in 30 patients with ileal neobladders, and in 23 with right colon neobladders compared to 11 patients after radical prostatectomy and 6 healthy control patients [173]. Clean catch mid-stream urine cultures were obtained weekly 3 times and at 6 months of follow-up. Of note, 43% of the patients with ileal neobladders received prophylactic antimicrobial suppression with trimethoprim 100 mg daily. Cultures were consistently negative in the controls and were positive in 67% and 80% of the patients with ileal neobladders without and with antimicrobial suppression, respectively. The rate of bacteriuria was 79% versus 46% (P = 0.003) for patients with postvoid residual urine volumes of greater than 20 mL versus less than 20 mL, respectively. Increased postvoid residual urine volumes also correlated with positive urine cultures (P < 0.005), but incontinence did not. The cultured organisms were potential uropathogens including *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Enterococcus faecalis*. Anaerobes were more common in ileal than in colonic neobladders. Intestinal neobladders lack the native immunologic defenses of the native bladder mucosa and prostatic secretions. Thus, bacterial colonization may progress to invasive tissue level infection more easily in urinary diversions. Nevertheless, virtually all investigators recommend against routine prophylactic antimicrobial suppression for asymptomatic bacteriuria in patients with neobladders to minimize the risk of developing drug-resistant species and to minimize cost and drug-related side effects.

e) Rupture

Multiple cases of spontaneous rupture of continent urinary diversions have been reported (*Level 3*, [81,88,282-292]). Recurrent episodes of pouch rupture in the same patient have also been reported [286,289]. The most common cause is acute or chronic overdistention of the diversion. Patients must be instructed to void every 3 to 4 hours even if they can maintain continence for longer intervals and do not feel pressure or a need to void. This is especially important in long-term follow-up as the pouch capacity may enlarge and the efficiency of voiding by Valsalva straining may decrease. Other causes include catheter trauma, mucus retention, and altered sensorium from alcohol intoxication. Neobladder

patients should be instructed in the technique of CIC in case an episode of mucus plugging and retention occurs when they do not have access to medical personnel who are familiar with continent urinary diversion. Some authors advocate that continent diversion patients should wear a medical alert bracelet [286]. The reported rates of spontaneous pouch rupture are 1.5% to 4.3% [81,286]. Pouch rupture should be considered in all patients with continent urinary diversion who present with acute abdominal pain. Catheterization to check for urinary retention and hematuria suggestive of pouch trauma should be performed initially while hematologic studies are pending. Pouchogram by standard radiography or preferably by computed tomography (CT) should be obtained. Radiographic pouchogram frequently fails to show extravasation in cases of proven rupture [19,88,286]. In contrast, free intraabdominal fluid (urine) usually will be detected by CT even if ongoing extravasation is not shown during the infusion CT cystogram. The overall clinical features of the patient dictate the necessary treatment. Patients who are hemodynamically stable, have uninfected urine, and lack signs of acute peritonitis may be treated with an indwelling catheter, broad spectrum antibiotics, and close observation [287,288,293]. Patients with overt sepsis, uncontrollable pain, or a rigid abdomen require surgical exploration and repair. Delayed diagnosis may lead to life-threatening infection with necrosis of the pouch and Fournier's type gangrene of the abdominal wall [285].

8. Types of Orthotopic Reconstruction With Confirmed Experience by Other Centers

Brief descriptions of the most common anatomic orthotopic neobladder reconstructions are presented in this section. Detailed analysis of the specific outcomes regarding results and complications were presented earlier in this chapter. Much credit is deserved for the early contribution of Camey and colleagues who created a U-shaped ileal segment orthotopic neobladder utilizing approximately 45 cm of ileum [277]. The inferior midpoint of the ileal segment was anastomosed to the urethra. The ureters were each anastomosed to the respective superior right and left limbs of the ileal segment with a unique antireflux anastomosis into a mucosal trough within the ileal segment [172]. The procedure is important in the historical evolution of orthotopic urinary diversion for its simplicity and the early recognition that a bowel segment could be anastomosed to the urethra just as the native bladder is reconnected following radical prostatectomy. The results reported by Camey and others were quite successful [277,278]. However, once the benefits of detubularization to lower pressure within a diversion were appreciated, routine detubularization of the bowel along the antimesenteric border became standard in all forms of continent urinary diversion. Initially most investigators utilized approximately 60 cm of ileum to create detubularized orthotopic neobladders.

These bowel segments were reconfigured in a variety of patterns (see below) to create large capacity, low pressure diversions adhering to the geometric and volume-pressure-wall tension relationships described earlier in this chapter. All of the detubularized diversions achieve low pressure and satisfactory capacity. Recently there is a trend to utilizing somewhat shorter ileal segments of 45 to 50 cm length to minimize the impact on the remaining small bowel function while still maintaining sufficient capacity of the orthotopic urinary diversion. The W-shaped ileal neobladder described by Hautmann and colleagues is created with 45 to 60 cm of ileum by folding 4 consecutive ileal segments of equal length into the shape of a W [9,19,55,178-180,217,294]. The entire segment is detubularized along the antimesenteric border. The adjacent edges of the ileal limbs are sutured together creating 3 vertical suture lines forming the posterior wall of the neobladder. The ureters are anastomosed either by direct refluxing or antirefluxing techniques to the superolateral posterior limbs of the diversion. The lateral limbs of the diversion are folded over to create the anterior wall suture line. The inferior most point of the diversion is anastomosed to the urethra. The W-shape creates a highly spherical neobladder and lends itself to a variety of antireflux ureteral reimplantation techniques if one so chooses.

A variety of minor variations upon this same configuration have been described, including an ileal S-pouch, J-pouch and so-called chimney modification leaving a short tubularized segment of ileum at each superolateral corner for direct anastomosis of the ureters [181,182,206]. The detubularized ileal neobladder with an intact tubularized afferent limb described by Studer and colleagues also is widely utilized [4,197,199,211,214,295]. The storage portion of the neobladder is created by folding a 30 to 45 cm segment of ileum into a vertically oriented U-shape. This segment is detubularized and the posterior wall edges are sutured. Then the pouch is cross folded and the anterior wall is sutured creating a

spherical shape. The lowest portion of the neobladder is anastomosed to the urethra. The ureters are anastomosed directly onto the upper portion of the intact afferent limb. The long afferent limb effectively prevents high pressure reflux to the kidneys from urine within the low pressure portion of the detubularized neobladder provided the patient is voiding effectively at appropriate intervals.

This neobladder configuration is particularly helpful if the available length of ureter is short. The ileal Kock pouch cutaneous reservoir was modified to create an orthotopic neobladder by eliminating the efferent limb and nipple while maintaining the afferent limb nipple to create an antirefluxing ureteral anastomosis [157,175,185,195,200,209,224]. Due to the complexity of nipple construction and the high rate of associated complications (stone formation on exposed metal staples; nipple stenosis, or necrosis secondary to ischemia), this procedure is no longer employed. The ileal T-pouch configuration represents a standard detubularized ileal segment reconfigured into a spherical shape for the storage chamber of the neobladder [3,176,296].

The ureters are anastomosed directly onto an intact ileal segment which is tunneled into the middle of the neobladder wall by an extraluminal, serosal trough technique similar to the principle of Abol-Enein and Ghoneim for antireflux ureteral anastomosis [280,281]. Segments of the colon also may be reconfigured and utilized for orthotopic neobladder construction. The cecoileal segment is particularly well-suited for orthotopic diversion due to a predictable blood supply from the ileocolonic artery and easy descent of the mobilized segment into the pelvis [33,43,54,158]. The high pressure contractions of the colon must be overcome by complete detubularization and or creation of teniomyotomies within the bowel wall. Redundant sigmoid colon also may be deconfigured and utilized for orthotopic neobladder construction [32]. However, the less predictable blood supply of the left colon in the elderly and the higher rate of intrinsic pathology such as diverticulitis and neoplasm limit the desirability of these procedures.

III. CONTINENT CUTANEOUS DIVERSION

1. Indications

In conjunction with radical cystectomy, today continent diversion to the skin generally is the second choice after orthotopic bladder substitution. The main indication is when urethral removal is deemed necessary because of a high risk of urothelial carcinoma recurrence. Occasionally, patients may prefer continent diversion to orthotopic reconstruction because of the risk of urine leakage with the latter.

2. Prerequisites

As with other types of continent reconstruction, large capacity under low pressure in the pouch is essential, and this is achieved through detubularization. The dynamic behavior of such pouches has been explained in general and biomechanical terms by Hinman Jr. and Colding-Jorgensen et al. (*Level 3*, [21,22]). The patient should have normal or near normal renal function, or the risk of electrolyte imbalance increases. However compliant the reservoir, its outlet must have an effective leakage-preventing mechanism, yet permitting easy catheterization. Further, it must be easy to construct. Numerous methods have been designed and reported once, but not reappeared in the literature, most often due to high complexity. The most commonly used methods have been the Kock pouch, the Indiana pouch or variation thereof, and pouches employing the appendix as an outlet. The stoma is usually in the right lower quadrant or in the umbilicus. Herein are described the most commonly used pouches and complications from the pouch that seem to be more common than in orthotopic substitutes.

3. The Kock Pouch

This was the first method that was accepted by the urological community after description by Kock et al. and refinement by Skinner´s group (*Level 3*, [297,298]). The ileal pouch has an afferent and an efferent ileal intussuscepted valve. The technique is elaborate with a long learning curve, and the initial enthusiasm has been considerably dampened by reports on high complication rates. Fatty mesentery can cause difficulties in fashioning the nipple valves,

and fixation of the efferent nipple base to the abdominal wall may present problems. Erosion by mesh, pinhole fistula, stenosis, and even sloughing of the valve as well as prolapse and sliding of the valve may occur with consequent urine leakage or difficult catheterization. Even with the large experience of this technique in Skinner´s department, the outlet failure rate after introducing several modifications was still as high as 15% in their last 239 patients (*Level 3*, [299]). In a long-term follow-up, Jonsson et al. reported that 31% of patients operated on since 1984 had outlet revision, which decreased to 21% in those operated on since 1993 (*Level 3*, [155]). Of surviving patients, 90% had a well-functioning reservoir.

For a detailed discussion of this technique and its historical significance, see Section III.8. The Intussuscepted Kock Ileal Nipple: A Technique of the Past.

4. The Indiana Pouch

Described by Rowland et al., this type of diversion uses the ascending colon patched with an ileal segment, the outlet being a 10 cm plicated or stapled ileal segment (*Level 3*, [300]). In the last report from that group, only 1 out of 81 patients needed outlet revision due to urine leakage (*Level 3*, [301]). Comparing this type of pouch with the Kock pouch, reports favor the former due to less complications (*Level 3*, [302-304]). The advantage with the technique is that it is simple; the disadvantage is that the outlet lacks an intraluminal closure mechanism.

Many modifications of the technique have been described. In the Florida pouch, a detubularized right colonic segment is used. In 74 patients followed for a mean of 11 years, Webster et al. reported that 7% became incontinent, requiring retapering of the outlet in some (*Level 3*, [305]). Stomal stenosis occurred in 3 patients and difficult catheterization due to limb elongation occurred in 1. This group recently reported that the addition of a cecal wrap to the efferent limb resulted in better urodynamics of the outlet and better continence (*Level 3*, [306]). The Indiana outlet incorporates the ileocecal valve, which is diminished in diameter and fixed to the cecal wall as a small flap valve. In a randomized study, this type of outlet proved equally effective as an ileal nipple valve, but with inferior urodynamic characteristics (*Level 2*, [307]). In the latest report on this technique, revision of the outlet due to leakage was necessary in 6 of 97 patients and 6 patients needed stomal revision due to stenosis (*Level 3*, [81]). All but 4 patients were continent at follow-up.

5. Appendiceal Outlet

The use of the appendix as a catheterizable outlet for vesicostomy was described by Mitrofanoff and later by Riedmiller et al. for continent cutaneous diversion (*Level 3*, [308,309]). Advantages with use of the appendix are that it is “ready-made” and that less amount of bowel is needed for the diversion. The main disadvantage is that it is sometimes lacking or too small to use. Familiarity with some other method for continent diversion is thus necessary. Several techniques for the use of appendix as a continent outlet have been described, but the most popular seems to be the embedded appendix as used in the Mainz Pouch I. Gerharz et al. reported that except for 3 of 118 patients who suffered ischemic necrosis of the appendix and needed reoperation, no other patients underwent revision due to incompetence of the outlet (*Level 3*, [310]). The main problem is the tendency to stomal stenosis, which required revision in 19 patients.

6. Complications of Continent Cutaneous Urinary Reservoirs

The evolution of urinary diversion over the past 25 years has included many technical advances and medical discoveries in the fields of medicine and oncology. Antibiotics, advances in anesthesia, more reliable blood products, and improved suture material and stapling devices have contributed to these developments. One of the most important advances in the entire field of diversion was Kock’s appreciation for the need to detubularize the bowel segment to decrease the intraluminal pressure of the reservoir in accordance with La Place’s law, allowing for a large capacity, low pressure system. Despite these improvements, complications in this generally elderly group of patients undergoing continent urinary diversion occur relatively frequently.

a) Complications Related to the Urinary Reservoir (Pouch)

1. Urine Leak

Probably the most common early diversion-related complication is a prolonged pouch urinary leak. Although the exact incidence is not difficult to determine, confirmation of the leak can be performed by assessment of the drain output for creatinine or radiographic evaluation of the reservoir. The majority of urine leaks are of no clinical consequence if they are appropriately drained. Most urine leaks close over time with appropriate drainage. In rare instances, placement of nephrostomy tubes bilaterally will facilitate the closure. Open surgical repair is

rarely needed if the abdomen is appropriately drained. A delayed urine leak is generally related to a spontaneous perforation of the reservoir. Although rare, this requires astute clinical evaluation. Patients may present with abdominal pain and signs of peritonitis. Importantly, urine leaks with a pouch perforation (usually secondary to overdistention) are unlikely to heal with drainage alone and often require open surgical repair.

2. Stone Formation

Pouch stones or calculi development in the lower urinary tract is usually dependent on the form of urinary diversion performed. Some studies suggest hypercalciuria and hyperoxaluria as causative factors [311] and several reports have noted that hypocitraturia is common in stone formers (*Level 3*, [312-314]). The incidence seems to increase with length of follow-up.

The highest incidence of stone has been reported in the Kock pouch ileal reservoir and is primarily related to the exposed staples required to construct the intussuscepted nipples [315]. Chronic bacteriuria, urinary stasis, mucus formation, and foreign bodies have been considered as important etiologic factors. Any exposed foreign body in the reservoir (such as staples) may lead to the development of stones. Furthermore, there is clearly a higher incidence of stones in continent cutaneous reservoirs compared to orthotopic neobladders. This finding is a result likely related to the state of chronic bacteriuria seen in up to 80% of patients with continent catheterizable cutaneous reservoirs. Additional factors that may contribute to stone formation include urinary stasis, mucus production, and metabolic abnormalities. The diagnosis of pouch stones is generally made radiographically. Urinary diversion calculi are commonly treated with endoscopic fragmentation via the cutaneous stoma or a percutaneous access if there is concern that transstomal manipulation may compromise the continence mechanism. Open surgery may be required for large stones.

3. Bacteriuria

Bacteriuria is a common finding of continent cutaneous urinary diversions in at least 80% of patients [316]. The source of bacteria is probably related to the clean (not sterile) catheterization technique employed by patients to empty the reservoir. There is little significance of bacteriuria, which is largely asymptomatic, unless the patient presents with pouch stones or upper tract infections with a refluxing continent cutaneous reservoir. Prophylaxis is needed, but little studies exist on this.

4. Rupture and Perforation

The incidence is 1% to 2% as found in a survey of patients operated upon in the Scandinavian countries (*Level 3*, [283]). The etiology can be trauma from catheterization, but it can also occur spontaneously, often with a full pouch. The investigational procedure of choice is CT scan and treatment is by laparotomy.

b) Complications Related to the Stoma

1. Parastomal Hernia

Parastomal hernia can occur in approximately 5% of patients with a continent urinary reservoir [263,317,318]. Parastomal hernias are a late diversion-related complication and may present with abdominal wall deformity, difficult catheterization, and urinary incontinence. Predisposing factors to parastomal hernias include obesity, multiple abdominal operations, wound infection, and poor surgical technique. Stomal location is important and should be positioned through the rectus muscle (not lateral), which may decrease the incidence of stomal hernia formation. Parastomal hernias can be difficult problems and are best managed surgically.

2. Stomal Stenosis

Stomal stenosis and difficult catheterization are primarily seen with the appendix and the Mitrofanoff technique. One review found an incidence of difficult catheterization or stomal stenosis of 18% in patients with the tunneled appendix, 9% with the intussuscepted valve (Mainz and Lund pouch), and 3% with a stapled-plicated limb (Indiana pouch) [263]. This complication can be minimized at the time of the original surgery by avoiding excess or redundant intestine, fixation of the reservoir to the abdominal wall, stabilization of the continence mechanism to the pouch wall, and intraoperative passage of a catheter through the catheterizable limb to ensure the ease of passage. Treatment may include gentle dilation followed by a strict intermittent catheterization schedule as a preventive measure. Ischemic stenosis of the cutaneous stoma usually requires open surgical revision.

c) Complications Related to the Antireflux Mechanism or Ureteral Stenosis

The need to prevent reflux in a continent cutaneous reservoir is not significantly debated and should be performed. Obstruction of the antireflux limb or ureter is seen in approximately 5% to 8% of patients [263]. In a comprehensive review, 7.5% of Le Duc type ureteral implantations demonstrated obstruc-

tion, compared to 10% with a Goodwin type, and 5% with a tunneled tenial ureteral reimplantation technique. Although the majority of strictures involving the ureterointestinal anastomosis occur within 1 to 2 years following construction of the urinary diversion, late strictures occur, underscoring the need for long-term follow-up. The majority of patients with obstruction are asymptomatic and diagnosed at the time of routine radiographic follow-up.

Anastomotic stenosis results in unilateral new-onset hydronephrosis (unless both ureteral reimplant sites are affected), as opposed to stenosis of an afferent nipple valve, which results in bilateral hydronephrosis, as the site of obstruction is distal to the ureteroileal anastomosis (3%-5% of the Kock ileal reservoir) [269,319]. The primary cause of stenosis of a ureterointestinal anastomosis or of an afferent intussuscepted nipple is ischemia. When dissecting the ureters at the time of radical cystectomy, it is important to maintain an adequate amount of periureteral and adventitial tissue so as not to devascularize the distal segment of ureter which is to be reimplanted. It is also important not to excessively angulate the ureter during reconstruction as that can also lead to postoperative obstruction. The diagnosis of ureteral strictures is made radiographically and best visualized with intravenous urography. Urinary decompression may be required and accomplished with percutaneous nephrostomy tube (PCN) insertion. An antegrade nephrostogram may help further delineate the stricture site. Placement of a PCN also allows access to be obtained prior to endoscopic therapy. In patients with a history of bladder cancer, it should be ensured that the stricture is not related to a malignant recurrence.

Initial treatment of ureteral strictures is usually endoscopic management. Balloon dilation has been employed with varying success in the management of ureterointestinal stricture. The primary indicators for failure of this technique include stricture length and time from surgery. Strictures less than 2 cm have a more favorable outcome [320-322], as do strictures less than 7 months' duration [323]. It also appears that ureterocolonic strictures are more difficult to manage endoscopically compared to ureteroileal strictures [318]. Endoscopic incision of a ureterointestinal stricture is an alternative minimally invasive technique. The outcomes are varied with recurrence-free stricture rates as high as 75% [324]. Cold-knife techniques are thought to avoid potential thermal injury with resultant ischemia, fibrosis, and restricture from hot-knife. If endourologic techniques fail in the correction of ureterointestinal strictures, then open revision may be necessary. The success rate of open revision of ureterointestinal strictures is greater than that for endourologic management of approximately 90% [325,326].

Although significant improvements in continent urinary diversion have occurred, complications do exist. Avoidance of these diversion-related complications with sound surgical technique is of utmost importance at the time of the initial surgery. However, even despite the best of surgical techniques, complications do occur. The vast majority of these diversion-related complications can be recognized early with proper follow-up and radiographic evaluation. The treatment of these complications in most cases is initially conservative or endoscopic; however, open surgical revision may be occasionally required.

8. The Intussuscepted Kock Ileal Nipple: A Technique of the Past

An important component in the evolution of urinary diversion over the past 25 years has been the development of a reliable and durable means to provide continence (via a catheterizable stoma) and prevent the reflux of the urinary constituents (to protect the upper urinary tract) in continent urinary reservoirs. The intussuscepted nipple valve was one technique that satisfied these goals [327]. The most recognizable pioneer in the development and clinical application of the intussuscepted nipple valve was Dr. Nils Kock. In 1973, Kock successfully reported on 37 patients who underwent creation of a continent detubularized ileostomy reservoir employing the intussuscepted nipple valve as the catheterizable continent limb [328]. This landmark experience paved the way for the continent Kock ileal urinary reservoir utilizing the intussuscepted nipple mechanism in 12 patients for a cutaneous urinary diversion [297]. The continent cutaneous Kock ileal reservoir subsequently became a common form of urinary diversion [175,329]. The continence and antireflux mechanism of this ileal reservoir required construction of intussuscepted nipple valves (efferent and afferent, respectively) as described by Kock. The evolution of the orthotopic neobladder resulted in the successful application of the Kock reservoir to the urethra, which utilized the afferent intussuscepted nipple valve as an antireflux mechanism in these patients [44,157,175,185,200]. Throughout this time period, significant technical advances and improvements in lower urinary tract reconstruction and continent diversion were made.

Although the principles of the continent Kock ileal reservoir (cutaneous and orthotopic form) are sound, complications occurred [269,311,314,316,330]. The Achilles' heel of the Kock ileal reservoir remained the intussuscepted nipple valve. Most complications associated with the Kock ileal reservoir involve either the antirefluxing (afferent limb) nipple or the continent catheterization (efferent limb) nipple. Despite several surgical modifications to improve upon the construction of the intussuscepted nipple valve, there remained complications and a certain reoperation rate. The era of the orthotopic bladder substitute reduced the need for continent cutaneous diversions and the application of the intussuscepted cutaneous Kock ileal nipple valve. The application of the afferent intussuscepted nipple remained a popular antirefluxing technique. An extensive review of the Kock ileal reservoir demonstrated a 10% complication rate associated with this antireflux nipple in over 800 patients (undergoing either a continent cutaneous or orthotopic Kock ileal reservoir) [269]. The most common complications associated with the intussuscepted afferent nipple included:

1. the formation of pouch calculi (usually on exposed staples that secure the afferent nipple valve) in 5%,
2. afferent nipple stenosis (thought to be caused by ischemic changes resulting from the mesenteric stripping required to maintain the intussuscepted limb) in 4%, and
3. extussusception (prolapse of the afferent limb) in 1% of patients.

Although the majority of these afferent nipple valve complications (60%) can be managed with endoscopic techniques, they nonetheless result in some morbidity. In fact, approximately 3% of all patients undergoing a continent Kock ileal reservoir will require an open surgical revision to repair a complication associated with the afferent nipple [269]. The need to improve upon the intussuscepted nipple valve was obvious. Elegant experimental and clinical reports from Abol-Enein and Ghoneim demonstrated a novel antirefluxing technique employing a ureteral extramural serous-lined tunnel in an orthotopic bladder substitute [280,294,331]. This serous-lined extramural technique was subsequently applied to a continent cutaneous urinary outlet [332,333]. This technique is clearly an important technical improvement that has helped pave the way for the extramural serous-lined ileal flap valve technique, called the T-mechanism [176,296]. The T-mechanism was first successfully incorporated as an afferent antireflux limb of an orthotopic reservoir (T-pouch) [176] and subsequently into an afferent antireflux and efferent continence limb of a cutaneous reservoir (Double-T-Pouch) [296]. The application of the serous-lined extramural tunnel, and the flap-valve T-mechanism has helped eliminate the complication associated with the intussuscepted nipple valve while maintaining an effective antireflux or continence mechanism. The concepts and principles of the continent Kock ileal reservoir ultimately paved the way for the development of the serous-lined extramural tunnel and T-mechanism techniques. These newer techniques have been found to be effective flap-valve mechanisms, eliminating the need for the intussuscepted nipple valve, which can provide antireflux and continent cutaneous mechanisms.

The principles of detubularization and reconfiguration of the Kock urinary reservoir should be maintained. However, the creation of the intussuscepted nipple has largely been abandoned. It would be beneficial for all surgeons interested in reconstructive urology to have a basic understanding of the history of the Kock intussuscepted nipple and the technical aspects of the surgical techniques. The historical perspective should provide a better understanding of the more contemporary technique and may also stimulate future improvement in the field of urinary diversion.

9. Revision Surgery for Nipple Failures

Critical components to the success of all forms of continent cutaneous urinary reservoirs include the ability to create a large capacity, low pressure system with an effective antireflux mechanism to protect the upper urinary tracts and an adequate continence mechanism to store urine. In general, continence and antireflux mechanisms in urinary diversions are dependent on the relationship between the outlet resistance and internal reservoir pressure. This mechanism should not only exceed intrareservoir pressures at rest, but also during change of position or posture and under Valsalva pressure. The basic surgical premise for the Kock ileal reservoir is sound - a low pressure, large capacity reservoir, employing the intussuscepted antirefluxing and continent nipple valves. The Achilles' heel of the Kock ileal reservoir remains, however, the intussuscepted nipple valve. Despite surgical modifications to improve upon the construction of the continent catheterizable intussuscepted nipple valve, there remain complications and a certain reoperation rate [314,325]. Complications and the need for revisional surgery of the efferent intussuscepted nipple valve are seen in at least 30%

of patients with the continent Kock ileal reservoir. These are technically demanding and require the reconstructive surgeon to be familiar with a variety of surgical techniques in order to construct a new continent catheterizable limb. In general, the intussuscepted Kock nipple valve is no longer commonly employed as a continence mechanism.

Several alternative techniques *(see Previous Sections)* may be applied to create a dependable, continent catheterizable efferent limb including:

1. appendiceal techniques,
2. tapered or imbricated terminal ileum and ileocecal valve, and
3. a flap-valve technique such as the serous-lined extramural tunnel or efferent T-mechanism.

Although these techniques may provide a catheterizable continence mechanism, each has its own limitations. The ideal outlet should be constructed from a readily available and surgically versatile intestinal segment without the need for synthetic materials. It should provide reliable continence and allow for easy catheterization in the long term. It is important to note that when revisional surgery is performed for the continence mechanism, the existing reservoir portion of the urinary diversion should be maintained (and, if necessary, augmented) with the new catheterizable efferent limb providing the continence mechanism.

The appendix may provide for an effective continence mechanism as was first described by Mitrofanoff [308]. The in situ appendix can be tunneled into a cecal tenia similarly to a ureterocolonic anastomosis (with preservation of the mesentery). The appendiceal continence mechanism has been criticized for 3 reasons. First, the appendix may be unavailable because of prior appendectomy. Second, the appendiceal stump may be too short to reach the anterior abdominal wall. Lastly, the caliber of the appendix may be small and may make reservoir urine and mucus more difficult to eliminate. However, if an appropriate appendix is available, it can provide for an effective continence mechanism. A slight modification of the Mitrofanoff principle was described by Monti in which a 2 to 3 cm segment of ileum is used and reconfigured into a tube; this tube can then be tunneled into the colon to provide a continence mechanism [334].

The second major type of continence mechanism that can be used for an intussuscepted nipple failure is the tapered or imbricated terminal ileum and ileocecal valve. The principle evolved from the Gilchrist procedure described in 1950 [335]. In this situation, imbrication and plication of the ileocecal valve region along with tapering of the more proximal ileum can provide an acceptable continence mechanism [300,336]. This technique can be easily performed. However, criticisms of this continent cutaneous mechanism include the loss of the ileocecal valve and potential for bowel dysfunction. In addition, this outlet relies mostly on passive tubular resistance (extraluminal valve) and will leak at higher reservoir pressures.

The third general type of procedure for developing a continence mechanism incorporates a flap-valve technique. The principle of embedding a tubular structure with a serous-lined extramural tunnel was first developed by Abol-Enein and Ghoneim [280,294,327,328,337]. This is a versatile technique that was used initially and successfully for reflux prevention in conjunction with an orthotopic ileal bladder [280,294]. Since the technique of embedding a tubular structure within a serous-lined extramural tunnel provides unidirectional flow of urine, the feasibility to construct a continent cutaneous outlet was explored and confirmed experimentally in animals first [327]. This technique was then applied using ileum or the appendix with good results in a clinical situation [328,332]. Continence is provided by a passive mechanism derived from tubular resistance of the anchored and tapered segment and, most importantly, a dynamic mechanism that results from embedding the outlet with the wall of the reservoir – a flap-valve technique. This combination prevents leakage even at high pressures within the reservoir (intraluminal valve). A modification of the serous-lined extramural tunnel was subsequently developed and coined the “T-mechanism.” This surgical technique incorporates an extramural serous-lined flap-valve technique. This technique was first developed in order to eliminate the inherent problems with the intussuscepted Kock nipple valve. This T-mechanism was initially applied as an antireflux technique in the T-pouch ileal neobladder [176], and subsequently applied to a continent cutaneous ileal reservoir; creating an afferent antireflux, and continent efferent catheterizable mechanism called the Double-T-pouch [296].

As previously mentioned, most reconstructive surgeons have abandoned the continent Kock ileal reservoir with the intussuscepted nipple valve largely due to the technical difficulties of pouch construction and the significant complication rate associated

with the intussuscepted nipple valve. Alternative and effective techniques for the creation of a continent cutaneous catheterizable mechanism have developed. This evolution in urinary diversion must not be viewed as a condemnation of the brilliant and pioneering work of Kock and his associates [297,323]. Rather, these are the natural improvements and refinement of reconstructive surgical techniques that occur over time.

Summary

Excellent functional results can be obtained with continent cutaneous diversion using the Kock pouch, the Indiana pouch, or with pouches using the appendix as the outlet. The former method carries a high risk of late complications. Stone formation in the pouch is not uncommon. Awareness of the possibility of pouch rupture or perforation is necessary.

IV. INCONTINENT URINARY DIVERSION

This is still the most commonly performed type of reconstruction in conjunction with cystectomy. Thus, 64% of all patients undergoing surgery within 3 months of diagnosis of locally advanced bladder cancer received a noncontinent form of diversion in Sweden in 2002, with corresponding figures for continent urinary diversion and orthotopic bladder substitution being 13% and 21%, respectively, with missing data in 3% (Swedish Bladder Cancer Registry, *Level 2*, [338]). According to data from the National Inpatient Sample of the Healthcare Utilization Project within the U.S Agency for Healthcare Research and Quality, constituting a representative 20% sample of the US population, 91% of the patients undergoing radical cystectomy in the years 1988 to 1999 received an ileal conduit, while 6.4% received an orthotopic neobladder, and 2.5% were incorrectly coded. The figure for continent cutaneous diversion may be included in the figure given for conduit diversion (B. Konety, personal communication). The high percentage of noncontinent diversion probably reflects that the mean age of cystectomy patients is high and that cystectomy is also performed outside major centers. Considerable improvements in the quality of the appliances and the development of enterostomal therapy into a specific field of its own have been of importance for the acceptance of noncontinent diversion.

1. Cutaneous Ureterostomy

Cutaneous ureterostomy (UCN) was initially described as a means of diversion in children. UCN was later used in adults with ureteral obstruction, generally from malignancy; however, a stomal stenosis rate of greater than 50% in an end-cutaneous ureterostomy has limited its application [339]. It was concluded that cutaneous ureterostomy no longer is indicated as a primary form of palliative diversion, since palliative diversion is now best initially attempted with percutaneous nephrostomy. Stomal stenosis and subsequent urinary tract infection are major complications. Feminella et al. pointed to the following elements as being likely to induce stomal stenosis: flush stoma, ureter smaller than 8 mm in diameter, and radiation exposure. The stricture rate was 64% of 70 cases that had undergone cutaneous ureterostomy. In terms of stricture patterns, the rate with an everted stoma was 56%, a flush stoma 92%, and an everted stoma of ureters greater than 8 mm in diameter 45% [340]. Other serious complications are renal dysfunction due to recurrent UTI and calculus formation. Although it occurs rarely, uretero-aortic fistula is a fatal complication of intubated cutaneous ureterostomy [341,342]. Since correct diagnosis is sometimes impossible preoperatively and fatal massive hemorrhage might occur, surgical treatment must be undertaken early even in the absence of absolute proof of diagnosis.

Considering these disadvantages, many urologists have thought of UCN as an abandoned surgical procedure. On the other hand, some urologists reported that UCN can be a practical alternative diversion in a select group of patients. Rainwater et al. reported that stomal stenosis could be avoided by restricting the application to patients with hydroureter and using skin flap interposition [343]. Indeed, the rate of stomal stenosis was only 4.5%, which is equivalent to that in patients with ileal conduits. Bracken et al. used double J stents for intubated cutaneous ureterostomy, which facilitates primary healing of the stoma and diminishes the late complication rate compared to balloon catheters [344]. Double J stents are commonly used for intubated cutaneous ureterostomy now. Claman et al. also reported the good clinical outcome of UCN for solitary functioning kidney [345]. They concluded that one could expect the transplant of even a normal caliber ureter to skin to succeed, as far as basic principles of preservation of blood supply and avoidance of angulation and tension are respected. Some other urologists tried to improve the surgical technique of UCN so that UCN

could be applied as not only temporary but also permanent urinary diversion for patients undergoing cystectomy but not intestinal segment urinary diversion due to high-risk medical conditions. Toyoda et al. presented a new technique for catheterless cutaneous ureterostomy [346**].** Interestingly, Yoshimura et al. reevaluated Toyoda's method in 2001, almost a quarter of a century after his report [347]. They performed this method in 61 patients (103 renal units), and, of these, 92 renal units (89%) remained tubeless. Within 3 months after surgery, acute pyelonephritis developed in 12 patients (20%), which was catheter induced in 5. After this period, acute pyelonephritis developed in 7 patients (11%) who were catheter-free. Although relatively common, this complication was only transient and was easily treated with antibiotic administration.

Another new technique was developed by Hirokawa et al. [348]. They applied this technique to patients with bilateral ureters with normal caliber. A 6 to 7 cm longitudinal incision is made to the distal segment of the carefully mobilized ureters. Both ureters, incised in strips, are then sutured together with a side-to-side anastomosis, omitting the distal 2.5 cm. Between the distal unsutured portion of the anastomosed ureters, a stoma is constructed by the interposition of 2 skin flaps that are made according to the Z-skin plasty technique with interrupted sutures. The rate of stomal stenosis was 8.3%. Loop cutaneous ureterostomy was developed to avoid stomal stenosis and mostly applied to children or kidney transplantation patients with permanently damaged lower urinary tracts [349,350]. A study by Rosen et al. of 20 children who underwent loop cutaneous ureterostomy reported no stoma-related complications in patients whose mean duration of diversion with ureterostomy was 12 months [345]. Thrasher et al. applied loop cutaneous ureterostomy to patients with advanced pelvic malignancies [351]. They applied this technique to patients with at least unilateral hydroureteronephrosis preoperatively and performed transureteroureterostomy for patients with bilateral functioning kidneys. No patient had ureteral stomal stenosis or retraction. Mean survival was 5 months, with the longest survival being 1 year. Loop cutaneous ureterostomy could be a realistic option for palliative urinary diversion.

At last, we mention laparoscopic cutaneous ureterostomy. Laparoscopic cutaneous ureterostomy is currently performed in 2 clinical settings. One is as a substitute for percutaneous nephrostomy tube (PCN) placement, and another is subsequent urinary diversion after laparoscopic cystectomy. PCN placement, which is a minimally-invasive and a well-established procedure, should be the first choice for inoperable pelvic malignancy with upper urinary tract obstruction. However, the life expectancy in these patients varies according to the primary disease. Fallon et al. reviewed 100 cases of surgical diversion (open nephrostomy) in patients with advanced pelvic malignancies of different histologic types [352]. In prostate cancer patients, the average survival from nephrostomy to death was 12.2 months; in cervical cancer patients, it was 18.0 months, and in bladder cancer patients only 4.5 months. Thus, more permanent urinary diversion such as UCN might be suitable for patients with a life expectancy of more than 1 year. Both laparoscopic bilateral and unilateral cutaneous ureterostomy have been reported [353,354]. A less invasive retroperitoneoscopic approach has also been performed recently [355].

At the time of laparoscopic cystectomy, cutaneous ureterostomy is the easiest urinary diversion requiring no further steps. Although total cystectomy with orthotopic neobladder using ileum has been performed laparoscopically in some institutions, laparoscopic cystectomy is generally thought to be a technically challenging operation [356,357]. Since the main purpose of cutaneous ureterostomy with cystectomy is to diminish operative invasiveness, further evaluation is needed.

2. Conduit Diversion

a) Ileal Conduit

This is the most common form of diversion in conjunction with cystectomy. A 15 to 20 cm long distal ileal segment is isolated and ureters are implanted in the proximal end. The stoma is usually below and to the right of the umbilicus. Few publications have appeared on ileal conduit diversion during the last decade. Comparison between series of cystectomy with ileal conduit diversion, continent cutaneous diversion, or orthotopic bladder substitution must be viewed cautiously as the patient characteristics differ. However, some series suggest that there are no major differences with regard to early complications (*Level 3*, [197,273]). Long-term follow-up complications of ileal conduit diversion are frequent, the most common being stomal or peristomal problems, parastomal hernia, conduit stenosis, and upper tract deterioration. The incidence of these correlates with length of follow-up.

1. Stomal and Peristomal Complications

These include erythematous, erosive, and pseudover-

rucous skin lesions and stenosis and retraction of the stoma. Studies show that these problems are common, being reported in up to 31% (*Level 3,* [152,358,359]). Parastomal hernia is seen in 10% to 15% of cases (*Level 3*, [152,354]). Recurrence is not uncommon following repair. For first-time parastomal hernia, stomal relocation may be superior to fascial repair (*Level 3,* [360]). Newer techniques with incision lateral and far from the stoma with closure of the fascial defect and using mesh material have been reported to give good results (*Level 3*, [361,362]). Conduit stenosis is seen only with ileal conduits and has never been described in other intestinal segments interposed on the urinary tract. The whole or part of the conduit is transformed into a thick-walled tube without peristalsis, causing upper urinary tract obstruction. Etiology may be chronic inflammation or vascular insufficiency. Treatment is by removal of the conduit or partial resection (*Level 3,* [363]).

2. Upper Urinary Tract Deterioration

Several case series during the 1970s and 1980s showed a high incidence of upper tract complications, supposedly caused by chronic bacteriuria, reflux, and obstruction. This is also confirmed in later studies. Singh et al. reported upper tract dilation in 34% after mean follow-up of 5 years (*Level 3*, [354]). Madersbacher et al. found radiographic or functional deterioration in 35% of patients with a minimum follow-up of 5 years, increasing to 50% in those followed for 15 years (*Level 3,* [152]).

b) Jejunal Conduit

Jejunal conduits received a bad reputation because of several reports in the 1970s on the "jejunal conduit syndrome," characterized by hypochloremia, hyponatremia, hyperkalemia, and acidosis, caused by the inherent absorptive characteristics of the jejunum. The clinical signs are dehydration and lethargy and treatment is by intravenous saline, which often has to be followed by oral salt supplementation for some period of time. Fontaine et al., however, expressed satisfaction with this type of diversion and found a low incidence of electrolyte problems (*Level 3*, [154]). They stressed that a short conduit should be used.

c) Colonic Conduit

A colonic conduit in the adult population is most often used when high dose irradiation has been given previously. When an ileal conduit is used in such patients, the risk of complications is very high [364]. The governing rule should be to use nonirradiated tissue, the "stay away" principle. Ureters should be divided high. If conduit diversion is the most suitable alternative for the patient, transverse colon is usually the best choice [365].

Summary

Ileal conduit diversion remains the most commonly used method for reconstructing the urinary tract in conjunction with radical cystectomy. It is technically easier than continent reconstruction. However, the complications, early as well as late, are *legion.* Several studies confirm a high incidence of upper tract complications, probably increasing with length of follow-up.

V. ANAL SPHINCTER-CONTROLLED URINARY DIVERSION

Attempts to create a bladder substitute controlled by the anal sphincter date back over 100 years when Simon introduced ureterosigmoidostomy [366]. Thereafter, the procedure underwent many technical modifications. By 1936, more than 60 methods of anal sphincter-controlled bladder substitutes could be cited by Hinman and Weyrauch [367]. Anal sphincter-controlled bladder substitutes can be classified into 3 main categories: without fecal diversion, with partial fecal diversion, and with total fecal diversion.

1. Anal Sphincter-controlled Bladder Substitutes Without Fecal Diversion

a) Ureterosigmoidostomy

1. Preoperative Considerations

The success of ureterosigmoidostomy depends highly on proper patient selection. Factors that should be considered include anal sphincteric function, renal function, liver function, degree of ureteral dilation, history of prior radiation therapy, primary colonic disease, and patient's compliance with long-term medications [7]. Paramount to success is an adequate anal sphincter mechanism. This should be assured both by history and preoperative testing using large volume enemas with the patient assuming normal activities. Inability of the patient to retain 400 to 500 mL in the upright position for 1 hour is a contraindication to ureterosigmoidostomy [7]. Patients with

neurogenic bladder are not suitable candidates for ureterosigmoidostomy, as there may be associated anal sphincter dysfunction [8]. Preoperative evaluation of the patient selected for ureterosigmoidostomy should include studies for bowel disease that might contraindicate the operation. The presence of diverticulitis or colon polyps may be investigated by barium enema or colonoscopy [7]. Compromised renal function results in accentuation of hyperchloremic acidosis that results from ureterosigmoidostomy. Consequently, patients should have normal renal function to avoid this complication [368]. Inability to handle the excess ammonia absorption has been reported to lead to hyperammonemic encephalopathy. Therefore, ureterosigmoidostomy should be avoided in patients with liver disease [42]. In the presence of ureteral dilation, creation of a nonrefluxing anastomosis may be difficult to achieve. Hendren in 1973 offered an alternative in this situation. In his staged procedure, an antirefluxing colon conduit was created in which the absence of reflux can be tested before the second stage, in which the colon is connected end-to-side to the sigmoid [369]. Previous radiation therapy of the pelvis carries an increased risk of leakage or stenosis of the ureterocolic anastomosis. Compliance with long-term medication, such as antibiotics and bicarbonate, is mandatory in patients with ureterosigmoidostomy [7].

2. Preoperative Preparation

An adequate bowel preparation is mandatory prior to ureterosigmoidostomy to avoid infectious complications. The regimen includes a low residue diet, oral laxatives, cleansing enemas, and oral intestinal antiseptics for 3 days preoperatively [7].

3. Advantages

In 1973, Wear and Barquin enumerated the following advantages of ureterosigmoidostomy over Bricker's ileal loop: voluntary sphincteric control of urination without an external stoma and its complications, no indwelling tubes or external collecting device, shorter operating time and easier technique, ability to stage the operation, ability to perform via intraperitoneal or extraperitoneal approach, requires 2 rather than 5 suture lines, and is better accepted by the patient and his relatives [370,371].

4. Complications

• Early Complications

- Postoperative Anuria

The most serious immediate complication from ureterosigmoidostomy is anuria if the anastomosis is not stented. Anuria after removal of the ureteral stents indicates bilateral obstruction caused by tissue edema. In both cases, percutaneous nephrostomy tubes should be placed, especially in case of fever or flank pain [372].

- Urine Leakage

Leakage of urine occurs as an early complication of ureterosigmoidostomy with a reported incidence of 3.5% after combined technique of ureterocolic anastomosis [373].

Small leaks usually seal spontaneously. Extensive leaks, especially those associated with prolonged ileus or signs of peritonitis, are indications for immediate reoperation. Bilateral percutaneous nephrostomy tubes and defunctioning colostomy are viable conservative therapeutic options [367].

- Pelvic Abscess

This diagnosis should be considered if a patient develops otherwise unexplained fever. Ultrasonography and computed tomography with or without aspiration establish the diagnosis in most cases. Once diagnosed, open or percutaneous drainage should be carried out [367].

• Late Complications

- Reflux

Reflux is rare except after the Nesbit technique of direct mucosa-to-mucosa anastomosis [374]. The incidence is high with dilated ureters, so if one or both ureters are significantly dilated, ureterosigmoidostomy should not be considered [366]. Allen (1993) interposed an ileal nipple valve between the dilated ureters and the sigmoid colon to solve this problem [375].

- Pyelonephritis

Pyelonephritis is one of the most common and most dangerous complications of ureterosigmoidostomy, even with the combined or transcolonic techniques. Wear and Barquin reported an incidence of 81% with the older refluxing techniques of Coffey [376] and Nesbit [369], as compared with an incidence of 5.7% after the Leadbetter's [377] combined technique [366]. Williams et al. (1969) reported an incidence of 45% with the Goodwin transcolonic technique [378,379]. Zincke and Segura (1975) reported an incidence of 20% with the combined technique of ureterosigmoidostomy [380]. The combination of high bacterial counts inside rectal contents and the

high rectosigmoid pressure during voiding might be responsible for the high incidence of pyelonephritis. Thus, long-term antibacterial suppressive therapy is recommended for patients with ureterosigmoidostomy [381].

- Ureterocolic Anastomotic Stricture

Ureteral obstruction at the ureterocolic anastomotic site may occur as a late complication in 32% of patients when the Leadbetter technique [372] is used, and in 49% with other types of ureterocolic anastomosis [366]. The incidence of upper tract dilation after ureterosigmoidostomy with a submucosal tunnel remained significant in the publications of the last 2 decades **(Table 12)** [373,384,387,391,392].

- Incontinence

Incontinence after ureterosigmoidostomy is a drastic social problem. It can be attributed to high rectal pressure. Patients should be advised to void on a regular basis, including once or twice during the night [376]. Imipramine hydrochloride at bedtime is indicated for those with persistent nocturnal enuresis [390]. Continence rates after ureterosigmoidostomy in the last 2 decades' publications are illustrated in **Table 13** [373,384,387,391,392].

- Carcinogenesis

The incidence of neoplasia occurring at the ureterointestinal anastomotic site in patients with ureterosigmoidostomy varies between 6% and 29% with a mean of 11% [391,393,394]. Polypoid lesions may develop in up to 40% of the patients if followed long enough [395]. There is generally a 10- to 20-year delay before the cancer manifests (range 5-50 yrs). A 500-fold increase in the incidence of cancer is reported; however, if the urinary diversion is performed before age 25 years there is a 7,000-fold increase in the incidence of cancer [396]. The most common type of tumor is adenocarcinoma, accounting for approximately 85% of all cases. Urothelial (transitional cell) carcinoma is the next most common, accounting for 10%. Signet ring carcinoma, undifferentiated carcinoma, adenomatous polyps, and sarcoma account for the remaining 5%. The development of these tumors is most commonly reported in patients with ureterosigmoidostomy. However, it has been reported in patients with ileal conduits, colon conduits, and bladder augmentation cystoplasties using either ileum or colon [381].

The pathogenesis of this complication is not clearly defined. Using a rat model, Crissey et al. (1980)

Table 12. Ureteral Obstruction After Ureterosigmoidostomy With Submucous Tunnel

Authors	Year	No. of Patients	Indication	Incidence
Jacobs and Young [382]	1980	28	Cancer	36%
Pagano et al. [383]	1984	33	Cancer	12.8%
Mesrobian et al. [384]	1988	40	Exstrophy	45%
Connor et al. [385]	1989	40	Exstrophy	40%
Kalble et al. [386]	1990	31	Cancer & Exstrophy	32%
Stockle et al. [387]	1990	39	Exstrophy	21.7%
Stein et al. [388]	1995	35	Exstrophy	28.6%
Bissada et al. [162]	1995	63	Cancer & Exstrophy	23%
Benchekroun et al. [389]	1998	35	Cancer & Exstrophy	17%

Table 13. Continence Rates After Ureterosigmoidostomy

Authors	Year	No. of Patients	Daytime	Nighttime
Zabbo and Kay [391]	1986	34	97%	88%
Mesrobian et al. [384]	1988	40	83%	83%
Stockle et al. [387]	1990	39	97%	92%
Wynant et al. [392]	1991	19	95%	95%
Koo et al. [373]	1996	27	92%	58%

showed that the development of intestinal tumors after urinary diversion was due to the effect of urine and feces on the colonic mucosa [397]. The same group postulated that an initial colostomy for 1 to 3 months might offer some protection against later development of tumors. Stewart et al. (1981) suggested that urinary nitrates are converted by fecal bacteria into nitrosamines that act as an active carcinogen [398]. However, this contention has been challenged by Shands et al. (1989), who drastically decreased the production of nitrosamines in urine by ascorbic acid. Nevertheless, urocolonic tumors continued to appear in the treated animals [399]. Additionally, Kalble et al. (1991) clearly showed that colon carcinomas occur in a rat model for ureterosigmoidostomy without evidence of nitrosamine formation [400]. Increased concentration of ornithine decarboxylase, the key enzyme for polyamine synthesis, was detected at the urocolonic anastomosis. An inhibitor of this enzyme prevents the development of carcinogen-induced colon neoplasms. Various growth factors and cytokines could also promote carcinogenesis [401]. Regular use of aspirin and other nonsteroidal anti-inflammatory drugs at low doses may reduce the risk of fatal colon cancer, perhaps mediated by inhibition of prostaglandin synthesis [402,403].

Summary

Although the mortality and initial morbidity following ureterosigmoidostomy have been significantly reduced, some inherent chronic complications remain problematic.

b) Modified Rectal Bladder (Augmented Valved Rectum)

Kock et al. (1988) introduced the modified rectal bladder (augmented valved rectum) [404]. The procedure entails functional isolation of the rectal bladder through a colonic intussusception valve and improving the functional capacity of the rectum by patching with a detubularized ileal segment. Defunctioning colostomy is performed at the time of surgery and closed 6 to 8 weeks postoperatively.

1. Experimental Verification

These concepts were tested in a series of elaborate experiments in dogs in the animal laboratories of the Department of Surgery, University of Goteborg, Sweden [405]. This investigation provided evidence that:

1) The intussusception valve constructed at the colorectal junction can effectively prevent regurgitation of fluid from the rectum to the proximal colon without obstruction of the fecal stream distally.

2) The rectal augmentation with a patch of ileum increased the capacity of the reservoir four- to fivefold within 6 months. The intraluminal pressure did not exceed 18 cmH_20 at maximal filling. As an indication of the good compliance of the rectal reservoir, no leakage through the anus was ever seen and no maceration around the anus was observed.

3) Incorporation of the ureters within the intussusception valve provided an efficient antireflux mechanism.

2. Clinical Implementation

• Surgical Techniques

The procedure entails 3 main principles: a) functional isolation of the rectal bladder using sigmoid valve, b) patching the rectal bladder with an ileal segment to improve the urodynamic characteristics, and c) antirefluxing ureteral reimplantation [399,406]. The authors described 3 techniques for ureteral reimplantation by either: a) leading them down between the leaves of the intussuscipiens to buttonholes created at the summit of the nipple valve, b) standard submucosal tunnel, or c) connection of the ureters to the reservoir through an ileal nipple valve created in conjunction with the ileal augmentation. The last technique is suitable for dilated ureters.

• Complications

- Nocturnal Enuresis

This problem was encountered in 10% of cases. All of them responded well to imipramine hydrochloride therapy [401].

- Urinary Tract Infection

The overall incidence of upper urinary tract bacteriuria was 20%, assessed by percutaneous urine sampling of the renal pelves and urine culture and sensitivity tests. However, clinical and radiologic pyelonephritis was documented in only 6% of patients [401].

- Reflux

Colonic reflux was encountered in 4% of cases, ureteral reflux in 4%, and both in 1% [401].

- Metabolic Complications

Subclinical acidosis was detected in 47% of cases. These cases returned to normal with low doses of alkalinizing drugs. Clinical manifestations of acidosis and renal impairment occurred in 2.2% of cases. Hypokalemia was encountered in 18% of cases, which was corrected by oral potassium supplementation [401]. In a later work, Shoma et al. reported a 31% incidence of metabolic acidosis in 42 patients with modified rectal bladder [407].

- Anastomotic Strictures

These caused upper tract deterioration in 7% of patients; half of them were managed endourologically [401].

- Carcinogenesis

There were no significant histopathologic changes in the rectal mucosa in the short-term. Longer-term follow-up with proctoscopy and biopsy in 10 patients showed normal rectal mucosa in 8, decrease in number of goblet cells in 1, and dysplastic mucosal changes in 1 [408].

Summary

The modified rectal bladder is legitimately criticized in view of its technical complexity and the need for a temporary colostomy. Nevertheless, interposition of an ileal segment between the ureters and rectum has been shown to decrease the risk of carcinogenesis in the experimental setting [394,409]. Moreover, functional isolation of the reservoir has been shown to be associated with lesser metabolic derangements [402].

c) Ileocecal Ureterosigmoidostomy

This modification of ureterosigmoidostomy was introduced by Kim et al. (1988) [410]. The procedure entails use of the ileocecal segment as an intervening urine conduit to the large bowel to achieve a continent diversion. The ureters are anastomosed end-to-end to the terminal ileum that is intussuscepted into the cecum. The cecum is joined to the lower sigmoid by an end-to-side anastomosis.

The procedure was performed in only 6 children with exstrophy/epispadias complex. The authors reported no reflux to the upper urinary tract. However, 2 of 6 patients developed febrile pyelonephritis. Kato et al. (1992) performed the same technique in 18 patients with satisfactory short-term results [411]. However, these results are at the expense of sacrificing the ileocecal valve.

d) Ureterorectal Diversion With Rectal Augmentation

Baron et al. (1991) eliminated the construction of the colorectal intussusception valve as a modification to simplify the modified rectal bladder in an experimental study [412,413]. This was followed by clinical application of the technique in 6 patients with satisfactory results in the short-term. They stated that metabolic consequences could be avoided by oral bicarbonates [414]. However, in an experimental study, Miller et al. compared the classic augmented valved rectum and a modified technique with no sigmoid intussusception valve. They reported significantly less biochemical changes in animals that had a sigmoid intussusception valve [415].

e) The Valved S-shaped Rectosigmoid Pouch

In a trial to improve the urodynamic characteristics of classic ureterosigmoidostomy and to avoid the technical complexity of augmented valved rectum, Sundin and Mansi (1992) introduced the valved S-shaped rectosigmoid pouch [416]. The procedure entails 2 main modifications of the classic augmented valved rectum. Patching of the reservoir by an ileal segment is replaced by single folding of the rectosigmoid, and transverse colostomy is replaced by a temporary cecostomy tube. The authors reported their preliminary results in 15 patients [417]. All patients were continent day and night. However, 13% of the renal units showed upper tract deterioration secondary to ureterocolic stricture. No reflux to the upper urinary tract was encountered.

Summary

The valved S-shaped rectosigmoid pouch is a faster and simpler surgical procedure compared with the augmented valved rectum. However, larger numbers of patients with longer follow-up periods are mandatory for proper evaluation of this technique.

f) The Sigma Rectum Pouch (Mainz Pouch II)

The sigma rectum pouch is another low pressure modification of ureterosigmoidostomy. The procedure was introduced by the Mainz group in 1993 [418]. The procedure entails single folding and antimesenteric splitting of the rectosigmoid to improve the urodynamic characteristics of the reservoir. The Goodwin technique is utilized for ureteral reimplantation [419]. In 1996, the same group reported on their experience with the sigma rectum

pouch in 73 patients [420]. Stenosis at the ureteral implantation site was encountered in 5 patients (6.8%). Daytime continence was achieved in 95% of patients. Nocturnal enuresis was encountered in only 2% of patients. All patients were on prophylactic alkalinization. Similar satisfactory short-term results were reported [69,421,422]. However, no long-term results were reported following this technique.

g) The Double-folded Rectosigmoid Bladder

The double-folded rectosigmoid bladder represents one of the low pressure modifications of ureterosigmoidostomy. The group of Mansoura introduced the procedure in 1993 [423]. The procedure includes double folding of the rectosigmoid to create a low pressure rectal reservoir and to create extramural tunnels for ureteral reimplantation. Ureteral reimplantation is performed utilizing the extramural serous-lined technique of Abol-Enein and Ghoneim, originally described for orthotopic ileal reservoirs and later utilized as a continent cutaneous outlet [326,332]. In 1997, the short-term results of the double-folded rectosigmoid bladder were reported for 64 patients with a mean follow-up of 19 months [418]. All patients were continent during the day with an emptying frequency of 2 to 4 times. Nocturnal enuresis was observed in 4 children who responded favorably to imipramine hydrochloride therapy. Upper urinary tract function was maintained or improved in 95% of the patients. No clinical evidence of acidosis was observed, since all patients were kept on prophylactic oral alkalization. Later, Shoma et al. reported an 89% incidence of metabolic acidosis in patients with a double-folded rectosigmoid bladder [402].

2. Anal Sphincter-controlled Bladder Substitutes With Partial Fecal Diversion

• The Rectal Bladder With Sigmoidoproctostomy

Borelius in 1903 was the first to consider a principle of partial exclusion of the sigmoid colon. The objective was to separate the urinary and fecal contents as a modification of ureterosigmoidostomy. He devised a method whereby a short-circuited loop of the sigmoid was partially excluded by a side-to-side anastomosis at its base. The ureters were anastomosed to the dome of the loop [424]. Descomps (1909), working with a cadaver, sectioned the upper rectum and carried out a termino-lateral implantation of the sigmoid to the anterior surface of the rectum. The ureters were implanted in the superior portion of the excluded rectum [425]. In 1936, Hinman and Weyrauch analyzed the early experience of these techniques. They concluded that the theoretical basis for such operations was unsound as supported by the initial poor results. In addition, they supposed that blind pockets act as traps for fecal matter rather than serving to protect the ureteral orifices from the fecal current [363]. In 1962, Modelski revised the procedure. While operating on a 6-year-old boy, he was unable to obtain an adequate length of the sigmoid colon to form a perineal colostomy. The sigmoid stump was anastomosed end-to-side to the distal segment of the rectum above the anal sphincter [426]. The same procedure was later reported by Leiter and Brendler and by Chargi et al. [427,428].

In 1985, Kamidono et al. used the ureterosigmoidostomy technique with end-to-side sigmoidoproctostomy for 7 patients with bladder cancer [429]. The technique was not expected to reduce the severity of metabolic acidosis as in patients with completely excluded rectal bladder as reported by Ghoneim in 1970 [430]. In 1996, Atta utilized the same principle, but with single folding and detubularization of an inverted U-shaped sigmoid colon with fixation of the left colon in continuity to the posterior wall of the rectal ampulla. The ureters were reimplanted into the sigmoid pouch using the nipple technique [431]. Later, Elabbady et al. modified the technique by dismembering the rectosigmoid instead of keeping the rectosigmoid in continuity [432].

3. Anal Sphincter-controlled Bladder Substitutes With Total Fecal Diversion

a) The Rectal Bladder With Terminal Colostomy

Mauclaire (1895) first described the isolated rectum as a bladder substitute in dogs. He diverted the fecal stream by a proximal colostomy [433]. The first clinical experience was acquired by Remedi (1906) [434]. The method of Mauclaire was reintroduced into clinical practice by Creevy and Reister (1952) and later advocated by others [435-437]. The use of an isolated rectal pouch as a urinary reservoir following cystectomy was favored in view of some theoretical considerations: desire for continent diversion, no need for sophisticated external appliance, the colostomy soon acquires a regular habit of emptying, and the operation is technically simple and can be staged [438]. The isolated rectum has a limited absorbent surface area, reducing the chances of biochemical disturbances. Since the urinary and fecal

streams are separated, the risk of ascending infection is minimized. The sum of these theoretical factors is a minimum incidence of pyelonephritis and hydronephrosis with a subsequent low incidence of renal failure and acidosis [439]. Ghoneim and Ashamallah (1974) reported that 2 main problems face this method of urinary diversion, namely loss of renal function due to pyelonephritis in 30% of their cases and nocturnal enuresis in 40% [440]. These 2 problems were addressed in a subsequent report. A submucosal tunnel for ureteral implantation is utilized for reflux prevention whenever the ureters are of normal caliber. Imipramine hydrochloride is given for the treatment of enuresis [377].

Summary

Although the isolated rectal bladder offers some advantages, it is a noncompliant reservoir with a significant incidence of enuresis. Furthermore, any advantages attained over ureterosigmoidostomy are at the expense of the presence of a terminal colostomy.

b) The Rectal Bladder With Perineal Colostomy

Gersuny (1898) described a surgical procedure intended to maintain fecal and urinary continence [441]. The trigone was implanted into an isolated rectal pouch. The proximal sigmoid was mobilized and pulled down through the perineum in front of the anus so that the anal sphincter would control the newly formed rectal bladder as well as the sigmoid, now functioning as an artificial anus. Heitz-Boyer and Hovelacque (1912) modified Gersuny's original operation [442]. They brought the sigmoid colon down posterior to the rectum and passed it directly underneath the anal mucosa to obtain full control of both the internal and external anal sphincter. Lowsley et al. (1953) revived these concepts [443]. They claimed that when this procedure was employed, continence of feces and urine could be achieved. Sporadic papers reporting good results followed this [444,445]. It is intriguing to note that none of these reports were followed up by a large series. Ghoneim and Shoukry (1974) applied the Gersuny-Lowsley procedure in 8 patients [446]. Cystectomy for bladder cancer was the indication of diversion in 6 cases and bladder exstrophy in 2. All patients achieved good urinary continence indicating that manipulations of the external anal sphincter do not interfere with its integrity. In addition, successful creation of a properly located, well-vascularized artificial anus was achieved in 7 of 8 cases. Despite the functioning sphincter, flatus or feces could pass suddenly without prior warning. Distension of the sigmoid colon in normal subjects produces a purely abdominal sensation of flatulence, whereas rectal distension causes a feeling of fullness interpreted by the patient as a need to pass gas or stool. Accordingly, the sigmoid cannot function as a proper reservoir since it is unable to mediate afferent sensation that could be interpreted by the patients as a need for defecation. Although the operation is technically feasible, the patients would have, in effect, an incontinent perineal colostomy.

The functional significance of creating a colorectal valve was studied by Shoma et al. [402]. Eighty-seven patients were included in a retrospective study to compare 42 patients with a modified rectal bladder and 45 with a double-folded rectosigmoid pouch without an intussuscepted valve. They reported that 69% of patients with a sigmoid valve had a normal acid base profile compared to only 12.6% of those without a valve. Long-term follow-up of the outcome of rectal reservoirs was studied by Hafez et al. in 33 children. The mean follow-up was 66 months (range 24-148 mos). All patients were continent day and night. The upper tract was improved or stabilized in 64 of 66 renal units. No patients had reflux to the upper urinary tract. Hyperchloremia was noted in 57% of patients. Arterial blood gases showed subclinical metabolic acidosis in 55%. Supine height measurements at last follow-up revealed that 19 of the 33 patients (57%) had decreased linear growth. All patients had significant reduction in bone density. The mean bone density corrected for age was 70% [447]. The augmented valved rectum and double-folded rectosigmoid bladder provide preservation of the upper urinary tract with excellent continence rates. Nevertheless, the use of rectal reservoir is becoming less popular. This trend is due to the increasing use of orthotopic reservoirs in men and women, successful construction of continent cutaneous urinary reservoirs, and emphasis on primary reconstructive surgery and undiversion in children.

VI. PALLIATIVE DIVERSIONS

1. INTRODUCTION

Urologists should first consider permanent urinary diversion for patients who undergo total cystectomy due to invasive bladder cancer. In fact, less attention has been directed to palliative urinary diversions in

the treatment of bladder cancer. However, mainly in 2 situations, this type of urinary diversion has significant meaning for patients with bladder cancer. First, patients who cannot have total cystectomy because of advanced stage or poor general condition sometimes require urinary diversion due to uncontrollable symptoms (hematuria, pain) or uremia. In this case, percutaneous nephrostomy (PCN) is preferable to cutaneous ureterostomy (UCN), because the prognoses of those patients are generally poor and PCN is a less invasive modality. Especially for patients with uremia due to ureteral obstruction, PCN should be the first choice because PCN is much more easily performed in patients with hydronephrosis.

Second, patients undergoing total cystectomy but not urinary diversion using intestinal segment are candidates for palliative urinary diversion. Patients with severe bowel adhesion or disease, or patients who need short and less invasive surgery due to medical conditions, need palliative urinary diversion. Contrary to the first situation, UCN is preferable to PCN in this setting, since UCN is much more easily performed at the time of cystectomy and might be a permanent urinary diversion when complete resection of bladder cancer is achieved. It has been said that tubeless cutaneous ureterostomy is suitable in patients with a solitary kidney, especially when the ureter is dilated [164,336]. Some papers have also shown good outcome of cutaneous ureterostomy for bilateral non-dilated ureters [342,343]. Moreover, laparoscopic or retroperitoneoscopic cutaneous ureterostomy has been performed in some institutes [348-350]. Considering that less invasive surgery should be applied to patients who need palliative urinary diversion, the introduction of laparoscopic or retroperitoneoscopic surgery is rational.

For a discussion of cutaneous ureterostomy, see Section IV.1. Incontinent Urinary Diversion: Cutaneous Ureterostomy.

2. Percutaneous Nephrostomy

The establishment of percutaneous nephrostomy (PCN) was undoubtedly a milestone of modern urology. Since PCN is a far less invasive technique compared to open nephrostomy or UCN, this procedure is used worldwide for patients with obstructive renal failure. The methodology of PCN has been well-described elsewhere [448]. There are several papers concerning PCN for malignant urinary tract obstruction [449-451]. All present the effectiveness for improvement of renal function with low morbidity. Ekici reported a relatively high overall complication rate (30%, 7/23), namely kinking or dislodgement of nephrostomy tubes [451]. Thus, for the patients with cureless malignancy but in whom rather long survival is expected, UCN can also be an optional urinary diversion, as previously described in this chapter. The average survival from nephrostomy to death in prostate cancer, cervical cancer, and bladder cancer patients was 12.2, 18.0, and 4.5 months, respectively. Thus, more permanent urinary diversion such as UCN might be suitable for patients with life expectancies of more than 1 year. Ekici's paper dealing with only bladder cancer patients showed a mean survival time of 4.9 months. Taken together, the prognosis of patients with inoperable bladder cancer who require palliative urinary diversion is worse than that of patients with prostate or cervical cancer who require palliative urinary diversion. In this sense, PCN might be an appropriate urinary diversion for patients with advanced bladder cancer. An indwelling double J stent is an alternative option for obstructive renal failure in patients with nonurologic pelvic malignancy, such as cervical cancer.

Summary

Tubeless UCN is the first choice for patients who can undergo cystectomy but not urinary diversion using a bowel segment. Although UCN had been abandoned because of high complication rates, mainly stomal stenosis and UTI, various improvements in surgical techniques and advances of laparoscopic surgery have made UCN a viable option for patients with bladder cancer. PCN is the first choice for patients with short life expectancies who develop obstructive renal failure due to incurable malignancy.

VII. OUTLOOK

Prosthetic organs have been successfully used in many regions of the human body. If a complex organ like the heart can be replaced by a mechanical pump, lay media suppose that a simple reservoir like the urinary bladder could also be easily replaced off the shelf. However, despite numerous attempts over the past 5 decades, this goal has not yet been reached. Recent advances in biomaterials, including advances in alloplasts, hold the door open for the total alloplastic artificial bladder. However, routine clinical use seems decades away.

Multiple “tissue-engineered artificial bladders” are being intensively investigated. Each approach has its own inherent advantages, disadvantages, and limitations. All authors evaluate both bladder augmentation and bladder replacement.

Engineering of neobladders from autologous urothelial smooth muscle cells cultured on biocompatible synthetic or naturally-derived substrates is now feasible in preclinical studies and may have clinical applicability in the not too distant future. The development of a bioartificial bladder would warrant the prevention of some metabolic shortcomings of intestinal neobladders. Two tissue-engineering techniques for bladder reconstruction have been tested in animals:

1) the in vivo technique, which involves the use of naturally-derived biomaterials for functional native bladder regeneration, and

2) the in vitro technique, which involves the establishment of autologous urothelial and smooth muscle cell cultures from the host’s urinary tract, after which the cells are seeded on a biodegradable matrix scaffold to grow a composite graft that is implanted into the same host for complete regeneration.

The creation of a complete tissue-engineered bladder with a trigone-shaped base as well as the realization of a conduit or a continent pouch using tissue-engineered material is awaited [452].

VIII. CONCLUSIONS

The disadvantages of conduits stimulated the development of orthotopic bladder substitutes. The early and late complication rates of orthotopic bladder substitutes are actually similar to or lower than the true rates of morbidity after conduit formation, in contrast to the popular view that conduits are simple and safe. Experience with orthotopic bladder substitution shows that patients who are highly motivated and carefully selected can achieve an outstanding outcome. For these patients, life is similar to that with a native lower urinary tract. However, enthusiasm for orthotopic reconstruction should be tempered by an understanding of its indications and how not to breach them [19].

RECOMMENDATIONS

I. GENERAL ASPECTS OF URINARY DIVERSION

1. Type of reconstruction at cystectomy is decided preoperatively after careful patient counselling with regard to possible advantages and disadvantages with the different methods. Age, general condition, tumor stage, and renal function are of importance in this context *(Grade C).*
2. Presently, data does not exist to allow recommendations with regard to type of diversion, choice of intestinal segment, and technique for ureterointestinal anastomosis in relation to renal function *(Grade D).*
3. Urodynamic evaluation is recommended in patients with ileal conduits who have recurrent UTIs. In patients with continent urinary reservoirs and orthotopic neobladders, UTI is not a serious complication, as long as urine is voided smoothly *(Grade C).*

II. ORTHOTOPIC RECONSTRUCTION

1. A simple end-to-side freely refluxing anastomosis into an afferent limb of a low pressure orthotopic reconstruction, in combination with regular voiding and close follow-up, is the procedure with the lowest overall complication rate. The potential benefits of "conventional" antireflux procedures in combination with orthotopic reconstruction seem outweighed by the higher complication and associated reoperation rates. The need to prevent reflux in a continent cutaneous reservoir is not significantly debated and should be performed *(Grade C).*
2. Prostate-sparing cystectomy should not routinely be performed due to the oncologic risks of prostate cancer and bladder cancer involving the prostate in men with urothelial carcinoma of the bladder. Sexuality-preserving cystectomy may be performed in highly selected young men with good functional results for nonurothelial malignancies. There is good data and evidence to suggest that preservation of sexuality with anterior vaginal wall-sparing radical cystectomy in women is appropriate from an oncologic perspective in most women undergoing cystectomy for bladder cancer *(Grade B).*

III. CONTINENT CUTANEOUS DIVERSION

- For continent urinary diversion, a tapered or stapled ileal segment or the appendix should be used as the outlet. Most reconstructive surgeons have abandoned the continent Kock ileal reservoir largely due to the significant complication rate associated with the intussuscepted nipple valve *(Grade B).*

IV. INCONTINENT URINARY DIVERSION

1. Ileal conduit diversion remains the most commonly used method for reconstructing the urinary tract in conjunction with radical cystectomy. It is technically easier than continent reconstruction. However, several studies confirm a high incidence of upper tract complications *(Grade B).*
2. To detect complications, should they occur, lifelong follow-up is mandatory. This includes stomal care by a stomal therapist and regular surveillance of morphology and function of the upper urinary tract. The EAU guidelines recommend follow-up by ultrasonography and plain film (*Level 4*, [453]). However, ultrasonography can never be a substitute for IVP or renography as obstruction can be present without gross dilation and vice versa. In addition, ultrasonography is user-dependent *(Grade B).*

VI. PALLIATIVE DIVERSIONS

1. Tubeless UCN is the first choice for patients who can undergo cystectomy but not urinary diversion using a bowel segment *(Grade B).*
2. Percutaneous nephrostomy is the first choice for patients with short life expectancies who develop obstructive renal failure due to incurable malignancy *(Grade B).*

APPENDICES

Appendix 1. Definitions of Continence [1]

Daytime		
Completely dry, without need for protection	Continent	Good
Completely dry, protection for safety		
No more than 1 pad/day; damp once or twice/week	Socially Continent	Satisfactory
No more than 1 pad/day, damp		
More than 1 pad/day, wet or soaked	Incontinent	Unsatisfactory
Nighttime		
Completely dry without need for protection	Continent	Good
Completely dry protection for safety		
Completely dry with 2 voids/night	Functionally Continent	Satisfactory
Completely dry with 3 voids/night		
No more than 1 pad/night, Socially damp once or twice/week	Continent	Satisfactory
No more than 1 pad/night, damp		
More than 1 pad/night, wet or soaked	Incontinent	Unsatisfactory

APPENDIX 2. NOCTURNAL LEAKAGE IN NEOBLADDERS: CONTRIBUTING FACTORS [19]

- Lack of detrusor-sphincter reflex (increases urethral closure pressure as bladder pressure increases)
- Lack of sensory vesical feedback to the brain to alert the patient when the neobladder is full, producing overflow incontinence
- New sensation of neobladder fullness
- Loss of the sensory afferent urethral innervation may result in loss of the external sphincter guarding reflex when urine leaks into the proximal urethra
- Decrease in continence with age
- Decrease in muscle tone at night
- Increased nocturnal diuresis
  - Secretion of hyperosmotic urine at night
  - Shift of free water into concentrated neobladder urine
- Interdependence among urine osmolality, neobladder compliance and pressure

APPENDIX 3. FAILURE TO EMPTY: CONTRIBUTING FACTORS [19]

- Angulation of urethra (pouchocele)
- Elongation/lengthening of neobladder neck
- Neobladder neck not the lowest portion of pouch
- Lack of funneling of neobladder neck during abdominal straining
- Preserved but dysfunctional native bladder neck
- Denervated proximal urethra
- Inadequate pelvic floor relaxation during voiding
- Neobladder too large (floppy bag)
- Ineffective Valsalva straining

REFERENCES

1. Hautmann RE, de Petriconi R, Gottfried HW, Kleinschmidt K, Mattes R, Paiss T: The ileal neobladder: complications and functional results in 363 patients after 11 years of followup. J Urol 161:422-427, 1999.
2. Montie JE and Wie JT: Formation of an orthotopic neobladder following radical cystectomy: historical perspective, patient selection, and contemporary outcomes. J pelv surgery 8: 141-147, 2000.
3. Stein JP and Skinner DG: Application of the T-mechanism to an orthotopic (T-pouch) neobladder: a new era of urinary diversion. World J Urol 18: 315-323, 2000.
4. Studer UE and Zingg EJ: Ileal orthotopic bladder substitutes. What we have learned from 12 years' experience with 200 patients. Urol Clin North Am 24:781-793, 1997.
5. Skinner DG, Studer UE, Okada K, et al: Which patients are suitable for continent diversion or bladder substitution following cystectomy or other definitive local treatment? Int J Urol 2 Suppl 2: 105-112, 1995.
6. Studer UE, Hautmann RE, Hohenfellner M, et al: Indications for continent diversion after cystectomy and factors affecting long-term results. Urol Oncol 4: 172-176, 1998.
7. Spirnak JP, and Caldamone AA: Ureterosigmoidostomy. Urol Clin North Am 13: 285-294, 1986.
8. Richie JP, and Skinner DG: Ureterointestinal diversion, in Walsh PC, Gittes RF, Perlmutter AD, et al. (Eds.): Campbell's Urology, 5th ed, Philadelphia, W.B. Saunders, 1986, pp.2601-2619.
9. Hautmann RE: 15 years experience with the ileal neobladder. What have we learned? Urologe A 40: 360-367, 2001.
10. Cajal SR: Los gangliosy plexos nerviosos del intestino de las mammiferos. Madrid Moya 1: 1893.
11. Faussone-Pellegrini MS: Histogenesis, structure and relationships of interstitial cells of Cajal (ICC): from morphology to functional interpretation. Eur J Morphol 30: 137-148, 1992.
12. Rumessen JJ, and Thuneberg L: Interstitial cells of Cajal in human small intestine. Ultrastructural identification and organization between the main smooth muscle layers. Gastroenterology 100: 1417-1431, 1991.
13. Huizinga JD, Thuneberg L, Kluppel M, Malysz J, Mikkelsen HB, Bernstein A. W/kit gene required for interstitial cells of Cajal and for intestinal pacemaker activity. Nature. 1995 Jan 26;373(6512):347-9.
14. Faussone-Pellegrini MS, Serni S, Carini M: Distribution of ICC and motor response characteristics in urinary bladders reconstructed from human ileum. Am J Physiol 273: G147-157, 1997.
15. Batra AK, Hanno PM, Ruggieri MR: Detubularization-induced contractile response change of the ileum following ileocystoplasty. J Urol 148: 195-199, 1992.
16. Philipson BM, Hockenstrom T, Akerlund S: Biological consequences of exposing ileal mucosa to urine. World J Surg 11: 790-797, 1987.
17. Aragona F, De Caro R, Parenti A, et al: Structural and ultrastructural changes in ileal neobladder mucosa: a 7-year follow-up. Br J Urol 81: 55-61, 1998.
18. Deane AM, Woodhouse CR, Parkinson MC: Histological changes in ileal conduits. J Urol 132:1108-1111, 1984.
19. Hautmann RE: Urinary diversion: ileal conduit to neobladder. J Urol 169: 834-842, 2003.
20. Moore JA, and Brading AF. Gastrointestinal tissue as a substitute for the detrusor. World J Urol 18: 305-314, 2000.
21. Hinman Jr F: Selection of intestinal segments for bladder substitution: physical and physiological characteristics. J Urol 139: 519-523, 1988.
22. Colding-Jorgensen M, Poulsen AL, Steven K: Mechanical characteristics of tubular and detubularized bowel for bladder substitution: theory, urodynamics and clinical results. Br J Urol 72: 586-593, 1993.
23. Akerlund S, Jagenburg R, Kock NG, et al: Absorption of L-phenylalanine in human ileal reservoirs exposed to urine. Urol Res 16: 321-323, 1988.
24. Davidsson T, Akerlund S, Forssell-Aronsson E, et al: Absorption of sodium and chloride in continent reservoirs for urine: comparison of ileal and colonic reservoirs. J Urol 151: 335-337, 1994.
25. Ekman I, Mansson W, Nyberg L: Absorption of drugs from continent cecal reservoir for urine. Br J Urol 64: 412-416, 1989.
26. Koch MO, Gurevitch E, Hill DE, et al: Urinary solute transport by intestinal segments: a comparative study of ileum and colon in rats. J Urol 143: 1275-1279, 1990.
27. Kollias G, Goulandris N, Kastriotis J, et al: Absorbability of mucosa in total replacement of urinary bladder with jejunum. An experimental study. Urology 23: 51-54, 1984.
28. Akerlund S, Forssell-Aronsson E, Jonsson O, et al: Decreased absorption of 22Na and 36Cl in ileal reservoirs after exposure to urine. An experimental study in patients with continent ileal reservoirs for urinary or fecal diversion. Urol Res 19: 249-252, 1991.
29. Mills RD, and Studer UE: Metabolic consequences of continent urinary diversion. J Urol 161: 1057-1066, 1999.
30. Koraitim MM, Atta MA, Foda MK: Early and late cystometry of detubularized and nondetubularized intestinal neobladders: new observations and physiological correlates. J Urol 154: 1700-1702, 1995.
31. Lytton B, and Green DF: Urodynamic studies in patients undergoing bladder replacement surgery. J Urol 141: 1394-1397, 1989.
32. Santucci RA, Park CH, Mayo ME, et al: Continence and urodynamic parameters of continent urinary reservoirs: comparison of gastric, ileal, ileocolic, right colon, and sigmoid segments. Urology 54: 252-257, 1999.
33. Kolettis PN, Klein EA, Novick AC, et al: The Le Bag orthotopic urinary diversion. J Urol 156: 926-930, 1996.
34. Berglund B, and Kock NG: Volume capacity and pressure characteristics of various types of intestinal reservoirs. World J Surg 11: 798-803, 1987.

35. Hohenfellner M, Burger R, Schad H, et al: Reservoir characteristics of Mainz pouch studied in animal model. Osmolality of filling solution and effect of oxybutynin. Urology 42: 741-746, 1993.

36. Goldwasser B, Barrett DM, Webster GD, et al: Cystometric properties of ileum and right colon after bladder augmentation, substitution or replacement. J Urol 138: 1007-1008, 1987.

37. Ferris DO, and Odel HM: Electrolyte pattern of the blood after bilateral ureterosigmoidostomy. JAMA 142: 634-640, 1950.

38. Koch MO, McDougal WS, Reddy PK: Metabolic alterations following continent urinary diversion through colonic segments. J Urol 145: 270-273, 1991.

39. Koch MO, McDougal WS, Thompson CO: Mechanisms of solute transport following urinary diversion through intestinal segments: an experimental study with rats. J Urol 146: 1390-1394, 1991.

40. McDougal WS, Stampfer DS, Kirley S: Intestinal ammonium transport by ammonium and hydrogen exchange. J Am Coll Surg 181: 241-248, 1995.

41. Stampfer DS, and McDougal WS: Inhibition of the sodium/hydrogen antiport by ammonium ion. J Urol 157: 362-365, 1997.

42. McDougal WS: Metabolic complications of urinary intestinal diversion. J Urol 147: 1199-1208, 1992.

43. Racioppi M, D'Addessi A, Fanasca A, Mingrone G, Capristo E, Benedetti G, Alcini A, Alcini E. Acid-base and electrolyte balance in urinary intestinal orthotopic reservoir: ileocecal neobladder compared with ileal neobladder. Urology 1999; 54: 629-635

44. Steven K and Poulsen AL: The orthotopic Kock ileal neobladder: functional results, urodynamic features, complications and survival in 166 men. J Urol 164: 288-295, 2000.

45. Williams RE, Davenport TJ, Burkinshaw L: Changes in whole body potassium associated with uretero-intestinal anastomosis. Br J Urol 39:676-680, 1967.

46. McDougal WS, and Koch MO: Effect of sulfate on calcium and magnesium homeostasis following urinary diversion. Kidney Int 35: 105-115, 1989.

47. Koch MO, and McDougal WS: The pathophysiology of hyperchloremic metabolic acidosis after urinary diversion through intestinal segments. Surgery 98: 561-570, 1985.

48. McDougal WS, Heimburger S, Wilmore DW: The effect of exogenous substrate on hepatic metabolism and membrane transport during endotoxemia. Surgery 84: 55-61, 1978.

49. Edwards RH: Hyperammonemic encephalopathy related to ureterosigmoidostomy. Arch Neurol 41: 1211-1212, 1984.

50. Bowyer GW, and Davies TW: Methotrexate toxicity associated with an ileal conduit. Br J Urol 60: 592-593, 1987.

51. Fossa SD, Heilo A, Bormer O: Unexpectedly high serum methotrexate levels in cystectomized bladder cancer patients with an ileal conduit treated with intermediate doses of the drug. J Urol 143: 498-501, 1990.

52. Davidsson T, Akerlund S, White T: Mucosal permeability of ileal and colonic reservoirs for urine. Br J Urol 78: 64-68, 1996.

53. Sridhar KN, Samuell CT, Woodhouse CR: Absorption of glucose from urinary conduits in diabetics and non- diabetics. Br Med J (Clin Res Ed) 287: 1327-1329, 1983.

54. Alcini E, D'Addessi A, Racioppi M, et al: Results of 4 years of experience with bladder replacement using an ileocecal segment with multiple transverse teniamyotomies. J Urol 149: 735-738, 1993.

55. Lee KS, Montie JE, Dunn RL, Lee CT: Hautmann and Studer orthotopic neobladders: a contemporary experience. J Urol 169: 2188-2191, 2003.

56. Sagalowsky AI, and Frenkel EP: Cobalamin profiles in patients after urinary diversion. J Urol 167: 1696-1700, 2002.

57. Yakout H, and Bissada NK: Intermediate effects of the ileocaecal urinary reservoir (Charleston pouch 1) on serum vitamin B12 concentrations: can vitamin B12 deficiency be prevented? BJU Int 91: 653-655, 2003.

58. Pfitzenmaier J, Loiz J, Faldum A, et al: Metabolic evaluation of 94 patients 5 to 16 years after ileocecal pouch (Mainz Pouch I) continent urinary diversion. J Urol 170: 1884 – 1887, 2003.

59. Fujisawa M, Nakamura I, Yamanaka N, et al: Changes in calcium metabolism and bone demineralization after orthotopic intestinal neobladder creation. J Urol 163: 1108-1111, 2000.

60. Koch MO, and McDougal WS: Bone demineralization following ureterosigmoid anastomosis: an experimental study in rats. J Urol 140: 856-859, 1988.

61. Koch MO, McDougal WS, Hall MC: Long-term metabolic effects of urinary diversion: a comparison of myelomeningocele patients managed by clean intermittent catheterization and urinary diversion. J Urol 147: 1343-1347, 1992.

62. Gros DA, Dodson JL, Lopatin UA: Decreased linear growth associated with intestinal bladder augmentation in children with bladder exstrophy. J Urol 164: 917-920, 2000.

63. Siklos P, Davie M, Jung RT: Osteomalacia in ureterosigmoidostomy: healing by correction of the acidosis. Br J Urol 52: 61-62, 1980.

64. Perry W, Allen LN, Stamp TC: Vitamin D resistance in osteomalacia after ureterosigmoidostomy. N Engl J Med 297: 1110-1112, 1977.

65. Bettice JA, and Gamble JL Jr: Skeletal buffering of acute metabolic acidosis. Am J Physiol 229: 1618-1624, 1975.

66. McDougal WS, Koch MO, Shands C 3rd: Bony demineralization following urinary intestinal diversion. J Urol 140: 853-855, 1988.

67. Lee SW, Russell J, Avioli LV: 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol: conversion impaired by systemic metabolic acidosis. Science 195: 994-996, 1977.

68. Arnett TR, and Dempster DW: Effect of pH on bone resorption by rat osteoclasts in vitro. Endocrinology 119: 119-124, 1986.

69. Stein R, Fisch M, Beetz R: Urinary diversion in children and young adults using the Mainz Pouch I technique. Br J Urol 79: 354-361, 1997.

70. Mundy AR, and Nurse DE: Calcium balance, growth and skeletal mineralization in patients with cystoplasties. Br J Urol 69: 257-259, 1992.

71. Tschopp AB, Lippuner K, Jaeger P: No evidence of osteopenia 5 to 8 years after ileal orthotopic bladder substitution. J Urol 155: 71-75, 1996.

72. Campanello A, Herlitz H, Lindstedt G: Bone mineral and related biochemical variables in patients with Kock ileal reservoir or Bricker conduit for urinary diversion. J Urol 155: 1209-1213, 1996.

73. Davidsson T, Lindergard B, Obrant K: Long-term metabolic effects of urinary diversion on skeletal bone: histomorphometric and mineralogic analysis. Urology 46: 328-333, 1995.

74. Kawakita M, Arai Y, Shigeno C: Bone demineralization following urinary intestinal diversion assessed by urinary pyridinium cross-links and dual energy x-ray absorptiometry. J Urol 156: 355-359, 1996.

75. Poulsen AL, Overgaard K, Steven K: Bone metabolism following bladder substitution with the ileal urethral Kock reservoir. Br J Urol 79: 339-347, 1997.

76. Hossain M: The osteomalacia syndrome after colocystoplasty; a cure with sodium bicarbonate alone. Br J Urol 42: 243-245, 1970.

77. Gillon G and Mundy AR: The dissolution of urinary mucus after cystoplasty. Br J Urol 63: 372-374, 1989.

78. George VK, Gee JM, Wortley MI, et al: The effect of ranitidine on urine mucus concentration in patients with enterocystoplasty. Br J Urol 70: 30-32, 1992.

79. Bushman W and Howards SS: The use of urea for dissolution of urinary mucus in urinary tract reconstruction. J Urol 151: 1036-1037, 1994.

80. Varol C and Studer UE: Managing patients after an ileal orthotopic bladder substitution. BJU Int 93: 266-270, 2004.

81. Mansson W, Davidsson T, Konyves J, et al: Continent urinary tract reconstruction - the Lund experience. BJU Int 92: 271-276, 2003.

82. Leibovitch IJ, Ramon J, Chaim JB, et al: Increased urinary mucus production: a sequela of cystography following enterocystoplasty. J Urol 145: 736-737, 1991.

83. Abol-Enein H and Ghoneim MA: Functional results of orthotopic ileal neobladder with serous-lined extramural ureteral reimplantation: experience with 450 patients. J Urol 165: 1427-1432, 2001.

84. Sheffner AL: The reduction in vitro in viscosity of mucoprotein solutions by a new mucolytic agent, N-acetyl-L-cysteine. Ann N Y Acad Sci. 106: 298-310, 1963.

85. Waldron-Edward D, and Skoryna SC: The mucolytic activity of amides: a new approach to mucus dispersion. Can Med Assoc 94: 1249-1256, 1966.

86. Marriott C: The effect of drugs on the structure and secretion of mucus. Pharmacy Int 4: 320-323, 1983.

87. Benderev TV: Acetylcysteine for urinary tract mucolysis. J Urol 139: 353-354, 1988.

88. Haupt G, Pannek J, Knopf HJ, et al: Rupture of ileal neobladder due to urethral obstruction by mucous plug. J Urol 144: 740-741, 1990.

89. N'Dow J, Robson CN, Matthews JN, et al: Reducing mucus production after urinary reconstruction: a prospective randomized trial. J Urol 165: 1433-1440, 2001.

90. Hendren WH and Hendren RB: Bladder augmentation: experience with 129 children and young adults. J Urol 144: 445-453, 1990.

91. Murray K, Nurse DE, Mundy AR: Secreto-motor function of intestinal segments used in lower urinary tract reconstruction. Br J Urol 60: 532-535, 1987.

92. Goldstein MJ, Melamed MR, Grabstald H, et al: Progressive villous atrophy of the ileum used as a urinary conduit. Gastroenterology 52: 859-864, 1967.

93. Philipson BM, Kock NG, Jagenburg R, et al: Functional and structural studies of ileal reservoirs used for continent urostomy and ileostomy. Gut 24: 392-398, 1983.

94. Gatti R, Ferretti S, Bucci G, et al: Histological adaptation of orthotopic ileal neobladder mucosa: 4-year follow-up of 30 patients. Eur Urol 36: 588-594, 1999.

95. Mansson W, Colleen S, Low K, et al: Immunoglobulins in urine from patients with ileal and colonic conduits and reservoirs. J Urol 133: 713-716, 1985.

96. Chang SS, Cookson MS, Hassan JM, et al: Routine postoperative intensive care unit monitoring is not necessary after radical cystectomy. Journal of Urology 167: 1321-1324, 2002.

97. Brodner G, Van Aken H, Hertle L, et al: Multimodal perioperative management—combining thoracic epidural analgesia, forced mobilization, and oral nutrition—reduces hormonal and metabolic stress and improves convalescence after major urologic surgery. Anesthes Analg 92: 1594-1600, 2001.

98. Cheatham ML, Chapman WC, Key SP, et al: A meta-analysis of selective versus routine nasogastric decompression after elective laparotomy. Annals of Surgery 221: 469-478, 1995.

99. Donat SM, Slaton JW, Pisters LL, et al: Early nasogastric tube removal combined with metoclopramide after radical cystectomy and urinary diversion. J Urol 162: 1599-1602, 1999.

100. Inman BA, Harel F, Tiguert R, et al: Routine nasogastric tubes are not required following cystectomy with urinary diversion: a comparative analysis of 430 patients. J Urol 170: 1888-1891, 2003

101. Mohler JL and Flanigan RC: The effect of nutritional status and support on morbidity and mortality of bladder cancer patients treated by radical cystectomy. J Urol 137: 404-407, 1985.

102. Black JM, Hawks JH, Keene A. (Eds.) (2001). Medical-surgical nursing: Clinical management for positive outcomes (6th ed.). Philadelphia: Saunders

103. Ankem MK, Han K-R, Hartanto V, et al: Routine pouchograms are not necessary after continent urinary diversion. Urology 63: 435-437, 2003.

104. Perimenis P and Studer UE: Orthotopic continent urinary

diversion. An ileal low pressure neobladder with an afferent tubular segment: how I do it. EJSO 30: 454-459, 2004.

105. Kane AM: Nursing management of neobladder surgery: The Studer pouch. Urologic Nursing 20, 189-199, 2004.

106. Razor BR: Continent urinary reservoirs. Seminars in Oncology Nursing 9, 272-285, 1993.

107. LeMone P and Burke KM: Nursing care of clients with urinary tract disorders. In P. LeMone and K.M. Burke (Eds.), Medical-surgical nursing: Critical thinking in client care (906-918). Menlo Park, CA: Addison-Wesley, 1996.

108. Montie JE: Follow-up after cystectomy for carcinoma of the bladder. Urol Clin North Am 21: 639, 2004.

109. Sung DJ, Cho SB, Kim YH, et al: Imaging of the various continent urinary diversions after cystectomy. J Comput Assist Tomogr 28: 299, 2004.

110. Tempany CM, Masoudi FA, Marshall FF: The use of dynamic magnetic resonance imaging to evaluate orthotopic continent urinary diversion. Urology 45: 886, 1995.

111. Varol C, Thalmann GN, Burkhard, FC, et al: Treatment of urethral recurrence following radical cystectomy and ileal bladder substitution. J Urol 172: 937, 2004.

112. Watarai Y, Satoh H, Matubara M, et al: Comparison of urine cytology between the ileal conduit and Indiana pouch. Acta Cytologica 44: 748-751, 2000.

113. Wolinska, WH, Melamed MR, Schellhammer PF, et al: Urethral cytology following cystectomy for bladder carcinoma. Am J Surg Pathol 1: 225, 1977

114. Hickey DP, Soloway MS, Murphy WM: Selective urethrectomy following cystoprostatectomy for bladder cancer. J Urol 136: 828, 1986.

115. Clark PB: Urethral carcinoma after cystectomy: the case for routine urethrectomy. J Urol 90: 173, 1984.

116. Poole-Wilson DS, and Barnard RJ: Total cystectomy for bladder tumours. Br J Urol 43: 16, 1971.

117. Tongaonkar HB, Dalal AV, Kulkarni JN, et al: Urethral recurrences following radical cystectomy for invasive transitional cell carcinoma of the bladder. Br J Urol 72: 910, 1993.

118. Lin DW, Herr HW, Dalbagni G: Value of urethral wash cytology in the retained male urethra after radical cystoprostatectomy. J Urol 169: 961, 2003.

119. Wood DP Jr., Bianco FJ Jr., Pontes JE, et al: Incidence and significance of positive urine cultures in patients with an orthotopic neobladder. J Urol 169: 2196, 2003.

120. Henningsohn L, Steven K, Brohm Kallestrup E, et al: Distressful symptoms and well-being after radical cysectomy and orthotopic bladder substitution compared with a matched control population. J Urol 168: 168-175, 2002.

121. Månsson Å, Henningsohn L, Steineck G, et al: A neutral third party versus treating institution for evaluating quality of life after radical cystectomy. Eur Urol. In press

122. Kulaksizoglu H, Toktas G, Kulaksizoglu IB, et al: When should quality of life be measured after radical cystectomy? Eur Urol 42: 350-355, 2002.

123. Hardt J, Filipas D, Hohenfellner R, et al: Quality of life in patients with bladder carcinoma after cystectomy: first results of a prospective study. Quality of Life Res 9: 1-12, 2000.

124. Hardt J, Petrak F, Filipas D, et al: Adaptation to life after surgical removal of the bladder – an application of graphical Markov models for analysing longitudinal data. Statist Med 23: 649-666, 2004.

125. Bjerre B, Johansen C, Steven K: Health-related quality of life after urinary di-version: continent diversion with the Kock pouch compared with ileal conduit. A questionnaire study. Scand J Urol Nephrol; Suppl 157: 113-118, 1994.

126.Castagnola C, Marechal J-M, Hanauer M-T, et al: Qualite´ de vie et dérivations urinaires cutanées. Résultats d´un questionnaire ad-resse´ à 73 patients. Progrès en Urologie 6: 207-216, 1996.

127. Gerharz EW, Weingärtner K, Dopatka T, et al: Quality of life after cystectomy and urinary diversion: results of a retrospective interdisciplinary study. J Urol 158: 778-785, 1997.

128. Okada, Y, Oishi K, Shichiri Y, et al: Quality of life survey of urinary diversion patients: comparison of continent urinary diversion versus ileal conduit. Int J Urol 4: 26-31, 1997.

129. Filipas D, Egle UT, Budenbender C, et al: Quality of life and health in patients with urinary diversion: a comparison of incontinent versus continent urinary diversion. Eur Urol 32: 23-9, 1997.

130. Bjerre BD, Johansen C, Steven K: Health-related quality of life after cystectomy: bladder substitution compared with ileal conduit diversion. A questionnaire survey. Br J Urol 75: 200-205, 1995.

131. Bjerre BD, Johansen C, Steven K: Sexological problems after cystectomy: bladder substitution compared with ileal conduit diversion. Scand J Urol Nephrol 32: 187-193, 1998.

132.Conde Redondo C, Estébanez Zarranz J, Rodriguez Tovez A, et al: Estudio de la calidad de vida en pacientes sometidos a sustitucion vesical ortotópica versus ileostomia cutánea. Actas Urologica Espangnol 25: 435-444, 2001.

133. Hobisch A, Tosun K, Kinzl J, et al: Life after cystectomy and orthotopic neobladder versus ileal conduit urinary diversion. Semin Urol Oncol 19: 18-23, 2001.

134. Fujisawa M, Isotani S, Gotoh A, et al: Health-related quality of life with orthotopic neobladder versus ileal conduit according to SF-36 survey. Urology 55: 862-865, 2000.

135. Salinas Sanchez AS, Segura Martin M, Lorenzo Romero JG, et al: Calidad de vita de los pacientes tras la cirugia radical del cancer vesical. Archivas Espanol de Urologia 54: 787-795, 2001.

136. Dutta SC, Chang SS, Coffey CS, et al: Health related quality of life assessment after radical cystectomy: comparison of ileal conduit with continent orthotopic neobladder. J Urol 168: 164-167, 2002.

137. Hara I, Miyake H, Hara S, et al: Health-related quality of

life after radical cystectomy for bladder cancer: a comparison of ileal conduit and orthotopic bladder replacement. BJU Int 89: 10-13, 2002.

138. Månsson Å, Colleen S, Hermerén G, et al: Which patients will benefit from psychosocial intervention after cystectomy for bladder cancer? Br J Urol 80: 50-57, 1997.

139. Månsson Å, Christensson P, Johnson G, et al: Can preoperative psychological defensive strategies, mood and type of lower urinary tract reconstruction predict psychosocial adjustment after cystectomy in patients with bladder cancer? Br J Urol 82: 348-356, 1998.

140. Hart S, Skinner EC, Meyerowitz BE, et al: Quality of life after radical cystectomy for bladder cancer in patients with an ileal conduit, or cutaneous or urethral Kock pouch. J Urol 162: 77-81, 1999.

141. Kitamura H, Miyao N, Yanase M, et al: Quality of life in patients having an ileal conduit, continent reservoir or orthotopic neobladder after cystectomy for bladder carcinoma. Int J Urol 6: 393-399, 1999.

142. McGuire MS, Grimaldi G, Grotas J, et al: The type of urinary diversion after radical cystectomy significantly impacts on the patient´s quality of life. Ann Surg Oncol 7: 4-8, 2000.

143. Hennigsohn L, Wijkstrom H, Steven K, et al: Relative importance of sources of symptom-induced distress in urinary bladder cancer survivors. Eur Urol 43: 651-662, 2003

144. Weijerman PC, Schurmans JR, Hop WC, et al: Morbidity and quality of life in patients with orthotopic and heterotopic continent urinary diversion. Urology 51: 51-56, 1998.

145. Sullivan LD, Chow VDW, Ko DSC, et al: An evaluation of quality of life in patients with continent urinary diversion after cystectomy. Br J Urol 81: 699-704, 1998.

146. Månsson Å, Davidsson T, Hunt S, et al: The quality of life in men after radical cystectomy with a continent cutaneous diversion or orthotopic bladder substitution: is there a difference? BJU Int 90: 386-389, 2002.

147. Satoh S, Sato K, Habuchi T, et al: Health-related quality of life of ileocecal rectal bladder compared with ileal conduit diversion: a questionnaire survey. Int J Urol 9: 385-391, 2002.

148. Kristjansson A, Wallin L, Mansson W: Renal function up to 16 years after conduit (refluxing or anti-reflux anastomosis) or continent urinary diversion. 1. Glomerular filtration rate and patency of uretero-intestinal anastomosis. Br J Urol 76: 539-545, 1995

149. Kristjansson A, Bajc M, Wallin L, et al: Renal function up to 16 years after conduit (refluxing or anti-reflux anastomosis) or continent urinary diversion. 2. Renal scarring and location of bacteriuria. Br J Urol 76: 546-550, 1995

150. Studer UE, Danuser H, Thalmann GN, et al: Antireflux nipples or afferent tubular segments in 70 patients with ileal low pressure bladder substitutes: long-term results of a prospective randomized trial. J Urol 156: 1913-1917, 1996.

151. Osman Y, Abol-Enein H, Nabeeh A, et al: Long-term results of a prospective randomized study comparing two different antireflux techniques in orthotopic bladder substitution. Eur Urol 45: 82-86, 2004.

152. Madersbacher S, Schmidt J, Eberle JM, et al: Long-term outcome of ileal conduit diversion. J Urol 169: 985-990, 2003

153. Iborra I, Casanova JL, Solsona E, et al: Tolerance of external urinary diversion (Bricker) followed for more than 10 years. Eur Urol 39 (suppl 5): 146-147, 2001.

154. Fontaine E, Barthelemy Y, Houlgatte A, et al: Twenty-year experience with jejunal conduits. Urology 50: 207-213, 1997.

155. Jonsson O, Olofsson G, Lindholm E, et al: Long-time experience with the Kock ileal reservoir for continent urinary diversion. Eur Urol 40: 632-640, 2001.

156. Thoeny HC, Sonnenschein MJ, Madersbacher S, et al: Is ileal orthotopic bladder substitution with an afferent tubular segment detrimental to the upper urinary tract in the long term? J Urol 168: 2030-2034, 2002.

157. Elmajian DA, Stein JP, Esrig D, et al: The Kock ileal neobladder: updated experience in 295 male patients. J Urol 156: 920-925, 1996.

158. Leissner J, Stein R, Hohenfellner R, et al: Radical cystoprostatectomy combined with Mainz pouch bladder substitution to the urethra. BJU Int 83: 964-970, 1999.

159. Pantuck AJ, Han KR, Perrotti M, et al: Ureteroenteric anastomosis in continent urinary diversion: long-term results and complications of direct versus nonrefluxing techniques. J Urol 163: 450-455, 2000.

160. Hohenfellner R, Black P, Leissner J, et al: Refluxing ureterointestinal anastomosis for continent cutaneous urinary diversion. J Urol 168: 1013-1017, 2002.

161. Echtle D, Müller E, Kontaxis D, et al: Why it works so well. Akt Urol 31: 263-268, 2000.

162. Bissada NK, Morcos RR, Morgan WM, et al: Ureterosigmoidostomy: is it a viable procedure in the age of continent urinary diversion and bladder substitution? J Urol 153: 1429-1431, 1995.

163. Bastian PJ, Albers P, Hanitzsch H, et al: The modified ureterosigmoidostomy (Mainz pouch II) as a continent form of urinary diversion. Urologe A, 2004 in press

164. Wandschneider G, Petek R, Pummer K, et al: The permanent ureterocutaneostomy (UCST). Int Urol Nephrol 24: 381-387, 1992.

165. Matsuda S, Nagatani Y, Kanematsu M, et al: Study of urinary infection in tubeless cutaneous ureterostomy-pathognomonic meaning of bacterial flora in the renal pelvis and methods of collecting urine. Nippon Hinyokika Gakkai Zasshi 78: 76-82, 1987.

166. Bruce AW, Reid G, Chan RC, et al: Bacterial adherence in the human ileal conduit: a morphological and bacteriological study. J Urol 132: 184-188, 1984.

167. Middleton AW Jr., and Hendren WH. Ileal conduits in children at the Massachusetts General Hospital from 1955 to 1970. J Urol 115: 591-595, 1976.

168. Minton JP, Kiser WS, Ketcham AS: A Study of the Func-

tional Dynamics of Ileal Conduit Urinary Diversion with Relationship to Urinary Infection. Surg Gynecol Obstet 119: 541-550, 1964.

169. Akerlund S, Campanello M, Kaijser B, et al: Bacteriuria in patients with a continent ileal reservoir for urinary diversion does not regularly require antibiotic treatment. Br J Urol 74: 177-181, 1994.

170. Mansson W, Colleen S, Mardh PA: The microbial flora of the continent cecal urinary reservoir, its stoma and the peristomal skin. J Urol 135: 247-250, 1986.

171. Terai A, Arai Y, Okada Y, et al: Urinary bacteriology of continent urinary reservoirs and calculus formation. Int J Urol 1: 332-336, 1994.

172. Le Duc A, Camey M, Teillac P: An original antireflux ureteroileal implantation technique: long-term followup. J Urol 137: 1156-1158, 1987.

173. Wullt B, Holst E, Steven K, et al: Microbial flora in ileal and colonic neobladders. Eur Urol 45: 233-239, 2004.

174. Nakano Y, Fujisawa M, Matsui T, et al: The significance of the difference in bacterial adherence between bladder and ileum using rat ileal augmented bladder. J Urol 162: 243-247, 1999.

175. Skinner DG, Boyd SD, Lieskovsky G, et al: Lower urinary tract reconstruction following cystectomy: experience and results in 126 patients using the Kock ileal reservoir with bilateral ureteroileal urethrostomy. J Urol 146: 756-760, 1991.

176. Stein JP, Lieskovsky G, Ginsberg DA, Bochner BH, Skinner DG: The T pouch: an orthotopic ileal neobladder incorporating a serosal lined ileal antireflux technique. J Urol 159: 1836-1842, 1998.

177. Studer UE, Danuser H, Merz VW, et al: Experience in 100 patients with an ileal low pressure bladder substitute combined with an afferent tubular isoperistaltic segment. J Urol 154: 49-56, 1995.

178. Hautmann RE. The ileal neobladder to the female urethra. Urol Clin North Am 24: 827-835, 1997.

179. Hautmann RE. The ileal neobladder. Atlas Urol Clin North Am 9: 85 – 99, 2001.

180. Hautmann RE, Egghart G, Frohneberg D, et al: The ileal neobladder. J Urol 139: 39-42, 1988.

181. Hollowell CM, Christiano AP, Steinberg GD: Technique of Hautmann ileal neobladder with chimney modification: interim results in 50 patients. J Urol 163: 47-50, 2000.

182. Lippert MC, and Theodorescu D: The Hautmann neobladder with a chimney: a versatile modification. J Urol 158: 1510-1512, 1997.

183. Montie JE: Ileal conduit diversion after radical cystectomy: pro. Urology 49: 659-662, 1997.

184. Hautmann RE, Paiss T, de Petriconi R: The ileal neobladder in women: 9 years of experience with 18 patients. J Urol 155: 76-81, 1996.

185. Stein JP, Stenzl A, Esrig D, et al: Lower urinary tract reconstruction following cystectomy in women using the Kock ileal reservoir with bilateral ureteroileal urethrostomy: initial clinical experience. J Urol 152: 1404-1408, 1994.

186. Stenzl A, Draxl H, Posch B, Colleselli K, Falk M, Bartsch G. The risk of urethral tumors in female bladder cancer: can the urethra be used for orthotopic reconstruction of the lower urinary tract? J Urol 1995; 153: 950-955

187. Hautmann RE and Simon J: Ileal neobladder and local recurrence of bladder cancer: patterns of failure and impact on function in men. J Urol 162: 1963-1966, 1999.

188. McGuire EJ, Woodside JR, Borden TA, et al: Prognostic value of urodynamic testing in myelodysplastic patients. J Urol 126: 205-209, 1981.

189. Pitts WR Jr, and Muecke EC: A 20-year experience with ileal conduits: the fate of the kidneys. J Urol 122: 154-157, 1979.

190. Schmidt JD, Hawtrey CE, Flocks RH, et al: Complications, results and problems of ileal conduit diversions. J Urol 109: 210-216, 1973.

191. Akerlund S, Delin K, Kock NG, et al: Renal function and upper urinary tract configuration following urinary diversion to a continent ileal reservoir (Kock pouch): a prospective 5 to 11-year followup after reservoir construction. J Urol 142: 964-968, 1989.

192. Light JK: Continence mechanisms following orthotopic bladder substitution. Scand J Urol Nephrol Suppl 142: 95-97, 1992.

193.Steers WD: Voiding dysfunction in the orthotopic neobladder. World J Urol 18: 330-337, 2000.

194. Borirakchanyavat S, Aboseif SR, Carroll PR, et al: Continence mechanism of the isolated female urethra: an anatomical study of the intrapelvic somatic nerves. J Urol 158: 822-826, 1997.

195. Stein JP, Grossfeld GD, Freeman JA, Esrig D, Ginsberg DA, Cote RJ, Skinner EC, Boyd SD, Lieskovsky G, Skinner DG. Orthotopic lower urinary tract reconstruction in women using the Kock ileal neobladder: updated experience in 34 patients. J Urol 1997; 158: 400-405

196. Thuroff JW, Mattiasson A, Andersen JT, et al: The standardization of terminology and assessment of functional characteristics of intestinal urinary reservoirs. International Continence Society Committee on Standardization of Terminology. Subcommittee on Intestinal Urinary Reservoirs. Br J Urol 78: 516-523, 1996.

197. Gburek BM, Lieber MM, Blute ML: Comparison of Studer ileal neobladder and ileal conduit urinary diversion with respect to perioperative outcome and late complications. J Urol 160: 721-723, 1998.

198. Arai Y, Okubo K, Konami T, Kin S, Kanba T, Okabe T, Hamaguchi A, Okada Y: Voiding function of orthotopic ileal neobladder in women. Urology 54: 44-49, 1999.

199. Studer UE, Danuser H, Hochreiter W, Springer JP, Turner WH, Zingg EJ: Summary of 10 years' experience with an ileal low-pressure bladder substitute combined with an afferent tubular isoperistaltic segment. World J Urol 14: 29-39, 1996.

200.Ghoneim MA, Shaaban AA, Mahran MR, Kock NG: Further experience with the urethral Kock pouch. J Urol 147: 361-365, 1992.

201. Kurzrock EA, Tomasic NA, Razi SS, Skinner DG, Ben-

nett CJ. Fluorourodynamic and clinical evaluation in males following construction of a Kock ileal-urethral reservoir. Urology 1995; 46: 801-803

202. Stenzl A, Colleselli K, Poisel S, Feichtinger H, Bartsch G: The use of neobladders in women undergoing cystectomy for transitional-cell cancer. World J Urol 14: 15-21, 1996.

203. El Bahnasawy MS, Osman Y, Gomha MA, Shaaban AA, Ashamallah A, Ghoneim MA: Nocturnal enuresis in men with an orthotopic ileal reservoir: urodynamic evaluation. J Urol 164: 10-13, 2000.

204. Lin DW, Santucci RA, Mayo ME, Lange PH, Mitchell ME. Urodynamic evaluation and long-term results of the orthotopic gastric neobladder in men. J Urol 2000; 164: 356-359

205. Mills RD, and Studer UE: Female orthotopic bladder substitution: a good operation in the right circumstances. J Urol 163: 1501-1504, 2000.

206. Constantinides C, Manousakas T, Chrisofos M, et al: Orthotopic bladder substitution after radical cystectomy: 5 years of experience with a novel personal modification of the ileal s pouch. J Urol 166: 532-537, 2001.

207. Beduk Y, Turkolmez K, Baltaci S, et al: Comparison of clinical and urodynamic outcome in orthotopic ileocaecal and ileal neobladder. Eur Urol 43: 258-262, 2003.

208. Nesrallah LJ, Srougi M, Dall'Oglio MF: Orthotopic ileal neobladder: the influence of reservoir volume and configuration on urinary continence and emptying properties. BJU Int 93: 375-378, 2004.

209. Shaaban AA, Mosbah A, El-Bahnasawy MS, Madbouly et al: The urethral Kock pouch: long-term functional and oncological results in men. BJU Int 92: 429-435, 2003.

210. Hugonnet CL, Danuser H, Springer JP, et al: Decreased sensitivity in the membranous urethra after orthotopic ileal bladder substitute. J Urol 161: 418-421, 1999.

211. Hugonnet CL, Danuser H, Springer JP, Studer UE. Urethral sensitivity and the impact on urinary continence in patients with an ileal bladder substitute after cystectomy. J Urol 2001; 165: 1502-1505

212. Madersbacher S, Mohrle K, Burkhard F, et al: Long-term voiding pattern of patients with ileal orthotopic bladder substitutes. J Urol 167: 2052-2057, 2002.

213. Tchetgen MB, Sanda MG, Montie JE, et al: Collagen injection for the treatment of incontinence after cystectomy and orthotopic neobladder reconstruction in women. J Urol 163: 212-214, 2000.

214. Cancrini A, De Carli P, Pompeo V, et al: Lower urinary tract reconstruction following cystectomy: experience and results in 96 patients using the orthotopic ileal bladder substitution of Studer et al. Eur Urol 29: 204-209, 1996.

215. Pagano F, Artibani W, Ligato P, et al: Vescica Ileale Padovana: a technique for total bladder replacement. Eur Urol 17: 149-154, 1990.

216. Mikuma N, Hirose T, Yokoo A, et al: Voiding dysfunction in ileal neobladder. J Urol 158: 1365-1368, 1997.

217. Smith E, Yoon J, Theodorescu D: Evaluation of urinary continence and voiding function: early results in men with neo-urethral modification of the Hautmann orthotopic neobladder. J Urol 166: 1346-1349, 2001.

218. Ghoneim MA: Orthotopic bladder substitution in women following cystectomy for bladder cancer. Urol Clin North Am 24: 225-239, 1997.

219. Ali-el-Dein B, el-Sobky E, Hohenfellner M, et al: Orthotopic bladder substitution in women: functional evaluation. J Urol 161: 1875-1880, 1999.

220. Shimogaki H, Okada H, Fujisawa M, et al: Long-term experience with orthotopic reconstruction of the lower urinary tract in women. J Urol 161: 573-567, 1999.

221. Cancrini A, De Carli P, Fattahi H, et al: Orthotopic ileal neobladder in female patients after radical cystectomy: 2-year experience. J Urol 153: 956-958, 1995.

222. Stenzl A, Colleselli K, Poisel S, Feichtinger H, Pontasch H, Bartsch G. Rationale and technique of nerve sparing radical cystectomy before an orthotopic neobladder procedure in women. J Urol 1995; 154: 2044-2049

223. Stenzl A, Colleselli K, Bartsch G: Update of urethra-sparing approaches in cystectomy in women. World J Urol 15: 134-138, 1997.

224. Grossfeld GD, Stein JP, Bennett CJ, et al: Lower urinary tract reconstruction in the female using the Kock ileal reservoir with bilateral ureteroileal urethrostomy: update of continence results and fluorourodynamic findings. Urology 48: 383-388, 1996.

225. Stein JP, Lieskovsky G, Cote R, et al: Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. J Clin Oncol 19: 666-675, 2001.

226. Erckert M, Stenzl A, Falk M, et al: Incidence of urethral tumor involvement in 910 men with bladder cancer. World J Urol 14: 3-8, 1996.

227. Slaton JW, Swanson DA, Grossman HB, et al: A stage specific approach to tumor surveillance after radical cystectomy for transitional cell carcinoma of the bladder. J Urol 162: 710-714, 1999.

228. Lebret T, Herve JM, Barre P, et al: Urethral recurrence of transitional cell carcinoma of the bladder. Predictive value of preoperative latero-montanal biopsies and urethral frozen sections during prostatocystectomy. Eur Urol 33: 170-174, 1998.

229. Robert M, Burgel JS, Serre I, et al: Urethral recurrence after cysto-prostatectomy for bladder tumor. Prog Urol 6: 558-563, 1996.

230. Freeman JA, Tarter TA, Esrig D, et al: Urethral recurrence in patients with orthotopic ileal neobladders. J Urol 156: 1615-1619, 1996.

231. Freeman JA, Esrig D, Stein JP, et al: Management of the patient with bladder cancer. Urethral recurrence. Urol Clin North Am 21: 645-651, 1994.

232. Esrig D, Freeman JA, Elmajian DA, et al: Transitional cell carcinoma involving the prostate with a proposed staging classification for stromal invasion. J Urol 156: 1071-1076, 1996.

233. Iselin CE, Robertson CN, Webster GD, et al: Does prostate transitional cell carcinoma preclude orthotopic bladder reconstruction after radical cystoprostatectomy for bladder cancer? J Urol 158: 2123-2126, 1997.

234. Nixon RG, Chang SS, Lafleur BJ, et al: Carcinoma in situ and tumor multifocality predict the risk of prostatic

urethral involvement at radical cystectomy in men with transitional cell carcinoma of the bladder. J Urol 167: 502-505, 2002.

235. Stein JP, Esrig D, Freeman JA, et al: Prospective pathologic analysis of female cystectomy specimens: risk factors for orthotopic diversion in women. Urology 51: 951-955, 1998.

236. Ali-El-Dein B, Gomha M, Ghoneim MA: Critical evaluation of the problem of chronic urinary retention after orthotopic bladder substitution in women. J Urol 168: 587-592, 2002.

237. Coloby PJ, Kakizoe T, Tobisu K, et al: Urethral involvement in female bladder cancer patients: mapping of 47 consecutive cysto-urethrectomy specimens. J Urol 152: 1438-1442, 1994.

238. Chen ME, Pisters LL, Malpica A, Pettaway CA, Dinney CP. Risk of urethral, vaginal and cervical involvement in patients undergoing radical cystectomy for bladder cancer: results of a contemporary cystectomy series from M. D. Anderson Cancer Center. J Urol 1997; 157: 2120-2123.

239. Maralani S, Wood DP Jr, Grignon D, Banerjee M, Sakr W, Pontes JE. Incidence of urethral involvement in female bladder cancer: an anatomic pathologic study. Urology 50: 537-541, 1997.

240. Schoenberg MP, Walsh PC, Breazeale DR, Marshall FF, Mostwin JL, Brendler CB. Local recurrence and survival following nerve sparing radical cystoprostatectomy for bladder cancer: 10-year followup. J Urol 1996; 155: 490-494.

241. Turner WH, Danuser H, Moehrle K, Studer UE. The effect of nerve sparing cystectomy technique on postoperative continence after orthotopic bladder substitution. J Urol 1997; 158: 2118-2122.

242. Strasser H, Ninkovic M, Hess M, Bartsch G, Stenzl A. Anatomic and functional studies of the male and female urethral sphincter. World J Urol 2000; 18: 324-32

243. Leungwattanakij S, Bivalacqua TJ, Usta MF, Yang DY, Hyun JS, Champion HC, Abdel-Mageed AB, Hellstrom WJ. Cavernous neurotomy causes hypoxia and fibrosis in rat corpus cavernosum. J Androl 2003; 24: 239-245

244. Van der Werf BA, Creed KE. Mechanical properties and innervation of the smooth muscle layers of the urethra of greyhounds. BJU Int 2002; 90: 588-595.

245. Colleselli K, Stenzl A, Eder R, Strasser H, Poisel S, Bartsch G. The female urethral sphincter: a morphological and topographical study. J Urol 1998; 160: 49-54

246. Stenzl A, Jarolim L, Coloby P, Golia S, Bartsch G, Babjuk M, Kakizoe T, Robertson C. Urethra-sparing cystectomy and orthotopic urinary diversion in women with malignant pelvic tumors. Cancer 2001; 92: 1864-1871

247. Lebret T, Herve JM, Yonneau L, et al: After cystectomy, is it justified to perform a bladder replacement for patients with lymph node positive bladder cancer? Eur Urol 42: 344-349, 2002.

248. Oberneder R, Staudte S, Waidelich R, et al: Local recurrence in patients after radical cystectomy and orthotopic ileal neobladder: impact on function. Int Urol Nephrol 35: 175-179, 2003.

249. Tefilli MV, Gheiler EL, Tiguert R, et al: Urinary diversion-related outcome in patients with pelvic recurrence after radical cystectomy for bladder cancer. Urology 53: 999-1004, 1999.

250. Hautmann RE: Complications and results after cystectomy in male and female patients with locally invasive bladder cancer. Eur Urol 33 Suppl 4: 23-24, 1999.

251. Ali-el-Dein B, Abdel-Latif M, Ashamallah A, et al: Local urethral recurrence after radical cystectomy and orthotopic bladder substitution in women: a prospective study. J Urol 171: 275-278, 2004.

252. Chang SS, Cole E, Cookson MS, Peterson M, Smith JA Jr. Preservation of the anterior vaginal wall during female radical cystectomy with orthotopic urinary diversion: technique and results. J Urol 2002; 168: 1442-1445

253. Vallancien G, Abou El Fettouh H, Cathelineau X, Baumert H, Fromont G, Guillonneau B. Cystectomy with prostate sparing for bladder cancer in 100 patients: 10-year experience. J Urol 2002; 168: 2413-2417

254. Colombo R, Bertini R, Salonia A, Naspro R, Ghezzi M, Mazzoccoli B, Deho' F, Montorsi F, Rigatti P. Overall clinical outcomes after nerve and seminal sparing radical cystectomy for the treatment of organ confined bladder cancer. J Urol 2004; 171: 1819-1822

255. Horenblas S, Meinhardt W, Ijzerman W, Moonen LF. Sexuality preserving cystectomy and neobladder: initial results. J Urol. 2001; 166: 837-840

256. Revelo MP, Cookson MS, Chang SS, Shook MF, Smith JA Jr, Shappell SB. Incidence and location of prostate and urothelial carcinoma in prostates from cystoprostatectomies: implications for possible apical sparing surgery. J Urol 2004; 171: 646-651

257. Montie JE, Wood DP Jr, Pontes JE, Boyett JM, Levin HS. Adenocarcinoma of the prostate in cystoprostatectomy specimens removed for bladder cancer. Cancer 1989; 63: 381-385

258. Kabalin JN, McNeal JE, Price HM, Freiha FS, Stamey TA. Unsuspected adenocarcinoma of the prostate in patients undergoing cystoprostatectomy for other causes: incidence, histology and morphometric observations. J Urol 1989; 141: 1091-1094

259. Wood DP Jr, Montie JE, Pontes JE, VanderBrug Medendorp S, Levin HS. Transitional cell carcinoma of the prostate in cystoprostatectomy specimens removed for bladder cancer. J Urol 1989; 141: 346-349

260. Spitz A, Stein JP, Lieskovsky G, Skinner DG. Orthotopic urinary diversion with preservation of erectile and ejaculatory function in men requiring radical cystectomy for nonurothelial malignancy: a new technique. J Urol 1999; 161: 1761-1764

261. Stein JP, Cote RJ, Freeman JA, Esrig D, Elmajian DA, Groshen S, Skinner EC, Boyd SD, Lieskovsky G, Skinner DG. Indications for lower urinary tract reconstruction in women after cystectomy for bladder cancer: a pathological review of female cystectomy specimens. J Urol 1995; 154: 1329-1333

262. Stein JP, Skinner DG. Radical cystectomy in women. In: Montie J, ed., Atlas of the Urologic Clinics of North America, Philadelphia, W.B. Saunders; 5: 65 – 78, 1997

263.Rowland RG: Complications of continent cutaneous reservoirs and neobladder – series using contemporary techniques. AUA Update Series, Vol XIX, lessons 25, 201 – 214, 1995.

264. Muraishi O, Yamashita T, Ishikawa S, et al: Improvement of ureteroileal anastomosis in orthotopic ileal neobladder with modified le duc procedure: short submucosal tunnel technique. J Urol 165: 798-801, 2001.

265. Schwaibold H, Friedrich MG, Fernandez S, et al: Improvement of ureteroileal anastomosis in continent urinary diversion with modified Le Duc procedure. J Urol 160: 718-720, 1998.

266. Lugagne PM, Herve JM, Lebret T, et al: Ureteroileal implantation in orthotopic neobladder with the Le Duc-Camey mucosal-through technique: risk of stenosis and long-term follow-up. J Urol 158: 765-767, 1997.

267. Shaaban AA, Gaballah MA, el-Diasty TA, et al: Urethral controlled bladder substitution: a comparison between the intussuscepted nipple valve and the technique of Le Duc as antireflux procedures. J Urol 148: 1156-1161, 1992.

268. Sagalowsky AI: Further experience with split-cuff nipple ureteral reimplantation in urinary diversion. J Urol 159: 1843-1844, 1998.

269. Stein JP, Freeman JA, Esrig D, et al: Complications of the afferent antireflux valve mechanism in the Kock ileal reservoir. J Urol 155: 1579-1584, 1996.

270. Roth S, van Ahlen H, Semjonow A, et al: Does the success of ureterointestinal implantation in orthotopic bladder substitution depend more on surgeon level of experience or choice of technique? J Urol 157: 56-60, 1997.

271. Papadopoulos I, and Weichert-Jacobsen K: Experiences with the entero-ureteral anastomosis via the extramural serous-lined tunnel: procedure of Abol-Enein. Urology 57: 234-238, 2001.

272. Parekh DJ, Clark T, O'Connor J, Jung C, Chang SS, Cookson MS, Smih JA Jr: Orthotopic neobladder following radical cystectomy in patients with high perioperative risk and co-morbid medical conditions. J Urol 168: 2454-2456, 2002.

273. Parekh DJ, Gilbert WB, Koch MO, Smith JA Jr: Continent urinary reconstruction versus ileal conduit: a contemporary single-institution comparison of perioperative morbidity and mortality. Urology 55: 852-855, 2000.

274. Turner WH, Bitton A, Studer UE: Reconstruction of the urinary tract after radical cystectomy: the case for continent urinary diversion. Urology 49: 663-667, 1997.

275. Benson MC, Slawin KM, Wechsler MH, et al: Analysis of continent versus standard urinary diversion. Br J Urol 69: 156-162, 1992.

276. Skinner DG. Intussuscepted ileal nipple valve-development and present status. Scand J Urol Nephrol 142 (suppl): 63 – 65, 1992.

277. Lilien OM, and Camey M: 25-year experience with replacement of the human bladder (Camey procedure). J Urol 132: 886-891, 1984.

278. Allen TD, Peters PC, Sagalowsky AI, et al: The camey procedure: preliminary results in 11 patients. World J Urol 3: 167-171, 1985.

279. De Carli P, Micali S, O'Sullivan D, et al: Ureteral anastomosis in the orthotopic ileal neobladder: comparison of 2 techniques. J Urol 157: 469-471, 1997.

280. Abol-Enein H, and Ghoneim MA: A novel uretero-ileal reimplantation technique: the serous lined extramural tunnel. A preliminary report. J Urol 151: 1193-1197, 1994.

281. Bochner BH, Stein JP, Ginsberg DA, et al: A serous lined antireflux valve: in vivo fluorourodynamic evaluation of antireflux continence mechanism. J Urol 160: 112-115, 1998.

282. Parsons JK, and Schoenberg MP: Successful conservative management of perforated ileal neobladder. J Urol 165: 1214-1215, 2001.

283. Mansson W, Bakke A, Bergman B, et al: Perforation of continent urinary reservoirs. Scandinavian experience. Scand J Urol Nephrol 31: 529-532, 1997.

284. Desgrandchamps F, Cariou G, Barthelemy Y, et al: Spontaneous rupture of orthotopic detubularized ileal bladder replacement: report of 5 cases. J Urol 158: 798-800, 1997.

285. Kyriakidis A: Fournier's gangrene following delayed rupture of an ileal neobladder (Hautmann). Br J Urol 76: 668, 1995.

286. Nippgen JB, Hakenberg OW, Manseck A, et al: Spontaneous late rupture of orthotopic detubularized ileal neobladders: report of five cases. Urology 58: 43-46, 2001.

287. Baseman AG, Young RR Jr, Young AK, et al: Conservative management of spontaneous rupture of Kock orthotopic ileal reservoir. Urology 49: 629-631, 1997.

288. Choong SK, and Gleeson M: Conservative management of a spontaneous rupture of a continent cutaneous urinary diversion. Br J Urol 82: 592-593, 1998.

289. Kristiansen P, Mansson W, Tyger J: Perforation of continent caecal reservoir for urine twice in one patient. Scand J Urol Nephrol 25: 279-281, 1991.

290. Chen YC, Lee YH, Huang JK: Spontaneous perforation of a modified Camey neobladder. Urol Int 59: 48-49, 1997.

291. Martinez Jabaloyas JM, Vera Donoso CD, Morera Martinez JF, et al: Spontaneous rupture of a neobladder. Eur Urol 25: 259-261, 1994.

292 Thompson ST, and Kursh ED: Delayed spontaneous rupture of an ileocolonic neobladder. J Urol 148:1890-1891, 1992.

293. Benson MC, Olsson CA: Continent urinary diversion. In: Cambell's Urology, 7th ed. Edited by Walsh PC, Vaughn ED jr, Retik AB et al. Philadelphia: WB Saunders, 3190, 1998

294. Abol-Enein H, and Ghoneim MA: Further clinical experience with the ileal W-neobladder and a serous-lined extramural tunnel for orthotopic substitution. Br J Urol 776: 558 – 564, 1995.

295. Huguet J, Palou J, Serrallach M, et al: Management of urethral recurrence in patients with Studer ileal neobladder. Eur Urol 43: 495-498, 2003.

296. Stein JP, and Skinner DG: T-mechanism applied to uri-

nary diversion: the orthotopic T-pouch ileal neobladder and cutaneous double-T-pouch ileal reservoir. Tech Urol 7: 209-222, 2001.

297. Kock NG, Nilson AE, Nilsson LO, et al: Urinary diversion via a continent ileal reservoir: clinical results in 12 patients. J Urol 128: 469-475, 1982.

298. Skinner DG, Lieskovsky G, Boyd SD: Continuing experience with the continent ileal reservoir (Kock pouch) as an alternative to cutaneous urinary diversion: An update after 250 cases. J Urol 137: 1140-1145, 1987.

299. Skinner DG, Lieskovsky G, Boyd SD: Continent urinary diversion. J Urol 141: 1323-1327, 1989.

300. Rowland RG, Mitchell ME, Bihrle R, et al: Indiana continent urinary reservoir. J Urol 137: 1136-1139, 1987.

301. Rowland RG: Present experience with the Indiana pouch. World J Urol 14: 92-98, 1996.

302. Arai Y, Kawakita M, Terachi T, et al: Long-term followup of the Kock and Indiana pouch procedures. J Urol 150: 51-55, 1993.

303. Carr LK, and Webster GD: Kock versus right colon continent urinary diversion: comparison of outcome and reoperation rate. Urology 48: 711-714, 1996.

304. Okada Y, Shichiri Y, Terai A, et al: Management of late complications of continent urinary diversion using the Kock pouch and the Indiana pouch procedures. Int J Urol 3: 334-339, 1996.

305. Webster C, Bukkapatnam R, Seigne JD, et al: Continent colonic urinary reservoir (Florida pouch): long-term surgical complications (greater than 11 years). J Urol 169: 174-176, 2003.

306. Shukla AR, Pow-Sang JM, Helal MA, et al: Urinary incontinence after continent urinary diversion using a cecal wrap or plicated ileum: a patient questionnaire review. Urology 61: 328-331, 2003.

307. Davidsson T, Hedlund H, Månsson W: Detubularized right colonic reservoir with intussuscepted ileal nipple valve or stapled ileal (”Lundiana”) outlet. World J Urol 14: 78-84, 1996.

308. Mitrofanoff P : Cystostomie continent transappendiculaire dans le traitement des vessies neurologiques. Chir Ped 21: 297-305, 1980.

309. Riedmiller H, Bürger R, Müller S, et al: Continent appendix stoma. A modification of the Mainz pouch technique. J Urol 143: 1115-1117, 1990.

310. Gerharz EW, Köhl UN, Melekos MD, et al: Ten years´experience with the submucosally embedded in situ appendix in continent cutaneous diversion. Eur Urol 40: 625-631, 2001.

311. Takeda M, Katayama Y, Takahashi H, et al: Incidence of pouch stones and risk factors for urolithiasis in patients with continent urinary diversion or neobladder using intestine. Urol Int 52: 21-25, 1994.

312. Edin-Liljegren A, Grenabo L, Hedelin H, et al: Concrement formation and urease-induced crystallization in urine from patients with continent ileal reservoirs. Br J Urol 78: 57-63, 1996.

313. Osther PJ, Poulsen AL, Steven K: Stone risk after bladder substitution with the ileal-urethral Kock reservoir. Scand J Urol Nephrol 34: 257-261, 2000.

314. Woodhouse CRJ, and Lennon: Management and etiology of stones in intestinal urinary reservoirs. Eur Urol 39: 253-259, 2001.

315. Ginsberg D, Huffman JL, Lieskovsky G, et al: Urinary tract stones: a complication of the Kock pouch continent urinary diversion. J Urol 145: 956-959, 1991.

316. Akerlund S, Berglund B, Kock NG, et al: Voiding pattern, urinary volume, composition and bacterial contamination in patients with urinary diversion via a continent ileal reservoir. Br J Urol 63: 619-623, 1989.

317. Lieskovsky G, Skinner DG, Boyd SD: Complications of the Kock pouch. Urol Clin North Am 15: 195-205, 1988.

318. Helal M, Austin P, Spyropoulos E, et al: Evaluation and management of parastomal hernia in association with continent urinary diversion. J Urol 157: 1630-1632, 1997.

319. Stein JP, Huffman JL, Freeman JA, et al: Stenosis of the afferent antireflux valve in the Kock pouch continent urinary diversion: diagnosis and management. J Urol 151: 338-340, 1994.

320. Netto NR Jr, Ferreira U, Lemos GC, et al: Endourological management of ureteral strictures. J Urol 144: 631-634, 1990.

321. Banner MP, and Pollack HM. Dilatation of ureteral stenoses: techniques and experience in 44 patients. AJR Am J Roentgenol 143: 789-793, 1984.

322. Shapiro MJ, Banner MP, Amendola MA, et al: Balloon catheter dilation of ureteroenteric strictures: long-term results. Radiology 168: 385-387, 1988.

323. Johnson CD, Oke EJ, Dunnick NR, et al: Percutaneous balloon dilatation of ureteral strictures. AJR Am J Roentgenol 148: 181-184, 1987.

324. Schneider AW, Conrad S, Busch R, et al: The cold-knife technique for endourological management of stenoses in the upper urinary tract. J Urol 146: 961-965, 1991.

325. Wilson TG, Moreno JG, Weinberg A, et al: Late complications of the modified Indiana pouch. J Urol 151: 331-334, 1994.

326. Kramolowsky EV, Clayman RV, Weyman PJ: Management of ureterointestinal anastomotic strictures: comparison of open surgical and endourological repair. J Urol 139: 1195-1198, 1988.

327. Skinner DG: Intussuscepted ileal nipple valve – development and present status. Scand J Urol Nephrol 142: 63-65, 1992.

328. Kock NG: Continent ileostomy. Progr Surg 12: 180-185, 1973.

329. Skinner DG, Boyd SD, Lieskovsky G: Clinical experience with the Kock continent ileal reservoir for urinary diversion. J Urol 132: 1101-1107, 1984

330. Lieskovsky G, Boyd SD, Skinner DG: Management of late complications of the Kock pouch form of urinary diversion. J Urol 137: 1146-1150, 1987.

331. Abol-Enein H, and Ghoneim MA: Optimization of uretero-intestinal anastomosis in urinary diversion; an

experimental study in dogs. III. An new anti-reflux technique for uretero-ileal anastomosis; a serous-lined extramural tunnel. Urol Res 21: 135–138, 1993.

332. Abol-Enein H, and Ghoneim MA: Serous-lined, extramural ileal valve as a new continent urinary diversion: an experimental study in dogs. Urol Res 23: 193-199, 1995.
333. Abol-Enein H, and Ghoneim MA: A technique for creation of a continent urinary outlet: the serous-lined extramural ileal valve. Br J Urol 78: 791-796, 1998.
334. Monti PR, Lara RC, Dutta MA, et al: New techniques for construction of efferent conduits based on the Mitrofanoff principle. Urology 49: 112-114, 1997.
335. Gilchrist RK, Merricks JW, Hamlin HH, et al: Construction of substitute bladder and uretra. Surg Gynec Obst 90: 752-755, 1950.
336. Lockhart JL: Remodeled right colon: an alternative urinary reservoir. J Urol 138: 730-734, 1987.
337. Abol-Enein H, and Ghoneim MA: Serous lined extramural ileal valve: a new continent urinary outlet. J Urol 161: 786-791, 1999.
338. Swedish Bladder Registry, 2003.
339. MacGregor PS, Montie JE, Straffon RA : Cutaneous ureterostomy as palliative diversion in adults with malignancy. Urology 30: 31-34, 1987.
340. Feminella JG Jr., and Lattimer JK: A retrospective analysis of 70 cases of cutaneous ureterostomy. J Urol 106: 538-540, 1971.
341. De Wilde P, Oosterlinck W, De Sy WA: Uretero-aortic fistula: a severe complication of ureterocutaneostomy. Eur Urol 17: 262-263, 1990.
342. Dervanian P, Castaigne D, Travagli JP, et al: Arterioureteral fistula after extended resection of pelvic tumors: report of three cases and review of the literature. Ann Vasc Surg 6: 362-369, 1992.
343. Rainwater LM, Leary FJ, Rife CC: Transureteroureterostomy with cutaneous ureterostomy: a 25-year experience. J Urol 146: 13-15, 1991.
344. Bracken RB, and Kinder B: Intubated cutaneous ureterostomy: option for high-risk patients needing supravesical urinary diversion. Urology 25: 45-48, 1985.
345. Claman M, Schapiro AE, Orecklin JR: Cutaneous ureterostomy, the preferred diversion of the solitary functioning kidney. Br J Urol 51: 352-356, 1979.
346. Toyoda Y: A new technique for catheterless cutaneous ureterostomy. J Urol 117: 276-278, 1977.
347. Yoshimura K, Maekawa S, Ichioka K, et al: Tubeless cutaneous ureterostomy: the Toyoda method revisited. J Urol 165: 785-788, 2001.
348. Hirokawa M, Iwasaki A, Yamazaki A, et al: Improved technique of tubeless cutaneous ureterostomy and results of permanent urinary diversion. Eur Urol 16: 125-132, 1989.
349. Tsai SY, Wong CC, Smith EK, et al: Terminal loop cutaneous ureterostomy in renal transplantation. Urology 40: 280-282, 1992.
350. Rosen MA, Roth DR, Gonzales ET, Jr: Current indications for cutaneous ureterostomy. Urology 43: 92-96, 1994.
351. Thrasher JB, and Wettlaufer JN: Transureteroureterostomy and terminal loop cutaneous ureterostomy in advanced pelvic malignancies. J Urol 146: 977-979, 1991.
352. Fallon B, Olney L, Culp DA: Nephrostomy in cancer patients: to do or not to do? Br J Urol 52: 237-242, 1980.
353. Puppo P, Perachino M, Ricciotti G, et al: Laparoscopic bilateral cutaneous ureterostomy for palliation of ureteral obstruction caused by advanced pelvic cancer. J Endourol 8: 425-428, 1991.
354. Loisides P, Grasso M, Lui P: Laparoscopic cutaneous ureterostomy: technique for palliative upper urinary tract drainage. J Endourol 9: 315-317, 1995.
355. Yoshimura K, Ichioka K, Terada N, et al: Retroperitoneoscopic tubeless cutaneous ureterostomy. BJU Int 89: 964-966, 2002.
356. Simonato A, Gregori A, Lissiani A, et al: Laparoscopic radical cystoprostatectomy: a technique illustrated step by step. Eur Urol 44: 132-138, 2003.
357. Matin SF, and Gill IS: Laparoscopic radical cystectomy with urinary diversion: completely intracorporeal technique. J Endourol 16: 335-341, 2002.
358. Nordström GM, Borglund E, Nyman CR: Local status of the urinary stoma – the relation to peristomal skin complications. Scand J Urol Nephrol 24: 117-122, 1990.
359. Singh G, Wilkinson JM, Thomas DG: Supravesical diversion for incontinence: a long-term follow-up. BJU Int 79: 348-353, 1997.
360. Rubin MS, Schoetz DJ Jr, Matthews JB: Parastomal hernia. Is stoma relocation superior to fascial repair? Arch Surg 129: 413-418, 1994.
361. Amin SN, Armitage NC, Abercrombie JF, et al: Lateral repair of parastomal hernia. Ann R Coll Surg Engl 83: 206-209, 2001.
362. Franks ME, and Hrebinko Jr RL: Technique of parastomal hernia repair using synthetic mesh. Urology 57: 551-553, 2001.
363. Magnusson B, Carle´n B, Bak-Jensen E, et al: Ileal conduit stenosis – an enigma. Scand J Urol Nephrol 30: 193-197, 1996.
364. Leissner J, Black P, Fisch M, et al: Colon pouch (Mainz Pouch III) for continent urinary diversion efter pelvic irradiation. Urology 56: 798-802, 2000.
365. Ravi R, Dewan AK, Pandey KK: Transverse colon conduit urinary diversion in patients treated with very high dose pelvic irradiation. Br J Urol 73: 51-54, 1994.
366. Simon J: Ectopia vesicae; operation for directing the orifices of the ureters in the rectum, temporary success, subsequent death; autopsy. Lancet 568-570, 1852.
367. Hinman F, and Weyrauch HM. A critical study of the different principles of surgery, which have been used in ureterointestinal implantation. Trans Am Assoc Genitourin Surg 29:15-16, 1936.
368. McDougal WS, and Koch MO: Accurate determination of renal function in patients with intestinal urinary diversions. J Urol 135:1175-1178, 1986.

369. Hendren WH: Reconstruction of previously diverted urinary tracts in children. J Pediatr Surg 8:135-150, 1973.

370. Bricker EM: Bladder substitution after pelvic evisceration. Surg Gynecol Obstet 30: 1511-1521, 1950.

371.Wear JB Jr and Barquin OP: Ureterosigmoidostomy. Long-term results. Urology 1: 192-200, 1973.

372. Truss MC: Supravesical diversion, First Edition ed, vol Chap.49. Philadelphia, Lippincott Company, 1994

373. Koo HP, Avolio L, Duckett JW Jr: Long-term results of ureterosigmoidostomy in children with bladder exstrophy. J Urol 156: 2037-2040, 1996.

374. Nesbit R: Ureterosigmoid anastomosis by direct elliptical correction. J Urol 61:728-734, 1949.

375. Allen TD: Salvaging the obstructed ureterosigmoidostomy using an ileal interposition technique. J Urol 150: 1195-1198, 1993.

376. Coffey RC: Physiologic implantation of the severed ureter or common bile duct into the intestine. JAMA 56: 397, 1911.

377. Leadbetter WF: Considerations of problems incident to performance of ureteroenterostomy: Report of a technique. Trans Am Assoc Genitourin Surg 42: 39, 1950.

378. Goodwin WE, Harris AP, Kaufman JJ: Open transcolonic ureterointestinal anastomosis. Surg Gynecol Obstet 97: 295-300, 1953.

379. Williams DF, Burkholder GV, Goodwin WE: Ureterosigmoidostomy: a 15-year experience. J Urol 101: 168-170, 1969.

380. Zincke H and Segura JW: Ureterosigmoidostomy: critical review of 173 cases. J Urol 113: 324-327, 1975.

381. Duckett JW and Gazak JM: Complications of ureterosigmoidostomy. Urol Clin North Am 10: 473-481, 1983.

382. Jacobs JA, Young JD, Jr.: The Strickler technique of ureterosigmoidostomy. J Urol 124(4):451-4., 1980.

383. Pagano F, Cosciani-Cunico S, Dal Bianco M, et al: Five years of experience with a modified technique of ureterocolonic anastomosis. J Urol 132(1):17-8., 1984.

384. Mesrobian HG, Kelalis PP, Kramer SA: Long-term follow-up of 103 patients with bladder exstrophy. J Urol 139(4):719-22., 1988.

385. Connor JP, Hensle TW, Lattimer JK, et al: Long-term follow-up of 207 patients with bladder exstrophy: an evolution in treatment. J Urol 142(3):793-5; discussion 795-6., 1989.

386. Kalble T, Tricker AR, Friedl P, et al: Ureterosigmoidostomy: long-term results, risk of carcinoma and etiological factors for carcinogenesis. J Urol 144(5):1110-4., 1990.

387. Stockle M, Becht E, Voges G, et al: Ureterosigmoidostomy: an outdated approach to bladder exstrophy? J Urol 143(4):770-4; discussion 774-5., 1990.

388. Stein R, Fisch M, Stockle M, et al: Urinary diversion in bladder exstrophy and incontinent epispadias: 25 years of experience. J Urol 154(3):1177-81., 1995.

389. Benchekroun A, Lachkar A, Soumana A, et al: [Ureterosigmoidostomies. 35 cases]. Ann Urol 32(2):95-8, 1998.

390. Ghoneim MA, Shehab-El-Din AB, Ashamallah AK: Evolution of the rectal bladder as a method for urinary diversion. J Urol 126: 737-740, 1981.

391. Zabbo A and Kay R: Ureterosigmoidostomy and bladder exstrophy: a long-term follow-up. J Urol 136: 396-398, 1986.

392. Wynant HP, Morelle V, Fonteyne E, et al: Ureterosigmoidostomy: reevaluation of a “forgotten” continent urinary diversion. Acta Urol Belg 59(4):103-7, 1991.

393. Stewart M, Macrae FA, Williams CB: Neoplasia and ureterosigmoidostomy: a colonoscopy survey. Br J Surg 69: 414-416, 1982.

394. Schipper H and Decter A: Carcinoma of the colon arising at ureteral implant sites despite early external diversion: pathogenetic and clinical implications. Cancer 47: 2062-2065, 1981.

395. Husmann DA and Spence HM: Current status of tumor of the bowel following ureterosigmoidostomy: a review. J Urol 144: 607-610, 1990.

396. Harzmann R, Kopper B, Carl P: Cancer induction by urinary drainage or diversion through intestinal segments? Urologe A 25: 198-203, 1986.

397. Crissey MM, Steele GD, Gittes RF: Rat model for carcinogenesis in ureterosigmoidostomy. Science 207: 1079-1080, 1980.

398. Stewart M, Hill MJ, Pugh RC: The role of N-nitrosamine in carcinogenesis at the ureterocolic anastomosis. Br J Urol 53: 115-118, 1981.

399. Shands C 3rd, McDougal WS, Wright EP: Prevention of cancer at the urothelial enteric anastomotic site. J Urol 141: 178-181, 1989.

400. Kalble T, Tricker AR, Hoang J: Effect of vitamin C on endogenous formation of N-nitrosamines in ureterosigmoidostomy patients. Urol Int 46: 22-26, 1991.

401. Gregoire M, Kantoff P, DeWolf WC: Synchronous adenocarcinoma and transitional cell carcinoma of the bladder associated with augmentation: case report and review of the literature. J Urol 149: 115-118, 1993.

402. Reddy BS, Tokumo K, Kulkarni N: Inhibition of colon carcinogenesis by prostaglandin synthesis inhibitors and related compounds. Carcinogenesis 13: 1019-1023, 1992.

403. Thun MJ, Namboodiri MM, Heath CW Jr: Aspirin use and reduced risk of fatal colon cancer. N Engl J Med 325: 1593-1596, 1991.

404. Kock NG, Ghoneim MA, Lycke KG: Urinary diversion to the augmented and valved rectum: preliminary results with a novel surgical procedure. J Urol 140: 1375-1379, 1988.

405. Kock NG, Berglund B, Ghoneim MA: Urinary diversion to the augmented and valved rectum. An experimental study in dogs. Scand J Urol Nephrol 22: 227-233, 1988.

406. Ghoneim MA, Ashamallah AK, Mahran MR: Further experience with the modified rectal bladder (the augmented and valved rectum) for urine diversion. J Urol 147: 1252-1255, 1992.

407. Shoma AM, Ashamallah A, Ghoneim MA: Rectosig-

moid urinary diversion: the functional significance of creating an intussuscepted colorectal valve. J Urol 161: 415-417, 1999.

408. Dawaba MS, Dawood A, Ghoneim MA: The modified rectal bladder in children: long-term follow-up. World J Urol 14: 73-77, 1996.

409. Kalble T, Busse K, Amelung F: Tumor induction and prophylaxis following different forms of intestinal urinary diversion in a rat model. Urol Res 23: 365-370, 1995.

410. Kim KS, Susskind MR, King LR: Ileocecal ureterosigmoidostomy: an alternative to conventional ureterosigmoidostomy. J Urol 140: 1494-1498, 1988.

411. Kato T, Sato K, Miyazaki H: The uretero-ileoceco-proctostomy (ileocecal rectal bladder): early experiences in 18 patients. J Urol 150: 326-331, 1993.

412. Baron JC, Arhan P, Boccon-Gibod L: Ureterorectal diversion with rectal augmentation. Morphological and manometric study in the dog. Urol Res 20: 247-251, 1992.

413. Baron JC, Arhan P, Boccon-Gibod L: Urinary diversion to the rectum with rectal widening. Experimental study and initial clinical results. Acta Urol Belg 59: 109-113, 1991.

414. Baron JC, and Boccon-Gibod L: Uretero-rectal diversion with rectal enlargement. Clinical results. Prog Urol 2: 874-881, 1992.

415. Miller K, Matsui U, Hautmann R: The functional rectal bladder - prevention of hyperchloremic acidosis following vesico-sigmoidostomy in dogs. J Urol 144: 375-380, 1990.

416. Sundin T, and Mansi M: The valved S-shaped rectosigmoid pouch for urinary diversion. Scand J Urol Nephrol Suppl 142: 91-94, 1992.

417. Sundin T, and Mansi MK: The valved S-shaped rectosigmoid pouch for continent urinary diversion. J Urol 150: 838-842, 1993.

418. Fisch M, Wammack R, Muller SC: The Mainz pouch II (sigma rectum pouch). J Urol 149: 258-263, 1993.

419. Mathisen W: A new method of ureterointestinal anastomosis: A preliminary report. Surg Gynecol Obstet 96: 255-258, 1953.

420. Fisch M, Wammack R, Hohenfellner R: The sigma rectum pouch (Mainz pouch II). World J Urol 14: 68-72, 1996.

421. Gerharz EW, Kohl UN, Weingartner K: Experience with the Mainz modification of ureterosigmoidostomy. Br J Surg 85: 1512-1516, 1998.

422. Obek C, Kural AR, Ataus S: Complications of the Mainz pouch II (sigma rectum pouch). Eur Urol 39: 204-211, 2001.

423. El Mekresh MM, Hafez AT, Abol-Enein H: Double folded rectosigmoid bladder with a new ureterocolic antireflux technique. J Urol 157: 2085-2089, 1997.

424. Borelius J: Eine neue Modifikation der Maydl'schen Operationsmethode bei angeborener Blasenktopie. Zentrbl Chir 30: 780-782, 1903.

425. Descomps P : Abouchement ureteral dans le rectum exclu. Ureterocolostomie haute terminale apres sigmoido-rectostomie basse termino-laterale. Arch Gen Chir 4: 892-909, 1909.

426. Modelski W: The transplantation of ureters into the partially excluded rectum. J Urol 87: 122-124, 1962.

427. Leiter E and Brendler H: A method of urinary diversion, which preserves continence. J Urol 92: 37-41, 1964.

428. Chargi A, Charbonneau J, Cholette JP: A method of urinary diversion by anastomosis of the ureters into a sigmoid pouch. J Urol 94: 376-379, 1965.

429. Kamidono S, Oda Y, Hamami G: Urinary diversion: anastomosis of the ureters into a sigmoid pouch and end-to-side sigmoidorectostomy. J Urol 133: 391-394, 1985.

430. Ghoneim MA: The rectosigmoid bladder for urinary diversion. Br J Urol 42: 429-433, 1970.

431. Atta MA: Detubularized isolated ureterosigmoidostomy: description of a new technique and preliminary results. J Urol 156: 915-919, 1996.

432. Elabbady AA, Elabbasy WI, Arafa AF: A simple technique for urinary diversion: the dismembered detubularized rectosigmoid bladder with distal colorectostomy. J Urol 160: 714-717, 1998.

433. Mauclaire P : De quelques essais de chirurgie experimental applicables de l'exstrophie de la vessie et de anus contre nature complexes. Ann Mal Org Genitourin 13: 1080-1081, 1895.

434. Remedi V: Un caso de estrofia della vesica. La Clin Chir 14: 608-640, 1906.

435. Creevy CD, and Reister MP: Observations upon the absorption of urinary constituents after ureterosigmoidostomy. The importance of renal damage. Surg Gynecol Obstet 95: 589-596, 1952.

436. Paul DP, and Hodges CV: The rectosigmoid colon as a bladder substitute. J Urol 74: 360-367, 1955.

437. Hanley HG: The rectal bladder. Br J Surg 53: 678-681, 1966.

438. Pyrah LN: The rectosigmoid bladder as a method of urinary diversion. J Urol 90: 189-192, 1963.

439. Irvine WT, Allan C, Webster DR: Prevention of late complications of ureterosigmoidostomy by methods of fecal exclusion. Br J Surg 43: 650-658, 1956.

440. Ghoneim MA, and Ashamallah A: Further experience with the rectosigmoid bladder. Br J Urol 46: 511-519, 1974

441. Gersuny R: Cited by Foges: Offizielles Protokoll der KK-Gesellschaft in Wien. Wien Klin Wschr 11: 990, 1898

442. Heitz-Boyer M, Hovelacque A: Creation d'uno nouvelle vessie et d'uno nouvel uretre. J Urologie 1912; 1: 237-258

443. Lowsley OS, Johnson TH, Rueda AE: A new operation for diversion of the urine with voluntary control of faeces and urine. J Int Coll Surg 20: 457-464, 1953.

444. Hinman FJ: The techniques of Gersuny operation (ureterosigmoidostomy with perineal colostomy) in vesical exstrophy. J Urol 81: 126-129, 1959.

445. Stonington OG, and Eiseman B: Perineal sigmoidostomy in cases of total cystectomy. J Urol 76: 74-82, 1956.

446. Ghoneim MA, and Shoukry I: Rectal bladder with perineal colostomy for urinary diversion. Urology 4: 278-281, 1974.

447. Hafez AT, El-Shirbiny MT, Dawaba MS, et al: Long term outcome analysis of low pressure rectal reservoirs in 33 children with bladder exstrophy. J Urol 156: 2414-2417, 2001.

448. McDougall EM, Liatsikos EN, Dinlenc CZ, et al: Percutaneous appraoaches to the upper urinary tract. In: Walsh PC, Retik AB, Vaughan ED, J. WA, Kavoussi LR, Novick AC, et al., editors. Campbell's Urology. 8 ed. Philadelphia: Saunders; 2002. p. 3320-336

449. Kinn AC, and Ohlsen H: Percutaneous nephrostomy—a retrospective study focused on palliative indications. APMIS Suppl 66-70, 2003.

450. Watkinson AF, A'Hern RP, Jones A, et al: The role of percutaneous nephrostomy in malignant urinary tract obstruction. Clin Radiol 47: 32-35, 1993.

451. Ekici S, Sahin A, Ozen H: Percutaneous nephrostomy in the management of malignant ureteral obstruction secondary to bladder cancer. J Endourol 15: 827-829, 2001.

452. Alberti C, Tizzani A, Piovano M, et al: What's in the pipeline about bladder reconstructive surgery? Some remarks on the state of the art. Int J Artif Organs 27: 737 – 738, 2004.

453. Oosterlinck W, Lobel B, Jakse G, Malmstrom PU, Stockle M, Sternberg C; European Association of Urology (EAU) Working Group on Oncological Urology. Guidelines on bladder cancer. Eur Urol. 2002 Feb;41(2):105-12.

Committee 8

Urothelial Carcinoma of the Prostate

Chair

J. Palou (Spain)

Members

J. Baniel (Israel)

L. Klotz (Canada)

D. Wood (USA)

M. Cookson (USA)

S. Lerner (USA)

S. Horie (Japan)

M. Schoenberg (USA)

J. Angulo (Spain)

P. Bassi (Italy)

CONTENTS

Urothelial Carcinoma of the Prostate

J. Palou

J. Baniel, L. Klotz, D. Wood, M. Cookson, S. Lerner, S. Horie, M. Schoenberg
J. Angulo, P. Bassi

I. ANATOMICAL AND HISTOPATHOLOGICAL BACKGROUND

1. Background

The prostate is a single midline organ situated under the bladder base. In 1953, Gil Vernet divided the prostate into cranial, caudal, and intermediate portions, according to the location of the glandular duct openings in the urethral lumen (*Level 3,* [1]). McNeal later proposed a topographical description similar to that of Gil Vernet (*Level 3,* [2]). He divided the glandular zones into central (25%), transitional and periurethral - close to the verumontanum - (5%-10%), and peripheral (65%-70%). These glandular groups are formed by acini and excreting ducts and surrounded by connective stroma and smooth muscle fibers (*Level 3,* [3]). The glands drain to the posterior aspect of the prostate near the verumontanum.

The fundamental histological structure of the gland is a double cell layer with secreting cells close to the lumen and basal cells close to the basal membrane contiguous with the prostatic stroma.

Urothelial carcinoma of the prostate may originate from the mucosa that covers the prostatic urethra or in the prostatic ducts. The tumor may progress via the prostatic ducts to involve acini and prostatic stroma **(Figure)**. Prostatic urethral involvement usually arises by direct extension from bladder cancer with surface down-growth or implantation from tumors in the bladder. Furthermore, urothelial carcinoma may originate multifocally and separately, involving both prostatic urethra and bladder.

Rarely, however, prostatic ductal, acinar, or stromal involvement is identified in the absence of urothelial carcinoma in the prostatic urethra or bladder. Ende et al. hypothesized that urothelial carcinoma originates in the periurethral and prostatic ducts at the juncture of the columnar and transitional epithelium (*Level 3,* [4]). A diagnosis of primary urothelial carcinoma of the prostate requires excluding CIS or urothelial carcinoma of the bladder.

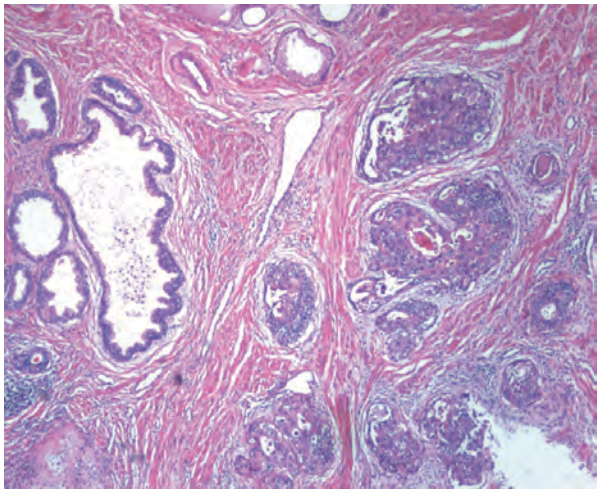


Figure. Urothelial Carcinoma Involving the Prostatic Stroma (Courtesy of Dr. Merce Jorda)

Urothelial carcinoma of the prostate may also occur by direct extension of an invasive bladder cancer through the bladder wall.

Since urothelium (transitional cell epithelium) lines the prostatic urethra, it is logical that it has the same etiological factors as urothelial carcinoma of the bladder (*Level 3,* [5]).

2. Classification of Urothelial Carcinoma of the Prostatic Urethra

According to studies that have evaluated the rela-

tionship between anatomical extent and prognosis, the main anatomical landmark for tumor spread in urothelial carcinoma of the prostate is the basement membrane of the prostatic urethra, periurethral glands, and prostatic ducts or acini (*Level 3,* [6-13]).

Schellhammer et al. elaborated a classification (**Table 1**) based on the microscopic extent of prostatic involvement by urothelial carcinoma (*Level 3,* [6]). When the neoplasia did not invade the basal membrane and prostatic stroma was not involved, prostatic involvement did not alter the prognosis. Tumors invading the basal membrane were not amenable to cure with endovesical therapy and were associated with an aggressive and lethal phenotype. They advocated that the staging of bladder carcinoma should include independent evaluation and staging of prostatic lesions. Kirk proposed a new classification (**Table 2**) that grouped tumors as superficial (i.e., that did not affect the basal membrane) or invasive (Groups 1 and 4) (*Level 3,* [7]). The poor prognosis associated with invasion has been described by Whitmore and Marshall and Greene and colleagues (*Level 3,* [8,9]).

Table 1. Microscopic Pattern of Prostatic Involvement by Urothelial (Transitional Cell) Carcinoma According to Schellhammer et al. [6]

1. Ductal disease	A. Without stromal invasion
	B. With stromal invasion
2. Glandular and ductal disease	A.Without stromal invasion
	B. With stromal invasion
3. Stromal invasion exclusively	

Chibber et al. identified 3 categories (**Table 3**) (*Level 3,* [10]). He stressed the importance of correctly evaluating the extent of prostatic involvement. In 1988, Hardeman and Soloway presented a new classification (**Table 4**) with a more logical histopathologic approach, considering mucosa, ducts, and stroma of the prostate (*Level 3,* [11]). TNM staging of bladder cancer defines invasion of the prostate by urothelial carcinoma as T4a (**Table 5**) [12]. The different level of involvement of the prostatic urethra by urothelial carcinoma is clarified in the explanatory notes of the TNM staging. There is a separate staging system for urothelial carcinoma involving the prostate that is not contiguous with the primary bladder lesion **(Table 6)**. The extension of the associated in situ component into the prostate does not qualify for classification as T4. It may be indicated by the suffix "(is)", e.g., T2 (is).

It may be further indicated by the suffix "(is pu)" (extension into the prostatic urethra) or "(is pd)" (extension into the prostatic ducts), e.g., T2 (is pu) or T2 (is pd). Invasion of the prostatic urethra (extension of invasive urinary bladder carcinoma into the prostatic urethra with invasion of the latter) is included in prostatic invasion and therefore classified as T4a in the bladder TNM. Direct invasion of the large or small intestine should be classified as T4a. The same applies to invasion through the peritoneum covering the bladder. Invasion of seminal vesicles by bladder tumors should be classified as T4a [13].

Pagano et al. defined the impact of prostate involvement and the degree of prostate invasion on survival rate (**Table 7**) (*Level 3,* [14]). The patients were divided into 2 groups: (1) contiguous involvement, defined as urothelial carcinoma of the bladder extending into the prostate through the bladder wall and (2) noncontiguous, defined as the simultaneous presence of urothelial carcinoma of the prostate and bladder, the latter not directly infiltrating into the prostate. In the noncontiguous group, stage was also classified as urethral mucosa, ductal or acinar, stromal, and extracapsular (**Table 7**). Donat et al. described another pattern of prostatic stromal invasion through the bladder neck directly into the prostatic stroma (*Level 3,* [15]).

Esrig et al. confirmed the difference in survival between contiguous and noncontiguous prostatic stromal invasion (*Level 3,* [16]). They also combined prostatic and bladder staging in order to improve the prognostic value of the pathological classification. These comparisons are based on a limited number of patients in each group. This group proposed a definition of pT4a as contiguous stromal invasion, to be differentiated from pT3b of the bladder plus noncontiguous stromal invasion. Superficial or muscle-invasive bladder cancer (pT3a or less) and noncontiguous prostatic invasion had a prognosis defined by the bladder stage. These authors suggested a modified staging system based on the primary bladder tumor with a subcategory of prostatic urethral involvement or prostatic stromal invasion. They proposed to define pT1str (stromal invasion plus T1 in the bladder) or pT2str (stromal invasion plus pT2 in the bladder) in order to categorize the disease more accurately.

Volkmer et al. analyzed in more detail those patients

Table 2. Prostatic Involvement by Urothelial (Transitional Cell) Carcinoma – Classification Proposed by Kirk et al. [7]

Group 1	Invasion of prostate by a bladder tumor
Group 2	Previous bladder tumor: prostatic recurrence
Group 3	Diffuse CIS
Group 4	Primary prostatic tumor

Table 3. Classification of Prostatic Urothelial Carcinoma According to Chibber et al. [10]

Group 1	CIS of prostatic urethra and ducts, with or without similar disease in the bladder
Group 2	Superficial papillary bladder tumor of prostatic urothelium and major ducts with similar bladder tumor
Group 3	Invasive tumor of bladder base and neck with prostatic extension

Table 4. Classification of Prostatic Involvement According to Hardeman and Soloway [11]

Stage 1	Tumor confined to prostatic urothelium
Stage 2	Invasion of ducts and acini, but confined to the basal membrane
Stage 3	Stromal invasion

Table 5. TNM Classification (1997) of T4 Urothelial (Transitional Cell) Carcinoma of the Bladder [12]

T4	Tumor invades any of the following: prostate, uterus, vagina, pelvic wall, abdominal wall
	T4a Tumor invades prostate or uterus or vagina
	T4b Tumor invades pelvic wall or abdominal wall

Table 6. TNM (1997) Classification of Prostatic Urothelial (Transitional Cell) Carcinoma [13]

Tis pu	CIS, affecting prostatic urethra
Tis pd	CIS, affecting prostatic ducts
T1	Tumor invading subepithelial connective tissue
T2	Tumor invading prostatic stroma, spongiosum body, or periurethral muscle
T3	Tumor invading cavernous body prostatic capsule or bladder neck (extraprostatic extension)
T4	Tumor that invades surrounding organs

Table 7. Classification of Involvement of the Prostate According to Pagano et al. [14]

Stage	**Patients (%)**	**Survival (%)**
Contiguous	44 (61)	7
Noncontiguous	28 (39)	46
Urethral mucosa	6	100
Ductal/acinar	14	50
Stromal	8	40
Extracapsular invasion	0	-

with an extravesical or contiguous pattern of prostate invasion and found that seminal vesicle invasion had a worse prognosis than prostate invasion alone (*Level 3,* [17]). Daneshmand et al. suggested that seminal vesicle invasion would better be classified as T4b, since these patients had a poor disease-specific survival (*Level 3,* [18]).

Summary

Several different classifications have been published regarding the level of involvement of the prostate by urothelial carcinoma. The classifications reflect the involvement of mucosa, ducts, and stroma. Stromal invasion may be contiguous (through the bladder wall) or noncontiguous (not directly infiltrating into the prostate from the bladder).

The TNM classification of urothelial carcinoma of the bladder defines pT4a as prostatic stromal invasion. When involvement of the prostate is superficial only, the classification refers to the bladder tumor stage only. In these cases, a suffix must be added to include information about prostatic involvement, such as T2 (is pu).

II. SUPERFICIAL UROTHELIAL CARCINOMA AND CARCINOMA IN SITU OF THE PROSTATIC URETHRA

1. INCIDENCE

a) Primary or Recurrent Tumor

Ortega et al. were the first to describe carcinoma "in situ" (CIS) of the prostatic urethra in 1953 (*Level 3,* [19]). In approximately 90% of the cases, CIS is associated with a papillary or solid tumor. However, in about 10% of cases, it may present as an isolated lesion. It is often diagnosed in the context of multifocal disease of the bladder (*Level 3,* [20,21]). Prostatic urethra involvement by CIS is relatively rare (*Level 3,* [22]). Its' prevalence and significance has been clarified by the use of routine random biopsies including the prostatic urethra in patients with superficial bladder tumors or positive urine cytology. In 1529 patients with primary bladder tumors that had random biopsies, 19% had carcinoma in situ., and 2.7% had CIS in the prostatic urethra (*Level 3,* [23]). Secondary tumor involvement of the prostatic urethra and ducts in bladder cancer may be detected in 10% to 15% of patients with high-risk superficial bladder disease within 5 years and in 20% to 40% within 15 years (*Level 3,* [24-26]). The majority of patients also relapse in the bladder (*Level 3,* [25]).

b) Cystectomy Specimens

Most reports of prostatic urethral involvement at the time of radical cystectomy are not only retrospective but lack careful pathologic assessment of the prostate and thus are likely to underreport the true incidence of involvement with urothelial carcinoma. However, the incidence of prostatic urethral involvement approaches 50% in series where detailed pathologic assessment of the prostate is performed. Wood et al. reported a 43% incidence of urothelial carcinoma of the prostate in cystectomy specimens (*Level 3,* [27]). In this series, 94% of those with prostatic involvement had disease present in the prostatic urethra, including 67% with CIS of the prostatic ducts or acini. Risk factors included CIS of the bladder neck or trigone, prior intravesical therapy, and ureteral involvement by urothelial carcinoma. In a prospective pathologic assessment, Revelo et al. reported results of 121 consecutive cystoprostatectomy specimens analyzed by whole mount (*Level 3,* [28]). Of 121 prostates, 58 (48%) had urothelial carcinoma involving the prostatic urethra, of which 19 (33%) had apical involvement. All patients with prostatic apical involvement by urothelial carcinoma uniformly had involvement of more proximal (toward the base) portions of the prostate. These results validate the concept of cystoprostatectomy.

Nixon et al. reviewed 192 consecutive radical cystectomy specimens and noted prostatic urethral involvement in 30 (15.6%) specimens (*Level 3,* [29]). Of patients with CIS in the bladder specimen, 31.3% (25/80) had prostatic urethral involvement. Similarly, 34.7% (25/72) with multifocal urothelial carcinoma of the bladder had prostatic urethral involvement. Multivariate analysis revealed the risk of prostatic urethral involvement to be 12- to 15-fold higher if CIS or multifocal urothelial carcinoma of the bladder was present.

Esrig et al. analyzed their findings of prostatic involvement in 143 of 489 cystectomy specimens (*Level 3,* [16]). Nineteen cases showed direct penetration from bladder to prostate and had a bad prognosis. The remaining 124 patients had different stages of indirect prostatic involvement. Thirty-seven had low grade tumor or CIS and 29 had pro-

static disease involving the ducts only; these patients had a relatively good prognosis.

2. Diagnosis of Superficial Urothelial Carcinoma or CIS in the Prostatic Urethra

The staging of bladder carcinoma should include independent evaluation and staging of any prostatic lesions (**Tables 4 and 6**) (*Level 3,* [6]). Involvement of the prostate by CIS is almost always associated with bladder CIS (*Level 3,* [30]).

Superficial disease in the prostate is sometimes evident as a papillary tumor. More commonly, it is silent and insidious with no evidence of macroscopic disease.

Urothelial (transitional cell) carcinoma of the prostate is often understaged; careful selection and correct diagnosis has to be achieved in order to avoid progression due to undetected stromal invasion (*Level 3,* [16,25]). Once stromal invasion is detected, the management changes completely *(see Section III. Prostatic Stromal Invasion)*.

Cystoscopy is a valuable measure of prostatic urethral involvement in macroscopic lesions, with a sensitivity of 83.3% and specificity of 95.1% (*Level 3,* [29]). But it is not always a valuable tool; in patients with recurrent superficial urothelial disease after BCG treatment, when considering suspicious or visible lesions, Orihuela et al. had a 48% negative biopsy rate (*Level 3,* [31]).

CIS in the prostatic urethra is common in high-risk superficial bladder cancer (9%-25%), and can evolve to prostatic stromal disease (*Level 3,* [32]). Rikken et al. stress the need to perform a biopsy of the prostatic urethra in every patient with high grade superficial bladder cancer, with the intention of identifying patients with tumors in that location to allow better therapeutic planning (*Level 3,* [20]). Eight of 9 patients with CIS of the prostatic urethra have coexistent CIS in the bladder.

Resectoscope loop biopsies of the prostatic urethra are taken from the lateral lobes and floor beginning distal to the bladder neck and extending just proximal to the verumontanum. In 1 study, 76.5% of 17 prostatic urethral biopsies contained identifiable prostatic ducts, and ductal urothelial carcinoma was identified in 7 [33].

Hillyard et al. recommended taking a biopsy of the prostatic urethra with the resectoscope loop from the lateral lobes distal to the bladder neck and performing a complete resection of the prostatic urethra (*Level 3,* [34]). Bretton et al. also recommended performing a complete resection with 1 to 3 passes and separate identification to determine the extent of prostatic involvement (*Level 3,* [35]). In a prospective histopathologic study by Sakamoto et al., 31 of 134 cystoprostatectomy specimens in patients with primary bladder cancer revealed prostatic involvement (*Level 3,* [36]). They differentiated between superficial (periurethral) and deep prostatic glands and demonstrated that there was prostatic urothelial carcinoma involvement of superficial glands around the verumontanum in 93% of the cases, and at 5 and 7 o'clock in 84%; only 1 patient had deeper gland involvement without superficial gland involvement.

The only way to approach 100% accuracy would be to perform an extensive transurethral resection of the prostate, an impractical approach for routine staging of patients with bladder cancer (*Level 3,* [21]). Multiple random biopsies of the bladder and prostatic urethra is not recommended as a normal routine in superficial bladder cancer. There is a very low incidence of CIS in that location, but this means that CIS of the prostate will be undetected in patients with primary bladder tumors (*Level 3,* [21]). Solsona et al. recommended a prostatic biopsy in patients with positive cytology or in those with macroscopic lesions in the prostate (*Level 3,* [21]).

Donat et al. reported a 39% rate of prostate relapse in patients with superficial bladder cancer (*Level 3,* [15]). They recommended a systematic transurethral loop biopsy extending through the bladder neck, trigone, and prostatic urethra, and ultrasound-guided biopsy of the prostate to evaluate patients with high grade superficial disease; they do not justify the proposed timing or frequency (**Table 8**).

Survival is optimized if radical treatment precedes stromal invasion (*Level 3,* [25]). The detection of prostatic relapse, particularly early stromal invasion, is difficult. That is why frequent and lifelong biopsies of the bladder neck and prostate are recommended in patients with recurrent high grade papillary and in situ tumors of the bladder (*Level 3,* [25]).

3. Treatment

a) General Comments

The prognostic implications of detecting CIS of the prostatic urethra are defined by the risk of progression (*Level 3,* [32]). Some authors feel that this finding mandates the need to offer radical cystoprostatectomy as primary therapy (*Level 3,* [33,37]). Esrig et

Table 8. Incidence of Tumor in the Prostatic Urethra in the Follow-up of Superficial Bladder Carcinoma

	Patients	Tumor in the prostatic urethra	Follow-up
Herr and Donat, 1999 [25]	186	39% 62% noninvasive 38% stromal inv.	15 years
Hardeman et al., 1988 [11]	63	16%	43 months
Solsona et al., 1991 [21]	276	13.3%	34.3 months

al. analyzed their findings of prostatic involvement at radical cystectomy; 37 of their patients with low grade tumors or CIS and 29 with ductal only prostatic disease had a relatively good prognosis (*Level 3,* [16]).

Both the prostatic urethra and distal ureter have been considered extravesical locations of urothelial neoplasms that cannot be managed with intravesical therapy. Since Morales introduced bacillus Calmette-Guérin (BCG) as intravesical therapy of superficial urothelial carcinoma of the bladder, several authors have evidenced its efficacy both on bladder CIS and on CIS of the prostatic urethra (*Level 3,* [6,38-41]).

Superficial tumors of the prostate can be treated conservatively if they are completely resected and treated with intravesical instillations. TUR with intravesical BCG provides a significantly better prophylaxis of tumor recurrence in Ta and T1 bladder cancer than TUR alone (*Level 2,* [42]). However, topical antineoplastic agents may not gain sufficient access to the prostatic urothelium (*Level 3,* [43]). In a few patients, there is contact of the chemotherapeutic agent with the prostatic urethra, but in the majority it is only during micturition. In a non-randomized study comparing BCG and epirubicin, there seemed to be a better prostate response to BCG (*Level 3,* [43]).

Hillyard et al. advocates radical surgery in patients with ductal and stroma involvement; however, this is not justified with numbers (*Level 3,* [34]). Solsona et al. also advocated radical surgery in patients with ductal involvement (*Level 3,* [44]). Although it seems that these patients do worse with conservative treatment, this is likely due to selection bias (**Table 9**).

b) BCG Penetration in the Prostatic Urethra

There is not complete agreement on the degree of BCG penetration of the prostatic urethra in bladder instillations. Some authors propose a primary resection of the bladder neck to obtain direct contact between the drug or immunotherapy and the prostatic urothelium [10,11,40]. Several studies on the prostatic tissue of patients who received BCG without prior resection of the prostate have demonstrated the presence of granulomas, indicating that BCG penetrates into the prostate (*Level 3,* [45-47]). Oates et al. performed biopsy in 13 of 32 patients that received BCG because a prostatic nodule or enhanced consistency of the gland was palpated, and granulomas were found in all of them (*Level 3,* [45]). Mukamel et al. diagnosed granulomas in 40% of the patients and distinguished an early period (1.5-3 months after BCG) during which these granulomas formed caseum (*Level 3,* [46]). At a later stage (4-14.5 months after BCG) they did not. Hillyard et al. performed several cystograms in patients without resection of the bladder neck or prostate and only occasionally observed contrast medium in the prostatic urethra (*Level 3,* [34]). However, patients with previous TUR of the prostate show good opening of the bladder neck on the one hand, and reflux to the prostatic ducts on the other. Both changes could facilitate the penetration of BCG into the prostatic gland.

Leibovici et al. found a clinically significant elevation of prostate specific antigen (PSA) in 41.6% of the patients receiving BCG therapy, which reverted to normal in 3 months (*Level 3,* [48]). In a recent study, the variation of PSA levels following instillation of BCG was evaluated (*Level 3,* [49]). The vari-

Table 9. Response to BCG in Patients with Ductal Involvement

	Patients	Response (%)
Bretton et al., 1989 [35]	4	3 (75)
Schellhammer et al., 1995 [33]	7	4 (57)
Hardeman et al., 1988 [11]	7 4 radical surgery 3 conservatively	2 (66)

ation was higher in patients that had previously undergone TUR of the prostate (**Table 10**), which may be related to better penetration of BCG into the prostate. Given these results, resection of the bladder neck or prostate is advisable, with separate superficial and deep sampling at 5 and 7 o'clock on both sides of the verumontanum. This allows better initial staging and gives the best chance to detect prostatic duct involvement. This maneuver will also facilitate penetration of BCG in the prostate.

Table 10. Total PSA Values During BCG Instillations in Patients With and Without TURP [49]

	TURP	No TURP
Before BCG	1.2	2.1
1st instillation	7.7	3.4
2nd instillation	10.9	3.5
3rd instillation	8.8	3.8
4th instillation	7.1	4.5
5th instillation	6.2	4.7
One month	5.3	4.7
Three months	3.5	3.2

c) BCG Treatment

The response rate of bladder CIS to BCG immunotherapy is approximately 70%. When only the mucosa of the prostatic urethra is involved, this form of prostatic involvement should also respond to BCG. In fact, treatment of CIS of the prostatic urethra associated with superficial bladder tumor has resulted in complete response rates of 70% to 100% in the prostatic urethra and 47% to 72% when both the bladder and prostate are considered (**Table 11**).

In the series of Bretton et al., therapeutic failure has always been evidenced as disease progression in the bladder; they believe that transurethral resection of the prostate contributed significantly to the successful control of tumor in the prostatic urethra (*Level 3,* [35]). Hillyard et al. described 2 cases in which radical cystoprostatectomy was performed to treat tumor progression in the prostatic urethra or due to progression in the bladder (*Level 3,* [34]). Schellhammer et al. reported an update of the series of Hillyard et al. and described persistence or recurrence of disease in 9 of 17 patients (*Level 3,* [33]). Seven were treated with radical surgery. Four presented with recurrence or progression in the bladder, 1 in the prostate and 2 in both bladder and prostate. They obtained good results in 8 of 10 patients with mucosal carcinoma and in 4 of 7 patients with ductal involvement. Therefore, a more aggressive approach is warranted in cases with ductal or acinar involvement.

In a series of 33 patients, general progression of disease was evidenced in 8 cases, 3 of them at the prostatic urethra (*Level 3,* [51]). The therapeutic response of this form of disease reaches 70%, while the global vesicoprostatic response is only 40%. Therefore, the results support the view that BCG is a valid option to treat carcinoma in situ of the prostatic urethra even without previous transurethral resection and that it achieves an improved response. However, with longer follow-up, disease progression occurs in 24% of the cases. These patients have a high disease-specific mortality. A good staging should be initially performed, comprising a transurethral resection of the prostate, together with strict follow-up and aggressive management of recurrence or persistence of ductal disease.

Very few cases of recurrence in the prostatic urethra after BCG failure have been treated conservatively. Orihuela et al. treated 5 patients, and only 2 patients with papillary lesions sustained complete response (*Level 3,* [31]). The other 3 patients with CIS or high grade tumors recurred and progressed. Hardeman and Soloway had 2 patients with ductal invasion after BCG - one had no disease after radical surgery and the other had persistence (*Level 3,* [11]).

Initial management of superficial prostatic urethral disease with endovesical treatment with BCG has reasonably good results with a response rate of approximately 70%. Patients who progress and those with urothelial carcinoma of the bladder undergoing radical cystectomy should be considered for prostatectomy as well, given the high degree of prostatic involvement (*Level 3,* [27-29]).

4. Follow-up of the Prostatic Urethra

With increasing number of patients receiving initially longer courses of intravesical therapy for high grade superficial bladder cancer or CIS rather than radical surgery, there will be an increased number of patients at risk of developing urothelial carcinoma of the prostate. Urothelial carcinoma of the prostate may occur in 8% to 48% of patients (*Level 3,* [27-29,31,34,35]). Prostatic urethral involvement tends to be more common in patients with CIS of the bladder, as well as those with multifocal tumors and involvement of the bladder neck (*Level 3,* [27,29,31,35]).

Table 11. Reported Series of CIS of the Prostatic Urethra in Patients with Superficial Bladder Tumors

Author (year)	N	%	Response % Global / prostate	Follow-up (months)	TURP
Breton et al., 1989 [35]	23	8.7	56/100	42	
Hillyard et al., 1988 [34]	8	28	62,5/75	22.3	Yes
Rikken et al., 1987 [20]	9	18	--/--	--	
Ovesen et al., 1993 [50]	1	23.8	--/80	26	Yes
Schellhammer et al., 1995 [33]	17	0.5	47/70	64	No
Palou et al., 1995 [42]	18	8.6	77.7/83.3	31.1	No
Palou et al., 2001 [51]	33	20.7*	39.4/69.6	64	No

* incidence in patients with bladder CIS

In the series of Herr and Donat, with a minimum follow-up of 15 years, 39% of patients with superficial bladder cancer (72% with associated CIS treated with BCG) relapsed in the prostate at a median follow-up of 28 months (*Level 3,* [35]). In 62%, the tumors were noninvasive and in 38% there was stromal invasion.

Solsona et al. strongly recommend frequent random biopsies of the prostatic urethra during initial and repeated cystoscopic examinations (*Level 3,* [21]). Details of frequency and technique were not provided.

For patients with positive cytology in follow-up in the absence of macroscopic bladder carcinoma, it is mandatory to evaluate the bladder and the prostatic urethra with multiple biopsies (*Level 3,* [21]). With a positive cytology during the first 6 months of follow-up after conservative management of a superficial bladder carcinoma, bladder recurrence is most likely to be the cause (*Level 3,* [52]). The prostatic urethra should be considered if there has been associated carcinoma in situ, tumor near the bladder neck, or multifocal disease (*Level 3,* [29,35,53]). If positive cytology appears in longer term follow-up, the upper urinary tract should be evaluated (*Level 3,* [54]).

Summary

The incidence of prostatic involvement in primary superficial bladder tumors is low. The risk increases with multifocality or CIS of the bladder.

Any suspicious lesion in the prostatic urethra should be biopsied. When superficial disease is diagnosed, intravesical instillations with BCG should be offered.

In patients with prostatic duct involvement, there is insufficient data to support conservative treatment. In the follow-up of superficial high grade carcinoma or CIS of the bladder, biopsies of the prostatic urethra should be undertaken if bladder recurrence or positive cytology occurs.

III. PROSTATIC STROMAL INVASION

1. INCIDENCE

The incidence of prostatic stromal invasion by urothelial carcinoma of the prostate may be related to the extent of pathologic evaluation of the radical cystectomy specimen.

Most reports of prostatic urethral involvement at the time of radical cystectomy are not only retrospective, but lack careful pathologic assessment of the prostate. Underreporting of the true incidence of prostatic involvement is common.

Series of patients who underwent cystectomy for urothelial carcinoma of the bladder report an incidence of urothelial carcinoma of the prostate from 12% to 48% (**Table 12**) with stromal invasion in 7.6% to 16.6% [6,14,16,25,27-29,55-57].

Wood et al. performed a prospective study to identify urothelial carcinoma of the prostate in patients undergoing radical cystectomy for bladder cancer (*Level 2,* [58]). Twenty-five men underwent a transurethral resection of the prostate, prostate needle biopsy, and fine-needle aspiration of the prostate prior to radical cystectomy. Of the 10 (40%) patients

Table 12. Incidence of Urothelial Carcinoma of the Prostate in Cystectomy Specimens

Author	Journal	Year	Patients	TCC in prostate (%)
Schellhammer et al. [6]	J Urol	1977	300	12
Coutts et al. [55]	Brit J Urol	1985	43	23
Wood et al. [27]	J Urol	1989	84	36
Reese et al. [56]	J Urol	1992	115	29
Pagano et al. [14]	J Urol	1996	570	13
Esrig et al. [16]	J Urol	1996	489	29.2
Herr et al. [25]	J Urol	1999	186	39
Njinou et al. [57]	J Urol	2003	283	27
Revelo et al. [28]	J Urol	2004	121	48
Nixon et al. [29]	J Urol	2002	192	15.6

with urothelial carcinoma of the prostate, 5 (25% of total) had stromal invasion.

Revelo et al. reported the results of 121 consecutive cystoprostatectomy specimens analyzed by whole mount (*Level 3,* [28]). Of 121 prostates, 58 (48%) had urothelial carcinoma involving the prostate with stromal involvement in 24 and noninvasive urothelial carcinoma or CIS/severe dysplasia in the prostatic urethra or periurethral ducts in 34. Nineteen (33%) had apical involvement. All patients with prostatic apical involvement by urothelial carcinoma had involvement of more proximal (toward the base) portions of the prostate.

The prostate is a site of relapse for patients with superficial bladder cancer who have been treated with intravesical therapy. Herr et al. found that of those patients who underwent cystectomy after intravesical treatment with BCG and had prostatic recurrence, 38% had stromal invasion and 62% had noninvasive urothelial carcinoma of the prostate (*Level 3,* [25]).

The prostate is a site of relapse for patients with superficial bladder cancer who have been treated with intravesical therapy. Herr et al. evaluated 186 consecutive men with superficial bladder tumors who were treated with transurethral resection and BCG therapy (*Level 3,* [25]). Thirty-nine percent of the patients relapsed in the prostate: 38% had stromal invasion and 62% had noninvasive urothelial carcinoma. Hardeman et al. reported that 5 of 63 male patients treated with intravesical therapy for superficial bladder cancer developed prostatic stromal invasion (7.9%) (*Level 3,* [60]).

2. Diagnosis

Donat et al. evaluated 416 male patients who underwent radical cystectomy; 246 of these men had transurethral biopsies of the prostatic urethra (*Level 3,* [59]). The sensitivity of transurethral biopsy for prostatic stromal invasion was 53% and the specificity was 77%, for a positive predictive value of 45% and negative predictive value of 82%. Wood et al. evaluated transurethral resection biopsy of the prostate, prostate needle biopsies, and fine needle aspirations of the prostate to identify urothelial carcinoma of the prostate in 25 consecutive men undergoing radical cystectomy for invasive bladder cancer (*Level 2,* [58]). These authors reported a 40% incidence of prostatic involvement by urothelial carcinoma. The accuracy of transurethral biopsies of the prostatic urethra was highest at 90%, followed by 40% for fine needle aspiration and 20% for transrectal needle biopsies. The accuracy of detecting stromal invasion, however, was poor for all 3 modalities. Transurethral resection biopsy of the prostate and fine needle aspiration identified 2 of 5 patients with stromal invasion, and needle biopsies of the prostate identified only 1 of 5 patients with prostatic stromal invasion.

3. Prognostic Factors Predictive of Prostatic Stromal Invasion

There are no articles evaluating prognostic factors and the risk of prostatic stromal invasion. Numerous articles evaluate prognostic factors and the development of prostatic urethral involvement, but not specifically prostatic stromal invasion. Wood et al.

identified carcinoma in situ of the trigone, bladder neck, periurethral structures, and ureter and use of intravesical chemotherapy as predictors of prostatic urethral involvement (*Level 3,* [27]). Nixon et al. reviewed a series of 192 cystectomies (*Level 3,* [29]). Of the patients with CIS of the bladder, 31.3% had concomitant urothelial carcinoma of the prostate, whereas only 4.5% of the patients with no bladder CIS had prostatic urethral involvement. Likewise, 34.7% with multifocal tumors had prostatic involvement compared to 4.2% in patients with no multifocality. Stromal invasion was not addressed.

4. TREATMENT

a) Cystectomy

Historically, the outcome following radical cystectomy for T4 disease was exceedingly poor with 5-year survival probabilities of less than 10%. Improvements in perioperative and postoperative care, recognition of the importance of the node dissection, and the use of perioperative chemotherapy to reduce the risk of progression have led to modest improvements in the long-term survival of patients with prostatic stromal invasion. In patients who are surgical candidates, radical cystoprostatectomy is the treatment of choice, as durable cancer control rates with radiation with or without radiosensitizing chemotherapy are poor, and there are too few patients treated on clinical trials of trimodal therapy to determine the efficacy of this approach for T4a disease (discussed below).

1. OUTCOME ANALYSIS - DISEASE-FREE AND OVERALL SURVIVAL

Survival probability following cystectomy is influenced by the path of prostate stromal invasion, the degree of prostate stroma invasion (superficial or deep), and the presence or absence of lymph node metastases. Prostate stromal invasion can occur via direct extension into the prostate contiguous with the bladder primary or by invasion via the prostatic urethra, separated in space from the bladder primary. Two important papers published in 1996 call attention to the degree and pattern of prostate involvement. Esrig and colleagues from USC studied 146 patients with prostate involvement following radical cystectomy (*Level 3,* [16]). Nineteen patients had direct extension from the bladder tumor into the prostate (the less common route). The 5-year survival probability for this group was 21% compared to 36% for the 58 patients with prostate invasion via the prostatic urethra. For this latter group, survival was further influenced by the primary bladder tumor stage where patients with pT1 bladder tumors and stromal invasion had a significantly better survival of 65% versus 21% for patients whose bladder tumor directly invaded the prostate (pT4a). Patients with pT2 to pT3b bladder tumors and prostatic stromal invasion had a similar 5-year survival to patients with pT4a tumors. The 5-year survival for patients with only CIS of the urethra or ducts was determined by the pathologic stage of the primary bladder tumor and node status. Pagano et al., from University of Padova in Italy, described outcomes for 72 patients following radical cystectomy. Survival with direct involvement of the prostate stroma via the bladder neck was 7% versus 40% for patients with stromal invasion that was not contiguous with the bladder primary (via the prostatic urethra) (*Level 3,* [14]). In a contemporary analysis, Ngninkeu et al. reported similar findings regarding the pattern of invasion on 76 patients with prostatic urothelial carcinoma (*Level 3,* [57]). The 5-year survival following cystectomy for patients with direct extension was 22% versus 43% for patients with invasion via the prostatic urethra.

Recent studies utilizing whole mount step section analysis indicate a potential stratification scheme for prostatic invasion via the prostatic urethra. Patients with superficial involvement of the stroma (equivalent to lamina propria involvement) have a less aggressive biology compared to patients with established, or deep, involvement of the prostatic stroma.

2. EXTENT OF PELVIC LYMPHADENECTOMY

Lymph node metastases occur in 40% to 50% of patients with prostatic stroma invasion and have a profound negative effect on survival (*Level 3,* [61,62]). Survival estimates in the studies discussed above were 44% to 61% for patients who were node-negative versus 13% to 34% for patients who were node-positive [16,57]. In the contemporary series from USC, Stein and colleagues reported on 79 pT4 patients with node-negative disease with 44% and 23% 5-and 10-year overall survival, respectively. Of 58 patients with pT4a disease and nodal metastases, survival probabilities were 26% and 20%, respectively [63].

Recent studies report data strongly suggesting that the number of nodes removed has a direct impact on survival in both node-negative and node-positive patients (*Level 3,* [64,65]). The ratio of positive nodes to the total number of nodes removed or the so-called “lymph node density” may provide a more

accurate means of assessing prognosis as it accounts for both the number of positive nodes as well as the total number of nodes removed (*Level 3,* [66,67]). This latter variable is affected both by the pathologist's ability to identify and count nodes and the extent of the lymphadenectomy (*Level 3,* [68]). In a recent study of patients with muscle-invasive bladder cancer who underwent radical cystectomy in the SWOG intergroup trial, there was a significantly longer survival if 10 or more nodes were removed at cystectomy (HR 0.51, $P = 0.0001$) (*Level 2,* [69]). The quality of surgery really is an independent prognostic factor for outcome.

Two published mapping studies provide important data regarding the incidence and location of node metastases in patients with pT4 disease. Leissner et al. reported results of a prospective multi-center study of 290 patients who underwent extended lymphadenectomy, including 20 patients with pT4a and pT4b disease, of whom 40% and 80%, respectively, had node metastases (*Level 3,* [62]). Stage-specific data were not reported; however, 7% of patients overall had node metastases in the common iliac or presacral region only, indicating the importance of including these fields in the dissection in order to accurately assess the presence of and the extent of nodal disease.

Vazina and colleagues reported on a series of 176 consecutive patients operated on by a single surgeon, 90% of whom had an extended node dissection that included the common iliac and presacral nodes in all patients (*Level 3,* [61]). Stage specific maps were constructed. One-half of the 24 patients with pT4 disease had positive nodes. Presacral, right and left common iliac, and aortic nodes were positive in 8.3%, 16.7%, 25%, and 8.3% of patients, respectively. In the overall study, 51% of patients with positive nodes had these in multiple sites.

b) Chemotherapy

Systemic chemotherapy may be used as monotherapy or as an adjunct to locoregional therapy, either radical cystectomy or radiation. The results from clinical trials utilizing a single agent such as cisplatin as adjuvant therapy or for treatment of measurable metastatic disease are clearly inferior to results using multi-agent regimens (*Level 1,* [70,71]). The role of neoadjuvant and adjuvant chemotherapy is discussed in other chapters and the results of neoadjuvant chemotherapy as applied to prostatic stroma invasion are discussed below.

1. Neoadjuvant Chemotherapy

Neoadjuvant trials utilizing chemotherapy (M-VAC) followed by cystectomy clearly demonstrate that a portion of patients could be managed by transurethral resection and chemotherapy alone for control of locoregional disease as evidenced by the findings of negative lymph nodes and pT0 in the cystectomy specimen. In the recently reported SWOG trial comparing 3 cycles of neoadjuvant M-VAC followed by cystectomy versus cystectomy alone, 48 of 126 (38%) patients in the neoadjuvant chemotherapy arm had no residual disease in the cystectomy specimen including 30% of patient with T3 or T4a disease (*Level 1,* [72]).

Chemotherapy as monotherapy has been studied in a limited fashion but conceptually it can be considered in highly selected patients who are able to comply with a rigorous follow-up schedule and have organ function that permits full-dose cisplatin-based therapy. Sternberg et al. treated 104 consecutive patients with T2 to T4N0M0 tumors (8 had T4 disease) with 3 cycles of M-VAC (*Level 3,* [73]). Depending on the response, subsequent treatment was transurethral resection (TUR), partial cystectomy, or radical cystectomy. Of the 52 patients in the TUR group, 3 refused the TUR. No residual cancer was found in 37 patients (T0), 5 had Ta, 2 had CIS, 4 had T1, and 1 had T2 with rapid progression to bone metastases. Of the T0 patients, 11 recurred with non-muscle-invasive cancer; 7 were treated with BCG and 4 with salvage cystectomy. Nineteen of these patients (51%) remained alive with intact bladders. Of the 8 patients with T4 disease, 4 were T0 at TUR, 2 were T1, and 2 refused TUR.

Meta-analyses of Patients With T4 Disease Treated With Neoadjuvant Chemotherapy and Cystectomy

Meta-analyses have been utilized to examine the cumulative reported data on the use of neoadjuvant chemotherapy in combination with either radical cystectomy or radiation. Separate studies have been reported using aggregate data for each trial and individual patient data (*Level 1,* [74,75]). A total of 10 studies (2524 patients) were reviewed, including 4 trials that used single agent cisplatin [74]. The hazard ratio was 0.9 (95% CI, 0.81 to 1.00), suggesting borderline results in favor of chemotherapy. The follow-up meta-analysis using updated individual patient data from all randomized trials (2688 patients) was subsequently reported by the United Kingdom's Medical Research Council [75]. The findings were that platinum-based combination chemotherapy showed a 5% absolute benefit at 5

years, overall survival increased from 45% to 50% (combined hazard ratio 0.87), and there was a 13% reduction in risk of death. There were 227 patients with T4 tumors (207 T4a and 20 T4b) equally distributed between the neoadjuvant chemotherapy and no chemotherapy arms. There was no difference in the chemotherapy effect when analyzed by type of locoregional therapy (cystectomy, radiation, radiation plus cystectomy). T and N category did not affect outcome; however, these analyses were restricted to 4 and 5 trials, respectively. Tumor diameter may have an effect. The authors concluded that for T4 disease, neoadjuvant chemotherapy may improve survival at 5 years from 25% to 30%.

Chin and colleagues separately reported the results of their meta-analysis. A total of 2605 patients from 11 randomized trials were included, and the authors reported a 6.5% improvement in overall survival in the neoadjuvant chemotherapy arm. There was no analysis stratified by clinical stage, however [76].

2. Adjuvant Chemotherapy

There are 4 randomized trials of adjuvant chemotherapy published to date in peer-reviewed journals and none are considered adequate regarding defining clinical practice [71,77-80]. The data suggest a benefit regarding time to progression but no conclusive benefit regarding overall survival. None of the trials are adequately powered to permit evaluation of patients with T4 tumors. Given the high incidence of lymph node metastases with prostate stromal invasion and the high long-term mortality rate, most patients are offered adjuvant chemotherapy following radical cystoprostatectomy.

Perioperative chemotherapy, whether delivered as neoadjuvant or adjuvant, utilizing a multi-agent regimen with M-VAC or CMV as the gold standard (the only regimens that have been reported to date in randomized trials), is the current standard of care given the data from the International and the SWOG trials [14,22], the high incidence of positive nodes, and the high risk of occult metastatic disease [72,81].

c) Radiation Therapy

Radical cystectomy is the gold standard for the treatment of invasive bladder cancer. Radiation-based treatment is usually offered to patients who are not felt to be surgical candidates. Radiation has been used extensively as monotherapy for invasive bladder cancer. Initial local control rates are acceptable, but long-term durable cancer control appears to be inferior to cystectomy. Poor prognostic features are hydronephrosis, T3b and T4 tumors, solid morphology, large size, and low hemoglobin.

The addition of chemotherapy as a radiosensitizing agent has led to improved cancer control rates. For patients treated with radiation alone, the addition of cisplatin, 5-FU, paclitaxel (Taxol), or gemcitabine improves the overall survival by 10% to 15%. The completeness of the TURBT may, however, be the most significant predictor of response to therapy (*Level 1,* [82]). This has led to the development of an integrated treatment approach designed to spare the bladder, which is commonly referred to as trimodal therapy (*Level 1,* [83]). This approach begins with a complete TUR of all visible tumor, down to fat. Induction radiation therapy integrated with chemotherapy follows, then the response is determined by pathologic staging with cystoscopy and biopsy. Complete responders get additional radiochemotherapy, and incomplete responders are recommended to proceed with radical cystectomy. The most important predictors of success are the ability to completely resect the tumor transurethrally and stage T2 disease (*Level 2,* [84]). A negative predictor is hydronephrosis, while age and gender do not affect outcome [84].

1. Outcome Analysis – Disease-free and Overall Survival

Overall survival rates are suggested to be equivalent to radical cystectomy and consistently approach 50% at 5 years (*Level 1,* [83]). Disease-free survival is lower due to non-muscle-invasive recurrences in the retained bladder, including CIS, which is frequently resistant to radiation and systemic chemotherapy. This review focuses on the 6 randomized trials conducted by the Radiation Therapy Oncology Group (RTOG) that address the role of radiation therapy as the primary method of local control. The studies progressed from testing the combination of radiation and cisplatin as a radiosensitizing agent (RTOG 85-12) (*Level 1,* [83]), to adding neoadjuvant methotrexate, cisplatin, and vinblastine (MCV), which did not improve outcome (RTOG 88-02 and 89-03) (*Level 1,* [85,86]), to moving the MCV to adjuvant therapy following radiation and cisplatin (RTOG 97-06) (*Level 1,* [87]), and, most recently, adding adjuvant chemotherapy with gemcitabine and cisplatin and combining paclitaxel (Taxol) with cisplatin as radiosensitizing agents (RTOG 99-06) (*Level 1,* [88]). Four of these trials included patients with T4a disease, and results from 3 of the 4 have been reported to date. Of these 3 trials, 2 included patients with T4a, and the third reported results utilizing a com-

bined stage grouping of T3 and T4a. Patients with prostatic stroma invasion have not been specifically identified, and patients with T4a disease make up no more than 10% of the reported patients. In the absence of specific data regarding the outcomes of patients with T4a disease in sufficient numbers, it is difficult to make any statement regarding the outcomes of these patients. The RTOG is arguably one of the best examples in urology of the important role that a cooperative group plays in answering important clinical questions in the management of patients with invasive bladder cancer.

2. Salvage Cystectomy

The patient populations treated in these clinical trials are the same that are considered for radical cystectomy regarding stage and performance status. An important issue, therefore regarding survival probabilities is the finding that at most 75% of patients enrolled in these trials complete the prescribed therapy and the potential negative impact on survival for patients who are incomplete responders who go on to cystectomy or refuse cystectomy [83,88]. Shipley et al. reported on 190 patients with long-term follow-up (median 6.6 years) in these RTOG studies (*Level 1,* [88]). A total of 66 patients (35%) ultimately underwent radical cystectomy - 41 for less than a complete response and an additional 25 for recurrent invasive tumors. Five- and 10-year survival probabilities for the 100 patients in the combined stage grouping T3 to T4a were 47% and 31%, respectively. The 5- and 10-year disease-specific survival probabilities were 63% and 59%, respectively. For the 66 patients who went on to cystectomy, the 5- and 10-year disease-specific survival rates were 48% and 41% for patients with T3 to T4a tumors.

d) Prostate-sparing or Apex-sparing Surgery

This strategy assumes that improved sexual function and continence with orthotopic neobladder can be achieved with sparing of all or a portion of the prostate and or seminal vesicles at the time of cystectomy. Colombo et al. demonstrated proof of principle in 8 patients with refractory non-muscle-invasive bladder cancer by performing transurethral resection of the prostate, pelvic lymphadenectomy, and radical cystectomy while sparing the vas deferens, seminal vesicles, and neurovascular bundles (*Level 3,* [89]). All patients reported normal sexual function, 7 had retrievable sperm, and all maintained diurnal continence. Vallencien et al. followed 100 patients with a typical spectrum of urothelial carcinoma of the bladder treated in a similar fashion and noted no affect on oncologic outcomes. Potency was preserved in 82%, and diurnal continence was achieved in 95% (*Level 3,* [90]). Muto et al. performed a modified form of this surgery on 63 patients (all but 5 had non-muscle-invasive cancer) by establishing a plane of dissection between the bladder and seminal vesicles in order to preserve the vas deferens, seminal vesicles, prostatic capsule, and neurovascular bundles (*Level 3,* [91]). Continence rates were similar to those reported for cystoprostatectomy and orthotopic neobladder, while normal erectile function was maintained in 95% of patients. These studies suggest that the quality of life gain in preservation of sexual function and the high likelihood of diurnal continence are achievable in the majority of patients. However, they are all uncontrolled and retrospective analyses. A prospective randomized study design comparing this modified approach to standard radical cystoprostatectomy with sparing of the neurovascular bundles using validated quality of life and erectile and sexual function questionnaires is necessary to demonstrate superiority of the modified approach and validate the safety from an oncologic standpoint.

The risks of these modified procedures relate to the high incidence of occult prostate adenocarcinoma and prostatic involvement by TCC. While prostate cancer is found in up to 40% of patients undergoing radical cystoprostatectomy, reflecting the advanced age of this patient population, these cancers are usually small and incidental, confined to the capsule, and clinically insignificant. Ravelo et al. analyzed 121 consecutive patients using whole mount step section analysis of the prostate removed at cystectomy (*Level 3,* [28]). Prostate cancer was found in 50 (41%), of which only 52% were considered clinically insignificant (defined as volume less than 0.5 cc and no Gleason 4 or 5). The prostatic apex was involved in 60% of the patients with prostate cancer. Urothelial carcinoma of the urethra, ducts, or stroma occurred in 58 (48%) patients, and 19 (33%) had prostatic apical involvement by urothelial carcinoma. Overall, only 32 of 121 patients (26%) had no prostate cancer or urothelial carcinoma involvement of the prostate. The high incidence of prostate involvement by urothelial carcinoma confirms previous observations by Wood et al. and Sakamoto et al. (*Level 2,* [36,58]).

Summary

The incidence of urothelial carcinoma of the prostate varies from 12% to 48% in cystectomy specimens. Stromal invasion is present in 7.6% to 16.6%. Underreporting of prostatic involvement is common. Although transurethral biopsy of the prostatic urethra is the best method of diagnosis, it lacks accuracy. Radical cystoprostatectomy is the treatment of choice. Disease-free survival is a function of the pattern of invasion. Direct extension from the bladder is associated with a worse prognosis than prostate invasion via the prostatic urethra.

Recent studies strongly suggest that the number of nodes removed has a direct impact on survival.

Data on neoadjuvant chemotherapy suggest a modest survival benefit. In patients with stromal invasion, there are insufficient data to draw any conclusions regarding the use of adjuvant chemotherapy and/or radiotherapy.

IV. PRIMARY UROTHELIAL CARCINOMA OF THE PROSTATE

1. Concept

Primary urothelial (transitional cell) carcinoma of the prostate is a rare clinicopathological entity originating in the urothelium (transitional epithelium) of the intraprostatic, periurethral ducts, in the area of the junction of the glandular epithelium and urothelium. It is a distinct histologic variety of prostate carcinoma, to be distinguished both from adenocarcinoma and endometrioid carcinoma of the prostate gland.

The literature describing this entity consists of individual case reports and short case series. By definition, primary urothelial carcinoma of the prostate is not preceded by any form of urothelial carcinoma or carcinoma in situ arising elsewhere in the urinary tract and must be distinguished from any form of prostatic involvement caused by previous or simultaneous urothelial carcinoma of the bladder. This infrequent tumor accounts for between 0.4% and 2% of all prostate neoplasms [92-96]. It has a propensity for extensive local invasion. It occasionally is diagnosed at an early stage within prostatic ducts or acini. Primary urothelial carcinoma of the prostate may be pure or mixed with squamous cell carcinoma or adenocarcinoma. Small cell differentiation may also occur [97]. Rare cases of primary squamous cell carcinoma of the prostate have also been described. Both the histogenesis of this tumor and its responsiveness to chemotherapy remain very controversial [98-101]. Prostatic adenocarcinoma and primary urothelial carcinoma of the prostate may coexist in the same patient, with an incidence similar to that of pure urothelial carcinoma of the prostate [95,102,103]. The association between transitional cell ductal carcinoma of high stage with a papillary or cribriform pattern and ductal adenocarcinoma in the same prostate likely reflects a shared causality. This may represent a new pattern of carcinoma with mixed features. The urothelial carcinoma component displays a positive reactivity for thrombomodulin and negative or weaker reactivity for PAP and PSA than the prostatic adenocarcinoma component in the same tumor [104].

2. Diagnosis

Presentation is usually late, generally with obstructive voiding complaints and, less frequently, macroscopic hematuria. However, specific presentations as rectal ulcer or hematochezia have also been described [105,106]. Primary urothelial carcinoma of the prostate is occasionally diagnosed in the histopathologic study of a transurethral resection specimen of the prostate performed for benign prostatic hyperplasia [107-110]. Histopathological examination usually reveals high grade urothelial carcinoma invading the prostate stroma, but low or intermediate grade urothelial carcinoma without submucosal invasion may also be seen [9,111].

To confirm the diagnosis of primary prostatic urothelial carcinoma, transrectal needle biopsy of the prostate and cystoscopy with random biopsy of the urinary bladder must be performed, in order to rule out prostate adenocarcinoma and urothelial carcinoma of the bladder.

Urine cytology at presentation may reveal malignant cells suggesting urothelial neoplasia, but cystoscopy and sonography fail to reveal a malignant lesion. Digital rectal examination, imaging, and marker studies are often normal. A hard prostatic mass on digital rectal examination is a sign of advanced disease [112]. PSA and tartrate-inhibited fractions of serum acid phosphatase are uniformly not elevated. Transrectal and transperineal prostate biopsies may be negative in early disease. In advanced disease,

they often reveal high grade urothelial carcinoma with negative prostatic acid phosphatase and PSA inmunostaining [113]. This neoplasia should be suspected when obstructive symptoms appear in relatively young patients diagnosed with prostate adenocarcinoma, especially if it is rapidly progressive and unresponsive to hormonal therapy [113,114].

Pelvic CT scan and MRI are the preferred preoperative staging modalities. They may reveal extraprostatic extension and lymph node metastasis in the iliac artery region [112]. Metastatic disease develops more frequently in lung and bone [115]. Osseous metastases are osteolytic, often with elevations of serum alkaline or acid phosphatase levels [9].

3. TREATMENT

Due to the limited accumulated experience with this form of disease and the absence of randomized clinical trials, optimal definitive therapy of primary urothelial carcinoma of the prostate remains uncertain. Traditional methods of therapy for adenocarcinoma of the prostate such as hormonal manipulation are ineffective, because these neoplasms are not hormonally dependent [9,94,116,117].

Some initial experiences suggested that preoperative pelvic irradiation followed by radical cystoprostatourethrectomy was the treatment of choice in low stage disease, and combined radiation therapy and chemotherapy was indicated for disease invading beyond the prostate [114]. However, current practice does not incorporate preemptive radiation before surgery in localized disease.

Transurethral resection of the prostate may be an appropriate therapy for the incidental form of primary urothelial carcinoma of the prostatic ducts localized to the gland, especially in cases of low grade urothelial carcinoma without submucosal invasion [118,119]. However, radical surgery (prostatectomy and cystoprostatectomy, sometimes including urethrectomy, or even pelvic exenteration) offers better locoregional control of the disease. It achieves good long-term results in some patients [111,113]. Radical prostatectomy (without cystectomy) has been favored in many reports, possibly because of the poor prognosis and the high tendency for metastatic spread [96]. Other authors prefer early cystoprostatectomy, as they believe it achieves better results [111]. No comparative study has been performed to address this point.

Some reports suggest that external beam radiotherapy has achieved good local control in the short-term, but long-term follow-up is lacking [95,106]. Despite the absence of definite clinical-based evidence at present regarding optimum therapy, most recent authors believe the best form of treatment is radical ablation of the prostate; radiation therapy is considered second line therapy for this indication.

Adjuvant chemotherapy (M-VAC) has also been reported to delay tumor recurrence [108,109]. Currently, the use of adjuvant chemotherapy even in favorable cases has been favored, but the degree of clinical-based evidence in this respect is still scarce. Neoadjuvant systemic chemotherapy has also proved to be effective in isolated case reports and in the institutional experience of the Memorial Sloan Kettering Cancer Center, with a clinical complete remission rate of 60% in pure urothelial carcinoma [120]. Induction chemotherapy has also achieved complete histopathological response, permitting radical cystoprostatectomy in cases with otherwise previously unresectable disease [112,121]. However, evidence supporting this is limited.

Due to the fact that therapy with M-VAC is ineffective against mixed histological tumors and in preventing development of new Tis lesions (carcinoma in situ of the prostatic ducts and carcinoma in situ of the bladder), surgical resection of the prostate (or prostate and bladder) is required and is not obviated by the use of induction chemotherapy [120].

Combination chemotherapy with cisplatin and cyclophosphamide may achieve complete or partial responses in some patients with metastatic disease [115,116]. Complete response in patients with isolated brain metastases has been described [115]. Metastatic disease refractory to M-VAC has been treated in one case with mitoxantrone, achieving a transient partial remission [122]. New chemotherapeutic drugs and schedules merit further evaluation.

4. PROGNOSIS

The literature uniformly emphasizes the aggressive behavior of primary urothelial carcinoma of the prostate once the prostatic stroma is infiltrated by the tumor [107]. Compared to acinar prostate adenocarcinoma, this tumor shows a hormone-resistant aggressive biology and poor prognosis, with local invasion and a propensity to distant metastases.

Long-term survival rates are uncertain, based on the absence of a prospective accumulated experience. Prognosis reported in most case series has been dismal, with a mean overall survival ranging from 4.6 to

10.6 months, and up to 60% of patients dying within the first 6 months after diagnosis [7,92,93,96].

Average survival for patients treated with radical surgery alone was 2 years, similar to that of a more recent retrospective analysis of patients treated with radiotherapy (mean survival 26.6 months, range 4-60) [94,95]. Complete responses have been achieved in metastatic cases with cisplatin-based chemotherapy programs. However, early diagnosis in a curable stage and subsequent radical treatment is the only option available to control urothelial carcinoma of the prostate and increase the life expectancy of these patients [96,117].

Summary

By definition, primary urothelial carcinoma of the prostate is not preceded by any form of urothelial carcinoma or carcinoma in situ arising elsewhere in the urinary tract. It must be distinguished from prostatic involvement caused by previous or simultaneous urothelial carcinoma of the bladder.

To diagnose primary urothelial carcinoma of the prostate, urothelial disease of the bladder and adenocarcinoma of the prostate must be ruled out.

Radical treatment is the only option available to control the disease. Beyond this, optimal therapy is not yet defined.

V. URETHRAL RECURRENCE

The risk of recurrent anterior urethral urothelial carcinoma following radical cystectomy is 8% to 14% (*Level 3*, [123]). Previously routine prophylactic urethrectomy was recommended in conjunction with the cystectomy based on the poor results of therapeutic urethrectomy in patients with recurrence. Retrospective analyses of cystectomy series have identified specific pathological characteristics of the bladder primary urothelial carcinoma that predict an increased risk for urethral recurrence, including multifocal tumors, carcinoma in situ, involvement of the prostatic urethra, particularly invasion of the stroma of the prostate, and, in the most recent studies, a positive urethral margin (*Level 3*, [123]).

1. Prognostic Factors

Initially, prophylactic urethrectomy was recommended when risk factors were found in the bladder; later, evidence of the importance of prostatic involvement for urethral recurrence changed the concepts for surgical decision-making. Levinson et al. and Hardeman and Soloway disputed that patients with spread of urothelial carcinoma into the prostate are at risk for urethral recurrence (*Level 3*, [124,125]). Levinson et al. showed in their retrospective analysis of 124 male patients who had initial cystoprostatectomy and unsuspected urethral malignancies that 4 of 24 (17%) patients whose tumors extended into the prostate developed recurrence. Notably 3 of 10 (30%) with stromal invasion developed urethral recurrence. In a retrospective analysis of patients undergoing radical cystoprostatectomy by Hardeman and Soloway, 11 of 30 patients (37%) who had prostatic involvement by urothelial carcinoma developed recurrence. Among those 30 patients, no patients of 8 whose tumor was confined to the urethra developed recurrence, while 2 of 8 (25%) patients who had duct involvement and 9 of 14 (64%) patients who had stromal invasion developed recurrence. Pathologically, none of the urethral recurrences had invasion beyond the urothelium. Tongaonkar et al. retrospectively analyzed urethral recurrences in 164 patients who underwent radical cystectomy (*Level 3*, [126]). Seven of 10 patients who had prostatic involvement, a positive urethral margin, or multifocal disease developed urethral recurrence. Diffuse CIS has been suggested as a risk factor for urethral recurrence [123]. Tobisu et al. examined the involvement of the anterior urethra in patients who underwent en bloc urethrectomy during radical cystectomy (*Level 3*, [127]). In 4 of 19 patients with diffuse CIS extending to the prostatic urethra, the anterior urethra was affected by urothelial carcinoma. This paper emphasized the risk of CIS recurrence involving the anterior urethra if primary bladder CIS extends to the prostatic urethra.

2. Predictive Value of Preoperative Transurethral Biopsy

Since prostatic involvement at biopsy or cystectomy translated into a higher risk of urethral recurrence, transurethral prostatic biopsy has been widely performed prior to cystectomy. If prostatic involvement was detected by transurethral biopsy, should a prophylactic urethrectomy be recommended? Lebret et al. evaluated the predictive value of preoperative latero-montanal biopsies and urethral frozen sections during radical cystectomy (*Level 3*, [128]). Preoperative endoscopic latero-montanal biopsies were nonspecific. Among the 106 patients with a negative frozen urethral resection margin, no urethral recur-

rence was observed. Donat et al. suggest that the predictive value of prostate involvement is insufficient to warrant a urethrectomy (*Level 3,* [59]). In their retrospective analysis, 80 of 246 patients were found positive on TUR loop prostate biopsy (20 superficial and 24 stromal). Eleven of 80 patients (14%) developed recurrence. Eight of 44 patients (18%) who were found to have prostatic involvement in cystectomy specimens developed recurrence. However, no deaths were related to urethral recurrence. There were 13 positive urethral margins at cystectomy, of which 11 (84.6%) have not been associated with urethral recurrence. These 2 studies concluded that prostatic involvement diagnosed by TUR biopsy should not be an absolute contraindication to urethral diversion.

3. Intraoperative Frozen Section Analysis of the Apical Urethral Margin

The important issues are the accuracy of frozen section for the diagnosis of CIS and the predictive value for subsequent urethral "recurrence".

Unfortunately, there are very little data that address this specific issue. A recent study using whole mount step section analysis of the prostate from cystoprostatectomy specimens found that one-fourth of patients had prostate cancer involving the prostatic apex and 79% of these were considered biologically significant (*Level 3,* [28]). A total of 19 of 121 patients had urothelial cancer involving the apex. Overall, only 39% had involvement of the apex by either prostate or urothelial cancer, and only 30% had involvement by clinically significant prostate or urothelial cancer. Only 9 patients in this study had intraoperative frozen section of the apical margin, of which one was positive. The frozen section findings correlated with the final pathology in all 9 patients. **These data suggest that while apical involvement with either biologically significant adenocarcinoma of the prostate or urothelial cancer is uncommon, an accurate means of determining this preoperatively or by frozen section at the time of cystectomy is imperative.**

The accuracy of frozen section of the prostatic apical margin has been addressed by Lebret et al. who performed preoperative prostatic urethral biopsies and intraoperative frozen section biopsies of the apical urethral margin in 118 consecutive cystoprostatectomies (*Level 3,* [128]). Twelve patients had positive biopsies on both and underwent en bloc urethrectomy. Of the remaining patients, 9 had positive preoperative prostatic urethra biopsies, but all had negative frozen section biopsies and the urethra was preserved in all patients without long-term sequelae (second primary tumors of the retained urethra). Vallancien et al. reported on a prostate-sparing approach, but no patients with T4 tumors were included and none had T4 disease on final pathology. However, there were 3 patients with adenocarcinoma of the prostate and 1 had a false negative frozen section of the prostate margin (*Level 3,* [90]). Iselin and associates reported on 70 patients followed long-term after orthotopic neobladder construction (*Level 3,* [129]). None had a positive intraoperative frozen section or permanent section of the prostatic apex, and 14 (20%) had urothelial carcinoma of the prostate. There were 2 patients with urethral recurrence, 1 early and 1 late, of which 1 had prostatic stromal invasion. Bochner et al. reported on 214 radical cystectomies with orthotopic neobladder creation and identified 1 patient with a positive apical margin who had an anastomotic recurrence that led to local and distant recurrence and subsequent death (*Level 3,* [68]). Two other patients developed second primary tumors in the urethra.

The current EAU guidelines for bladder cancer recommend that the decision to perform urethrectomy may be based on the results of a frozen section analysis of the urethral margins (*Level 4,* [130]).

4. Urethral Recurrence in the Patient With an Orthotopic Neobladder

The decision to preserve the urethra and perform orthotopic neobladder construction requires a motivated patient who desires to be "bag-free" and void per urethra, a low risk of developing a second primary tumor in the retained urethra, and a high likelihood of achieving diurnal continence and evidence of a functionally intact external sphincter. In the case of a patient with stromal invasion, the decision rests solely on the perceived risk of "urethral recurrence" or, more properly termed, a second primary tumor of the urethra.

Formerly, prostatic urethral involvement has been a relative contraindication to orthotopic neobladder creation. But, there is indirect evidence that a neobladder may reduce the risk of urethral recurrence compared to an abdominal diversion, due to the flushing effect of urine through the retained urethra (*Level 3,* [131]). However, until now many feel that a 30% risk is too high and a prophylactic urethrectomy should be performed at the time of cystec-

tomy. This argument must be weighed against the high-risk nature of T4 disease, including a 40% to 50% risk of pelvic nodal metastases and a 5-year survival probability of less than 50%. These adverse statistics modify the risk of developing a second primary in the retained urethra. Additionally, a neobladder enhances quality of life compared to an abdominal diversion. Management of prostatic stromal invasion diagnosed after surgery is not well-defined. Most urologists simply monitor the urethra with wash cytology and perform urethrectomy if a new tumor is identified.

Freeman et al. analyzed 174 men with a Kock ileal neobladder and 262 with a cutaneous urinary diversion for time to urethral recurrence (*Level 3,* [131]). They found 5 urethral recurrences (2.9%). This incidence is low, particularly considering that 32% had prostatic involvement by urothelial carcinoma in the cystectomy specimens. Nonetheless, prostatic urethral involvement, particularly stromal invasion, significantly increased the probability of recurrence ($P < 0.001$). Patients with a Kock ileal neobladder had a significantly lower probability of recurrence compared to those with cutaneous diversion ($P = 0.015$), even when associated with prostatic urethral involvement. Another report showed that only 1 of 32 orthotopic bladder substitutes that had pathological prostatic involvement developed urethral recurrence (*Level 3,* [126]). Iselin et al. examined whether urethral preservation and orthotopic bladder replacement in patients with urothelial carcinoma within the prostatic urethra or prostate placed these patients at risk for urethral recurrence or death (*Level 3,* [129]). The urethra was sacrificed only if the distal prostatic urethral margin was positive for urothelial carcinoma. They observed 2 urethral recurrences (2.8%) among 70 patients with orthotopic neobladders; all of them with tumor-free urethral frozen sections. Of the 14 patients who had prostatic urothelial carcinoma, only 1 had urethral recurrence (7%), and this recurrence was not the cause of death.

Huguet et al. examined 138 patients who were reconstructed with orthotopic neobladders and 5 (3.6%) developed urethral recurrences (*Level 3,* [132]). Bulbul et al. challenged the value of cystoscopy, prostate biopsy, and frozen section urethral biopsy prior to orthotopic neobladder substitution (*Level 3,* [133]). In their retrospective analysis, 40 men with a cystoscopically normal prostatic fossa had negative prostatic biopsies and had orthotopic neobladder substitution. Pathological examination showed that 3 of these 40 men had urothelial carcinoma involving the prostate. None of the patients developed urethral or neobladder recurrence. They argued that TUR biopsy of the prostatic urethra prior to cystectomy, or biopsy of the prostatic urethral margin at the time of cystectomy in patients with a cystoscopically normal, tumor-free prostatic urethra, has limited value in selecting candidates for orthotopic neobladder substitution. The lower rate of urethral recurrence than expected in neobladder series suggests that orthotopic bladder substitution may decrease the incidence of urethral recurrences compared to cutaneous diversions, based on the diluting effect of urine on urothelium. This remains an open question.

Summary

The risk of anterior urethral urothelial carcinoma following radical cystectomy is 8% to 14%. It is associated with multifocal disease, diffuse CIS, and prostatic involvement.

The biopsy of the apex of the prostatic urethra seems to accurately identify patients at risk for urethral recurrence.

RECOMMENDATIONS

I. ANATOMIC AND HISTOPATHOLOGIC BACKGROUND

1. There is a clear difference in disease-specific survival related to mucosal/ductal involvement and stromal invasion by urothelial carcinoma in the prostatic urethra *(Grade B).*

2. Surgeons must be cognizant of the different mechanisms of prostatic stromal invasion when evaluating patients at risk for prostatic urethral disease *(Grade C).*

3. The TNM classification of urothelial carcinoma of the bladder including the urothelial (TCC) tumors in the prostatic urethra as pT4a should be clarified: pT4a should be used when there is invasion of the prostate by urothelial carcinoma, and when there is only superficial involvement of the prostate, a suffix "is pu" (extension into prostatic urethra) or "is pd" (extension into prostatic ducts) may be added to the bladder staging *(Grade C).*

4. It is advisable to make a distinction between direct invasion of the bladder tumor into the prostate and prostatic urethral involvement leading to prostatic stromal invasion *(Grade C).*

5. The extravesical invasion of the seminal vesicles is an ominous sign of locally advanced and metastatic disease *(Grade C).*

II. SUPERFICIAL UROTHELIAL CARCINOMA OF THE PROSTATE

1. Macroscopic evidence of superficial bladder cancer in the prostatic urethra is highly specific.

   Transurethral resection of any macroscopic or suspicious lesion is required in order to determine stage and grade of the tumor in the prostatic urethra. Once a superficial high grade tumor or CIS of the bladder is diagnosed, careful follow-up of the prostatic urethra is mandatory *(Grade C).*

2. High and low grade superficial urothelial carcinoma and CIS of the prostate should be treated with intravesical BCG *(Grade C).*

3. The evidence (level 3) shows that transurethral resection may improve contact of BCG with the prostatic urethra. It remains to be demonstrated if there is an increase in response rates to BCG *(Grade C).*

4. CIS or tumor in the prostatic ducts warrant further study, since very few patients have been treated and there are no conclusive results using conservative therapy. It is advisable to perform radical surgery until proven otherwise and to avoid understaging in patients with prostatic duct involvement *(Grade C).*

5. Patients with superficial urothelial carcinoma who fail conservative therapy should be considered for cystoprostatectomy *(Grade C).*

6. Patients with intermediate- to high-risk superficial urothelial carcinoma of the bladder or CIS, especially with involvement of the bladder neck and multifocality, need monitoring of the prostatic urethra in these patients with prostatic duct involvement *(Grade B/C).*

III. PROSTATIC STROMAL INVASION

1. The incidence of prostatic urothelial carcinoma in men with superficial or invasive bladder cancer ranges from 12% to 48%, and 7.6% to 16.6% have stromal invasion. The prostate is a site of relapse for patients with superficial bladder cancer after intravesical therapy *(Grade C).*

2. Transurethral biopsies of the prostatic urethra are effective at identifying prostatic involvement, but do not accurately determine the extent of prostatic involvement, particularly stromal invasion.

   New methods for detection of prostatic stromal invasion are necessary *(Grade C).*

3. Retrospective and prospective studies are needed to determine prognostic factors for prostatic stromal invasion .

4. Radical cystoprostatectomy is the treatment of choice for locoregional control for patients with prostatic stromal invasion *(Grade B).*

5. In patients with pT4 disease, the incidence of positive nodes ranges from 40% to 50% and node mapping studies indicate that multiple sites are involved *(Grade C).*

6. There is some data showing that the extent of lymphadenectomy may have an impact on survival *(Grade C).*

7. There are sufficient data from randomized trials of neoadjuvant chemotherapy combined with radical cystectomy that suggest a modest benefit to cisplatin-based multi-agent chemotherapy in patients with documented prostatic stromal invasion *(Grade B).*

8. The data from randomized trials of adjuvant chemotherapy after cystectomy however, are limited

and therefore insufficient to draw any conclusions regarding the efficacy of adjuvant chemotherapy for patients with prostate stromal invasion *(Grade C).*

9. The number of patients with prostatic stromal invasion treated in radiation therapy trials is too small to make definitive conclusions regarding survival outcome *(Grade C).*

10. Though the data are limited and the number of patients with prostate stromal invasion cannot be determined from the literature, the use of radical cystectomy as a salvage procedure does not appear to diminish disease-specific or overall survival probabilities *(Grade C).*

11. Prostate-sparing cystectomy is contraindicated in the setting of prostate stromal invasion documented preoperatively *(Grade C).*

IV. PRIMARY UROTHELIAL CARCINOMA OF THE PROSTATE

1. To diagnose primary TCC of the prostate a transrectal needle biopsy of the prostate and cystoscopy with random biopsy of the urinary bladder must be performed, in order to rule out prostate adenocarcinoma and TCC of the bladder *(Grade C).*

2. Pelvic CT scan and MRI are the preferred preoperative staging modalities *(Grade C).*

3. Optimal definitive therapy of primary urothelial carcinoma of the prostate remains undefined *(Grade C).*

4. There is no agreement on the optimal radical surgery (radical prostatectomy vs. cystoprostatectomy) *(Grade C).*

5. Adjuvant radiotherapy and chemotherapy may delay tumor recurrence *(Grade C).*

6. Early diagnosis and subsequent radical treatment is the only option available to control urothelial carcinoma of the prostate and increase disease-specific survival *(Grade C).*

V. URETHRAL RECURRENCE

1. Urothelial carcinoma of the prostate diagnosed by TUR of the prostatic urethra is not an absolute indication for prophylactic urethrectomy *(Grade C).*

2. Frozen section biopsy of the prostatic urethra appears to be accurate in identifying patients with a negative biopsy who are at very low risk for developing a second primary tumor of the urethra *(Grade C).*

3. The finding of a positive biopsy should be considered a contraindication to an orthotopic neobladder *(Grade C).*

4. In patients with orthotopic neobladders, due to exposure of the urethra to urine or by other unknown causes, there is a decreased incidence of urethral recurrence *(Grade C).*

REFERENCES

1. Gil Vernet S. Patología Urogenital. Biología y Patología de la próstata. Tomo II. Vol 1. Paz Montalvo, Madrid, 1953.
2. McNeal JE. Regional morphology and pathology of the prostate. Am J Clin Pathol 1968, 49:347-357.
3. Algaba F, Moreno A, Trías I. Uropatología tumoral. Correlación morfológica, molecular y clínica. Pulso, Barcelona, 1996.
4. Ende N, Woods LP, Shelley HS. Carcinoma originating in ducts surrounding the prostatic urethra. Amer J Clin Pathol 1963; 40:183.
5. Johnson DE, Hogan JM, Ayala AC. Transitional cell carcinoma of the prostate: a clinical and morphological study. Cancer 1972; 36:514.
6. Schellhammer PF, Bean MA, Whitmore WFJ. Prostatic involvement by transitional cell carcinoma: pathogenesis, patterns and prognosis. J Urol 1997; 118:399-403.
7. Kirk D, Hinton CE, Shaldon C. Transitional cell carcinoma of the prostate. Br J Urol 1979; 51:575-578.
8. Whitmore WF and Marshall VF. Radical total cystectomy for cancer of the bladder: 230 consecutive cases five years later. J Urol 1962, 87:853-868.
9. Greene LF, O´Dea MJ, Dockerty MB. Primary transitional cell carcinoma of the prostate. J Urol 1976, 116:761-763.
10. Chibber PJ, McIntrye MA, Hindmarsh JR, Hargreave JB, Newsam JF, Chisholm GD. Transitional cell carcinoma involving the prostate. Br J Urol 1981; 53:605-609.
11. Hardeman SW and Soloway MS. Transitional cell carcinoma of the prostate: diagnosis, staging and management. Word J Urol 1988; 6:170-174.
12. International Union Against Cancer: TNM classification of Malignant Tumours, 6th ed. Edited by M.H. Harmer. Geneva: International Union Against Cancer, 2002.
13. Wittekind Ch, Henson DE, Hutter RVP, Sobin LH. TNM supplement. 2nd Edition. A commentary on uniform use. Wiley-liss, a John Wiley & Sons, Inc., Publication. 2001.
14. Pagano F, Bassi PF, Ferranti GL, Piazza N, Abantagelo G, Pappagallo GL, Garbeglio A. Is stage pT4a (D1) reliable assessing transitional cell carcinoma involvement of the prostate in patients with a concurrent bladder cancer? A necessary distinction for contiguous or noncontiguous involvement. J Urol 1996; 155:244-247.
15. Donat SM, Genega EM, Herr HW, Reuter VE. Mechanisms of prostatic stromal invasion in patients with bladder cancer: clinical significance. J Urol 2001; 165:1117-1120.
16. Esrig D, Freeman JA, Elmajian DA, Stein JP, Chen S, Groshen S, Simoneau A, Skinner EC, Lieskovsky G, Boyd SD, Cote RJ, Skinner DG. Transitional cell carcinoma involving the prostate with a proposed staging classification for stromal invasion. J Urol 1996; 156:1071-1076.
17. Volkmer BG, Küfer R, Maier S, Bartsch G, Bach D, Hautmann RE, Gschwend JE. Outcome in patients with seminal vesicle invasion after radical cystectomy. J Urol 2003; 169:1299-1302.
18. Daneshmand S, Stein JP, Lesser T, Queck ML, Nichols PW, Miranda G, Cai J, Groshen S, Skinner EC, Skinner DG. Prognosis of seminal vesicle involvement by transitional cell carcinoma of the bladder. J Urol 2004; 172:81-84.
19. Ortega LM, Whitmore FRJ, Murphy AJ. In situ carcinoma of the prostate with intra-epithelial extension into the urethra and bladder. Cancer 1953; 6:898-923.
20. Rikken CHM, Van Helsdingen PJRO, Kazzaz BA. Are biopsies from the prostatic urethra useful in patients with superficial bladder carcinoma? Brit J Urol 1987; 59:145-147.
21. Solsona E, Iborra I, Ricós JV, Monrós JL, Dumont R, Casanova J, Calabuig C. Recurrence of superficial bladder tumors in the prostatic urethra. Eur Urol 1991; 19:89-92.
22. Matzkin H, Soloway MS, Hardeman S. Transitional cell carcinoma of the prostate. J Urol 1991; 146:1207-1212.
23. Millan-Rodriguez F, Chechile-Toniolo G, Salvador-Bayarri J, Palou J, Vicente-Rodriguez J. Multivariate analysis of the prognostic factors of primary superficial bladder cancer. J Urol 2000, 163:73-78.
24. Davis JW, Sheth SI, Doviak MJ, Schellhammer PF. Superficial bladder carcinoma treated with bacillus Calmette-Guerin: progression-free and disease specific survival with minimum 10-year followup. J Urol. 2002 Feb;167(2 Pt 1):494-500; discussion 501.
25. Herr HW and Donat SM. Prostatic tumor relapse in patients with superficial bladder tumors: 15 year outcome. J Urol 1999;161:1854-1857.
26. Bassi PF. BCG (bacillus Calmette Guerin) therapy of high risk superficial bladder cancer. Surg Oncol 2002;11:77-83.
27. Wood DP Jr, Montie JE, Pontes JE, VanderBrug Medendorp S, Levin HS. Transitional cell carcinoma of the prostate in cystoprostatectomy specimens removed for bladder cancer. J Urol 1989;141:346-349.
28. Revelo MP, Cookson MS, Chang SS, Shook MF, Smith JA Jr, Shappell SB. Incidence and location of prostate and urothelial carcinoma in prostates from cystoprostatectomies: implications for apical sparing surgery . J Urol 2004; 171:646-651.
29. Nixon RG, Chang SS, Lafleur BJ, Smith JA JA, Cookson MS. Carcinoma in situ and tumor multifocality predict the risk of prostatic urethral involvement at radical cystectomy in ment with transitional cell carcinoma of the bladder. J Urol 2002; 167:502-505.
30. Seemayer TA, Knaack J, Thelmo WL, Wang N, Ahmed NM. Further observations on carcinoma in situ of the urinary bladder: silent but extensive intraprostatic involvement. Cancer 1975; 36:514-520.
31. Orihuela E, Herr WH, Whitmore WF. Conservative treatment of superficial transitional cell carcinoma of the prostatic urethra with intravesicla BCG. Urology 1989; 34:231-237.
32. Thelmo WL, Seemayer TA, Madarnas P, Mount BMM, Mackinnon KJ. Carcinoma in situ of the bladder with associated prostatic involvement. J Urol 1974; 111:491-494.
33. Schellhammer PF, Ladaga LE, Morarty RP. Intravesical Bacillus Calmette-Guerin for treatment of superficial transitional cell carcinoma of prostatic uretthra in association with carcinoma of the bladder. J Urol 1995; 153:53-56.
34. Hillyard RW, Ladaga L, Schellhammer PF: Superficial tranansitional cell carcinoma of the Bladder associated with mucosal involvement of the prostatic urethra:Results of treatment with Intravesical Bacillus Calmette-Guerin. J Urol 1988; 139:290-293.
35. Bretton PR, Herr HW, Whitmore WF Jr, Badalament RA, Kimmel M, Provet J, Oettgen HF, Melamed MR, Fair WR. Intravesical bacillus Calmette-Guerin therapy for in situ transitional cell carcinoma involving the prostatic urethra. J Urol 1989; 141:853-856.
36. Sakamoto N, Tsuneyoshi M, Naito S, Kumazawa J. An adequate sampling of the prostate to identify prostatic involvement by urothelial carcinoma in bladder cancer patients. J Urol 1993; 149:318-321.
37. Lamm RL, Stodgill UD, Stodgill BJ, Crispen RG. Complicacions of Bacillus Calmett-Guerin immunotherapy in 1,278 patients with bladder cancer. J Urol 1986; 135:272-274.
38. Morales A, Eidinger D, Bruce AW. Intracavitary bacillus Calmette-Guerin in the treatment of superficial bladder tumors. J Urol 1976; 116:180-183.

39. Herr HW. Carcinoma in situ of the bladder. Sem Urol 1983; 1:15-19.

40. Lamm DL. BCG immunotherapy in bladder cancer. J Urol 1985; 134:40-47.

41. de Kernion JB, Hvany MY, Linanfr A, Smith RB, Kaufman J. The management of superficial bladder tumors and carcinoma in situ with intravesical Bacillus Calmette-Guerin. J Urol 1985; 133:598-601.

42. Palou J, Xavier B, Laguna P, Montlleo M, Vicente J. In situ transitional cell carcinoma involvement of prostatic uretra: Bacillus Calmette-Guérin therapy without previous transurethral resection of the prostate. Urology 1996; 47:482-484.

43. Canda AE, Tuzel E, Mungan MU, Yorukoglu K, Kirkali Z. Conservative management of mucosal prostatic involvement in patients with superficial transitional cell carcinoma of the bladder. Eur Urol 2004 Apr;45(4):465-9; discussion 469-70.

44. Solsona E, Iborra I, Ricós JV, Monrós JL, Casanova JL, Almenar S. The prostate involvement as prognostic factor in patients with superficial bladder cancer. J Urol 1995; 154:1710-1713.

45. Oates RD, Stilmant MM, Freedlund MC, Siroky MB. Granulomatous prostatitis following bacillus Calmette-Guèrin Immunotherapy of bladder cancer. J Urol 1988, 140:751-754.

46. Mukamel E, Konichezky M, Engelstein D, Cytron S, Abramovici A, Servadio C. Clinical and pathological findings in prostates following intravesical bacillus Calmette-Guèrin instillations. J Urol 1990, 144: 1399-1400.

47. LaFontaine PD, Middleman BR, Graham SD, Danders WH. Incidence of granulomatous postatitis and Acid-fast bacilli after intravesical BCG therapy. Urology 1997;49:363-366.

48. Leibovici D, Zisman A, Chen-Levyi, Cypele H, Siegel YI, Faitelovich S, Lindner A. Elevated prostate specific antigen serum levels after intravesical instillation of bacillus Calmette-Guerin. J Urol 2000;164:1546-1549.

49. Palou J, López H, Millán F, Oliver A, Salvador J, Vicente J. Effect of intravesical instillations of BCG on total PSA. Preliminary results. BJU International 2000; 86, suppl.3:254.

50. Ovesen H, Poulsen AL, Steven K. Intravesical Bacillus Calmette-Guerin with the Danish strain for treatment of carcinoma in situ of the bladder. Br J Urol. 1993 Nov;72(5 Pt 2):744-748.

51. Palou J, Salvador J, Parada R, Chéchile G, Millán F, Vicente J. Carcinoma in situ of the prostatic urethra: the role of intravesical BCG. Urol Integr Invest 2001;6(2):165-170.

52. Schwalb DM, Herr HW, Fair WR. The management of clinically unconfirmed poaitive urine cytology. J Urol 1993; 150:1751-1756.

53. Pieras E, Palou J, Rodriguez L, Millán F, Salvador J, Vicente J. Seguimiento cistoscópico de los tumores vesicales G3T1 iniciales tratados con BCG. Arch Esp de Urol 2001; 54:211-217.

54. Schwalb DM, Herr HW, Sogani PC, Russo P, Sheinfeld J, Fair WR. Positive urine cytology following complete response to intravesical bacillus Calmette Guerin therapy: pattern of recurrence. J Urol 1994; 152:382-387.

55. Coutts AG, Grigor KM, Fowler JW. Urethral dysplasia and bladder cancer in cystectomy specimens. Br J Urol 1985; 57:535-541.

56. Reese JH, Freiha FS, Gelb AB, Lum BL, Torti FM. Transitional cell carcinoma of the prostate in patients undergoing radical cystoprostatectomy. J Urol. 1992 Jan;147(1):92-5.

57. Njinou Ngninkeu B, Lorge F, Moulin P, Jamart J, Van Cangh PJ. Transitional cell carcinoma involving the prostate: a clinicopathological retrospective study of 76 cases. J Urol 2003; 169:149-152.

58. Wood DP Jr, Montie JE, Pontes JE, Levin HS. Identification of transitional cell carcinoma of the prostate in bladder cancer patients: a prospective study. J Urol 1989; 142:83-85.

59. Donat SM, Wei DC, McGuire MS, Herr HW. The efficacy of transurethral biopsy for predicting the long-term clinical impact of prostatic invasive bladder cancer. J Urol 2001; 165:1580-1584.

60. Hardeman SW, Perry A, Soloway MS. Transitional cell carcinoma of the prostate following intravesical therapy for transitional cell carcinoma of the bladder. J Urol 1988; 140:289.

61. Vazina A, Dugi D, Shariat SF, Evans J, Link R, Lerner SP. Stage specific lymph node metastasis mapping in radical cystectomy specimens. J Urol 2004; 171(5):1830-1834.

62. Leissner J, Ghoneim MA, Abol-Enein H, Thuroff JW, Franzaring L, Fisch M, Schulze H, Managadze G, Allhoff EP, el-Baz MA, Kastendieck H, Buhtz P, Kropf S, Hohenfellner R, Wolf HK. Extended radical lymphadenectomy in patients with urothelial bladder cancer: results of a prospective multicenter study. J Urol 2004; 171(1):139-144.

63. Stein JP, Lieskovsky G, Cote R, Groshen S, Feng AC, Boyd S, Skinner E, Bochner B, Thangathurai D, Mikhail M, Raghavan D, Skinner DG. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. J Clin Oncol. 2001 Feb 1;19(3):666-675.

64. Leissner J, Hohenfellner R, Thuroff JW, Wolf HK. Lymphadenectomy in patients with transitional cell carcinoma of the urinary bladder; significance for staging and prognosis. BJU Int 2000; 85(7):817-823.

65. Herr HW, Bochner BH, Dalbagni G, Donat SM, Reuter VE, Bajorin DF. Impact of the number of lymph nodes retrieved on outcome in patients with muscle invasive bladder cancer. J Urol 2002;167(3):1295-1298.

66. Herr HW. Superiority of ratio based lymph node staging for bladder cancer. J Urol 2003;169(3):943-945.

67. Stein JP, Cai J, Groshen S, Skinner DG. Risk factors for patients with pelvic lymph node metastases following radical cystectomy with en bloc pelvic lymphadenectomy: concept of lymph node density. J Urol 2003;170(1):35-41.

68. Bochner BH, Herr HW, Reuter VE. Impact of separate versus en bloc pelvic lymph node dissection on the number of lymph nodes retrieved in cystectomy specimens. J Urol 2001; 166(6): 2295-2296.

69. Herr HW, Faulkner JR, Grossman HB, Natale RB, DeVere White R, Sarosdy MF, Crawford ED. Surgical factors influence bladder cancer outcomes: a cooperative group report. J Clin Oncol 2004; 22:2781-2789.

70. Loehrer PJ Sr, Einhorn LH, Elson PJ, Crawford ED, Kuebler P, Tannock I, Raghavan D, Stuart-Harris R, Sarosdy MF, Lowe BA, et al. A randomized comparison of cisplatin alone or in combination with methotrexate, vinblastine, and doxorubicin in patients with metastatic urothelial carcinoma: a cooperative group study. J Clin Oncol 1992; 10(7):1066-1073.

71. Studer UE, Bacchi M, Biedermann C, Jaeger P, Kraft R, Mazzucchelli L, Markwalder R, Senn E, Sonntag RW. Adjuvant cisplatin chemotherapy following cystectomy for bladder cancer: results of a prospective randomized trial. J Urol 1994; 152(1):81-84.

72. Grossman HB, Natale RB, Tangen CM, Speights VO, Vogelzang NJ, Trump DL, deVere White RW, Sarosdy MF, Wood DP Jr, Raghavan D, Crawford ED. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. N Engl J Med 2003;349(9):859-866.

73. Sternberg CN, Pansadoro V, Calabro F, Schnetzer S, Giannarelli D, Emiliozzi P, De Paula F, Scarpone P, De Carli P, Pizzo M, Platania A, Amini M. Can patient selection for bladder preservation be based on response to chemotherapy? Cancer 2003; 97(7):1644-1652.

74. Sternberg CN and Parmar MK. Neoadjuvant chemotherapy is

not (yet) standard treatment for muscle-invasive bladder cancer. J Clin Oncol 2001;19(18 Suppl):21S-26S.

75. Advanced Bladder Cancer Meta-analysis Collaboration. Neoadjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis. Lancet 2003; 361(9373):1927-1934.
76. Winquist E, Kirchner TS, Segal R, Chin J, Lukka H; Genitourinary Cancer Disease Site Group, Cancer Care Ontario Program in Evidence-based Care Practice Guidelines Initiative. Neoadjuvant chemotherapy for transitional cell carcinoma of the bladder: a systematic review and meta-analysis. J Urol. 2004 Feb;171(2 Pt 1):561-9.
77. Freiha F, Reese J, and Torti FM. A randomized trial of radical cystectomy versus radical cystectomy plus cisplatin, vinblastine and methotrexate chemotherapy for muscle invasive bladder cancer. J Urol 1996;155(2):495-499.
78. Stockle M, Meyenburg W, Wellek S, Voges GE, Rossmann M, Gertenbach U, Thuroff JW, Huber C, Hohenfellner R. Adjuvant polychemotherapy of nonorgan-confined bladder cancer after radical cystectomy revisited: long-term results of a controlled prospective study and further clinical experience. J. Urol 1995;153(1):47-52.
79. Stockle M, Meyenburg W, Wellek S, Voges G, Gertenbach U, Thuroff JW, Huber C, Hohenfellner R. Advanced bladder cancer (stages pT3b, pT4a, pN1 and pN2): improved survival after radical cystectomy and 3 adjuvant cycles of chemotherapy. Results of a controlled prospective study. J. Urol 1992;148(2 Pt 1):302-306.
80. Skinner DG, Daniels JR, Russell CA, Lieskovsky G, Boyd SD, Nichols P, Kern W, Sakamoto J, Krailo M, Groshen S. The role of adjuvant chemotherapy following cystectomy for invasive bladder cancer: a prospective comparative trial. J Urol 1991; 145(3):459-464.
81. Neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: a randomised controlled trial. International collaboration of trialists. Lancet 1999; 354 (9178):533-540.
82. Sauer R, Birkenhake S, Kuhn R, Wittekind C, Schrott KM, Martus P. Efficacy of radiochemotherapy with platin derivatives compared to radiotherapy alone in organ-sparing treatment of bladder cancer. Int J Radiat Oncol Biol Phys 1998;40(1):121-127.
83. Shipley WU, Kaufman DS, Tester WJ, Pilepich MV, Sandler HM; Radiation Therapy Oncology Group. Overview of bladder cancer trials in the Radiation Therapy Oncology Group. Cancer 2003;97(8 Suppl):2115-2119.
84. Michaelson MD, Shipley WU, Heney NM, Zietman AL, Kaufman DS. Selective bladder preservation for muscle-invasive transitional cell carcinoma of the urinary bladder. Br J Cancer 2004;90(3):578-581.
85. Shipley WU, et al. An RTOG phase III trial (#89-03) of neoadjuvant chemotherapy in patients with invasive bladder cancer treated with selective bladder preservation by combined radiation therapy and chemotherapy. ASCO Program/Proc 1998; 17:311a [Abstract 1197].
86. Tester W, Caplan R, Heaney J, Venner P, Whittington R, Byhardt R, True L, Shipley W. Neoadjuvant combined modality program with selective organ preservation for invasive bladder cancer: results of Radiation Therapy Oncology Group phase II trial 8802. J Clin Oncol 1996;14(1):119-126.
87. Hagan MP, Winter KA, Kaufman DS, Wajsman Z, Zietman AL, Heney NM, Toonkel LM, Jones CU, Roberts JD, Shipley WU. RTOG 97-06: initial report of a phase I-II trial of selective bladder conservation using TURBT, twice-daily accelerated irradiation sensitized with cisplatin, and adjuvant MCV combination chemotherapy. Int J Radiat Oncol Biol Phys 2003; 57(3):665-672.
88. Shipley WU, Kaufman DS, Zehr E, Heney NM, Lane SC, Thakral HK, Althausen AF, Zietman AL. Selective bladder preservation by combined modality protocol treatment: long-term outcomes of 190 patients with invasive bladder cancer. Urology 2002;60(1):62-67; discussion 67-68.
89. Colombo R, Bertini R, Salonia A, Da Pozzo LF, Montorsi F, Brausi M, Roscigno M, Rigatti P. Nerve and seminal sparing radical cystectomy with orthotopic urinary diversion for select patients with superficial bladder cancer: an innovative surgical approach. J Urol 2001;165(1):51-55; discussion 55.
90. Vallancien G, Abou El Fettouh H, Cathelineau X, Baumert H, Fromont G, Guillonneau B. Cystectomy with prostate sparing for bladder cancer in 100 patients: 10-year experience. J Urol 2002;168(6):2413-2417.
91. Muto G, Bardari F, D'Urso L, Giona C. Seminal sparing cystectomy and ileocapsuloplasty: long-term followup results. J Urol 2004;172(1):76-80.
92. Algaba F, Santaularia JM, Lamas M, Ayala G. Transitional cell carcinoma of the prostate. Eur Urol 1985; 11: 87-90.
93. Busto Castañón L, Sousa Escandon A, Rodriguez Garcia J, Guitian Barreiro D, Gomez Veiga F, Gonzalez Martin M. Transitional cell carcinoma of the prostate. Report of 2 cases (Article in Spanish) Actas Urol Esp 1990;14: 365-367.
94. Mottola A, Di Cello V, Lunghi F, Saltutti C, Natali A, Bianchi S. Diagnostic, clinical and therapeutic aspects of primary transitional cell carcinoma of the prostate (Article in Italian). Minerva Urol Nefrol 1991; 43: 37-9.
95. Queipo Zaragoza JA, Budia Alba A, Perez Ebri M, Vera Donoso CD, Vera Sempere F, Jimenez Cruz JF. Primary transitional carcinoma of the prostatic ductus (Article in Spanish). Actas Urol Esp 2000; 24: 406-412.
96. Mallen Mateo E, Gil Martinez P, Sancho Serrano C, Garcia de Jalon Martinez A, Pascual Regueiro D, Gil Sanz MJ, Rioja Sanz LA. Pure primary prostate transitional cell carcinoma. A review of our series (Article in Spanish). Actas Urol Esp 2004; 28:377-380.
97. Samsonov VA, Kolomoitsev SV. Dimorphic (transitional-anaplastic) ductal cancer of the prostate (Article in Russian). Arkh Patol 1984; 46: 71-73.
98. Wernert N, Goebbels R, Bonkhoff H, Dhom G. Squamous cell carcinoma of the prostate. Histopathology 1990; 17: 339-344.
99. Sarma DP, Weilbaecher TG, Moon TD. Squamous cell carcinoma of prostate. Urology 1991; 37: 260-262.
100. Okamoto T, Ogiu K, Sato M, Kaneko T, Suzuki Y, Tanji S, Fujioka T. Primary squamous cell carcinoma of the prostate: a case report (Article in Japanese). Hinyokika Kiyo 1996; 42: 67-70.
101. Majeed F, Javed TA, Khan AU, Koerber RK. Primary squamous cell carcinoma of the prostate: a novel chemotherapy regimen. J Urol 2002; 168: 640.
102. Yoshikawa H, Ikeuchi T, Onodera Y, Matsuda N, Sasaki H, Iguchi H, Kai Y. A case of transitional cell carcinoma of the prostate (Article in Japanese). Hinyokika Kiyo 1994; 40: 257-60.
103. Morikawa H, Cho M, Takada S, Fujimoto K, Uemura H, Ozono S, Hirao Y, Natsume O. A case of primary transitional cell carcinoma of the prostate (Article in Japanese). Hinyokika Kiyo 2003; 49: 357-360.
104. Mai KT, Collins JP, Veinot JP. Prostatic adenocarcinoma with urothelial (transitional cell) carcinoma features. Appl Immunohistochem Mol Morphol. 2002; 10: 231-236.
105. Marchal Escalona C, Caballero Alcantara J, Padilla Leon M, Villar Alvarez E, Villalobos J. Primary transitional cell carcinoma of the prostate. An infrequent tumor (Article in Spanish). Actas Urol Esp 1997; 21: 926-930.

106. Wadhwa P, Mandal AK, Singh SK, Goswami AK, Sharma SC, Joshi K, Sharma SK Primary transitional cell carcinoma of the prostate presenting as a rectal ulcer. Urol Int. 2004; 72: 176-177.

107. Varo Solis C, Soto Delgado M, Hens Perez A, Estudillo Gonzalez F, Sanchez Bernal C, Gonzalez Moreno D, Maximiano Vazquez R. Transitional carcinoma of the prostate (Article in Spanish). Actas Urol Esp 1999; 23: 806-810.

108. Konya E, Nose K, Kiwamoto H, Kataoka K, Kajikawa H, Kurita T. A case of primary transitional cell carcinoma of the prostate (Article in Japanese). Hinyokika Kiyo 1999; 45: 439-442.

109. Uemura M, Imamura R, Inoue H, Nishimura K, Mizutani S, Miyoshi S, Mise T. Primary transitional cell carcinoma of prostate: a case report (Article in Japanese). Hinyokika Kiyo. 2000 Jul;46(7):495-498

110. Parra Muntaner L, Verdu Martinez M, Kilani Elmasri S, Monsalve Rodriguez M, Gomez Cisneros S, Martin Castillo J, Garcia Alonso J. Transitional carcinoma of the prostate. Report of a case treated with chemotherapy (Article in Spanish). Arch Esp Urol 1993; 46: 909-912.

111. Greene LF, O'Dea MJ, Dockerty MB. Primary transitional cell carcinoma of the prostate. J Urol 1976; 116: 761-763.

112. Abe K, Ohishi Y, Onodera S, Kiyota H, Asano K. A case of primary transitional cell carcinoma of the prostate responsive to combination chemotherapy with methotrexate, epirubicin and cisplatin (Article in Japanese). Hinyokika Kiyo 1998; 44: 415-417.

113. Hashimoto H, Watanabe Y, Mizunaga M, Sasaki M, Kaneko S, Tokunaka S, Yachiku S, Fujita M. A case of primary transitional cell carcinoma of the prostate (Article in Japanese). Hinyokika Kiyo 1989; 35: 1235-1238.

114. Nicolaisen GS and Williams RD. Primary transitional cell carcinoma of prostate. Urology 1984; 24: 544-549.

115. Dexeus FH, Logothetis CJ, Samuels ML, Ayala AG, Hossan E. Complete responses in metastatic transitional cell carcinoma of the prostate with cisplatin regimens. J Urol 1987; 137: 122-125.

116. Alexander SJ, Lee SS, Bekhrad A. Transitional cell carcinoma of the prostate: response to treatment with cisplatinum and cyclophosphamide. J Urol 1984; 131: 975-977.

117. Sawczuk I, Tannenbaum M, Olsson CA, deVere White R. Primary transitional cell carcinoma of prostatic periurethral ducts. Urology 1985; 25: 339-343.

118. Hashimoto K, Ohnishi N, Katoh Y, Iguchi M, Hamada Y. Primary transitional cell carcinoma of the prostatic urethra: a case report (Article in Japanese) Hinyokika Kiyo 1996; 42: 385-387.

119. Tan MO, Tuncel A, Deniz N, Uzcum N, Dursun A, Bozkirli I. Case report: Incidental primary transitional cell carcinoma of the prostate treated with transurethral prostatectomy only. Tumori 2003; 89: 440-442.

120. Scher HI, Yagoda A, Herr HW, Sternberg CN, Morse MJ, Sogani PC, Watson RC, Reuter V, Whitmore WF Jr, Fair WR. Neoadjuvant M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) for extravesical urinary tract tumors. J Urol 1988;139: 475-477.

121. Takashi M, Sakata T, Nagai T, Kato T, Sahashi M, Koshikawa T, Miyake K. Primary transitional cell carcinoma of prostate: case with lymph node metastasis eradicated by neoadjuvant methotrexate, vinblastine, doxorubicin, and cisplatin (M-VAC) therapy. Urology 1990; 36: 96-98.

122. Stewart DJ and Dahrouge S. Mitoxantrone in the treatment of metastatic transitional cell carcinoma of the prostate. A case report. Am J Clin Oncol 1997; 20: 381-382.

123. Freeman JA, Esring D, Stein JP, Skinner DG. Management of the patient with bladder cancer. Urethral recurrence. Urol Clin North Am 1994;21:645.

124. Levinston AK, Johnson DE, Wishnow KI. Indications of urethrectomy in the era of continent urinary diversion. J Urol 1990;144:73.

125. Hardeman SW and Soloway MS. Urethral recurrence following radical cystectomy. J Urol 1990; 144:666.

126. Tongaonkar HB, Dalal AV, Kulkarni JN, Kamat MR. Urethral recurrences following radical cystectomy for invasive transitional cell carcinoma of the bladder.?Br J Urol 1993;72:910.

127. Tobisu K, Kanai Y, Sakamoto M, Fujimoto H, Doi N, Horie S, Kakizoe T. Involvement of the anterior urethra in male patients with transitional cell-carcinoma of the bladder undergoing radical cystectomy with simultaneous urethrectomy. Jpn J Clin Oncol 1997;27:406.

128. Lebret T, Herve JM, Barre P, Gaudez F, Lugagne PM, Barbagelatta M, et al. Urethral recurrence of transitional cell carcinoma of the bladder. Predictive value of preoperative latero-montanal biopsies and urethral frozen sections during prostatocystectomy. Eur Urol 1998;33:170.

129. Iselin CE, Robertson CN, Webster GD, Vieweg J, Paulson DF. Does prostate transitional cell carcinoma preclude orthotopic bladder reconstruction after radical cystoprostatectomy for bladder cancer? J Urol 1997;158:2123.

130. Jakse G, Algaba F, Fossa S, Stenze A, Sternberg C. EAU Guidelines of bladder cancer. Muscle invasive and metastatic. March 2004.

131. Freeman JA, Tarter TA, Esring D, Stein JP, Elmajian DA, Chen S, et al. Urethral recurrence in patients with orthotopic ileal neobladders. J Urol 1996;156:1615.

132. Huguet J, Palou J, Serrallach M, Sole Balcells FJ, Salvador J, Villavicencio H. Management of urethral recurrence in patients with Studer ileal neobladder. Eur Urol 2003;43:495.

133. Bulbul MA, Wazzan W, Nasr R, Hemady K. The value of cystoscopy, prostate biopsy and frozen-section urethral biopsy prior to orthotopic neobladder substitution. Can J Urol 2001;8:1290.

Committee 9

Chemotherapy for Bladder Cancer: Treatment Guidelines for Neoadjuvant Chemotherapy, Bladder Preservation, Adjuvant Chemotherapy, and Metastatic Cancer

Chair

C. Sternberg (Italy)

Members

S. M. Donat (USA)

J. Bellmunt (Spain)

R. E. Millikan (USA)

W. Stadler (USA)

P. De Mulder (Netherlands)

A. Sherif (Sweden)

H. von der Maase (Denmark)

T. Tsukamoto (Japan)

M. Soloway (USA)

CONTENTS

Chemotherapy for Bladder Cancer: Treatment Guidelines for Neoadjuvant Chemotherapy, Bladder Preservation, Adjuvant Chemotherapy, and Metastatic Cancer

C. Sternberg

S. M. Donat, J. Bellmunt, R. E. Millikan, W. Stadler, P. De Mulder, A. Sherif, H. von der Maase, T. Tsukamoto, M. Soloway

I. NEOADJUVANT CHEMOTHERAPY

Muscle-invasive bladder cancer is one of the most aggressive epithelial tumors, with a high rate of early systemic dissemination. Five-year survival rates depend principally upon pathologic stage and nodal status. With increasing T stage, especially when cancer extends outside of the bladder wall, the prognosis worsens. Failure is usually due to occult metastatic disease present at the time of the initial diagnosis.

1. What Do We Know About Survival From Cystectomy Series?

Cystectomy is considered to be the gold standard of treatment for clinically localized muscle-invasive bladder cancer. This idea has been fortressed by the widespread practice of performing orthotopic bladder substitutions. Five-year survival after cystectomy, however, is at best 65% (including patients with pT2), and, in major series from the University of Padua, Memorial Sloan Kettering Cancer Center, and the University of Southern California, varies from 36% to 48% *(Level 3,* [1-4]*)*. High-risk patients with pathologic stage T3 to T4 and/or positive nodes have an even worse 5-year survival that is somewhere between 25% and 35%.

2. Advantages and Disadvantages of Neoadjuvant Chemotherapy

Neoadjuvant chemotherapy is intended for patients with operable clinical stage T2 to T4a muscle-invasive disease. The rationale for giving chemotherapy prior to cystectomy or full-dose radiation therapy is based on the intent ***to treat micrometastatic disease*** present at diagnosis.

In this way, systemic chemotherapy is delivered very early when the burden of metastatic disease is minimal. The indications for neoadjuvant chemotherapy have additionally evolved to include programs where bladder preservation is planned [5]. Therapy is tolerated better prior to surgery or radiation than after *(Level 4)*. Toxicity is usually less than that seen in patients with metastatic disease, as subjects with localized disease usually have a better performance status *(Level 4)*.

Patients are clinically staged, which may lead to some difficulties in assessing response to therapy. ***A discrepancy between clinical and pathological staging can be expected in some 30% of cases*** **(Level 3,** [6,7]**)**. There is also a delay in cystectomy or radiation therapy during neoadjuvant chemotherapy administration. This may have a negative effect in those patients who don't respond to chemotherapy. In some series, an interval longer than 12 weeks between the diagnosis of muscle invasion and cystectomy is associated with a worse outcome *(Level 3,* [8,9]*)*.

It is unknown whether 3 or 4 cycles of therapy are needed since this question has never been systematically evaluated. Toxicity in the neoadjuvant setting can be determined from 2 large cooperative group randomized trials. In the EORTC/MRC (European

Organization for Research and Treatment of Cancer/Medical Research Council) trial of neoadjuvant CMV chemotherapy (cisplatin, methotrexate, and vinblastine), there was a 1% mortality rate due to CMV [10]. In the American intergroup trial coordinated by SWOG (Southwest Oncology Group), there were no deaths due to M-VAC chemotherapy (methotrexate, vinblastine, doxorubicin [Adriamycin], and cisplatin) *(Level 1,* [11]*)*.

Urologists are sometimes reluctant to pursue neoadjuvant chemotherapy because they fear that it may increase the incidence of perioperative morbidity. There have actually been very few reports to study this [12,13]. In a comparative study of neoadjuvant and adjuvant chemotherapy from the M. D. Anderson Cancer Center, neoadjuvant chemotherapy did not increase perioperative morbidity *(Level 1,* [12]*)*.

3. Randomized Trials - Does Neoadjuvant Chemotherapy Improve Survival?

Neoadjuvant chemotherapy should theoretically have a benefit for patients whether it is given prior to cystectomy or radiation therapy. In the United States and most of Europe, radical cystectomy is preferred for patients who have a good performance status.

Randomized trials have evaluated whether neoadjuvant chemotherapy improves survival. Initial studies were with single agent cisplatin, but more recent trials have employed cisplatin-containing combination chemotherapy. These trials have either shown a trend towards a small benefit or no survival benefit. What has emerged is that most of the trials probably didn't enlist sufficient numbers of patients to detect differences in survival. The results of randomized trials can be found in **Table 1.**

Results from the intergroup trial initiated by SWOG have been published in the New England Journal of Medicine [11]. Patients with cT2 to cT4a urothelial carcinoma of the bladder (TCC) were randomized between 3 cycles of M-VAC chemotherapy followed by cystectomy or cystectomy alone. Enrollment took place over an 11-year period at 126 institutions and patients were stratified according to age (less than 65 years or 65 years or greater) and stage (cT2 vs. cT3 or cT4a). Of the 317 patients entered, 307 were eligible. Only 82% in the M-VAC group and 81% in the surgery group actually underwent cystectomy.

Table 1. Randomized Phase III Trials of Neoadjuvant Chemotherapy

Study Group	Neoadjuvant Arm	Standard Arm	Patients	Survival
Cisplatin Chemotherapy Trials				
Australia/UK [23]	Cis/RT	RT	255	No difference
Canada/NCI [24]	Cis/RT or preop RT+Cystectomy	RT or preop RT+Cystectomy	99	No difference
Canada/NCI [24]	Cis/RT or preop RT+Cystectomy	RT or preop RT+Cystectomy	99	No difference
Spain (CUETO) [25]	Cis/Cystectomy	Cystectomy	121	No difference
Australia/UK [23]	Cis/RT	RT	255	No difference
Combination Chemotherapy Trials				
EORTC/MRC [10]	CMV/RT or Cystectomy	RT or Cystectomy	976	5.5% difference in favor of CMV
SWOG Intergroup [26]	M-VAC/Cystectomy	Cystectomy	298	Benefit with M-VAC ($P = 0.06$)
Italy (GUONE) [15]	M-VAC/Cystectomy	Cystectomy	206	No difference
Italy (GISTV) [27]	M-VEC/Cystectomy	Cystectomy	171	No difference
Genoa [28]	Cis/5FU/RT/Cystectomy	Cystectomy	104	No difference
Nordic 1	ADM/Cis/RT/Cystectomy	RT/Cystectomy	311	No difference, 15% benefit with ADM + Cis in T3-T4a
Nordic 2 [17]	MTX/Cis/Cystectomy	Cystectomy	317	No difference
Abol-Enein [29]	CarboMV/Cystectomy	Cystectomy	194	Benefit with CarboMV

5FU - 5-fluorouracil; ADM - doxorubicin (Adriamycin); Cis - cisplatin; CMV - cisplatin, methotrexate, vinblastine; CarboMV - carboplatin, methotrexate, vinblastine; MTX - methotrexate; M-VAC - methotrexate, vinblastine, doxorubicin, cisplatin; M-VEC - methotrexate, vinblastine, epirubicin, cisplatin; RT- radiation therapy

Median survival was 77 months in patients who received neoadjuvant M-VAC as compared to 46 months in patients who underwent cystectomy alone. The results at present do not show a statistically significant improvement in overall survival (2-sided testing, $P = 0.06$). However, the size of the study has only limited potential to discern a clinically meaningful difference and as such does not rule out the relevance of this approach. There was a trend towards improved survival in favor of M-VAC treated patients. The estimated risk of death was reduced by 25% (hazard ratio [HR]. 1.33) *(Level 1,* [11]*)*.

The EORTC/MRC trial is the largest neoadjuvant randomized trial in the literature. This trial was performed more or less in the same time period as the SWOG trial. In this trial, 976 patients were accrued over a 5 1/2 -year period from 106 institutions. CMV neoadjuvant chemotherapy versus no chemotherapy was evaluated. Since this trial sought to be all-inclusive, local therapy was left up to the choice of the investigators and included cystectomy and RT. When published in 1999, there was a nonsignificant trend towards improvement in survival in patients in the CMV arm [10]. In a 2002 ASCO update, with follow-up of 7.4 years, the data reached statistical significance ($P = 0.048$). There was a 5.5% benefit in favor of patients treated with CMV chemotherapy [14]. Survival at 5 years was 50% compared to 44%, and at 8 years was 43% as opposed to 37% in the CMV arm. Although Hall concluded that there was no change in absolute benefit, patients treated with CMV had a consistent survival benefit that was maintained over time *(Level 1)*.

An almost identical trial to the SWOG study was performed by the GUONE cooperative group in Italy. Over a 6 1/2-year period, 206 patients were randomized to neoadjuvant M-VAC prior to cystectomy versus cystectomy alone [15]. No clear differences in survival were demonstrated as 3-year survival was 62% for the M-VAC treated patients and 68% for the cystectomy alone arm *(Level 2)*.

The Nordic cystectomy I trial evaluated neoadjuvant doxorubicin, cisplatin, and preoperative radiation therapy prior to cystectomy versus preoperative radiation therapy and cystectomy alone. A 15% survival difference in favor of patients treated with chemoradiotherapy was seen in only a subset analysis of patients with T3 or T4 disease [16]. These investigators were unable to confirm this survival advantage in the subsequent Nordic cystectomy II trial in which 317 patients were randomized between cystectomy or cystectomy preceded by methotrexate and cisplatin (without radiation therapy) [17]. However, combining the 2 trials provided positive results in favor of neoadjuvant chemotherapy *(Level 2,* [18]*)*.

What is the value of neoadjuvant chemotherapy [19]? Although more than 2000 patients were evaluated in neoadjuvant chemotherapy randomized trials, the real value of neoadjuvant chemotherapy in terms of survival has not been clarified. For this reason, a meta-analysis of 10 neoadjuvant chemotherapy trials was performed [20]. Unfortunately, original data from the SWOG trial were not available. Overall survival for the whole group and for a subgroup of patients treated with single agent cisplatin was not affected by neoadjuvant chemotherapy. In a subset of patients treated with ***cisplatin-containing combination chemotherapy, a 5% difference (P = 0.016, 95% confidence interval [CI]. 1% to 9%) in favor of neoadjuvant chemotherapy was demonstrated.*** This reflected a change in survival from 45% to 50%, also consistent with only a 1% to 7% difference in survival. The majority of patients were from the EORTC/MRC trial, and, thus, the results are similar to the results in that trial *(Level 2)*.

A very similar meta-analysis of neoadjuvant randomized controlled trials was conducted in Canada [21]. A total of 16 eligible trials with 3315 patients were identified, and 2605 patients provided data suitable for a meta-analysis of overall survival. The pooled HR was 0.90 (95% CI 0.82 to 0.99, $P = 0.02$). Eight trials used cisplatin-based combination chemotherapy and the pooled HR was 0.87 (95% CI 0.78 to 0.96, $P = 0.006$), consistent with an absolute overall survival benefit of 6.5% from 50% to 56.5% (95% CI 2% to 11%). A major pathological response was associated with improved overall survival in 4 trials. Neoadjuvant cisplatin-based chemotherapy improved overall survival in muscle-invasive urothelial carcinoma, but the size of the effect was modest *(Level 2)*.

Surgical factors were evaluated in 268 patients with muscle-invasive bladder cancer who underwent radical cystectomy in the SWOG intergroup trial [22]. Cystectomies were performed by 106 surgeons in 109 institutions. Half of the patients received neoadjuvant M-VAC. Five-year postcystectomy survival and local recurrence rates in all patients receiving cystectomy were 54% and 15%, respectively. Surgical variables associated with longer postcystectomy survival were negative margins (HR 0.37, $P = 0.0007$), and 10 or more nodes removed (HR0.51, *P*

= 0.0001). These associations did not differ by treatment arms (P > 0.21 for all tests of interactions between treatment and surgical variables). Predictors of local recurrence were positive margins (odds ratio [OR]. 11.2, P = 0.0001) and fewer than 10 nodes removed (OR 5.1, P = 0.002). ***The quality of surgery was an independent prognostic factor for outcome after adjustment for pathologic factors and neoadjuvant chemotherapy usage*** **(Level 2).**

Available data suggest that for "average risk" cT2 patients, there is at best a modest benefit of adding chemotherapy to local therapy. Likewise, available studies suggest a much more substantial benefit for patients with high-risk disease, such as cT3b cancers *(Level 2)*.

Furthermore, in cases where there are small differences in survival, it is always regrettable that there are not enough data on quality of life.

Summary

Cystectomy is considered to be the gold standard of treatment for localized muscle-invasive bladder cancer. Neoadjuvant chemotherapy was intended for patients with operable clinical stage T2 to T4a muscle-invasive disease. The rationale for giving chemotherapy prior to cystectomy or full-dose radiation therapy is based on the intent to treat micrometastatic disease present at diagnosis. A discrepancy between clinical and pathological staging can be expected. Toxicity and mortality associated with neoadjuvant chemotherapy is acceptable. Available data suggest that for "average risk" cT2 patients, there is at best a modest benefit of adding chemotherapy to local therapy. Likewise, available studies suggest a much more substantial benefit for patients with high-risk disease, such as cT3b cancers. The quality of the surgery is a confounding factor in these studies. Meta-analysis of cisplatin-containing combination neoadjuvant chemotherapy trials revealed a 5% difference in favor of neoadjuvant chemotherapy. Unfortunately, in this case where there are small differences in survival, it is regrettable that there are not enough data on quality of life.

II. BLADDER PRESERVATION

1. Muscle-Invasive Bladder Cancer: Can Bladder Preservation Achieve Equivalent Survival to Radical Cystectomy ?

The goal of any organ preservation strategy should be to achieve equivalent cancer survival to extirpative surgery, while maintaining quality of life in the patient. Improvement in surgical techniques and the development of continent urinary diversions has resulted in decreased morbidity and better postoperative quality of life for patients undergoing radical cystectomy for muscle-invasive bladder cancer [30], leading some to suggest that bladder preservation is not necessary.

Although mortality rates with radical cystectomy have decreased by half since the 1990s, survival rates with surgery alone have remained steady, with 5-year survival rates of 66% for pathologic stage T2, 35% for pT3, and 27% for pT4 disease (**Table 2**) *(Level 3,* [1,2,11,31-42]*)*. In addition, up to 15% of patients with muscle-invasive disease will have no pathologic residual disease at the time of cystectomy, indicating the potential curability of select patients with transurethral resection alone. These findings suggest that while bladder preservation can be a viable option to radical cystectomy in selected patients, transurethral resection alone will be successful in only a small percentage of patients. ***The risk of clinical understaging in 30% to 50% of patients*** **(Level 3, [43-45]),** ***the limited effectiveness of surgery alone, and the advent of more effective combination chemotherapy have led to a multidisciplinary approach to bladder preservation.***

Prior to effective chemotherapy, early attempts at bladder preservation included the use of transurethral resection of bladder tumors (TURBT) or partial cystectomy alone for solitary tumors amenable to complete surgical resection. ***There are no randomized trials comparing survival with TURBT alone versus cystectomy for the management of muscle-invasive disease***. Five-year overall survival rates in case series from 1951 to 1988 utilizing TURBT alone were 61% for T2a disease and 36% for T2b disease (**Table 3**, [46-52]). similar to radical cystectomy series reported during the same time period (**Table 2**) *(Level 3,* [1,2,11,31-42]*)*. Two large series have now reported similar long-term 10-year survival rates indicating TURBT alone may be an effective bladder-sparing technique in select

Table 2. Comparison of 5-Year Survival for Radical Cystectomy Series Based on Pathologic Stage

Series	Year	N	No Residual Disease at Cystectomy	Operative Mortality	% Survival by Pathologic Stage		
					P2	P3	P4
Richie	1975	134	8%	8.5%	40%	20%	--
Bredael	1980	174	--	4%	51%	25%	18%
Mathur	1981	58	7%	3.4%	77%	33%	29%
Skinner	1984	197	10%	2%	64%	44%	36%
Montie	1984	99	10%	9%	69%	57%	--
Giuliani	1985	202	--	12%	56%	19%	0%
Totals		**864**	**9%**	**7%**	**60%**	**33%**	**21%**
Roehrborn	1991	280	--	2.1%	63%	36%	24%
Pagano	1991	261	9%	1.8%	57%	15%	21%
Wishnow	1992	188	5%	1.1%	79%	46%	33%
Waehre	1993	227	25%	--	61%	36%	29%
Vieweg	1999	686	--	--	58%	22%	15%
Stein	2001	633	6%	3%	72%	48%	33%
Dalbagni	2001	284	10.7%	--	59%	25%	29%
Studer	2003	507	--	4.5%	74%	52%	36%
Grossman*	2003	154	15%	0.6%	75%	--	24%†
Totals		**3220**	**12%**	**2.2%**	**66%**	**35%**	**27%**

* - SWOG 8710 trial Cystectomy alone arm; † - pathologic stage T3 and 4a combined.

Table 3. Early Experience for Muscle-Invasive Bladder Cancer Treated With Transurethral Resection Alone

Series	Year	No. Pts.	B1 (T2a)*	B2 (T2b)*	5-Year Overall Survival
Flocks	1951	142	56%	43%	47%
Milner	1954	88	57%	23%	53%
Barnes et al.	1967	114	--	--	40%
O'Flynn et al.	1975	123	59%	20%	53%
Barnes et al.	1977	75	--	--	31%
Herr	1987	44	70%	57%	68%
Henry et al.	1988	43	63%	38%	--
Totals		**629**	**61%**	**36%**	**49%**

* - Marshall-Jewett (comparable TNM) clinical stage

patients with small tumors. Solsona (1998) reported 10-year follow-up in 176 patients with muscle-invasive disease treated with transurethral resection alone compared to 76 patients with node-negative muscle-invasive disease who underwent radical cystectomy during the same time period [53]. Disease-specific survival rates in those receiving TURBT alone were 81% at 5 years and 75% at 10 years, with 83% maintaining their native bladder at 5 years and 80% at 10 years *(Level 3)*. Of note, all patients treated with TURBT alone in this series had a negative restaging TURBT. Herr reported 10-year follow-up on 99 patients undergoing TURBT alone for muscle-invasive bladder cancer versus 52 patients undergoing immediate cystectomy [54]. The 10-year disease-specific survival for TURBT alone was 76% with 56% maintaining their native bladder, compared to a 71% disease-specific survival in those undergoing immediate radical cystectomy. Interestingly, 73 patients (74%) in the TURBT alone group had no residual tumor on their restaging TURBT and enjoyed an 82% 10-year survival, compared to a 57% 10-year survival in the 26 patients with residual T1 tumor on their restaging TURBT *(Level 3)*.

These data denote the therapeutic importance that TURBT can play in multimodality bladder preservation strategies and the difficulty in interpreting the contribution of each component of a multimodality bladder-sparing approach to survival in reported series. Restaging TURBT has not been performed as standard practice in all combined modality series; therefore, it is difficult to know the impact the TURBT alone may have had on survival. One would expect patients who have been rendered clinical pT0 by either TURBT alone or TURBT plus chemotherapy prior to radiation or cystectomy to have better long-term survival, [55]. and this has been demonstrated in several prospective case series (**Table 4**) *(Level 3,* [56-61]*)* . ***Clinical factors in these studies associated with a better chance of a complete clinical response to TURBT alone or TURBT plus chemotherapy and thus better survival are clinical stage (organ-confined), tumor size less than 3 to 5 cm, no hydronephrosis, no palpable mass, and unifocal disease, [46-61]. although none have been prospectively verified in a randomized trial.***

From phase II trials, bladder preservation may be possible in select patients who respond to neoadjuvant chemotherapy *(Level 3,* [6,57,62]*)*. The question is, Can we preserve the bladder and achieve the same survival as with radical cystectomy? Response to chemotherapy is clearly an important prognostic factor [5,6,11,15]. However, this may represent patient selection, as it is possible that patients who do well have characteristics that would make them survive longer whether or not they were treated with chemotherapy. In the EORTC and SWOG trials, improved survival was clearly shown in patients who

Table 4. Partial Cystectomy/TURBT + Neoadjuvant Chemotherapy for Stage T2-T4a [6,56-61,65]

Series	Year	No. Patients (surgery type)	Chemo	% Clinical CR	% Survival / Years	% Alive with Bladder / Years
Hall et al.	1984	57 (54 TURBT/ 3 PC)	M	58% (33/57)	59% (31/54) / 2 yrs 46% / 3 yrs	79% (19/24) / 2 yrs
Simon et al.	1994	36 (30 completed; 4 PC/12 RC)	M-VAC	47% (14/30)	78% (7/9) / 3 yrs 50% / 5 yrs	20% / 5 yrs
Herr, Bajorin, Scher	1998	60/111 (15 PC/ 28 TURBT/ 17 RC)	M-VAC	54% (60/111)		58% (25/43) / 10 yrs
Thomas et al. (Hall)	1999	50 (44 TURBT/ 6 PC)	CM	76% (38/50)	74% (32/43) / 10 yrs	60% / 4 yrs
	1984	61 (TURBT)	M	--		48% (29/61) overall / 5 yrs 25% for persistent T2 versus 75% for CRs and <T2
Flores et al.	1996	71 (TURBT)	CMV	33% (20/61)	47% / 5 yrs	55% (11/20) of CRs and 0% of PRs / 3 yrs 18% (11/61) overall / 3 yrs
Sternberg et al.	1999	87	M-VAC	51% (40/87)	59% / 5 yrs	57% (24/87) / 4.5 yrs
	1993	TURBT/PC/RC 28 PC	M-VAC		75% / 3 yrs	
de la Rosa et al.	2002	40 (TURBT)	CMV	53% (21/40)	50% for T2 and 25% for T3/4a / 5 yrs 35% / 7 yrs	52% (11/21) CRs / 7 yrs 28% overall / 7 yrs
Sternberg et al.	2003	104 (52 TURBT/ 13 PC/39 RC)	M-VAC	47% (49/104)	60% (31/52) / 5 yrs 69% PC / 7 yrs	44% (23/52) / 5 yrs 31% (4/13) / 7 yrs

CM - cisplatin, methotrexate; CMV - cisplatin, methotrexate, vinblastine; CR - complete response; M - methotrexate; M-VAC - methotrexate, vinblastine, doxorubicin, cisplatin; PC - partial cystectomy; PR - partial response; RC - radical cystectomy; TURBT - transurethral resection of the bladder tumor alone

were pT0 at cystectomy. These may be the same patients who would have benefited from a bladder preservation strategy.

In the SWOG trial, the pT0 rate in patients who received M-VAC was 38% compared to 15% for patients who underwent cystectomy alone ($P < 0.001$).The pT0 rate after CMV in the EORTC/MRC trial was similarly 33%. After two cycles of neoadjuvant M-VAC chemotherapy, the pT0 rate was 40% in the M. D. Anderson trial of M-VAC given both before and after cystectomy (neoadjuvant and adjuvant) versus adjuvant alone [12].

In Rome, 104 patients with clinical T2 to T4N0M0 tumors of the bladder were treated with neoadjuvant M-VAC [6]. After clinical restaging, 52 patients underwent TURBT alone, 13 patients had a partial cystectomy, and 39 patients had a radical cystectomy. Median survival for the entire group was 7.49 years (95% CI 4.86 to 10.00 years). At the TURBT following M-VAC, 49 patients (49%) were T0. Responding patients underwent TURBT or partial cystectomy alone following chemotherapy. Sixty percent of the patients who had M-VAC and TURBT alone were alive at a median follow-up of 56 months (range 10 to 160+). Forty-four percent of the patients in the TURBT group maintained an intact bladder. Of the responding patients with monofocal lesions who underwent partial cystectomy, only 1 required salvage cystectomy and the 5-year survival was 69%.

Of note, in 77 patients who had downstaging to T0 or superficial disease, the 5-year survival was 69%. This is in contrast to the 5-year survival of only 26% in 27 patients who failed to respond and were T2 or greater after chemotherapy. Median survival for 27 patients above 70 years old (median 73 years, range 70-82) was surprisingly long at 90 months (7.5 years). For elderly patients who underwent TURBT and partial cystectomy, the 5-year survival was 67% with a median survival of 9 years. Forty-seven percent preserved their bladders.

Patients who undergo neoadjuvant chemotherapy and bladder preservation should be highly informed, willing to undergo frequent follow-up and multiple cystoscopies, and understand the possibility that cystectomy may become necessary. ***It is the patients with residual disease at the first cystoscopy (within 3 months) after TURBT alone or neoadjuvant chemotherapy plus TURBT in whom we must critically assess the effectiveness of combined modality approaches in comparison to immediate radical cystectomy.***

2. What Can Be Obtained By Adding Radiation Therapy to Neoadjuvant Chemotherapy?

Combining systemic chemotherapy with radiation therapy may allow bladder preservation while sensitizing the tumor to radiation therapy and also treating occult metastases. Trials of combined neoadjuvant chemotherapy and radiation therapy are shown in **Table 5**. This approach has been used by the RTOG (Radiation Therapy Oncology Group), at Massachusetts General Hospital, [62]. and by investigators in Erlangen and Paris [63,64]. Selection criteria for chemoradiation are similar to those that predict a good prognosis after cystectomy. Patients with small T2 or T3 lesions without hydronephrosis who undergo a thorough TURBT tend to fare best *(Level 3)*.

Most patients undergo TURBT followed by chemoradiation, restaging TURBT, and then consol-

Table 5. Trials of Combined Chemotherapy and Radiotherapy

Series	Year	No. Pts	Chemo	5-year survival	5-year survival with intact bladder
Radiation Therapy Oncology Group-study 85-121 [66]	1993	42	DDP	52%	42%
Radiation Therapy Oncology Group-study 88-02 [67]	1996	91	MCV +RT and DDP	62%*	44%
Radiation Therapy Oncology Group-study 89-03 [68]	1998	123	MCV +RT and DDP	48%	36%
University of Erlangen [63,69]	2001	199	DDP or Carbo	52%	41%
University of Paris [64,70]	2001	120	DDP/5FU	63%	
Massachusetts General [71]	2002	190	MCV or DDP/5FU	54%	46%

*4-year survival data; 5FU – 5-fluorouracil; Carbo – carboplatin; DDP – cisplatin; MCV – methotrexate, cisplatin, and vinblastine; RT – radiation therapy

idative radiation therapy in responding patients and cystectomy in nonresponders. Five-year survival rates ranging from 42% to 63%, with organ preservation in approximately 40% of patients, have been reported. ***Although survival is similar to that in contemporary cystectomy series, the combined morbidity of chemotherapy and radiation therapy can be significant.***

The use of newer active chemotherapeutic agents such as gemcitabine and the taxanes in the neoadjuvant setting or as concomitant therapy with radiation remains experimental, but is being incorporated into treatment protocols. Neoadjuvant gemcitabine, paclitaxel, and carboplatin followed by observation or immediate cystectomy is being studied by SWOG. Molecular markers, recurrence rates, and cystectomy-free survival are being evaluated.

As in the case with neoadjuvant chemotherapy alone, patients should be highly motivated to preserve their bladders and understand the possible side effects of combined therapy.

Summary

The goal of any organ preservation strategy should be to achieve equivalent cancer survival to extirpative surgery, while maintaining quality of life in the patient. The risk of clinical understaging in 30% to 50% of patients, the limited effectiveness of surgery alone, and the advent of more effective combination chemotherapy have led to a multidisciplinary approach to bladder preservation. There are no randomized trials comparing survival with TURBT alone versus cystectomy for the management of muscle-invasive disease. Clinical factors associated with a better chance of a complete clinical response to TURBT alone or TURBT plus chemotherapy and thus better survival are clinical stage (organ-confined), tumor size less than 3 to 5 cm, no hydronephrosis, no palpable mass, and unifocal disease. Patients with residual disease at the first cystoscopy (within 3 months) after TURBT alone or neoadjuvant chemotherapy plus TURBT are those in whom we must critically assess the effectiveness of combined modality approaches in comparison to immediate radical cystectomy. Although survival is similar to that in contemporary cystectomy series, the combined morbidity of chemotherapy and radiation therapy can be significant.

III. ADJUVANT CHEMOTHERAPY

Advantages and Disadvantages of Adjuvant Chemotherapy

Adjuvant chemotherapy is widely used after cystectomy in patients with pT3-pT4a and/or pN+ M0 disease in an effort to delay recurrence and prolong survival. This approach of giving chemotherapy after local treatment has led to increases in survival in patients with several other solid tumors [5,72,73].

The rationale for giving adjuvant chemotherapy is that ***local treatment is performed immediately. Treatment decisions are based on pathologic criteria after careful examination of the cystectomy specimen. The availability of sufficient tissue for increasingly sophisticated analysis of putative molecular prognostic and predictive markers is also an advantage. Surgery is not delayed***, and there is no time wasted for those patients who wouldn't respond to chemotherapy. If micrometastases are present, they are treated when at a low volume, rather than waiting for overt metastatic disease.

The advent of ***orthotopic bladder substitutions and the decreased morbidity of cystectomy*** has increased the tendency of urologists to operate early, await the pathologic stage, and then consider adjuvant chemotherapy.

The major disadvantage is that the bladder is not preserved and that there is a delay in starting systemic therapy for occult metastases while focusing first upon the primary tumor. Response cannot be easily evaluated, and the only clinical endpoint that can be assessed is the time to tumor recurrence. An additional disadvantage is the difficulty in administering chemotherapy to patients following cystectomy.

Despite its appeal, there have been very few randomized trials evaluating adjuvant chemotherapy (**Table 6**). Two studies have received attention. In an American phase III prospective trial, Skinner showed a significant increase in time to progression and survival in patients randomized to receive chemotherapy following cystectomy [74]. This study has been criticized for its methodology. Specifically, only a small percentage of potentially eligible patients were entered into the study, therapy varied and changed during the course of the study, and the primary benefit was identified in a subgroup not prospectively identified in the study plan *(Level 2)*.

Table 6. Adjuvant Chemotherapy Following Cystectomy

Investigator	Year	Chemo	Chemo	No Chemo	Results
Logothetis	1988	CISCA	62	71	Benefit, but not randomized
Skinner	1991	CAP	47	44	Benefit, few pts received therapy
Stockle	1992	M-VAC/M-VEC	26	23	Benefit, few pts, no treatment at relapse
Studer	1994	DDP	40	37	No benefit, DDP alone inadequate
Bono	1995	CM	48	35	No benefit for N0M0
Freiha	1996	CMV	25	25	Benefit in relapse-free survival only
Otto	2001	M-VEC	55	53	No benefit

CAP - cyclophosphamide, doxorubicin (Adriamycin), and cisplatin; CISCA - cisplatin, cyclophosphamide, and doxorubicin (Adriamycin); CM - cisplatin, methotrexate; CMV - cisplatin, methotrexate, vinblastine; DDP - cisplatin; M-VAC - methotrexate, vinblastine, doxorubicin (Adriamycin), cisplatin; M-VEC - methotrexate, vinblastine, epirubicin, cisplatin

Another adjuvant chemotherapy trial conducted in Germany was published by Stockle [75,76]. Patients were randomized to cystectomy or cystectomy followed by M-VAC or M-VEC (methotrexate, vinblastine, epirubicin, and cisplatin). Patients had poor risk factors; 60% had positive nodes and most were stage T4. The study was prematurely discontinued with only small patient numbers after an interim analysis showed a benefit for patients randomized to chemotherapy. There was a 27% progression rate in treated versus 82% progression in control patients. Survival was different between the 2 groups as well. Five-year progression-free survival was 59% after the recommendation to receive chemotherapy versus 13% after the recommendation to receive cystectomy alone *(Level 2,* [76]*)* . Biases introduced by early stopping of non-blinded phase III trials have been well-recognized. In addition, and contrary to current standard practice, the investigators did not offer chemotherapy to patients in the observation group at the time of recurrence. Whether this had an effect on the observed survival advantage remains an open question. Of note, in a more recent German series comparing M-VEC to observation after cystectomy, no difference in survival was confirmed *(Level 2,* [77]*)* .

Due to the difficulty in interpretation of these adjuvant chemotherapy trials, a systematic review of published randomized trials of adjuvant cisplatin-containing combination chemotherapy in locally advanced bladder cancer was undertaken. A difference in favor of adjuvant chemotherapy was suggested, but serious methodological flaws were found in all the studies. Major deficiencies included an insufficient sample size, inappropriate early stopping of patient entry, inappropriate statistical analyses, and insufficient reporting of results, all leading to poorly substantiated and supported conclusions *(Level 2,* [78]*)*. More specifically, it was concluded that the ***available trials provide insufficient evidence to support the routine use of adjuvant chemotherapy in clinical practice***.

To address these questions, 2 separate adjuvant studies have been initiated. The EORTC together with other international cooperative groups ***have begun a large randomized adjuvant trial in patients at high risk for relapse***. This patient population was chosen on the basis that chemotherapy is commonly administered to these patients already and the fact that generally fewer patients are required to detect a statistically significant survival advantage in such a population. This study evaluates 4 cycles of immediate chemotherapy versus therapy at the time of relapse in patients with pT3, pT4, or node-positive disease. Three different chemotherapy regimens are permitted: standard dose M-VAC, high dose M-VAC, and gemcitabine-cisplatin (GC) [79-81].

Although it is common to select patients for adjuvant therapy based on risk of recurrence, this does not necessarily imply that these patients are the most likely to benefit from the administered therapy. To this end, a multi-center international adjuvant trial seeks to make therapeutic decisions based upon p53 status. Numerous studies suggest that p53 alterations select a group of patients at high risk for relapse, and data from the University of Southern California also suggest that these patients are most likely to benefit from cisplatin-containing chemotherapy. Therefore, patients with mutant p53 (IHC positive) pT1 or pT2 tumors are randomized after surgery to M-VAC versus observation. Eligible

patients include those with pT1 or pT2 disease, or patients who had T1 or T2 disease at the TURBT and are pT0 at cystectomy.

This is the first randomized study that seeks to use molecular markers to define a group of patients with locally advanced bladder cancer to be targeted for cytotoxic therapy.

Summary

The rationale for giving adjuvant chemotherapy is that local treatment is performed immediately. Treatment decisions are based on pathologic criteria after careful examination of the cystectomy specimen. The availability of sufficient tissue for increasingly sophisticated analysis of putative molecular prognostic and predictive markers is also an advantage. Surgery is not delayed, and there is no time wasted for those patients who wouldn't respond to chemotherapy. If micrometastases are present, they are treated when at a low volume, rather than waiting for overt metastatic disease.

The advent of orthotopic bladder substitutions and the decreased morbidity of cystectomy has increased the tendency of urologists to operate early and then to consider adjuvant chemotherapy. Although it is common to select patients for adjuvant therapy based on risk of recurrence, this does not necessarily imply that these patients are the most likely to benefit from the administered therapy. Available trials provide insufficient evidence to support the routine use of adjuvant chemotherapy in clinical practice. The results of larger collaborative international adjuvant chemotherapy trials will be needed in order to determine the true value of adjuvant chemotherapy.

IV. CHEMOTHERAPY IN METASTATIC DISEASE

Systemic chemotherapy is the only modality that has been shown in phase III trials to improve survival in responding patients with advanced bladder cancer *(Level 1,* [82,83]*)*. The M-VAC regimen, first reported in 1985 by investigators from Memorial Sloan Kettering Cancer Center, revealed that urothelial carcinoma was sensitive to chemotherapy [84]. Patients with measurable lesions were found to have a remarkably high response rate (RR) of 72%, and 36% attained complete response (CR) [79]. Long-term survival was achieved in patients who attained CR. In addition, patients who achieved a CR with the combination of chemotherapy and surgery had twice the survival of patients who had only a partial response (PR) to chemotherapy and no further surgery *(Level 3,* [79]*)*. Overall survival for the whole group was 13.1 months. Chemotherapy was more effective in patients with nodal disease only than in those with visceral metastases [79,83].

In an update of these results, a retrospective analysis of 5 different M-VAC trials encompassing 203 patients from Memorial Sloan Kettering Cancer Center was reported. Among 194 evaluable patients, 46 patients achieved a CR (24%) and 84 patients a PR (43%), yielding an overall RR of 67%. The median survival for all 203 patients was 14.8 months, with a 5-year survival rate of 17% *(Level 3,* [85]*)*. The 5-year survival rate for the 46 patients with a CR after chemotherapy alone was 40%. An additional 30 patients achieved CR after chemotherapy followed by surgery with a 5-year survival rate of 33% *(Level 3,* [86]*)* .

Prognostic factors were predictive of response and survival in these patients. Three risk categories were established on the basis of Karnofsky performance status (KPS) and the presence or absence of visceral metastases. Two factors had an independent prognosis: KPS less than 80% and visceral (lung, liver, or bone) metastasis. Median survival times for patients who had 0, 1, or 2 risk factors were 33, 13.4, and 9.3 months, respectively ($P = 0.0001$). The median survival time of patient cohorts could vary from 9 to 26 months simply by altering the proportion of patients from different risk categories [85].

Prior M-VAC prognostic models for predicting increased toxicity and poor overall survival included the presence of visceral metastases, the presence of abnormal levels of alkaline phosphatase, and a low KPS *(Level 2,* [82,88,89]*)*. Similar findings regarding prognostic factors, risk categories, and survival have been seen when using the new agents in triple combination regimens *(Level 2,* [87]*)*. ***Prognostic factors of patients with metastatic disease in phase II trials can be as important as the therapy actually given to the patients and can be determinant of both response and survival*** **(Level 2).**

Randomized trials in the 1990s showed that M-VAC was superior to single agent cisplatin *(Level 1)* and to the CISCA [(cisplatin, cyclophosphamide, and doxorubicin [Adriamycin]). combination regimen

(Level 1, [82,83]*)*. Although M-VAC was found superior to single agent cisplatin, [82]. long-term survival of the M-VAC patients was poor [88]. In the years since M-VAC was developed, it has been considered the standard therapy for "fit" patients with advanced disease. In the Memorial Sloan Kettering Cancer Center experience, M-VAC has been associated with severe toxicity and long-term survival in only 15% of patients with visceral metastases and 30% with nodal disease. The need for improved efficacy and reduced toxicity has led investigators to continue to seek less toxic and more effective regimens.

Other extensively studied combination regimens in metastatic urothelial carcinoma are cisplatin and methotrexate (CM) and CMV (with vinblastine) *(Level 3,* [90-92]*)*. CMV has been shown to be superior to MV (methotrexate and vinblastine) in a randomized study of 214 patients undertaken by the Medical Research Council *(Level 1,* [93]*)*. The median survival was 7 months versus 4.5 months, and the one-year survival rate was 29% versus 16% for CMV and MV, respectively. The HR for overall survival was 0.48 in favor of CMV. This study demonstrated the significant survival impact of cisplatin and has helped to justify the routine use of cisplatin-based combination chemotherapy. Although CM, CMV, and M-VAC have never been compared in randomized studies, most centers have considered M-VAC as the standard regimen.

More recent combination regimens have shown better survival than was seen in the original M-VAC series (in the range of 14 to 15 months) (**Table 7**) *(Level 3,* [94-98]*)* . This may be the case for multiple reasons including case selection, stage migration (patients with locally-advanced disease mixed together with advanced metastatic disease), better radiological techniques, increased patient awareness, increased use of post-chemotherapy surgery, and newer active agents [99-101].

1. Single Agents

Anti-tumor activity has been demonstrated with several single agents, although these have rarely produced an improvement in survival *(Level 3,* [95,96]*)*. The RR to single agent cisplatin is 17% (12% in phase III trials) [82]. Carboplatin has also been widely used due to its ease of outpatient administration and its milder toxicity profile. Phase II studies in advanced urothelial cancer have shown a 12% to 14% RR [102,103].

Several other novel chemotherapeutic agents have activity in urothelial carcinoma including gemcitabine, the taxanes (paclitaxel and docetaxel), pemetrexed, the epothilones, and vinflunine [95,96,99, 104-106]. Gemcitabine is usually given weekly for 3 weeks, followed by a 1-week rest, in a 4-week schedule. When administered as a single agent, gemcitabine RRs from 23% to 28% have been obtained in both pretreated patients and in those who have not had prior therapy [94,99,104].

Following several phase II studies [104], gemcitabine and cisplatin (GC) were combined in a randomized international trial and compared to M-VAC. Eligibility criteria included patients with T4b, N2 or N3, or M1 disease. The trial revealed a similar effi-

Table 7. Phase III Randomized Trials of Chemotherapy in Metastatic Disease

Author	Chemo	n	RR	MDS	Best Arm
Loehrer [82]	M-VAC	126	39%	12.5	M-VAC
	DDP	120	12%	8.2	
Logothetis [83]	M-VAC	65	65%	12.6	M-VAC
	CISCA	55	46%	10.0	
von der Maase [81]	M-VAC	202	46%	14.8	M-VAC ~ GC
	GC	203	49%	13.8	
Sternberg [80]	HD-M-VAC	134	62%	14.5	HD-M-VAC ~ M-VAC
	M-VAC	129	50%	14.1	
Bamias [121]	M-VAC	109	54%	14.2	M-VAC
	DC	111	37%	9.3	

~ - equivalent; CISCA – cisplatin, doxorubicin (Adriamycin), and cyclophosphamide; DC – docetaxel and cyclophosphamide; DDP – cisplatin; GC – gemcitabine, cisplatin; HD-M-VAC – high dose M-VAC; MDS – median duration of survival; M-VAC – methotrexate, vinblastine, doxorubicin, cisplatin; RR – response rate

cacy with respect to response, time to progressive disease, and survival between the 2 treatment arms, whereas GC was significantly less toxic than M-VAC [81]. The median survival was 13.8 months for GC treated patients and 14.8 months for M-VAC treated patients with an HR of 1.04, but the study did not include enough patients (N=405) to prove that the two regimens had an equivalent efficacy. However, based on the favorable balance in the risk-benefit ratio in favor of GC *(Level 2*, [81]*)*. ***GC is now considered an alternative to M-VAC as a standard of care in patients with locally advanced and metastatic urothelial cancer.***

The 5-year update of the randomized GC versus M-VAC trial is awaited. However, in order to look for the first possible long-term results following treatment with GC, the data from the first 3 phase II studies on GC including a total number of 121 patients have been pooled [107,109]. The median survival for all patients was 13.2 months with an estimated 4-year survival rate of 13%. In patients without visceral metastases, the estimated 4-year survival rate was 20% [110].

High-dose paclitaxel at 250 mg/m^2 by 24-hour continuous infusion every 3 weeks resulted in a RR of 42%, including a 27% CR rate [111]. Since the kidneys are only minimally involved in the excretion of paclitaxel, it can be utilized in patients with impaired renal function [112]. Regimens of combined paclitaxel and cisplatin, usually every 3 weeks, have been evaluated in several phase II studies including more than 100 patients, with an overall RR rate ranging from 50% to 70% (CR rates from 15%-32%) [113-115].

Docetaxel, another widely used taxane, also has displayed activity in urothelial carcinoma. In previously treated patients, the RR was 13% with a median overall survival of 9 months [116]. In untreated patients, the RR was higher (38%) with a median duration of response of 6 months [117]. The combination of docetaxel and cisplatin every 3 weeks has been evaluated in 3 studies [118-120]. In more than 120 patients, the overall RR was 52% to 62% and the median overall survival ranged from 8.2 to 13.6 months.

Although phase II studies of 2-drug combinations of paclitaxel or docetaxel with cisplatin have shown activity in untreated patients with RRs that are similar to M-VAC, a recent randomized study reported by the Hellenic Group has shown inferior activity of the docetaxel and cisplatin (DC) combination compared to classical M-VAC. Although this study was designed to detect a survival advantage for DC, the investigators instead observed that survival was inferior for patients treated with DC. Because performance status was not used in this trial as a prospective stratification variable, the treatment arms were not appropriately balanced. After adjusting for prognostic factors, difference in time to progression remained significant (HR 1.61, P = 0.005), whereas survival difference was not significant at the 5% level (HR, 1.31; P = 0.089) *(Level 2*, [121]*)*.

2. Dose Intensification

In a phase III EORTC Genitourinary Group trial, high dose M-VAC given every 2 weeks with G-CSF (granulocyte colony stimulating factor) was compared to M-VAC [80]. It was possible to deliver twice the dose of cisplatin and doxorubicin with less toxicity, fewer dose delays, and in half the time if G-CSF was routinely added. This trial revealed less toxicity with high dose M-VAC due to the addition of G-CSF. Although there was not a significant difference found in median survival (more than 14 months in both arms), there was a significant difference in favor of high dose M-VAC in RR and CR rate. The 2-year survival was 35% with high dose M-VAC compared to 25% with M-VAC *(Level 1)*. One could conjecture that this regimen might be useful in the neoadjuvant or adjuvant setting since the cycle length is much shorter and it is delivered in half the time of traditional M-VAC *(Level 4)*.

3. Reducing Toxicity in Unfit or Elderly Patients

Strategies have been developed to minimize toxicity in patients who are unfit, elderly, or have compromised renal function [122]. Unfortunately, ***there is not a general consensus as to who is considered "unfit."***

The EORTC is evaluating gemcitabine and carboplatin compared to methotrexate, carboplatin, and vinblastine in patients ineligible for cisplatin-based chemotherapy [123].

Cisplatin-related toxicity is not inconsequential in elderly patients. Renal insufficiency limits wide applicability, and long-term survival remains poor.

These protocols seek less toxic treatments for patients that cannot undergo cisplatin-based regimens, primarily for medical reasons. One major problem is that "unfit" or "poor performance status"

(PS) patients are often mixed or confused with "elderly" and "renal-impaired patients." PS 2 patients are a very poor prognosis group but may still respond to chemotherapy. Clinical trials should be designed to clearly distinguish among these 3 groups of patients. Efficacy data about the use of chemotherapeutic combinations in clearly defined "unfit" patients as effective and safe palliative therapy are still scant. Outside of a clinical trial, M-CAVI (methotrexate, carboplatin, vinblastine), carboplatin-gemcitabine, CBDCA (carboplatin)-paclitaxel, gemcitabine-taxane, or monotherapy with gemcitabine, CBDCA, or a taxane can be considered for "unfit" patients on an individual basis *(Level 3)*.

The combination of gemcitabine and carboplatin has been evaluated in predefined "unfit" bladder cancer patients in a dose finding study (PS above 2 and or creatinine clearance less than 60 mL/min). Using this combination, investigators reported an overall RR of 43.5% with a median survival of 14.4 months in 16 patients ineligible for the cisplatin-based regimen ("unfit" patient population) [123]. The preliminary results found in this phase II trial using the carboplatin-gemcitabine doublet prompted an EORTC randomized phase II/III trial comparing carboplatin-gemcitabine with M-CAVI in patients ineligible for cisplatin-based chemotherapy, which is ongoing.

4. Doublet Combination Chemotherapy

Paclitaxel and carboplatin combination chemotherapy regimens have been routinely used in advanced urothelial carcinoma [124]. Several studies with carboplatin (AUC 5-6) and paclitaxel (150-225 mg/m^2) have reported RRs ranging from 21% to 63%, though many of the responses were partial [125-127]. In the SWOG study, the RR was only 14% with a very poor median survival of only 9 months [125]. This may have been due to a predominance of patients with poor PS and with visceral metastases, suggesting that the regimen was not necessarily to blame for the poor results. Nonetheless, a number of investigators now question whether or not it is ethical to give "fit" patients this combination.

Since no phase III trials have compared carboplatin and paclitaxel to the standard regimens of M-VAC or GC (the ECOG trial of M-VAC versus carboplatin and paclitaxel was closed early due to poor accrual), it is probably best not to use this regimen except in patients with extremely poor renal function who cannot tolerate cisplatin *(Level 3)*.

Carboplatin-based combinations reported in the 1990s (the combination of carboplatin with methotrexate and vinblastine [carbo-MV and M-CAVI].) have shown RRs of 30% to 40% and a median survival of 8 to 10 months [102,128], and, again, these results were inferior to those obtained with M-VAC. Two underpowered randomized studies also suggested the suboptimal efficacy of carboplatin-based chemotherapy *(Level 3,* [129,130]*)*.

The platinum-free combination of gemcitabine and paclitaxel combination chemotherapy has been evaluated in several studies with favorable results, even in pretreated patients [131,136]. In a phase II Italian and Israeli study, 40 patients who had been pretreated with M-VAC had a 60% overall RR (28% CR and 33% PR) when treated with paclitaxel 150 mg/m^2 and gemcitabine 2 500-3 000 mg/m^2 every 2 weeks on an outpatient basis [131]. Of note, the RR was 27% in patients who had failed prior chemotherapy for metastatic disease within the last year as compared to 80% for patients who received prior neoadjuvant or adjuvant M-VAC. The median survival for all patients was 14.4 months, equal to that seen in another American study [132].

Of concern was the pulmonary toxicity observed in the Hoosier group study in which a weekly regimen of this combination (gemcitabine 1 000 mg/m2 and paclitaxel 110 mg/m2 on days 1, 8, and 15 every 4 weeks) was utilized in patients who were not pretreated [133].

The combination of docetaxel 40 mg/m^2 and gemcitabine 800 mg/m^2 on days 1 and 8 every 3 weeks has been evaluated in pretreated patients by the ECOG [137]. Of 29 patients, 25 were evaluable for response. The authors concluded that this regimen was active with 5 patients attaining a PR (20% overall RR) and 10 having stable disease. A combination of doxorubicin and gemcitabine has been reported to lead to a 36% CR rate, but this has not been confirmed.

The combination of gemcitabine and a taxane is active and well-tolerated as first- or second-line treatment of patients with advanced urothelial carcinoma, as well as in patients with compromised renal function *(Level 3)*.

5. Triplet Combination Chemotherapy

Other combinations using the taxanes and gemcitabine have been put forth as possible alternatives to M-VAC. Both gemcitabine and paclitaxel have been incorporated into multi-agent chemotherapy combinations with cisplatin or carboplatin [98]. Phase II data from 2 gemcitabine-based triplets are currently available.

The Spanish regimen of gemcitabine, cisplatin, and paclitaxel (GCP) has led to a very high RR of around

78% (CR 28% and PR 50%) [138]. The first report from the phase I trial reported survival of 24 months, probably due to patient selection. In the multi-center phase II study, the median survival was 15.6 months, more consistent with other currently available regimens [139].

The American combination study of gemcitabine, paclitaxel, and carboplatin (rather than cisplatin) compared favorably to the Spanish regimen with a 14.7 month median survival and 1-year survival of 59%. The RR was 68% (CR 32% and PR 36%) [140].

In a third study from Memorial Sloan Kettering Cancer Center, the triplet ifosfamide, paclitaxel (Taxol), and cisplatin (Platinol) (ITP) revealed a 68% overall RR (CR 23% and PR 45%). Median survival was 20 months in this single center study [141].

Whether or not we are really improving upon survival with these new triplet regimens will be determined from the results of ongoing phase III trials.

Summary

Single agent chemotherapy has rarely produced improvement in survival. Systemic cisplatin-based combination chemotherapy is the only current modality which has been shown to improve survival in responding patients with advanced bladder cancer in randomized phase III trials. Prognostic factors of patients with metastatic disease in phase II trials can be as important as the therapy actually given to the patients and can be determinant of both response and survival. The randomized study comparing GC and M-VAC did not include enough patients to prove equivalency but, based on a similar efficacy of GC compared with M-VAC and a favorable risk-benefit ratio, GC is now considered an alternative to M-VAC as a standard of care in patients with locally advanced and metastatic urothelial cancer.

Phase II studies of two-drug combinations of paclitaxel or docetaxel with cisplatin have shown activity in untreated patients, with RRs similar to M-VAC, but, in one randomized trial (where treatment arms were not appropriately balanced), M-VAC has proved to be superior in terms of time to progression. When HD-M-VAC (given every 2 weeks with G-CSF) was compared to M-VAC, it was possible to deliver twice the dose of cisplatin and doxorubicin with less toxicity, fewer dose delays, and in half the time, with a significant difference in favor of HD-M-VAC in RR and CR rate but without a significant survival difference. Strategies have been developed to minimize toxicity in patients who are “unfit,” “elderly,” or have “compromised renal function.” Clinical trials should be designed to clearly distinguish among these 3 groups of patients. Outside of a clinical trial, MCAVI, carboplatin-gemcitabine, CBDCA-paclitaxel, gemcitabine-taxane, or monotherapy with gemcitabine, CBDCA, or a taxane could be used in “unfit” patients on an individual basis. Since no phase III trials have compared carboplatin and paclitaxel to M-VAC or to GC, this regimen should not be used in “fit” patients. Two small randomized studies using “classical” agents have suggested the suboptimal efficacy of carboplatin-based combination chemotherapy compared with M-VAC. Even with the incorporation of the “new” agents, carboplatin-based regimens should not be used in “fit” patients outside of a clinical trial. The combination of gemcitabine and a taxane is active and well-tolerated as first- or second-line treatment of patients with advanced urothelial carcinoma and in patients with compromised renal function.

Whether or not newer triplet regimens can improve survival remains to be seen in ongoing phase III trials.

RECOMMENDATIONS

I. NEOADJUVANT CHEMOTHERAPY

1. Cystectomy is considered the gold standard of treatment for localized muscle-invasive bladder cancer *(Grade B).*

2. In considering neoadjuvant chemotherapy, a discrepancy between clinical and pathological staging can be expected *(Grade B).*

3. Toxicity and mortality associated with neoadjuvant chemotherapy is acceptable *(Grade B).* However, there are few data available on quality of life.

4. Meta-analysis of cisplatin-containing combination neoadjuvant chemotherapy trials revealed a modest difference in favor of neoadjuvant chemotherapy *(Grade B).*

5. Available data suggest that for "average risk" cT2 patients, there is at best a modest benefit of adding chemotherapy to local therapy. Likewise, all available studies suggest a much more substantial benefit for patients with high-risk disease, such as cT3b cancers *(Grade B).*

6. The quality of the surgery is a confounding factor in these studies. *(Grade B)*

II. BLADDER PRESERVATION

1. The goal of any organ preservation strategy should be to achieve equivalent cancer survival to extirpative surgery, while maintaining quality of life in the individual patient *(Grade D).*

2. The risk of clinical understaging in 30% to 50% of patients, and the advent of more effective combination chemotherapy have led to a multidisciplinary approach to bladder preservation *(Grade C).*

3. There are no randomized trials comparing bladder-sparing approaches with radical cystectomy.

4. Clinical factors associated with a better prognosis with TURBT with or without chemotherapy include clinical stage (organ-confined), tumor size less than 3 to 5 cm, absence of hydronephrosis, unifocal disease, and no CIS *(Grade C).*

5. After TURBT alone or chemotherapy plus TURBT, if residual disease is found at the first cystoscopy (within 3 months), patients with muscle-invasive cancer should be considered for immediate radical cystectomy. *(Grade C)*

6. Although survival is similar to that in contemporary cystectomy series, the combined morbidity of chemotherapy and radiation therapy can be significant *(Grade C).*

7. Patients who undergo bladder preservation approaches should be highly motivated to preserve their bladders and understand the possible side effects of combined therapy and the burden of long-term follow-up *(Grade C).*

III. ADJUVANT CHEMOTHERAPY

1. The advent of orthotopic bladder substitutions and the decreased morbidity of cystectomy have increased the tendency of urologists to operate early and then consider adjuvant chemotherapy *(Grade C).*

2. With adjuvant chemotherapy following cystectomy, local treatment is performed immediately and treatment decisions can be based on pathologic criteria. The availability of sufficient tissue for increasingly sophisticated analysis of putative molecular prognostic and predictive markers is also an advantage *(Grade D).*

3. Available trials provide insufficient evidence to support the routine use of adjuvant chemotherapy in clinical practice *(Grade B).*

4. The results of larger collaborative international adjuvant chemotherapy trials will be needed in order to determine the true value of adjuvant chemotherapy *(Grade D).*

IV. CHEMOTHERAPY IN METASTATIC DISEASE

1. Single agent chemotherapy has rarely produced improvement in survival *(Grade A).*

2. Systemic cisplatin-based combination chemotherapy is the only current modality which has been shown to improve survival in responding patients with advanced bladder cancer in phase III trials *(Grade A).*

3. Prognostic factors of patients with metastatic disease in phase II trials can be as important as the therapy actually given to the patients and can be determinant of both response and survival *(Grade B).*

4. The randomized study comparing GC and M-VAC did not include enough patients to prove equivalency, but, based on a similar efficacy of GC compared with M-VAC and a favorable risk-benefit ratio, GC is now considered an alternative to M-VAC as a standard of care in patients with metastatic urothelial cancer *(Grade B).*

5. Phase II studies of 2 drug combinations of paclitaxel or docetaxel with cisplatin have shown activity in untreated patients with RRs similar to M-VAC, but in 1 randomized trial - where treatment arms may not have been perfectly balanced - M-VAC was superior *(Grade C).*

6. When HD-M-VAC (given every 2 weeks with G-CSF) was compared to M-VAC, it was possible to deliver twice the dose of cisplatin and doxorubicin with less toxicity, fewer dose delays, and in half the time, with a significant difference in favor of HD-M-VAC in RR and CR rate but without a significant survival difference *(Grade B)* .

7. Strategies have been developed to minimize toxicity in patients who are “unfit”, “elderly,” or have “compromised renal function”. Clinical trials should be designed to clearly distinguish among these 3 groups of patients. Low morbidity regimens are being developed for “unfit” patients *(Grade C).*

8. Since no phase III trials have compared carboplatin and paclitaxel to M-VAC or to GC, this regimen should not be used in “fit” patients *(Grade C).*

9. Routine use of carboplatin is not supported in fit patients with good creatinine clearance *(Grade C).*

10. Whether or not we can improve survival with newer triplet regimens will depend upon the results of ongoing phase III trials *(Grade D).*

REFERENCES

1. Stein JP, Lieskovs.ky G, Cote R, Groshen S, Feng AC, Boyd S, Skinner E, Bochner B, Thangathurai D, Mikhail M, Raghavan D, Skinner DG. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. J Clin Oncol 2001;19(3):666-75.
2. Dalbagni G, Genega E, Hashibe M, Zhang ZF, Russo P, Herr H, Reuter V. Cystectomy for bladder cancer: a contemporary series. J Urol 2001;165(4):1111-6.
3. Bassi P, Ferrante GD, Piazza N, Spinadin R, Carando R, Pappagallo G, Pagano F. Prognostic factors of outcome after radical cystectomy for bladder cancer: a retrospective study of a homogeneous patient cohort. J Urol 1999;161(5):1494-7.
4. Ghoneim MA, el-Mekresh MM, el-Baz MA, el-Attar IA, Ashamallah A. Radical cystectomy for carcinoma of the bladder: critical evaluation of the results in 1,026 cases. J Urol 1997;158(2):393-9.
5. Sternberg CN. Current perspectives in muscle invasive bladder cancer. Eur J Cancer 2002;38(4):460-7.
6. Sternberg CN, Pansadoro V, Calabrò F, Schnetzer S, Giannarelli D, Emiliozzi P, De Paula F, Scarpone P, De Carli P, Pizzo M, Platania A, Amini M. Can patient selection for bladder preservation be based on response to chemotherapy? Cancer 2003;97(7):1644-52.
7. Herr HW and Scher HI. Surgery of invasive bladder cancer: is pathologic staging necessary? Sem Oncol 1990;17:590-7.
8. Sanchez-Ortiz RF, Huang WC, Mick R, Van Arsdalen KN, Wein AJ, Malkowicz SB. An interval longer than 12 weeks between the diagnosis of muscle invasion and cystectomy is associated with worse outcome in bladder carcinoma. J Urol 2003;169(1):110-5.
9. Stein JP. Contemporary concepts of radical cystectomy and the treatment of bladder cancer. J Urol 2003;169(1):116-7.
10. Neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: a randomised controlled trial. International collaboration of trialists. Lancet 1999;354 (9178):533-40.
11. Grossman HB, Natale RB, Tangen CM, Speights VO, Vogelzang NJ, Trump DL, deVere White RW, Sarosdy MF, Wood DP Jr, Raghavan D, Crawford ED. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. N Engl J Med 2003;349(9):859-66. Erratum in: N Engl J Med 2003;349(19):1880.
12. Millikan R, Dinney C, Swanson D, Sweeney P, Ro JY, Smith TL, Williams D, Logothetis C. Integrated therapy for locally advanced bladder cancer: final report of a randomized trial of cystectomy plus adjuvant M-VAC versus cystectomy with both preoperative and postoperative M-VAC. J Clin Oncol 2001;19:4005-13.
13. Hall MC, Swanson DA, Dinney CP. Complications of radical cystectomy: impact of the timing of perioperative chemotherapy. Urol 1996;47(6):826-30.
14. Hall RR. Updated results of a randomised controlled trial of neoadjuvant cisplatin (C), methotrexate (M) and vinblastine (V) chemotherapy for muscle-invasive bladder cancer. Proc Annu Meet Am Soc Clin Oncol 21(1), 178a. 2002.
15. Bassi P, Pagano F, Pappagallo G, Cosciani S, Lembo A, Anselmo G, Sperandio P, Signorelli G, Di Tonno F, Hurwitz E, Lavelli D, Seren M, Piazza N, Faggiano L, Fiorentino M. Neoadjuvant M-VAC of invasive bladder cancer: The G.U.O.N.E. multicenter phase III trial. Eur Urol 33 Suppl 1, 142. 1998.
16. Malmstrom PU, Rintala E, Wahlqvist R, Hellstrom P, Hellsten S, Hannisdal E. Five year follow-up of a prospective trial of radical cystectomy and neoadjuvant chemotherapy. J Urol 1996;155:1903-6.
17. Sherif A, Rintala E, Mestad O, Nilsson J, Holmberg L, Nilsson S, Malmstrom PU; Nordic Urothelial Cancer Group. Neoadjuvant cisplatin-methotrexate chemotherapy of invasive bladder cancer - Nordic cystectomy trial 2. Scand J Urol Nephrol 2002;36(6):419-25.
18. Sherif A, Rintala E, Mestad O, Nilsson J, Holmberg L, Nilsson S, Malmstrom PU. Neoadjuvant Platinum based combination chemotherapy improves overall survival in patients with locally advanced bladder cancer. A Meta-analysis of two Nordic collaborative studies of 620 patients. J Urol 169, 307. 2003.
19. Sternberg CN and Parmar MKB. Neoadjuvant chemotherapy is not (yet) standard treatment for muscle invasive bladder cancer. J Clin Oncol 2001;19(Suppl 1):21S-6S.
20. Advanced Bladder Cancer Meta-analysis Collaboration. Neoadjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis. Lancet 2003;361(9373):1927-34.
21. Winquist E, Kirchner TS, Segal R, Chin J, Lukka H. Genitourinary Cancer Disease Site Group of Cancer Care Ontario Program in Evidence-based Care Practise Guidelines Initiative. Neoadjuvant Chemotherapy for Transitional Cell Carcinoma of the Bladder: A Systematic Review and Meta-Analysis. J Urol 2004;171(2):561-9.
22. Herr HW, Faulkner JR, Grossman HB, Natale RB, deVere White R, Sarosdy MF, Crawford ED. Surgical factors influence bladder cancer outcomes: a cooperative group report. J Clin Oncol 2004; 15:22(14);2781-9.
23. Wallace DM, Raghavan D, Kelly KA, Sandeman TF, Conn IG, Teriana N, Dunn J, Boulas J, Latief T. Neoadjuvant (pre-emptive) cisplatin therapy in invasive transitional cell carcinoma of the bladder. Br J Urol 1991;67:608-15.
24. Coppin CM, Gospodarowicz MK, James K, Tannock IF, Zee B, Carson J, Pater J, Sullivan LD. Improved local control of invasive bladder cancer by concurrent cisplatin and preoperative or definitive radiation. The National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 1996;14(11):2901-7.
25. Martinez Pineiro JA, Gonzalez Martin M, Arocena F. Neoadjuvant cisplatin chemotherapy before radical cystectomy in invasive transitional cell carcinoma of the bladder: prospective randomized phase III study. J Urol 1995;153:964-73.
26. Natale RB, Grossman HB, Blumenstein B, Vogelzang N, Trump DL, Speights VO, de Vere White R, Crawford ED. SWOG 8710 (INT-0080): Randomized phase III trial of neoadjuvant M-VAC and cystectomy versus cystectomy alone in patients with locally advanced bladder aancer. Proc Am Soc Clin Oncol 20(1), 2a. 2001.
27. GISTV (Italian Bladder Cancer Study Group). Neoadjuvant treatment for locally advanced bladder cancer: a randomized prospective clinical trial. J Chemother 1996;8:345-6.
28. Orsatti M, Curotto A, Canobbio L. Alternating chemo-radiotherapy in bladder cancer: a conservative approach. Int J Radiation Oncology Biol Phys 1995;33:173-8.
29. Abol-Enein H, El Makresh M, El Baz M, Ghoneim M. Neoadjuvant chemotherapy in treatment of invasive transitional bladder cancer: a controlled, prospective randomised study. Br J Urol 1997;80(suppl 2):49.
30. Hautmann RE. Urinary diversion: ileal conduit to neobladder. J Urol 2003;169(3):834-42.
31. Ritchie JP, Skinner DG, Kaufman JJ. Radical cystectomy for carcinoma of the bladder: 16 years of experience. J Urol 1975;113:186-9.
32. Bredael JJ, Croker BP, Glenn JF. The curability of invasive blad-

der cancer treated by radical cystectomy. Eur Urol 1980;6(4):206-10.

33. Mathur VK, Krahn HP, Ramsey EW. Total cystectomy for bladder cancer. J Urol 1981;125:784.-6.
34. Skinner DG, Lieskovsky G. Contemporary cystectomy with pelvic node dissection compared to preoperative radiation therapy plus cystectomy in the management of invasive bladder cancer. J Urol 1984;131:1069-72.
35. Montie JE, Straffon RA, Stewart BH. Radical cystectomy without radiation therapy for carcinoma of the bladder. J.Urol. 1984;131:477-82.
36. Giuliani L, Gilberti C, Martorrama G. Results of radical cystectomy for primary bladder cancer. Urol 1985; 26(3):243-45.
37. Roehrborn CG, Sagalowsky AI, Peters PC. Long-term patient survival after cystectomy for regional metastatic transitional cell carcinoma of the bladder. J Urol 1991;146(1):36-9.
38. Pagano F, Bassi P, Galetti TP, Meneghini A, Milani C, Artibani W, Garbeglio A. Results of contemporary radical cystectomy for invasive bladder cancer: a clinicopathological study with an emphasis on the inadequacy of the tumor, nodes and metastases classification. J Urol 1991;145:45-50.
39. Wishnow KI, Tenney DM. Will Rogers and the results of radical cystectomy for invasive bladder cancer. Urol Clin North Am 1991;18:529-37.
40. Waehre H, Ous S, Klevmark B, Kvarstein B, Urnes T, Ogreid P, Johansen TE, Fossa SD. A bladder cancer multi-institutional experience with total cystectomy for muscle invasive bladder cancer. Cancer, 1993; 72(10): 3044-3051.
41. Vieweg J, Gschwend JE, Herr HW, Fair WR. The impact of primary stage on survival in patients with lymph node positive bladder cancer. J Urol 1999;161(1):72-6.
42. Madersbacher S, Hochreiter W, Burkhard F, Thalmann GN, Danuser H, Markwalder R, Studer UE. Radical cystectomy for bladder cancer today-a homogenous series without neoadjuvant therapy. J Clin Oncol 2003;15;21(4)):690-6.
43. Frazier HA, Robertson JE, Dodge RK, Paulson DF. The value of pathologic factors in predicting cancer-specific survival among patients treated with radical cystectomy for transitional cell carcinoma of the bladder and prostate. Cancer 1993;71(12):3993-4001.
44. Amling CL, Thrasher JB, Frazier HA, Dodge RK, Robertson JE, Paulson DF. Radical cystectomy for stages Ta, Tis and T1 transitional cell carcinoma of the bladder. J Urol 1994;151(1):31-5.
45. Stein JP. Indications for early cystectomy. Sem Urol Oncol 2000;18:289-95.
46. Flocks RH. Treatment of patients with carcinoma of the bladder. JAMA 1951;145(5):295-301.
47. Milner WA. The role of conservative surgery in the treatment of bladder tumors. Br J Urol, 1954; 26:375-86.
48. Barnes RW, Bergman RT, Hadley HL, Love D. Control of bladder tumors by endoscopic surgery. J Urol 1967;97:864-8.
49. O'Flynn JD, Smith JD, Hanson JS. Transurethral resection for the assessment and treatment of vesical neoplasms. A review of 800 consecutive cases. Eur Urol 1975;1:38-40.
50. Barnes RW, Dick AL, Hadley HL, Johnston OL. Survival following transurethral resection of bladder carcinoma. Cancer Res. 1977;37:2895-8.
51. Herr HW. Conservative management of muscle-infiltrating bladder cancer: Prospective experience. J.Urol. 1987;138:1162-3.
52. Henry K, Miller J, Mari M, Loening SJ, Falow B. Comparison of transurethral resection to radical therapies for stage B bladder tumors. J Urol 1988;140:964-7.
53. Solsona E, Iborra I, Ricos JV, Monros JL, Casanova J, Calabuig C. Feasibility of transurethral resection for muscle infiltrating carcinoma of the bladder: long-term followup of a prospective study. J Urol 1998;159:95-9.
54. Herr HW. Transurethral resection of muscle-invasive bladder cancer: 10-Year outcome. J Clin Oncol 2001;19(1):89-93.
55. Herr HW. Uncertainty, stage, and outcome of invasive bladder cancer. J Urol 1994 Aug;152(2 Pt 1):401-402.
56. Hall RR, Newling DW, Ramsden PD, Richards B, Robinson MR, Smith PH. Treatment of invasive bladder cancer by local resection and high dose methotrexate. Br J Urol. 1984;56:668-72.
57. Herr HW, Bajorin DF, Scher HI. Neoadjuvant chemotherapy and bladder sparing surgery for invasive bladder cancer: ten-year outcome. J Clin Oncol 1998;16 (4):1298-301.
58. Thomas DJ, Roberts JT, Hall RR, Reading J. Radical transurethral resection and chemotherapy in the treatment of muscle invasive bladder cancer: a long-term follow-up. Br J Urol 1999;83(4):432-7.
59. Angulo JC, Sanchez-Chapado M, Lopez JI, Flores N. Primary cisplatin, methotrexate and vinblastine aiming at bladder preservation in invasive bladder cancer: multivariate analysis on prognostic factors. J Urol 1996;155 (6):1897-902.
60. Sternberg CN, Pansadoro V, Calabrò F, Marini L, van Rijn A, De Carli P, Giannarelli D, Platania A, Rossetti A. Neoadjuvant chemotherapy and bladder preservation in locally advanced transitional cell carcinoma of the bladder. Ann Oncol. 1999;10(11):1301-5.
61. De la Rosa F, Garcia-Carbonero R, Passas J, Rosino A, Lianes P, Paz-Ares L. Primary cisplatin, methotrexate and vinblastine chemotherapy with selective bladder preservation for muscle invasive carcinoma of the bladder: Long-term followup of a prospective study. J Urol 2002;167(6):2413-8.
62. Shipley WU, Kaufman DS, Tester WJ, Pilepich MV, Sandler HM, Radiation Therapy Oncology Group. Overview of bladder cancer trials in the Radiation Therapy Oncology Group. Cancer 2003;97(8 Suppl):2115-9.
63. Sauer R, Birkenhake S, Kühn R, Wittekind C, Martus P, Dunst J, Schrott KM. Muscle-Invasive Bladder Cancer: Transurethral Resection and Radiochemotherapy as an Organ-Sparing Treatment Option. In: Petrovich Z, Baert L, Brady LW. Carcinoma of the bladder. Springer, 1998:205-14.
64. Housset M, Dufour B, Maulard-Durdux C, Chretien Y, Mejean A. Concomitant fluorouracil (5-FU)-cisplatin (CDDP) and bifractionated split course radiation therapy (BSCRT) for invasive bladder cancer. Proc Am Soc Clin Oncol. 16,319A. 1997.
65. Srougi M and Simon SD. Primary methotrexate, vinblastine, doxorubicin and cisplatin chemotherapy and bladder preservation in locally invasive bladder cancer: a 5 year follow-up. J Urol 1994;151:593-7.
66. Tester W, Porter A, Asbell S. Combined modality program with possible organ preservation for invasive bladder carcinoma:results of RTOG protocol 85-12. Int J Radiation Oncology Biol Phys 1993;25:783-90.
67. Tester W, Caplan R, Heaney J. Neoadjuvant combined modality program with selective organ preservation for invasive bladder cancer: Results of Radiation Therapy Oncology Group phase II trial 8802. J Clin Oncol 1996;14 (1):119-26.
68. Shipley WU, Winter KA, Kaufman DS, Lee WR, Heney NM, Tester WR, Donnelly BJ, Venner PM, Perez CA, Murray KJ, Doggett RS, True LD. Phase III trial of neoadjuvant chemotherapy in patients with invasive bladder cancer treated with selective bladder preservation by combined radiation therapy and chemotherapy: initial results of Radiation Therapy Oncology Group 89-03. J Clin Oncol 1998;16(11):3576-83.

69. Sauer R and Rodel C. Biological selection for organ conservation. Eur J Cancer 37(Suppl 6), S286. 2001.

70. Durdux C, Housset M, Dufour B. Altered fractionation in chemo-radiation for bladder cancer. Eur J Cancer 37(Suppl 6), S286. 2001.

71. Shipley WU, Kaufman DS, Zehr E, Heney NM, Lane SC, Thakral HK, Althausen AF, Zietman AL. Selective bladder preservation by combined modality protocol treatment: long-term outcomes of 190 patients with invasive bladder cancer. Urol 2002;60(1):62-7.

72. Sternberg CN. Neoadjuvant and adjuvant chemotherapy of bladder cancer: Is there a role? Ann Oncol 2002;13 (Suppl 4):273-9.

73. de Braud F, Maffezzini M, Vitale V, Bruzzi P, Gatta G, Hendry WF, Sternberg CN. Bladder cancer. Crit Rev Oncol Hematol 2002;41(1):89-106.

74. Skinner DG, Daniels JR, Russell CA, Lieskovsky G, Boyd SD, Nichols P, Kern W, Sakamoto J, Krailo M, Groshen S. The role of adjuvant chemotherapy following cystectomy for invasive bladder cancer: a prospective comparative trial. J Urol. 1991;145:459-67.

75. Stockle M, Meyenburg W, Wellek S, Voges G, Gertenbach U, Thuroff JW, Huber C, Hohenfellner R. Advanced bladder cancer (stages pT3b, pT4a, pN1 and pN2): improved survival after radical cystectomy and 3 adjuvant cycles of chemotherapy. Results of a controlled prospective study. J Urol. 1992;148:302-7.

76. Stockle M, Meyenburg W, Wellek S. Adjuvant polychemotherapy of nonorgan-confined bladder cancer after radical cystectomy revisited: long term results of a controlled prospective study and further clinical experience. J Urol 1995;153:47-52.

77. Otto T, Börgemann C, Krege S, Rübben H, and participating clinicians*, *Hartung R, Haubensak K, Henning K, Hertle L, Jocham D, Kröpfl D, Rassweiler J, Roth S, Tauber R, Tschada R, Weissbach L. Adjuvant chemotherapy in locally advanced bladder cancer (PT3/PN1-2,M0) - a phase III study. Eur Urol 39 (Suppl 5), 147. 2001.

78. Sylvester R and Sternberg C. The role of adjuvant combination chemotherapy after cystectomy in locally advanced bladder cancer: What we do not know and why. Ann Oncol 2000;11(7):851-6.

79. Sternberg CN, Yagoda A, Scher HI, Watson RC, Geller N, Herr HW, Morse MJ, Sogani PC, Vaughan ED, Bander N, et al. Methotrexate, vinblastine, doxorubicin, and cisplatin for advanced transitional cell carcinoma of the urothelium. Efficacy and patterns of response and relapse. Cancer 1989;64:2448-58.

80. Sternberg CN, de Mulder PHM, Schornagel JH, Théodore C, Fossa SD, van Oosterom AT, Witjes F, Spina M, van Groeningen CJ, de Balincourt C, Collette L; European Organization for Research and Treatment of Cancer Genitourinary Tract Cancer Cooperative Group. Randomized phase III trial of high-dose-intensity methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) chemotherapy and recombinant human granulocyte colony-stimulating factor versus classic MVAC in advanced urothelial tract tumors: European Organization for Research and Treatment of Cancer Protocol no. 30924. J Clin Oncol 2001;19(10):2638-46.

81. von der Maase H, Hansen SW, Roberts JT, Dogliotti L, Oliver T, Moore MJ, Bodrogi I, Albers P, Knuth A, Lippert CM, Kerbrat P, Sanchez Rovira P, Wersall P, Cleall SP, Roychowdhury DF, Tomlin I, Visseren-Grul CM, Conte PF. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. J Clin Oncol 2000;18(17):3068-77.

82. Loehrer P, Einhorn LH, Elson PJ, Crawford ED, Kuebler P, Tannock I, Raghavan D, Stuart-Harris R, Sarosdy MF, Lowe BA, et al. A randomized comparison of cisplatin alone or in combination with methotrexate, vinblastine, and doxorubicin in patients with metastatic urothelial carcinoma: a cooperative group study. J Clin Oncol. 1992;10:1066-73.

83. Logothetis CJ, Dexeus FH, Finn L, Sella A, Amato RJ, Ayala AG, Kilbourn RG. A prospective randomized trial comparing MVAC and CISCA chemotherapy for patients with metastatic urothelial tumors. J Clin Oncol 1990;8:1050-5.

84. Sternberg CN, Yagoda A, Scher HI, Watson RC, Ahmed T, Weiselberg LR, Geller N, Hollander PS, Herr HW, Sogani PC, et al. Preliminary results of methotrexate, vinblastine, doxorubicin and cisplatin (M-VAC) for transitional cell carcinoma of the urothelium. J Urol 1985;133:403-7.

85. Bajorin DF, Dodd PM, Mazumdar M, Fazzari M, McCaffrey JA, Scher HI, Herr H, Higgins G, Boyle MG. Long-term survival in metastatic transitional-cell carcinoma and prognostic factors predicting outcome of therapy. J Clin Oncol 1999;17(10):3173-81.

86. Dodd PM, McCaffrey JA, Herr H, Mazumdar M, Bacik J, Higgins G, Boyle MG, Scher HI, Bajorin DF. Outcome of postchemotherapy surgery after treatment with methotrexate, vinblastine, doxorubicin, and cisplatin in patients with unresectable or metastatic transitional cell carcinoma. J Clin Oncol. 1999;17(8):2546-52.

87. Bellmunt J, Albanell J, Paz-Ares L, Climent MA, Gonzalez-Larriba JL, Carles J, de la Cruz JJ, Guillem V, Diaz-Rubio E, Cortes-Funes H, Baselga J; Spanish Oncology Genitourinary Group. Pretreatment prognostic factors for survival in patients with advanced urothelial tumors treated in a phase I/II trial with paclitaxel, cisplatin, and gemcitabine. Cancer 2002;95(4):751-7.

88. Saxman SB, Propert KJ, Einhorn LH, Crawford ED, Tannock I, Raghavan D, Loehrer PJ Sr, Trump D. Long-term follow-up of a phase III intergroup study of cisplatin alone or in combination with methotrexate, vinblastine, and doxorubicin in patients with metastatic urothelial carcinoma: a cooperative group study. J Clin Oncol 1997;15(7):2564-9.

89. Geller NL, Sternberg CN, Penenberg D, Scher H, Yagoda A. Prognostic factors for survival of patients with advanced urothelial tumors treated with methotrexate, vinblastine, doxorubicin, and cisplatin chemotherapy. Cancer 1991;67:1525-31.

90. Hillcoat BL, Raghavan D, Matthews J, Kefford R, Yuen K, Woods R, Olver I, Bishop J, Pearson B, Coorey G, et al. A randomized trial of cisplatin versus cisplatin plus methotrexate in advanced cancer of the urothelial tract. J Clin Oncol. 1989;7:706-9.

91. Stoter G, Splinter TA, Child JA, Fossa SD, Denis L, van Oosterom AT, de Pauw M, Sylvester R. Combination chemotherapy with cisplatin and methotrexate in advanced transitional cell cancer of the bladder. J Urol 1987;137:663-7.

92. Harker W, Meyers FJ, Freiha FS, Palmer JM, Shortliffe LD, Hanningan JF, McWhirter KM, Torti FM. Cisplatin, methotrexate, and vinblastine (CMV): an effective chemotherapy regimen for metastatic transitional cell carcinoma of the urinary tract. A Northern California Oncology Group study. J Clin Oncol 1985;3:1463-70.

93. Mead GM, Russell M, Clark P, Harland SJ, Harper PG, Cowan R, Roberts JT, Uscinska BM, Griffiths GO, Parmar MK. A randomized trial comparing methotrexate and vinblastine (MV) with cisplatin, methotrexate and vinblastine (CMV) in advanced transitional cell carcinoma: results and a report on prognostic factors in a Medical Research Council study. MRC Advanced Bladder Cancer Working Party. Br J Cancer 1998;78(8):1067-75.

94. Vogelzang NJ. Future directions for gemcitabine in the treatment of genitourinary cancer. Sem Oncol 2002;29 (1 Suppl 3):40-5.

95. Calabrò F and Sternberg CN. High-risk metastatic urothelial cancer: chances for cure? Curr Opin Urol 2002;12(5):441-8.

96. Calabrò F and Sternberg CN. New drugs and new approaches for the treatment of metastatic urothelial cancer. World J Urol 2002;20(3):158-66.

97. Sternberg CN. Second-line treatment of advanced transitional cell carcinoma of the urothelial tract. Curr Opin Urol 2001;11(5):523-9.

98. Hussain M, Vaishampayan U, Smith DC. Novel gemcitabine-containing triplets in the management of urothelial cancer. Sem Oncol 2002;29 (1 Suppl 3):20-4.

99. Sternberg CN. Gemcitabine in bladder cancer. Sem Oncol 2000;27(1):31-9.

100. Sengelov L, Kamby C, von der Maase H. Metastatic urothelial cancer: evaluation of prognostic factors and change in prognosis during the last twenty years. Eur Urol 2001;39(6)):634-42.

101. Juffs HG, Moore MJ, Tannock IF. The role of systemic chemotherapy in the management of muscle-invasive bladder cancer. Lancet Oncol 2002;3(12):738-47.

102. Bellmunt J, Albanell J, Gallego OS, Ribas A, Vicente P, Carulla J, De Torres J, Morote J, Lopez M, Sole LA. Carboplatin, methotrexate, and vinblastine in patients with bladder cancer who were ineligible for cisplatin-based chemotherapy. Cancer. 1992;70(7):1974-9.

103. Waxman J and Barton C. Carboplatin-based chemotherapy for bladder cancer. Cancer Treat Rev 1993;19(suppl. C):21-5.

104. von der Maase H. Gemcitabine in transitional cell carcinoma of the urothelium. Expert Rev Anticancer Ther 2003;3(1):11-9.

105. Misset JL. Brief communication: use of the multitargeted antifolate pemetrexed (Alimta) in genitourinary cancer. Semin.Oncol. 2002;29(1 Suppl 3):36-9.

106. Sternberg CN and Vogelzang NJ. Gemcitabine, paclitaxel, pemetrexed and other newer agents in urothelial and kidney cancers. Crit Rev Oncol Hematol 2003;46 Suppl:S105-15.

107. von der Maase H, Andersen L, Crino L, Weinknecht S, Dogliotti L. Weekly gemcitabine and cisplatin combination therapy in patients with transitional cell carcinoma of the urothelium: a phase II clinical trial. Ann Oncol 1999;10 (12):1461-5.

108. Kaufman D, Raghavan D, Carducci M, Levine EG, Murphy B, Aisner J, Kuzel T, Nicol S, Oh W, Stadler W. Phase II trial of gemcitabine plus cisplatin in patients with metastatic urothelial cancer. J Clin Oncol 2000;18 (9):1921-7.

109. Moore MJ, Winquist EW, Murray N, Tannock IF, Huan S, Bennett K, Walsh W, Seymour L. Gemcitabine plus cisplatin, an active regimen in advanced urothelial cancer: a phase II trial of the National Cancer Institute of Canada Trials Group. J Clin Oncol 1999;17(9):2876-81.

110. Stadler WM, Hayden A, von der Maase H, Roychowdhury D, Dogliotti L, Seymour L, Kaufmann D, Moore M. Long-term survival in phase II trials of gemcitabine plus cisplatin for advanced transitional cell cancer. Urol Oncol 2002;7(4)):153-7.

111. Roth BJ, Dreicer R, Einhorn LH. Significant activity of paclitaxel in advanced transitional cell carcinoma of the urothelium: a phase II trial of the Eastern Cooperative Oncology Group. J Clin Oncol 1994;12 (11):2264-70.

112. Dreicer R, Gustin DM, See WA, Williams RD. Paclitaxel in advanced urothelial carcinoma: its role in patients with renal insufficiency and as salvage therapy. J Urol 1996;156(5):1606-8.

113. Murphy BA, Johnson DR, Smith J, Koch M, DeVore R, Blanke C, Johnson DH. Phase II trial of paclitaxel and cisplatin for metastatic or locally unresectable urothelial cancer. Proc Amer Soc Clin Oncol Vol 15;1996. Abstract # 617, p. 245.

114. Dreicer R, Manola J, Roth BJ, Cohen MB, Hatfield AK, Wilding G. Phase II study of cisplatin and paclitaxel in advanced carcinoma of the urothelium: an Eastern Cooperative Oncology Group Study. J Clin Oncol 2000;18(5):1058-61.

115. Burch PA, Richardson RL, Cha SS, Sargent DJ, Pitot HC 4th, Kaur JS, Camoriano JK. Phase II study of paclitaxel and cisplatin in advanced urothelial carcinoma. J Urol 2000;164:1538-42.

116. McCaffrey JA, Hilton S, Mazumdar M. Phase II trial of docetaxel in patients with advanced or metastatic transitional cell carcinoma. J Clin Oncol 1997;15 (5):1853-7.

117. de Wit R, Kruit WH, Stoter G, de Boer M, Kerger J, Verweij J. Docetaxel (Taxotere): an active agent in metastatic urothelial cancer; results of a phase II study in non-chemotherapy pretreated patients. Br J Cancer 1998;78(10):1342-5.

118. Sengelov L, Kamby C, Lund B, Engelholm SA. Docetaxel and cisplatin in metastatic urothelial cancer: a phase II study. J Clin Oncol 1998;16(10):3392-7.

119. Dimopoulos MA, Bakoyannis C, Georgoulias V, Papadimitriou C, Moulopoulos LA, Deliveliotis C, Karayannis A, Varkarakis I, Aravantinos G, Zervas A, Pantazopoulos D, Fountzilas G, Bamias A, Kyriakakis Z, Anagnostopoulos A, Giannopoulos A, Kosmidis P. Docetaxel and cisplatin combination chemotherapy in advanced carcinoma of the urothelium: a multicenter phase II study of the Hellenic Cooperative Oncology Group. Ann Oncol 1999;10(11):1385-8.

120. Garcia del Muro X, Marcuello E, Guma J, Paz-Ares L, Climent MA, Carles J, Parra MS, Tisaire JL, Maroto P, Germa JR. Phase II multicentre study of docetaxel plus cisplatin in patients with advanced urothelial cancer. Br J Cancer 2002;86(3):326-30.

121. Bamias A, Aravantinos G, Deliveliotis C. Docetaxel and cisplatin with granulocyte colony-stimulating factor (G-CSF) versus M-VAC with G-CSF in advanced urothelial carcinoma: a multicenter, randomized, phase III study from the Hellenic Cooperative Oncology Group. J Clin Oncol 2004;22:220-8.

122. Sternberg CN and Calabrò F. The Management of Bladder Cancer in the Elderly. Tumori 2002;88 (1 Suppl 1):S128-S129.

123. Bellmunt J, de Wit R, Albanell J, Baselga J. A feasibility study of carboplatin with fixed dose of gemcitabine in 'unfit' patients with advanced bladder cancer. Eur J Cancer 2001;37(17):2212-5.

124. Stadler WM. Gemcitabine doublets in advanced urothelial cancer. Sem Oncol 2002;29 (1 Suppl 3):15-9.

125. Small EJ, Lew D, Redman BG, Petrylak DP, Hammond N, Gross HM, Eastham JA, Crawford ED. Southwest Oncology Group Study of paclitaxel and carboplatin for advanced transitional cell carcinoma: the importance of survival as a clinical trial end point. J Clin Oncol 2000;18 (13):2537-44.

126. Vaughn DJ, Malkowicz SB, Zoltick B, Mick R, Ramchandani P, Holroyde C, Armstead B, Fox K, Wein A. Paclitaxel plus carboplatin in advanced carcinoma of the urothelium: an active and tolerable outpatient regiment. J Clin Oncol. 1998;16(1):255-60.

127. Redman BG, Smith DC, Flaherty L, Du W, Hussain M. Phase II trial of paclitaxel and carboplatin in the treatment of advanced urothelial carcinoma. J Clin Oncol 1998;16(5):1844-8.

128. Boccardo F, Pace M, Guarneri D, Canobbio L, Curotto A, Martorana G. Carboplatin, methotrexate, and vinblastine in the treatment of patients with advanced urothelial cancer. A phase II trial. Cancer 1994;73(7):1932-6.

129. Bellmunt J, Ribas A, Eres N, Albanell J, Almanza C, Bermejo B, Sole LA, Baselga J. Carboplatin-based versus cisplatin-based chemotherapy in the treatment of surgically incurable advanced bladder carcinoma. Cancer 1997;80(10):1966-72.

130. Petrioli R, Frediani B, Manganelli A, Barbanti G, De Capua B, De Lauretis A, Salvestrini F, Mondillo S, Francini G. Comparison between a cisplatin-containing regimen and a carboplatin-

containing regimen for recurrent or metastatic bladder cancer patients: A randomized phase II study. Cancer 1996;77(2):344-51.

131. Sternberg CN, Calabrò F, Pizzocaro G, Marini L, Schnetzer S, Sella A. Chemotherapy with every-2-week gemcitabine and paclitaxel in patients with transitional cell carcinoma who have received prior cisplatin-based therapy. Cancer 2001;92(12):2993-8.
132. Meluch AA, Greco FA, Burris HA 3rd, O'Rourke T, Ortega G, Steis RG, Morrissey LH, Johnson V, Hainsworth JD. Paclitaxel and gemcitabine chemotherapy for advanced transitional-cell carcinoma of the urothelial tract: a Phase II trial of the Minnie Pearl Cancer Research Network. J Clin Oncol 2001;19(12):3018-24.
133. Parameswaran R, Fisch MJ, Ansari RH, Fox EP, Sweeney CJ, Einhorn LH. A hossier oncology group phase II study of weekly paclitaxel and gemcitabine in advanced transitional cell (TCC) carcinoma of the bladder. Proc Annu Meet Am Soc Clin Oncol 20(1), 200a. 2001.
134. Guardino AE and Srinivas S. Gemcitabine and paclitaxel as second line chemotherapy for advanced urothelial malignancies. Proc Annu Meet Am Soc Clin Oncol 21(2), 150b. 2002.
135. Fechner GH, Siener R, Reimann M, Strunk R, Golinski C, Heimbach D, Wiebusch HW, Langbein S, Ehlert C, Bannowsky A, Heidenreich A, Kühn M, Albers P. Randomized phase II trial of gemcitabine and paclitaxel with or without maintenance treatment in patients with cisplatin refractory transitional cell carcinoma. J Urol 167(4 Suppl), 284. 2002.
136. Kaufmann DS, Carducci MA, Kuzel T, Todd MB, Raghavan D, Oh WK, Smith MR, Nicol SJ, Stadler WW. Gemcitabine (G) and paclitaxel (P) every two weeks (GP2w): a completed multicenter phase II trial in locally advanced or metastatic urothelial cancer (UC). Proc Annu Meet Am Soc Clin Oncol 21(1), 192a. 2002.
137. Manola JB, Dreicer R, Wilding G. Gemcitabine and docetaxel in advanced carcinoma of the urothelium: report of a phase II Eastern Cooperative Oncology Group trial. Proc Annu Meet Am Soc Clin Oncol 2002;21(1):200a.
138. Bellmunt J, Guillem V, Paz-Ares L, González-Larriba JL, Charles J, Batiste-Alentorn E, Saenz A, Lopez-Brea M, Font A, Nogue M, Bastus R, Climent MA, de la Cruz JJ, Albanell J, Banus JM, Gallardo E, Diaz-Rubio E, Cortes-Funes H, Baselga J. Phase I-II study of paclitaxel, cisplatin, and gemcitabine in advanced transitional-cell carcinoma of the urothelium. Spanish Oncology Genitourinary Group. J Clin Oncol 2000;18(18):3247-55.
139. Bellmunt J, de Wit R, Albiol S, Tabernero JM, Albanell J, Baselga J. New drugs and new approaches in metastatic bladder cancer. Crit Rev Oncol Hematol 2003;47(2):195-206.
140. Hussain M, Vaishampayan U, Du W, Redman B, Smith DC. Combination paclitaxel, carboplatin, and gemcitabine is an active treatment for advanced urothelial cancer. J Clin Oncol 2001;19(9):2527-33.
141. Bajorin DF, McCaffrey JA, Dodd PM, Hilton S, Mazumdar M, Kelly WK, Herr H, Scher HI, Icasiano E, Higgins G. Ifosfamide, paclitaxel, and cisplatin for patients with advanced transitional cell carcinoma of the urothelial tract: final report of a phase II trial evaluating two dosing schedules. Cancer 2000;88(7):1671-8.

Committee 10

Radiotherapy for Bladder Cancer

Chairs

M. Milosevic (Canada)

M. Gospodarowicz (Canada)

A. Zietman (USA)

Members

F. Abbas (Pakistan)

K. Haustermans (Belgium)

L. Moonen (Netherlands)

C. Rödel (Germany)

M. Schoenberg (USA)

W. Shipley (USA)

CONTENTS

Radiotherapy for Bladder Cancer

M. Milosevic, M. Gospodarowicz, A. Zietman

F. Abbas, K. Haustermans, L. Moonen, C. Rödel, M. Schoenberg, W. Shipley

Radiotherapy has been used to treat cancer for over 100 years and is an effective tool in the armamentarium against many tumors, including bladder cancer. The goal of radiation is to eradicate tumor while preserving the structure and function of the surrounding normal tissues. The utility of radiation in treating cancer arises because of differences in the radiation response of tumors and normal tissues. In general, tumor cells are less able than normal cells to repair DNA strand breaks that are produced by radiation. These DNA breaks cause a cascade of downstream molecular events that eventually lead to cell death. Differences in the molecular response of tumor and normal tissue cells to radiation results in a favorable therapeutic ratio, where the beneficial effects of carefully planned and delivered radiation treatment outweigh the potential for serious toxicity.

Radiotherapy as radical treatment for bladder cancer has declined in many parts of the world because of 1) a perception that radical cystectomy is more effective at both controlling the index primary tumor and preventing the development of new bladder tumors, 2) improvements in surgical techniques for radical cystectomy, and 3) more acceptable alternatives for urinary diversion, including stomal and orthotopic neobladders, that arguably reduce the need for bladder conservation. However, parallel advances in high precision radiation treatment planning and delivery, along with an improved understanding of radiobiology, have reinforced the important role that radiotherapy plays in the treatment of this disease.

There has never been a phase 3 study of cystectomy versus radiotherapy with salvage cystectomy. There are, however, numerous reports of treatment with either modality alone. These studies are very difficult to compare for reasons that largely revolve around patient selection for one treatment versus the other. Patients who are most appropriate for radical cystectomy are usually young and otherwise healthy. They often have small tumors that are confined to the bladder and are able to tolerate adjuvant systemic treatment. In contrast, patients treated with radiation tend to be older with other serious illnesses and more extensive disease at diagnosis. This introduces bias in favor of surgically treated patients, which can only partially be corrected by accounting for obvious imbalances in known prognostic factors.

In general, surgery, radiotherapy, and chemotherapy should be thought of as complementary treatments for bladder cancer. There are numerous situations where combinations of these 3 modalities yield better results than any single modality alone. For example, transurethral resection of bladder cancer at diagnosis may improve the effectiveness of radical radiotherapy, and salvage cystectomy is an important component of the composite management plan for anyone receiving radiotherapy with curative intent. Radiation is now frequently combined with chemotherapy to treat muscle-invasive bladder cancer, with the aim of both improving the local effectiveness and preventing the development of distant metastases. This consensus guideline focuses on the optimal use of radiotherapy, either alone or in combination with these other modalities, in the ***radical treatment*** of bladder cancer. The following 5 questions will be addressed:

1. Can radiotherapy eradicate muscle-invasive bladder cancer and preserve normal bladder function without compromising overall patient survival?
2. Which patients with bladder cancer should be considered for curative treatment with radiotherapy?

3. How should radiotherapy optimally be delivered to maximize patient benefit?
4. What is the best radiation prescription for treating bladder cancer?
5. How should patients with bladder cancer optimally be managed after radiotherapy?

I. CAN RADIOTHERAPY ERADICATE MUSCLE-INVASIVE BLADDER CANCER AND PRESERVE NORMAL BLADDER FUNCTION WITHOUT COMPROMISING OVERALL PATIENT SURVIVAL?

There is substantial evidence that radiotherapy is effective treatment for bladder cancer. This is derived from numerous sources, including laboratory studies that demonstrate the high sensitivity of bladder cancer cell lines to radiation, large single-institution experiences with external and/or interstitial radiotherapy, population-based studies of bladder cancer treatment in defined geographic regions, phase 1 and 2 studies of radiotherapy with neoadjuvant or concurrent chemotherapy, and phase 3 randomized trials that include a radiotherapy control arm.

1. External Beam Radiotherapy

Table 1 summarizes the published experience with external beam radiotherapy alone as treatment for bladder cancer. Most are retrospective descriptions of the experience at a single institution over several decades, and often do not consider changes with time in patient assessment, imaging, stage classification, radiotherapy technique, and supportive treatment. Management strategies vary from institution to institution, including the criteria for salvage cystectomy, making detailed comparison of results problematic. Nevertheless, there are consistent patterns among the studies with respect to both short and long-term response to radiation.

Together, they provide strong evidence that a substantial proportion of patients, particularly those with small tumors at presentation, are cured with radiotherapy and maintain normal bladder function.

Radical external beam radiotherapy produces complete regression of muscle-invasive bladder cancer in approximately 70% of patients [1-7]. and 30% to 50% have sustained local control (complete tumor regression without subsequent recurrence in the bladder) [5,8,9]. Nevertheless, distant metastases develop in more than 50% of patients, [4]. and long-term overall survival is in the range of only 25% to 30% [1,4,10-12]. Salvage cystectomy for progressive or recurrent disease after radiotherapy, which is an important part of the integrated management plan, has historically been undertaken in less than 30% of patients [4,5,10,13]. This at least in part reflects the poor general health and prognosis of patients treated with radiation, who often have relative contraindications to surgery. Overall, approximately 80% of patients who survive long-term following external beam radiotherapy have intact, well-functioning bladders [14].

2. Interstitial Radiotherapy

Interstitial radiation, as an alternative to external beam treatment, allows a high dose of radiation to be delivered focally to a small area of the bladder with relative sparing of surrounding normal tissues. It has been used to treat selected, otherwise well patients with solitary tumors that are less than 5 cm in diameter and preferably confined to the bladder wall (pT1 or pT2) [15-20]. The largest experience to date with interstitial radiotherapy for bladder cancer was described by Rozan et al. based on 205 patients treated at 8 radiotherapy centers in France [19]. Most patients had solitary T1 or T2 tumors, and partial cystectomy was performed in 58% of cases prior to interstitial radiotherapy. Tumor recurred locally in 17% of patients, and frequently this was the only site of recurrence. The long-term overall survival was 67%. These results are superior to those generally described for external beam radiotherapy, probably reflecting the more favorable characteristics of patients suitable for interstitial treatment.

3. Preoperative Radiotherapy

Planned preoperative pelvic radiotherapy, while not commonly prescribed in modern practice because of the availability of effective systemic chemotherapy, was advocated in the past as a means of reducing pelvic recurrence. Patients most likely to benefit from this approach are those with locally extensive primary tumors (pT3b or pT4), which implies a 30% to 50% risk of lymph node metastases and a similar risk of pelvic recurrence after cystectomy alone [21-24]. Preoperative radiotherapy is unlikely to yield a significant improvement in survival since the clinical and surgicopathologic prognostic factors that predict

Table 1. External Beam Radiotherapy Alone for Muscle-invasive Bladder Cancer

Study, year	n	5-year Survival by T-category (%)			
		T2	T3 (T3a/T3b)	T4	Overall
Goffinet, 1975	384	35-42	20		
Yu, 1985	356	42	(35/23)		
Goodman, 1981	470				38
Duncan, 1986	963	40	26	12	30
Blandy, 1988	614	27	38	9	
Jenkins, 1988*	182	46	35		40
Gospodarowicz, 1991*	355	50	(38/28)		46
Jansson, 1991*	319	31	16	6	28
Davidson, 1990*	709	49	28	2	25
Greven, 1990	116	59	10	0	
Smaaland, 1991	146	26	10†		
Fossa, 1993	308	38‡	14§		24
Vale, 1993	60	38	12		
Pollack, 1994	135	42	20	0	26
Moonen, 1998	379	25	17		22
Borgaonkar, 2002*	163	48	26		45

International Consultation on Urological Diseases (ICUD) ***Level of Evidence 3*** for all studies

* - Cause-specific survival; † - T3/T4; ‡ - T2/T3a; § - T3b/T4

local recurrence also strongly predict distant recurrence.

The largest single-institution experience with preoperative radiotherapy for bladder cancer is from the M. D. Anderson Cancer Center [25]. Among 338 patients with T2 to T4 disease, pathologic downstaging occurred as a result of radiotherapy in 65% of cases, and 42% had no tumor whatsoever in the surgical specimen. The overall survival at 5 years was 44%. The pelvic and distant recurrence rates were 16% and 43%, respectively. Preoperative radiotherapy appeared to improve pelvic control in patients with T3b disease at presentation, relative to a more recent cohort treated with cystectomy alone (91% vs. 72%) [26].

There have been at least 3 randomized phase 3 studies comparing planned preoperative radiotherapy plus cystectomy to cystectomy alone, as summarized in **Table 2** [27-29]. Many of these studies included patients with early stage disease who were unlikely to benefit from preoperative radiation. Other problems include the use of relatively low doses of radiation and infrequent reporting of local control, which is the endpoint most likely to be enhanced by preoperative treatment. Only one of the studies individually showed a survival advantage in favor of preoperative radiotherapy, and it contained a high proportion of patients with schistosomiasis [29]. A meta-analysis that combined data from these studies found no effect of preoperative radiotherapy on survival [30].

Table 2 also summarizes the results of 3 studies in which patients were randomized to receive either planned preoperative radiotherapy and cystectomy or radical radiotherapy with cystectomy for salvage. The smallest showed a survival difference in favor of preoperative radiation and cystectomy, while there was no difference in the other 2 studies. A recent meta-analysis that combined these studies also suggested improved survival with immediate cystecto-

Table 2. Randomized Studies of Planned Preoperative Radiotherapy Plus Cystectomy versus Radiotherapy Alone or Cystectomy Alone

Study	n	Stage	Experimental Arm	Control Arm	3-5 year Survival‡	LOE
Smith, 1997	140	Tis-T3†	PreRT 20 Gy + Cyst	Cyst alone	43% vs. 53%, NS	2
Anderstrom, 1983	44	T1-T3		Cyst alone	75% vs. 61%	2
Ghoneim, 1985*	92		PreRT 20 Gy + Cyst	Cyst alone		2
Miller, 1977	68	T2-T3	PreRT 50 Gy + Cyst	RT 70Gy + salvage cyst	46% vs. 16%§, $P < 0.01$	2
Bloom, 1982	189	T3	PreRT 40 Gy + Cyst	RT 60 Gy + salvage cyst	38% vs. 29%, NS	1
Sell, 1991	183	T2-T4a	PreRT 40 Gy + Cyst	RT 60 Gy + salvage cyst	20% both arms, NS	1

‡ - Experimental versus control arm; † - 64% T3 tumors; * - Patients with schistosomiasis; § - Crude rather than actuarial results

Cyst – Cystectomy; LOE - International Consultation on Urological Diseases (ICUD) Level of Evidence; NS - Not significant; PreRT - Planned preoperative RT; RT - Radical radiotherapy

my [31]. Overall, the results are difficult to interpret, given methodologic problems, the evolution of surgical and radiotherapy techniques over the past 20 years since they were completed, the limited use of preoperative radiotherapy in modern practice, and the availability of effective systemic chemotherapy. They indicate that cystectomy and radical radiotherapy are both effective treatments for bladder cancer, but provide little evidence that one treatment is more effective than the other.

4. Combined Treatment with Radiotherapy and Chemotherapy

There is now substantial experience using radiotherapy in combination with chemotherapy to treat bladder cancer, with the aims of enhancing local tumor control, reducing metastasis development, and improving patient survival. Cisplatin is the most active single agent in the treatment of bladder cancer, and has been shown in preclinical studies to enhance the cytotoxic affects of radiation under both oxic and hypoxic conditions. Numerous case series and phase 3 randomized trials support the use of radiation and chemotherapy together in patients with muscle-invasive disease.

Rodel et al. recently updated their large accumulated experience in 415 patients with T1 to T4 bladder cancer [14]. More than 50% of patients had T3 or T4 disease. All were treated with transurethral resection followed by pelvic radiotherapy. Chemotherapy with cisplatin, carboplatin, and/or 5-fluorouracil (5-FU) was used concurrently with radiation in 289 patients. Complete tumor regression occurred in 72% of patients, as assessed by cystoscopy and biopsy 6 weeks after completing treatment. Among patients who achieved a complete response, 50% remained free of any relapse in the bladder at 10 years and 64% had no recurrence of muscle-invasive disease. Overall, 20% of patients underwent salvage cystectomy. Distant metastases developed in 35% of patients. The 10-year cause-specific survival was 42%.

The Massachusetts General Hospital has pursued an aggressive program of bladder conservation with conservative surgery, radiation, and chemotherapy in selected patients since 1986. Patients initially underwent a thorough transurethral resection, followed by induction treatment with radiotherapy to 40 Gy and concurrent cisplatin chemotherapy. Those with complete regression of disease proceeded to consolidative radiotherapy (a further 24-25 Gy with chemotherapy), while those with residual disease underwent cystectomy. Among 190 patients, 82% completed treatment according to protocol. Sixty percent of patients treated with chemo-radiation alone remained free of bladder cancer long-term. Superficial disease recurred in the bladder in 24 patients, and in the majority of cases was managed conservatively with further resection and intravesical chemotherapy. A muscle-invasive recurrence developed in 16%. The 10-year cause-specific survival rates were 60% overall, and 45% with an intact bladder. Bladder function was normal by urodynamic assessment in 75% of these patients [32,33].

Table 3 summarizes 7 phase 3 studies of cystectomy or radiotherapy, with or without neoadjuvant, concurrent, or adjuvant chemotherapy. The only phase 3 trial of radiotherapy and concurrent chemotherapy was conducted by the National Cancer Institute of Canada [34]. Patients with T2 to T4b urothelial carcinoma of the bladder received local regional therapy alone (full-dose radiotherapy or preoperative radiotherapy and cystectomy) with or without concurrent cisplatin. There was no difference in overall survival or distant relapse-free survival. However, patients who received concurrent chemotherapy had a significantly lower rate of pelvic recurrence than those treated with radiation alone. There was no difference in the risk of serious side effects.

Initial phase 2 studies of neoadjuvant chemotherapy suggested improved local control and prolonged survival [35-37]. However, phase 3 studies have, in general, failed to confirm these results. The largest phase 3 neoadjuvant study was comprised of 976 patients with T2 to T4 bladder cancer who were randomized to receive 3 cycles of chemotherapy with cisplatin, methotrexate, and vinblastine (CMV) followed by cystectomy or radiotherapy, versus the same treatment without chemotherapy [38]. A total of 485 patients underwent cystectomy, 415 were treated with radiotherapy, and 76 received preoperative radiation followed by cystectomy. There was no difference in overall survival between the chemotherapy and no chemotherapy arms (55% vs. 50%, respectively). Local regional control was not affected by chemotherapy, although there was a suggestion that the development of metastasis was delayed.

Although the results of individual phase 3 randomized studies of neoadjuvant chemotherapy have been disappointing, a recent meta-analysis that combined individual data from 2688 patients in 10 studies has shown a survival advantage to combination platinum-based chemotherapy [39]. There was a 13% relative reduction in the risk of death and an improvement in survival at 5 years from 45% to 50%. Local disease-free survival and metastasis-free survival were also improved (relative risk reductions of 13% and 18%, respectively).

Notwithstanding the results of these studies, several questions remain about how to optimally combine radiotherapy and chemotherapy. It is unclear which subgroups of patients are best treated with neoadjuvant versus concurrent chemotherapy, how many cycles of neoadjuvant chemotherapy are necessary, and whether pelvic radiotherapy is beneficial only in patients who have a complete clinical and radiographic response to neoadjuvant chemotherapy or also in those with residual pelvic tumor.

Table 3. Randomized Studies of Combination Radiation and Chemotherapy

Study	n	Stage	Experimental Arm	Control Arm	3-5 year Survival†	LOE
Richards, 1982	129	T3	± Adj Doxo + 5-Fu x4	RT alone	35% vs. 37%, NS	2
Shearer, 1988	423	T3	± Neo and Adj MTX	RT alone 64 Gy or PreRT 44 Gy + cyst	39% vs. 37%, NS	2
Wallace, 1991	255	T2-T4	± Neo Cis	RT alone	NS	2
Coppin, 1996*	99	T2-T4	± Con Cis x3 with induction RT	Induction RT 40Gy RT boost 20 Gy or Cyst	47% vs. 33%, NS	1
Shipley, 1998 (RTOG 89-03)	123	T2-T4	± Neo CMV x2 after TURBT	TURBT RT 39.6 Gy + Con Cis RT boost 25.2 Gy + Cis if CR Cyst if no CR	48% vs. 49%, NS	1
International, 1999	976	T2-T4	± Neo CMV x3	RT or Cyst	55% vs. 50%, NS	1
Senglov, 2002	153	T2-T4	± Neo Cis and MTX x3	RT or Cyst	29% vs. 29%, NS	1

† - Experimental versus control arm; * - Improved pelvic control

5-FU - 5-fluourouracil; Adj – Adjuvant; Cis – Cisplatin; CMV - Cisplatin, methotraxate, vinblastine; Con – Concurrent; CR - Complete response; Cyst – Cystectomy; Doxo – Doxorubicin; LOE - ICUD Level of Evidence; MTX – Methotrexate; n - Number randomized patients; Neo – Neoadjuvant; NS - Not significant; PreRT - Planned preoperative RT; RT – Radiotherapy; TURBT - Transurethral resection of bladder tumor

5. Population-based Studies

There are at least 2 population-based studies that have described the treatment of bladder cancer in well-defined geographic regions of Canada. Hayter et al. reported on over 20,000 cases of bladder cancer diagnosed in Ontario, Canada, between 1982 and 1994 [40]. This study included both superficial and muscle-invasive tumors treated in a variety of ways with transurethral resection, partial cystectomy, radical cystectomy, and radical radiotherapy. Among patients with muscle-invasive bladder cancer, there was no difference in survival between those treated with radiotherapy and those who underwent cystectomy. The 5-year cause specific survival for radiation-treated patients was 41%. Salvage cystectomy was performed in 28% of patients who received radiation initially. Scrimger et al. described the management of 285 patients with muscle-invasive bladder cancer diagnosed in Alberta, Canada, between 1984 and 1993 [41]. There was a relatively even distribution of patients treated with radical radiotherapy and cystectomy. The 5-year cause-specific survival was 37%, and this was independent of the type of treatment for bladder cancer. Taken together, these studies indicate that on a population basis, radical radiotherapy with cystectomy for salvage is comparable to initial cystectomy and has the advantage of preserving normal bladder function.

Summary

There is substantial experience worldwide with the use of radiotherapy to treat bladder cancer, either alone or in combination with surgery and chemotherapy. Muscle-invasive urothelial carcinoma of the bladder is an aggressive malignancy that is associated with a high mortality if untreated. There is ***consistent evidence*** from numerous studies to suggest ***that radiotherapy produces complete eradication of tumor, sustained local control, and prolonged survival*** of some patients who would otherwise have died of progressive disease *(Level 1)*. ***Planned preoperative radiotherapy*** improves pelvic control compared to cystectomy alone in high-risk patients *(Level 4)*, but has no effect on survival because of the competing risk of distant metastases. ***Cisplatin chemotherapy administered concurrently with radiotherapy*** improves local pelvic control *(Level 1)*. ***Neoadjuvant chemotherapy followed by consolidative pelvic radiotherapy*** improves patient outcome relative to radiotherapy alone *(Level 1)*. ***Interstitial radiotherapy*** is an effective alternative to external beam radiotherapy in selected patients with unifocal, small bulk disease *(Level 3)*.

II. WHICH PATIENTS WITH BLADDER CANCER SHOULD BE CONSIDERED FOR CURATIVE TREATMENT WITH RADIOTHERAPY?

Radiotherapy for bladder cancer, administered with the aim of permanently controlling the tumor and preserving normal bladder function, is most appropriate in situations where the prior probability of achieving this goal is high. Numerous factors may influence the success of radiotherapy in patients with bladder cancer, and can broadly be classified as those relating to the characteristics of the tumor, bladder, and patient. The evidence to support stratification of patients according to risk is derived mainly from multivariate prognostic factor analyses of patients accrued to retrospective and prospective studies. **Table 4** summarizes the results of multivariate analyses for local control and survival in several large contemporary series.

1. Superficial Bladder Cancer

Many of the largest series of patients treated with radiotherapy for bladder cancer contain a subgroup with superficial disease [1,8,14,42,43]. Patients may have solitary or multifocal, papillary or solid tumors with or without coexisting carcinoma in situ (CIS). Radiotherapy has been advocated as a bladder-sparing treatment for rapidly recurrent or extensive superficial disease that is not amenable to transurethral resection, and where the risk of progression to muscle-invasive disease is deemed to be high. As summarized in **Table 5**, complete response rates following radiotherapy with or without concurrent chemotherapy are in the range of 50% to 80% depending on histologic grade, tumor configuration (papillary vs solid), and multifocality [8,44,45]. Sustained local control in the bladder is seen in 30% to 60% of patients. Long-term cause-specific survival varies between 30% and 70%. Radiotherapy for T1 disease has never been compared in a randomized study to more conservative therapy consisting of transurethral resection with or without intravesical BCG or chemotherapy. In general, given the limited

Table 4. Prognostic Factors by Multivariate Analysis for Local Control and Survival Following Treatment With Radiotherapy, With or Without Chemotherapy

Study	n	Local Control	Survival
Gospodarowicz, 1991*	355	T-stage	Grade T-stage Tumor bulk Hydronephrosis
Fossa, 1993	308		Age Year of treatment‡ T-category Serum creatinine
Mameghan, 1995	342	Multifocal disease Hydronephrosis T-stage	
Moonen, 1998	379	Multifocal disease Radiation dose	Age T-category
Rodel, 2002	415	Multifocal disease	Age Extent of TURBT T-category Lymphatic invasion Treatment†

* - Cause-specific survival; † - Radiotherapy alone vs. radiotherapy + carboplatin vs. radiotherapy + cisplatin vs. radiotherapy +5- FU/cisplatin, $P = 0.06$; ‡ - 1980-85 vs. 1986-90

TURBT - Transurethral resection of bladder tumor prior to radiotherapy

Table 5. Radiotherapy for Superficial Bladder Cancer

Author	n	CR	Sustained Local Control	10 yr CSS
Quilty, 1986	190	48%	28%	33%†
Gospodarowicz, 1991				
T1 Solitary	42	69%	35%	70%
T1 Multiple	50	58%	20%	32%
Rodel, 2001	74*	84%	56%	66%

International Consultation on Urological Diseases (ICUD) ***Level of Evidence 3*** for all studies

† - Overall survival; * - 17 RT alone, 57 RT with concurrent chemotherapy

CR - Complete response; CSS - Cause-specific survival

evidence to support the use of radiotherapy in patients with superficial bladder cancer and the effectiveness and convenience of other management strategies, radiation should be reserved for circumstances where these other options have either been exhausted or are otherwise inappropriate for patient-specific reasons. The remainder of this discussion will focus on factors that influence the outcome of patients with muscle-invasive bladder cancer who are treated with curative intent using external beam radiotherapy.

2. Tumor Factors for Local Control

Sustained local control of muscle-invasive bladder cancer treated with radiotherapy is strongly influenced by the bulk of local disease at the time of treatment, and the propensity for new tumors to develop in the bladder after treatment. Advanced T category, large tumor size, the presence of an extravesical mass, and hydronephrosis have all been associated with either incomplete response to radiation or local disease recurrence [1,4,5,7,8,11,12,14]. Overall, approximately 50% of patients treated with external beam radiotherapy have complete regression of disease: 50% to 70% of those with T2 or T3a disease and 40% to 50% with T3 or T4a tumors [1-7]. Sustained local control can be expected in 30% to 50% and 20% to 30% of patients with T2 and T3 disease, respectively [5,8,9]. A gross complete transurethral resection of the bladder tumor before radiotherapy has been associated with improved local control, [14,47]. although this has not been a consistent observation [6,7,48].

Tumor factors in addition to bulk may influence local disease progression in the bladder following radiotherapy. Pollack et al. described a relationship between altered expression of the pRB-retinoblastoma and bcl-2 genes on the local response of patients to preoperative radiotherapy [49,50]. These genes are important in cell cycle regulation, DNA repair, and the control of spontaneous and radiation-induced apoptosis. Moonen et al. demonstrated improved local control in patients with wild-type p53 and a high pretreatment apoptotic index [51]. Other studies have also suggested that apoptotic index may be an independent prognostic factor for local control [52,53]. Further evaluation of molecular prognostic factors is essential to advancing the role of radiotherapy in the management of this disease.

Treatment of bladder cancer with radiotherapy is associated with a long-term risk of new tumor development in the preserved bladder. For example, Gospodarowicz et al. reported a continuous decline in local relapse-free rate and cause-specific cystectomy-free survival to beyond 10 years in 355 patients treated with radiotherapy alone [8]. Patients at greatest risk of new tumor development are those with multifocal superficial disease at presentation [8,12,14,42,43]. Extensive CIS, when present in association with muscle-invasive bladder cancer, is a particularly strong adverse prognostic factor for sustained local control with radiotherapy [4,54,55]. Wolf et al. reported the development of a new bladder cancer after radiotherapy in 58% of patients with dysplasia or CIS at initial presentation, but in none of the patients without concomitant CIS [55]. Zietman et al. described the Massachusetts General Hospital experience with superficial disease recurrence in 121 patients who presented initially with muscle-invasive cancer and were treated with a combination of surgery, radiation, and chemotherapy [56]. Superficial disease recurrence was seen at 57 sites in 32 patients (26%), at a median interval of 2.1 years from the completion of initial treatment. CIS associated with the original muscle-invasive tumor was a strong predictor of subsequent superficial recurrence. Conservative treatment with transurethral resection and intravesical therapy was undertaken in 27 patients, 10 of whom eventually required cystectomy because of further superficial recurrence or progression to invasive cancer. There was no difference in survival among patients who remained permanently free of disease following initial treatment and those who developed a superficial recurrence. These results indicate that, while CIS is associated with reduced long-term disease control in the bladder, it is not an absolute contraindication to the use of radiotherapy in patients with muscle-invasive disease, and should be considered in the context of other tumor- and patient-related factors when considering treatment options.

3. Tumor Factors for Survival

The prognostic factors for survival are similar to those for local control, and generally reflect primary tumor bulk. As indicated in **Table 1**, patients with T2 tumors have an expected survival of 30% to 50%, and those with T3 disease a survival of 15% to 35% [1-12,57-60]. In addition, advanced age at diagnosis, high histologic grade, and gross residual disease at the completion of transurethral resection prior to radiotherapy have all been associated with reduced survival [4,8,10,12,14].

Anemia has been shown to predict reduced local

control following radiotherapy [4,61], as well as a higher rate of distant metastases and death from bladder cancer [4]. This may be explained by either anemia-induced tumor hypoxia, leading to genetic instability and the emergence of more aggressive metastatic phenotypes [62], or the fact that patients who are anemic at diagnosis may be more likely to have advanced disease. Hoskin et al. evaluated tumor hypoxia in 64 patients with bladder cancer using the intrinsic hypoxic markers carbonic anhydrase IX (CA-IX) and glucose transporter-1 protein (GLUT-1) [63]. There was no association between hypoxia and control of the primary bladder tumor following treatment with radiotherapy, carbogen, and nicotinamide. However, hypoxia was strongly predictive of both cause-specific and overall survival independent of clinical prognostic factors. This is consistent with the results in cervical cancer and other tumors, where hypoxia has been shown to have only a minimal effect on local control with radiotherapy, but a profound effect on the development of lymph node and distant metastases [64,65].

Several surgical series have demonstrated pelvic lymph node metastases at diagnosis in 10% to 50% of patients with muscle-invasive bladder cancer depending on primary tumor extent [21-24]. Nodal metastases imply a high risk of occult distant metastases, a high risk of recurrence outside of the pelvis following local treatment alone, and significantly lower survival relative to node-negative patients. Despite this, the impact of nodal metastases on the outcome of bladder cancer patients treated with radiotherapy has not been extensively studied. This in part reflects the difficulty of reliably identifying subclinical nodal disease in the absence of surgical dissection. CT and MRI do not have sufficient resolution, [66,67]. and even PET scans are of limited value in the detection of disease less than a few millimeters in size [68]. Very few of the modern radiotherapy series have described the prognostic impact of nodal status at diagnosis. Rodel et al. showed that lymph node involvement was predictive of inferior local control by univariate analysis, but not by multivariate analyses [14]. However, patients with positive nodes were more likely to develop distant metastases independent of other tumor-, patient-, and treatment-related factors. The potential for radiotherapy with or without concurrent chemotherapy to control bulky nodal disease is limited by normal tissue toxicity, and the relatively modest doses that can safely be delivered [69]. In addition, these patients are at particularly high risk of having occult distant metastases. Patients in this situation may be more appropriately managed by multi-modality strategies that incorporate initial chemotherapy and consolidative pelvic radiotherapy for complete responders, or cystectomy and lymph node dissection followed by postoperative chemotherapy.

4. Patient Factors

Radiotherapy is generally tolerated well even in elderly patients and in those with concurrent medical problems, and this has contributed to an imbalance in the underlying likelihood of long-term survival between patients who undergo cystectomy and those treated with radiotherapy [70]. However, the benefit of definitive radiotherapy with bladder conservation is likely to be limited in situations where pretreatment bladder function is compromised and in patients at high risk of developing intolerable acute or long-term treatment complications. Those with severe irritable bladder symptoms at presentation due to factors such as long standing outflow obstruction, chronic infection, multiple prior transurethral resections, or prior intravesical chemotherapy may have permanent impairment of bladder function after radiotherapy that diminishes the benefit of organ preservation. Anatomic and technical factors that limit the accuracy and reproducibility of radiation delivery, such as atonic bladders and large bladder diverticula, may increase the risk of local tumor recurrence and treatment complications. Cystectomy may be preferred in these situations.

Summary

There is substantial *(Level 3)* evidence that the ideal candidate for curative external beam radiotherapy with or without concurrent chemotherapy has a ***small, solitary tumor less than 5 cm in size with no associated CIS, no evidence of lymph node or distant metastases, and a normally functioning bladder.*** The patient must be ***highly motivated to preserve a normal bladder and committed to life-long bladder surveillance and prompt treatment of new superficial or invasive disease.*** Advanced T category, extravesical disease, large tumor size, and hydronephrosis have been associated with reduced local control and survival *(Level 3)*. Thorough resection of intravesical tumor before radiotherapy increases the likelihood of achieving a complete response and sustained local control in the bladder *(Level 3)*. Multifocal disease and extensive bladder CIS at presentation have been consistently linked to

local recurrence and the development of new bladder tumors *(Level 3)*. The prognostic importance of pretreatment lymph node status in radiation-treated patients needs to be evaluated more thoroughly in future studies *(Level 4)*. A better understanding of the biologic factors that influence tumor radiation response will contribute to improved local control and patient survival *(Level 4)*.

III. HOW SHOULD RADIOTHERAPY OPTIMALLY BE DELIVERED TO MAXIMIZE PATIENT BENEFIT?

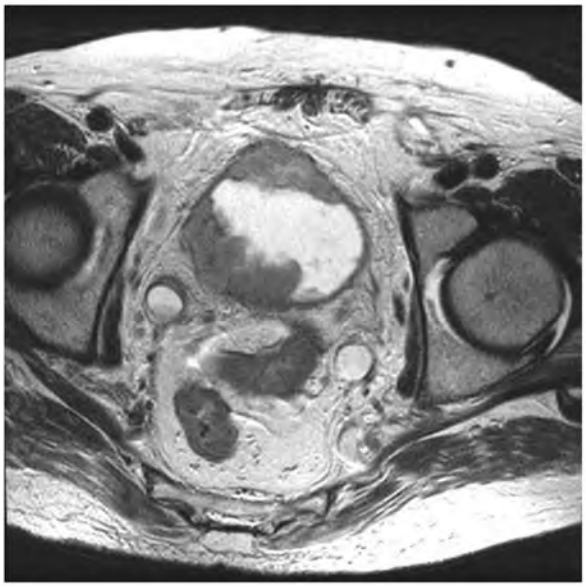
The goal of radiotherapy is to eradicate all gross and microscopic tumor in the bladder and often also in the pelvic lymph nodes, while minimizing patient toxicity. Therefore, the success of radiotherapy depends not only on the selection of appropriate patients, but also on knowledge of tumor patterns of spread, accurate localization of the primary tumor and lymph node metastases, selection of appropriate treatment volumes to encompass all tumor and exclude as much normal tissue as possible, and careful tracking of tumor movement. The bladder is not a fixed structure but rather varies in size and position as a function of urine volume and rectal contents. Compensation for bladder and tumor movement from day to day during a fractionated course of treatment is an important component of the radiotherapy treatment plan.

1. Radiotherapy for the Primary Bladder Tumor

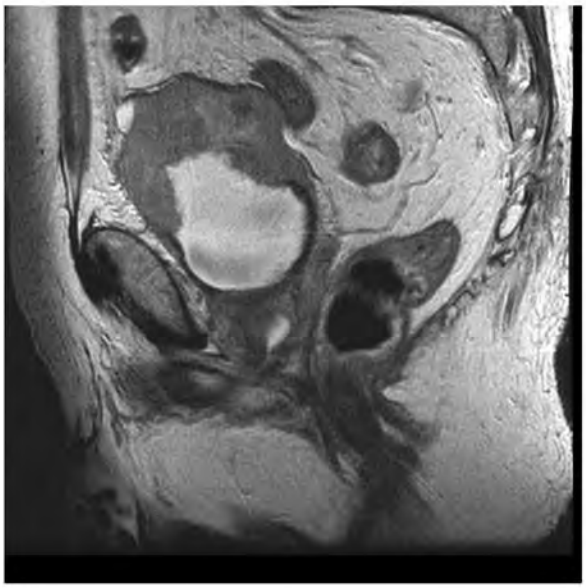
Radiotherapy for bladder cancer implies the need for accurate and reproducible delivery of multiple radiation fractions to the gross tumor and regions of subclinical disease extension. Microscopic infiltrative tumor is likely to be present in the lamina propria, muscularis propria, and lymphovascular spaces adjacent to the primary tumor, although the degree of extension beyond gross disease has not been studied and is likely highly variable. Disease may also extend into paravesical tissues. The location and extent of gross tumor from diagnostic and staging tests, including cystoscopy, pelvic CT, and pelvic MRI, should be integrated with CT imaging of the patient in the treatment position and used to develop a 3-dimensional radiotherapy plan. CT-based treatment planning has been shown to be more accurate than conventional planning techniques that rely on cystogram alone [71-74]. However, there is probably significant interobserver variability in the definition of gross tumor using CT, particularly in the region of the trigone and bladder neck [75,76]. This may be improved in the future with the use of planning MRI and registration of the CT and MR images. MRI provides greater soft tissue resolution than CT, and valuable information about the extent of local disease. **Figure 1** shows axial, sagittal, and coronal images of a tumor extensively involving the dome and posterior wall of the bladder causing ureteric obstruction and hydronephrosis.

The clinical target volume (CTV) for treatment of the primary bladder tumor is often considered to be the entire bladder. However, lateralized solitary tumors that can be accurately localized are probably safely treated with a reduced CTV that encompasses the gross tumor and a surrounding margin to account for microscopic disease extension. Cowan et al. [77] reported the results of a 3-arm phase 3 study in which patients with bladder cancer were randomized to either whole bladder treatment or escalated dose partial bladder treatment with 2 different dose regimens. The median irradiated pelvic volume was 61% lower in the partial volume arms of the study than in the whole bladder arm. There were no differences in complete response, sustained local control, long-term survival, or toxicity.

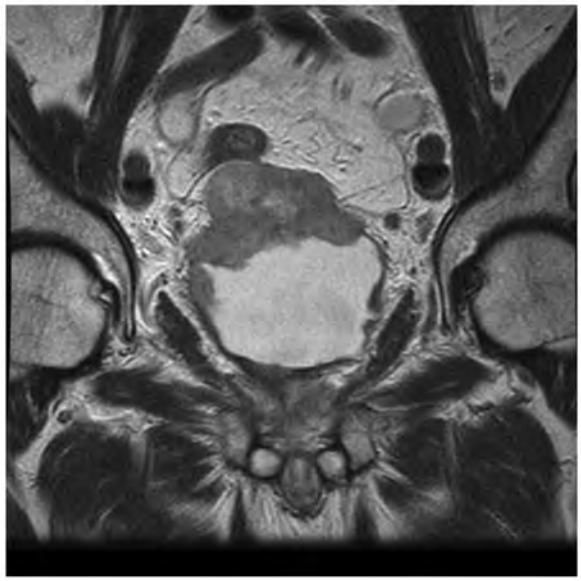
Variability in the position of the bladder tumor from day to day during a course of fractionated radiotherapy may theoretically be minimized by asking patients to completely empty their bladders immediately prior to imaging for treatment planning and prior to receiving each radiation fraction. However, the efficacy of this maneuver has not been rigorously evaluated, and there still may be significant changes in bladder volume depending on factors such as the interval between voiding and treatment delivery, the state of hydration of the patient, and the use of diuretic medications or beverages. Movement may also be influenced by extrinsic pressure, such as might arise from differences in rectal filling, [78]. and by the characteristics of the tumor including size and degree of extravesical extension. Turner et al. demonstrated interfraction bladder wall movement of at least 1.5 cm in 18 of 30 patients, with the greatest movement being seen in those with large initial bladder volumes [78]. Bladder movement resulted in inadequate coverage of the CTV in 10 patients. An isotropic planning target volume (PTV) of 2 cm



A



B



C

Figure 1. Axial (A), sagittal (B), and coronal (C) T2-weighted MR images of an extensive urothelial carcinoma involving the dome, right lateral wall, and posterior wall of the bladder causing ureteric obstruction and hydronephrosis. MR provides high resolution images of bladder cancer and valuable information about the extent of local disease for radiotherapy treatment planning.

around the CTV was recommended to account for random internal movement [78]. Muren et al. studied 20 patients with bladder cancer using weekly CT scans [79]. In 89% of the repeat scans during treatment, the bladder wall extended beyond the bladder contour as outlined using the original planning CT. The greatest displacements during treatment occurred along the superior, left, anterior, and posterior aspects of the bladder and measured up to 3.6 cm. Anisotropic margins (CTV to PTV) of 1.1 to 2.3 cm were necessary to simultaneously encompass all bladder displacements except in the most extreme cases. In good agreement, Meijer et al. advocated anisotropic margins (CTV-PTV) of 2.3 cm superiorly and 1 cm inferiorly (behind the symphysis) and laterally [76].

The choice of radiation treatment margin around the gross bladder tumor is likely to influence not only local control, but also toxicity. In a recent analysis, conformal 3- or 4-field treatment plans for 15 patients were developed using either isotropic margins of 1 cm around the bladder wall CTV, or wider anisotropic margins of 1.2 cm laterally and 2 cm elsewhere. The wider margins were associated with a 1.5- to 2.4-fold increase in the volume of small bowel and rectum receiving greater than 50% of the prescribed dose. The fractional rectal volume receiving greater than 75% of the prescribed dose was 3.6-

to 5-fold higher. The higher doses to critical normal structures correlated with model predictions of higher complication rates [80].

2. Radiotherapy for Pelvic Lymph Node Metastases

Pelvic lymph node metastases occur in 10% to 50% of patients with muscle-invasive bladder cancer. Radiotherapy treatment volumes historically have encompassed pelvic lymph nodes, whether or not there is radiographic evidence of gross nodal metastases. However, the benefit of nodal irradiation in bladder cancer has not been extensively studied. Several surgical series have suggested long-term survival of 15% to 30% in patients with nodal metastases who undergo thorough lymph node dissection at the time of cystectomy [22,23,81-87]. By extrapolation, there may also be a benefit of aggressive nodal treatment in patients who are managed primarily with radiotherapy. Pelvic lymph node radiation is typically delivered using a 4-field technique, which encompasses a large volume of small bowel and rectum. Therefore, the dose of radiation that can be prescribed safely is limited by the radiation tolerance of these critical normal tissues, and is probably inadequate to control gross or, in some cases, even "bulky" subclinical nodal disease that is near the threshold of radiographic detection. Intensity modulated radiotherapy, which allows the radiation dose to be "sculpted" in 3 dimensions to a predefined lymph node volume while excluding surrounding normal tissue, may facilitate higher lymph node doses in the near future [69].

Summary

Radiotherapy for bladder cancer requires the accurate and reproducible delivery of fractionated treatment to ***pelvic volumes that typically encompass both the primary bladder tumor and pelvic lymph nodes***. Radiation treatment plans need to account for ***differences in bladder and tumor position*** that occur as a result of variation in bladder and rectal filling. An ***isotropic margin of 2 cm around the gross tumor*** is sufficient to encompass interfraction tumor movement in most circumstances *(Level 3)*. However, ***anisotropic margins*** tailored to the location of the tumor within the bladder afford an opportunity to optimize radiation delivery and reduce normal tissue toxicity *(Level 3)*. ***Image-guided radiotherapy*** that allows day-to-day optimization of the treatment volumes should further reduce the possibility of accidentally underdosing tumor *(Level 4)*. There is limited *(Level 3)* evidence from radiotherapy series to support the treatment of clinically negative pelvic nodes but more substantial *(Level 3)* evidence from surgical series where patients underwent extensive pelvic lymph node dissection. New developments in precision radiotherapy delivery should allow higher doses to be safely delivered to pelvic lymph nodes, with an expectation of improved pelvic control *(Level 4)*.

IV. WHAT IS THE BEST RADIATION PRESCRIPTION FOR TREATING BLADDER CANCER?

The benefit of radiotherapy in the treatment of malignant disease including bladder cancer, in addition to careful planning and delivery, hinges on differences in the capacity of malignant and normal tissue cells to repair radiation-induced molecular damage. This is strongly influenced by intrinsic tumor and normal tissue biologic factors, and also by treatment factors including total radiation dose, dose per fraction, the interfraction interval, and the overall treatment time. A variety of fractionation schemes have been described for bladder cancer based on differences in these 4 parameters.

Radiation treatment plans, in addition to the primary bladder tumor, also frequently encompass pelvic lymph nodes. Using current radiation techniques, the dose that can be delivered safely to pelvic lymph nodes is limited by the radiation tolerance of the surrounding normal tissues, and is typically 40 to 50 Gy in 1.8 to 2.0 Gy daily fractions. The future implementation of precision intensity modulated radiotherapy techniques may allow escalation of the lymph node dose, with the expectation of improved nodal control [69]. The remainder of this discussion will focus on the best radiation prescription for treating the primary bladder tumor.

1. Conventional Radiation Fractionation

Conventional dose-fractionation, defined as 50 to 70 Gy in 1.8 to 2.5 Gy fractions over 4 to 7 weeks, is commonly used to treat bladder cancer worldwide. The clinical dose-response relationship for bladder

cancer is poorly defined, and it remains unclear to what extent differences in total dose in this range influence local tumor control and patient survival. In practice, the prescribed dose is usually determined by the radiation tolerance of the surrounding normal tissues on the assumption that a higher bladder cancer dose will always be desirable and produce improved local control. Therefore, phase 3 randomized studies comparing different conventionally –fractionated dose schedules have never been undertaken. At least 4 case series have suggested improved local tumor control with doses greater than 55 to 60 Gy [5,6,43,88], although others have found no evidence to support such a relationship [11,46]. The dose-response relationship in these and other retrospective studies may have been obscured to some extent by differences among the dose strata in the distribution of other important tumor-, patient-, and treatment-related factors.

Conventionally-fractionated radiotherapy to total doses of less than 70 Gy is typically well tolerated by patients with bladder cancer. Most experience acute gastrointestinal and lower urinary tract side effects during treatment that are usually easily controlled with dietary modification and medications. Late complications primarily affect the bowel and normal bladder and typically arise from 1 to 4 years after completing treatment. Approximately 75% of late complications are present by 3 years [1,9]. Late bladder side effects, which include urinary frequency, dysuria, and hematuria, have been reported in 7% to 15% of patients treated with modern radiation techniques [1,5,8,9,89], and in some circumstances necessitate cystectomy. Severe gastrointestinal toxicity is seen in 6% to 17% of patients [1,8,9]. Doses above 70 Gy are likely to be associated with an unacceptably high rate of serious complications if delivered using standard radiation techniques [11], but may be feasible in the future with image-guided intensity modulated radiotherapy.

2. Hyperfractionated Radiotherapy

Hyperfractionated regimens, defined as the delivery of a larger number of smaller fractions (usually 1.5 Gy or less) with no increase in overall treatment time, have been examined in patients with bladder cancer as a means of exploiting differences in the molecular response of tumor and normal tissues to radiation. In theory, hyperfractionation should allow an increase in radiation dose leading to a greater likelihood of tumor control with no increase in the risk of late radiation complications. Naslund et al. randomized 168 patients to receive 1 Gy 3 times daily to a total dose of 84 Gy, versus 2 Gy once daily to a total dose of 66 Gy [90]. Goldobenko et al. reported a 4-arm randomized study of 177 patients comparing conventional radiotherapy (60 Gy in 2 Gy fractions) to 3 hyperfractionated strategies (60 Gy and 70 Gy in 1 Gy fractions twice daily, 67.2 Gy in 1.2 Gy fractions twice daily) [91]. Both studies included a 2-week rest period midway through treatment. Clinical complete response and long-term local control were improved in the hyperfractionated arms relative to conventional fractionation. A meta-analysis based on the pooled data from these studies indicated a significant improvement in overall survival with hyperfractionated treatment [92].

3. Accelerated Radiotherapy

Laboratory and clinical studies have shown that tumor growth may increase during a course of fractionated radiotherapy relative to the pretreatment state as a result of changes in the balance between cellular proliferation and cell loss [93]. This may offset the beneficial effects of radiation and decrease the probability of tumor eradication. Poorly differentiated urothelial carcinoma has been reported to have a high labeling index and short potential doubling time [94-96], both indicators of rapid tumor growth [94-96]. Therefore, long total radiation treatment times may be deleterious in patients with bladder cancer. In a retrospective analysis, Maciejewski et al. reported a significant loss of local control when treatment of bladder cancer was prolonged from 40 to 55 days [97]. Conversely, studies by Moonen et al. in 379 patients and by De Neve et al. in 147 patients failed to show a correlation between overall treatment time and local control among patients treated with continuous course radiotherapy [43,98]. However, De Neve et al. demonstrated that split-course radiotherapy with a gap of 1 month midway through treatment and an overall treatment time greater than 75 days was associated with inferior local control [98].

Accelerated radiotherapy regimens are designed to deliver the same total dose of radiation in a shorter interval of time relative to conventionally fractionated regimens, and might be beneficial in patients with rapidly proliferating bladder tumors. At least 6 phase 2 studies of accelerated radiotherapy have reported encouraging locoregional control rates and acceptable toxicity [99-104]. Horwich et al. recently reported the results of a prospective study in which 229 patients with bladder cancer were randomly assigned

to receive accelerated radiation consisting of 60.8 Gy in 32 fractions over 26 days or conventional radiation with 64 Gy in 32 fractions over 45 days [105]. There was no difference in local control, time to metastases, or overall survival between the groups, but patients in the accelerated arm had a significantly higher rate of bowel complications.

4. Hypofractionated Radiotherapy

Hypofractionated radiation schedules, based on larger daily doses in the range of 2.5 to 6.0 Gy, have also been used to treat patients with bladder cancer, usually in the palliative setting. There has only been 1 small phase 3 study of curative hypofractionated radiotherapy in bladder cancer. Patients were randomized to receive either partially hypofractionated treatment (30 Gy in 3 Gy daily fractions, 4 week break, then 30 Gy in 1.5 Gy daily fractions) or hyperfractionated radiotherapy (60Gy in 1.5 Gy daily fractions). Survival was inferior (52% vs. 39%) in the hypofractionated arm [106]. Large fractions of 5.7 to 6.0 Gy administered once weekly to cumulative dose of 30 to 39 Gy have been reported to provide effective symptom palliation in elderly patients with poor performance status [107,108]. However, hypofractionated regimens have also been associated with an unacceptably high risk of serious late radiation complications. Salminen et al. reported late toxicity affecting the bladder, small bowel, or rectum in 29% of patients following 30 Gy in 6 fractions over 3 weeks [109]. Scholten et al., in a similar study of 36 Gy in 6 fractions over 3 weeks, found a 33% rate of late complications and a 9% rate of severe complications [110].

Summary

Conventional radiation fractionation regimens for bladder cancer have been derived from extensive experience to maximize patient benefit and minimize treatment complications. An initial large pelvic volume that delivers ***40 to 50 Gy in 1.8 to 2.0 Gy daily fractions over 4 to 5 weeks*** to the primary tumor and lymph nodes, followed by a small volume boost that escalates the cumulative primary tumor dose to ***55 to 65 Gy in 1.8 to 2.5 Gy fractions over 4 to 7 weeks***, with or without concomitant chemotherapy, produce complete tumor regression in about 70% of patients, sustained local control in 30% to 50%, and long-term survival in 25% to 30% *(Level 3)*. Treatment with doses in this range delivered using standard radiation techniques is safe with an acceptable risk of acute and late radiation complications. ***Hyperfractionated*** *(Level 1)* and ***accelerated*** *(Level 2)* regimens may be superior to conventional fractionation at least in situations where concurrent chemotherapy is not used, but this must be balanced against the potential for increased toxicity because of inadequate time between fractions for repair of molecular radiation damage. ***Hypofractionated*** treatment provides good symptom control in palliative situations *(Level 3)* but must be used carefully to prevent toxicity.

V. HOW SHOULD PATIENTS WITH BLADDER CANCER OPTIMALLY BE MANAGED AFTER RADIOTHERAPY?

Patients with muscle-invasive bladder cancer are at risk of developing progressive tumor both in the bladder and at metastatic sites after completing radiation treatment. This underscores the importance of life-long bladder surveillance and prompt treatment of bladder recurrences [56]. Several studies have demonstrated that new superficial disease in the bladder following radiotherapy, including new CIS, can often be managed effectively with transurethral resection and intravesical BCG [56,111,112]. However, persistent or new muscle-invasive cancer usually implies the need for salvage cystectomy. Many patients with high-risk muscle-invasive bladder cancer are at high risk of harboring occult metastatic disease at diagnosis and theoretically might benefit from adjuvant chemotherapy.

1. Salvage Cystectomy for Progression after Radiotherapy

The goal of treating muscle-invasive bladder cancer with radiotherapy is complete tumor eradication and preservation of normal bladder function. However, a decision to use radiotherapy initially should always be thought of as one component of a more comprehensive management strategy that includes salvage cystectomy for persistent or recurrent tumor. Most modern radiotherapy series have reported salvage cystectomy rates of only 20% to 30% of patients [5,8,10,13,14,89,113]. Many patients referred for radiotherapy have bulky unresectable tumors and a high risk of occult micrometastases, or concurrent medical problems, making them unsuitable for initial surgery. For the same reasons, these patients often

are not considered for salvage in the event of radiation failure. However, cystectomy frequently is the only remaining option for prolonged survival of patients with an isolated recurrence of muscle-invasive disease in the bladder. The benefit of salvage cystectomy may outweigh a higher risk of complications in some of these cases. In general, all patients with residual or recurrent bladder cancer following radiotherapy should be evaluated for cystectomy.

The rate of bladder cancer regression following radiotherapy influences both the optimal timing of cystoscopy to evaluate response and the optimal timing of salvage cystectomy. Several reports have identified disease status at the completion of radiotherapy (with or without concurrent chemotherapy) as an important prognostic factor for overall patient outcome [8,14]. In most radiotherapy series, response has been evaluated 1 to 3 months after completing treatment [8,14]. However, the Massachusetts General Hospital has adopted a policy of earlier evaluation [32]. After initial thorough transurethral resection, patients receive induction radiotherapy to a dose of approximately 40 Gy with concurrent cisplatin chemotherapy. Cystoscopy is performed 2 to 4 weeks later to allow disease regression. Patients who have had complete regression receive consolidative radiotherapy, while those with residual bladder cancer proceed to immediate cystectomy. The advantage is early cystectomy after only a modest dose of radiotherapy, which should maximize the curative potential of cystectomy and minimize toxicity. However, early response assessment before completion of full-course radical radiotherapy may theoretically decrease the likelihood of bladder preservation if slow-responders, who would have achieved complete regression of disease given sufficient time, are evaluated prematurely. In addition, the introduction of a treatment break in patients destined to receive radiotherapy alone may reduce the overall likelihood of sustained cancer control because of accelerated repopulating of the remaining malignant cells [93-96]. There has not been a randomized comparison of early versus delayed response assessment and cystectomy. However, the results from several series suggest comparable results with respect to local control, patient survival, the proportion of patients undergoing cystectomy, and treatment complications [8,12,14,32].

Long-term survival after salvage cystectomy has ranged from 40% to 60% [4,13,114-120]. The strongest predictor of survival following salvage cystectomy in several series has been the extent of tumor at the time of the procedure (Ta or Tis vs. T1 or T2 vs. T3) [114,116-118,121]. Postoperative morbidity and mortality of 25% to 35% and 5% to 8%, respectively, have been described [114,116,119]. However, other reports have suggested that salvage cystectomy can be performed safely, with a risk of complications that is not significantly different from cystectomy alone or planned preoperative radiation and cystectomy [4,120,122]. Previous high-dose pelvic radiation treatment does not preclude continent urinary diversion at the time of cystectomy [122,123].

2. Adjuvant Chemotherapy for High-Risk Bladder Cancer

Patients with high-risk muscle-invasive bladder cancer frequently have clinically and radiographically occult metastatic disease at diagnosis. Greater than 50% of patients treated with radiotherapy will eventually manifest metastatic disease, [4]. suggesting the potential for benefit with adjuvant chemotherapy. There has only been 1 phase 3 clinical study of adjuvant chemotherapy in radiation-treated patients. This study was from the pre-cisplatin era, and showed no difference in overall survival [124]. In contrast, there have been several randomized studies of chemotherapy following cystectomy in patients with either locally extensive primary tumors or involved pelvic lymph nodes [125-128]. Chemotherapy in these studies typically consisted of 2 to 4 cycles of cisplatin either alone or in combination with other drugs. In general, the results showed improved disease-free survival but no difference in overall survival. Chemotherapy administered at the time of recurrence was associated with a high likelihood of response, particularly in patients initially randomized to cystectomy alone.

Extrapolating from the surgical experience, there may also be a benefit of adjuvant chemotherapy in patients undergoing radiation. However, the indications for adjuvant chemotherapy following radiation are less well-defined, mainly because the detailed surgicopathologic prognostic information provided by cystectomy and pelvic lymphadenectomy is not usually available. In addition, the comorbidities that make patients ineligible for initial radical cystectomy may also limit their ability to tolerate chemotherapy. New drug combinations, like cisplatin and gemcitabine, have similar efficacy and less toxicity relative to previous regimens, and may be useful in this setting [129].

Summary

Radiotherapy for muscle-invasive bladder cancer implies the need for ***long-term bladder surveillance*** and prompt treatment of progressive or recurrent disease *(Level 3)*. ***Superficial recurrences*** can be treated initially with transurethral resection and intravesical BCG with the expectation of good response and continued bladder preservation *(Level 3)*. ***Salvage cystectomy*** should be considered in all patients who develop progressive or recurrent bladder cancer. ***Specific indications for salvage cystectomy*** include 1) failure to control the index muscle-invasive cancer, 2) a new muscle-invasive cancer after prior radiotherapy, and 3) new superficial bladder cancer or CIS in situations where the disease has previously demonstrated resistance to BCG *(Level 3)*. There is an important need to identify ***new clinical, radiographic, pathologic, and biologic factors that predict disease recurrence*** following radiotherapy as a guide to selecting patients for additional treatment *(Level 4)*.

RECOMMENDATIONS

An evidence-based approach to treating muscle-invasive urothelial carcinoma with radiotherapy is outlined in **Figure 2**, and is reflected in greater detail in the following recommendations:

1. Radiotherapy is effective treatment for muscle-invasive bladder cancer that produces complete eradication of tumor, sustained local control, and prolonged survival of selected patients who would otherwise die of the disease *(Grade A).* All patients with muscle-invasive bladder cancer should be evaluated for both cystectomy and radiotherapy, and the most appropriate treatment selected based on individual patient and tumor characteristics to yield the highest probability of cure and quality of life and the least toxicity.
2. The ideal candidate for curative external beam radiotherapy has a small, solitary muscle-invasive tumor less than 5 cm in size with no associated CIS, no evidence of lymph node or distant metastases, and a normally functioning bladder *(Grade B).* These patients have a high probability of being cured and maintaining their bladder *(Grade B).* Radiotherapy should be considered for all patients who meet these criteria, and should be administered concurrently with platinum chemotherapy *(Grade A).*
3. Patients with bulky T3 or T4 tumors, hydronephrosis, or imaging evidence of pelvic lymph node metastases are unlikely to be cured with radiotherapy alone *(Grade B).* These patients should be considered for neoadjuvant combination platinum-based chemotherapy followed by pelvic radiotherapy *(Grade A).*
4. Patients should undergo a thorough transurethral resection of intravesical tumor before radiotherapy to maximize the likelihood of achieving a complete response and sustained local control in the bladder *(Grade B).*
5. Carcinoma in situ (CIS), while associated with an increased risk of local recurrence and the development of new bladder tumors *(Grade B)*, is not an absolute contraindication to the use of radiotherapy in patients with muscle-invasive disease *(Grade B).* It should be considered in the context of other tumor- and patient-related factors when deciding between cystectomy and radiotherapy.
6. Radiotherapy treatment volumes for muscle-invasive bladder cancer should encompass the primary bladder tumor and pelvic lymph nodes *(Grade B).* A radiation dose of 50 to 70 Gy in 1.8 to 2.5 Gy fractions over 4 to 7 weeks should be delivered to the primary tumor, and 40 to 50 Gy in 1.8 to 2.0 Gy fractions over 4 to 5 weeks to the lymph nodes *(Grade B).*
7. There is insufficient evidence to recommend hyperfractionated or accelerated radiation regimens in routine clinical practice *(Grade B).* Further evaluation should be undertaken to determine which patients are most likely to benefit from these strategies in relation to clinical and biologic characteristics.
8. Hypofractionated radiotherapy with doses of 30 to 40 Gy in 3 to 6 Gy daily fractions should be considered for palliation of bladder cancer symptoms in incurable patients, but should be used judiciously to minimize side effects *(Grade B).*
9. Radiotherapy plans should be designed to account for differences in bladder and tumor position from day to day during treatment that occur as a result of variation in bladder and rectal filling. An isotropic margin of 2 cm around the gross tumor is sufficient to encompass inter-fraction tumor movement in most circumstances *(Grade B).* However, anisotropic margins tailored to the location of the tumor within the bladder and daily imaging during treatment should be considered as a means of optimizing radiation delivery and reducing normal tissue toxicity *(Grade B).*
10. All patients who receive radiotherapy for muscle-invasive bladder cancer should undergo life-long cystoscopic bladder surveillance and prompt treatment of progressive or recurrent disease *(Grade B).*
11. Focal superficial disease recurrence in the bladder following radiotherapy should be treated initially with transurethral resection and intravesical BCG with the expectation of good response and continued bladder preservation *(Grade B).*
12. Salvage cystectomy should be considered following radiotherapy for residual muscle-invasive cancer, the development of a new muscle-invasive cancer, or the development of superficial bladder cancer that is resistant to BCG *(Grade B).*
13. The prognostic importance of pretreatment lymph node status in radiation-treated patients should be evaluated in future studies *(Grade C).*
14. The biologic factors that influence bladder cancer progression and radiation response should be evaluated in future studies *(Grade C).*

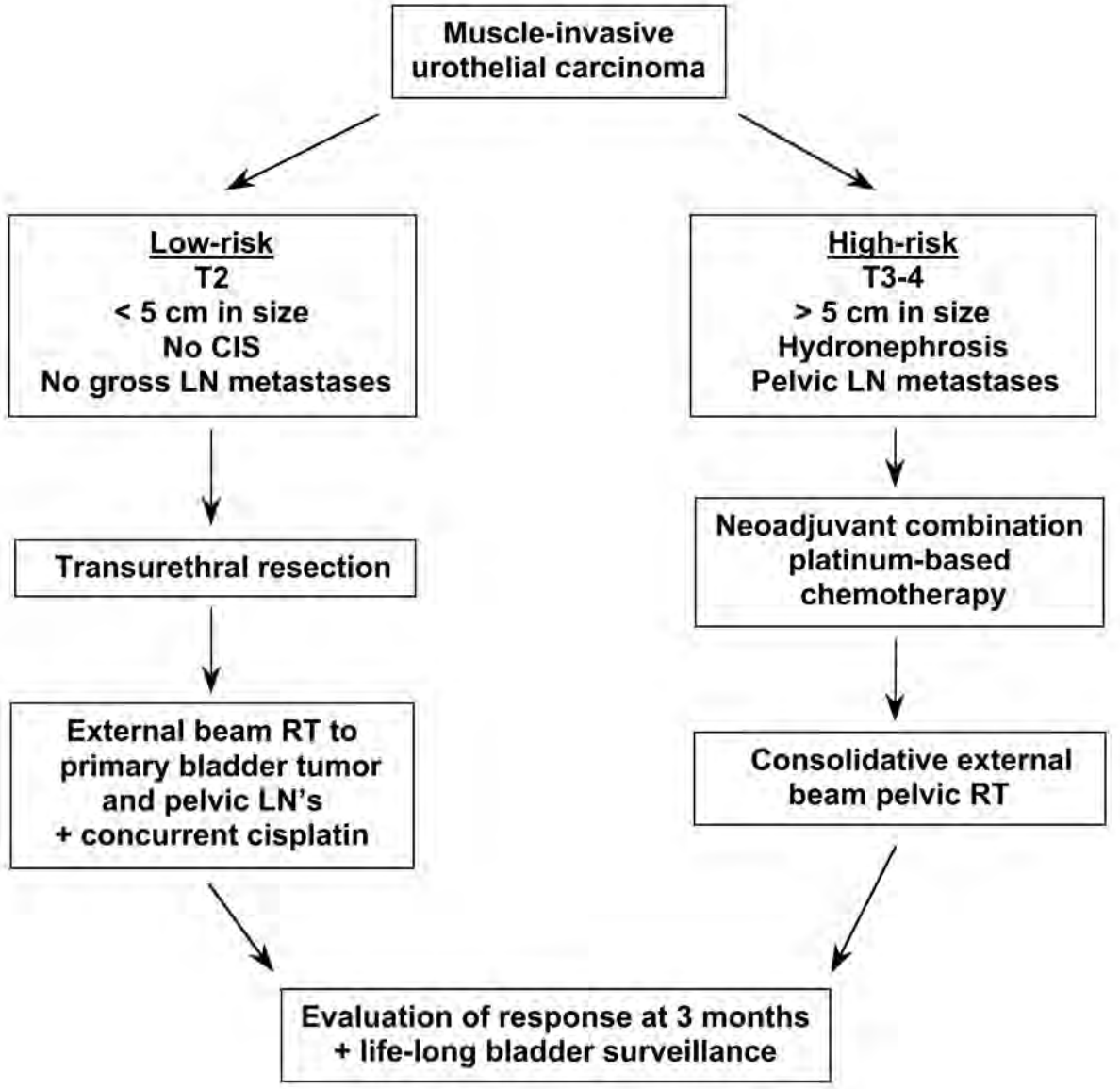


Figure 2. Evidence-based Approach to Treating Muscle-invasive Urothelial Carcinoma With Radiotherapy

REFERENCES

1. Duncan, W. and Quilty, P. M. The results of a series of 963 patients with transitional cell carcinoma of the urinary bladder primarily treated by radical megavoltage x-ray therapy. Radiother. Oncol., *7:* 299-310, 1986.
2. Blandy, J. P., Jenkins, B. J., Fowler, C. G., Caulfield, M., Badenoch, D. F., England, H. R., Hope, S. H. F., Mair, G. M., Mantell, B. S., and Oliver, R. T., et al Radical radiotherapy and salvage cystectomy for T2/3 cancer of the bladder. Progress In Clinical and Biological Research, *260:* 447-451, 1988.
3. Jenkins, B. J., Caulfield, M. J., Fowler, Badenoch, D. F., Tiptaft, R. C., Paris, A. M. I., Hope-Stone, H. F., Oliver, R. T. D., and Blandy, J. P. Reappraisal of the role of radical radiotherapy and salvage cystectomy in the treatment of invasive (T2/T3) bladder cancer. Br. J. Urol., *62:* 342-346, 1988.
4. Gospodarowicz, M. K., Hawkins, N. V., Rawlings, G. A., Connolly, J. G., Jewett, M. A. S., Thomas, G. M., Herman, J. G., Garrett, D. G., Chua, T., Duncan, W., Buckspan, M., Sugar, L., and Rider, W. D. Radical radiotherapy for the muscle invasive transitional cell carcinoma of the bladder: Failure analysis. J. Urol., *142:* 1448-1454, 1989.
5. Greven, K. M., Solin, L. J., and Hanks, G. E. Prognostic factors in patients with bladder carcinoma treated with definitive irradiation. Cancer, *65:* 908-912, 1990.
6. Smaaland, R., Akslen, L., Tonder, B., Mehus, A., Lote, K., and Albrektsen, G. Radical radiation treatment of invasive and locally advanced bladder cancer in elderly patients. Br. J. Urol., *67:* 61-69, 1991.
7. Vale, J. A., A'Hern, R. P., Liu, K., Hendry, W. F., Whitfield, H. N., Plowman, P. N., Sowter, C., and Slavin, G. Predicting the outcome of radical radiotherapy for invasive bladder cancer. Eur. Urol., *24:* 48-51, 1993.
8. Gospodarowicz, M. K., Rider, W. D., Keen, C. W., Connolly, J. G., Jewett, M. A. S., Cummings, B. J., Duncan, W., Warde, P., and Chua, T. Bladder cancer: long term follow-up results of patients treated with radical radiation. Clin. Oncol., *3:* 155-161, 1991.
9. Jahnson, S., Pedersen, J., and Westman, G. Bladder carcinoma - a 20-year review of radical irradiation therapy. Radiother. Oncol., *22:* 111-117, 1991.
10. Fossa, S. D., Waehre, H., Aass, N., Jacobsen, A. B., Olsen, D. R., and Ous, S. Bladder cancer definitive radiation therapy of muscle-invasive bladder cancer. A retrospective analysis of 317 patients. Cancer, *72:* 3036-3043, 1993.
11. Pollack, A., Zagars, G. K., and Swanson, D. A. Muscle-invasive bladder cancer treated with external beam radiotherapy: prognostic factors. Int. J. Radiat. Oncol. Biol. Phys., *30:* 267-277, 1994.
12. Moonen, L., Voet, H. v. d., Nijs, R. D., Hart, A. A., Horenblas, S., and Bartelink, H. Muscle-invasive bladder cancer treated with external beam radiotherapy: pretreatment prognostic factors and the predictive value of cystoscpic re-evaluation during treatment. Radiother. Oncol., *49:* 149-155, 1998.
13. Quilty, P. M., Duncan, W., Chisholm, G. D., Fowler, J. W., Hargreave, T. B., Newsam, J. E., and Tolley, D. A. Results of surgery following radical radiotherapy for invasive bladder cancer. Br. J. Urol., *58:* 396-405, 1986.
14. Rodel, C., Grabenbauer, G., Kuhn, R., Papadopoulos, T., Dunst, J., Meyer, M., Schrott, K., and Sauer, R. Combined-modality treatment and selective organ preservation in invasive bladder cancer: long-term results. J. Clin. Oncol., *20:* 3061-3071, 2002.
15. Werf-Messing, B. H. P. v. d. and Hop, W. C. L. Carcinoma of the urinary bladder (category T1NXM0) treated either by radium implant or by transurethral resection only. Int. J. Radiat. Oncol. Biol. Phys., *7:* 299-303, 1981.
16. Werf-Messing, B. v. d., Menon, R. S., and Hop, W. C. J. Cancer of the urinary bladder category T2, T3, (NXM0) treated by interstitial radium implant: second report. Int. J. Radiat. Oncol. Biol. Phys., *9:* 481-485, 1983.
17. Wijnmaalen, A., Helle, P. A., Koper, P. C. M., Jansen, P. P., Hanssens, P. E., Kruger, C. G. G. B., and Putten, W. L. J. v. Muscle invasive bladder cancer treated by transurethral resection, followed by external beam radiation and interstitial iridium-192. Int. J. Radiat. Oncol. Biol. Phys., *39:* 1043-1052, 1997.
18. De_Neve, W., Lybeert, M. L., Goor, C., Crommelin, M. A., and Ribot, J. G. T1 and T2 carcinoma of the urinary bladder: long term results with external, preoperative, or interstitial radiotherapy. Int. J. Radiat. Oncol. Biol. Phys., *23:* 299-304, 1992.
19. Rozan, R., Albuisson, E., Donnarieix, D., Giraud, B., Mazeron, J. J., Gerard, J. P., Pernot, M., Gerbaulet, A., Baillet, F., Douchez, J., and et, a. l. Interstitial iridium-192 for bladder cancer (a multicentric survey: 205 patients). Int. J. Radiat. Oncol. Biol. Phys., *24:* 469-477, 1992.
20. Moonen, L. M., Horenblas, S., van, der, Voet, Jc, Nuyten, M. J., and Bartelink, H. Bladder conservation in selected T1G3 and muscle-invasive T2-T3a bladder carcinoma using combination therapy of surgery and iridium-192 implantation. Br. J. Urol., *74:* 322-327, 1994.
21. Lerner, S. P., Skinner, D. G., Lieskovsky, G., Boyd, S. D., Groshen, S. L., Ziogas, A., Skinner, E., Nichols, P., and Hopwood, B. The rationale for en bloc pelvic lymph node dissection for bladder cancer patients with nodal metastases: long-term results. J. Urol., *149:* 758-764, 1993.
22. Frazier, H. A., Robertson, J. E., Dodge R.K., and Paulson, D. F. The value of pathologic factors in predicting cancer-specific survival among patients treated with radical cystectomy for transitional cell carcinoma of the bladder and prostate. Cancer, *71:* 3993-4001, 1993.
23. Bassi, P., Ferrante, G. D., Piazza, N., Spinadin, R., Carando, R., Pappagallo, G., and Pagano, F. Prognostic factors of outcome after radical cystectomy for bladder cancer: a retrospective study of a homogeneous patient cohort. J. Urol., *161:* 1494-1497, 1999.
24. Skinner, D. G., Tift, J. P., and Kaufman, J. J. High dose, short course preoperative radiation therapy and immediate single stage radical cystectomy with pelvic node dissection in the management of bladder cancer. J. Urol., *127:* 671-674, 1982.
25. Pollack, A., Zagars, G. K., Dinney, C. P., Swanson, D. A., and von Eschenbach, A. C. Preoperative radiotherapy for muscle-invasive bladder carcinoma. Long term follow-up and prognostic factors for 338 patients. Cancer, *74:* 2819-2827, 1994.
26. Cole, C. J., Pollack, A., Zagars, G. K., Dinney, C. P., Swanson, D. A., and von, E. A. Local control of muscle-invasive bladder cancer: preoperative radiotherapy and cystectomy versus cystectomy alone. Int. J. Radiat. Oncol. Biol. Phys., *32:* 331-340, 1995.
27. Anderstrom, C., Johansson, S., Nilsson, S., Unsgaard, B., and Wahlqvist, L. A prospective randomized study of preoperative irradiation with cystectomy or cystectomy alone for invasive bladder carcinoma. Eur. Urol., *9:* 142-147, 1983.
28. Smith, J., Crawford, E., Paradelo, J., Blumenstein, B., Herschman, B., Grossman, B., and Christie, D. Treatment of advanced bladder cancer with combined preoperative irradiation and radical cystectomy versus radical cystectomy alone: a phase III Intergroup study. J. Urol., *157:* 805-808, 1997.
29. Ghoneim, M. A., Ashamallah, A. K., Awaad, H. K., and Whitmore, W. F. Randomized trial of cystectomy with or without preoperative radiotherapy for carcinoma of the bilharzial bladder. J. Urol., *134:* 266-268, 1985.
30. Huncharek, M., Muscat, J., and Geschwind, J. F. Planned preoperative radiation therapy in muscle invasive bladder cancer; results of a meta-analysis. Anticancer Res, *18:* 1931-1934, 1998.
31. Shelley, M., Wilt, T., Barber, J., and Mason, M. A meta-analysis

of randomised trials suggests a survival benefit for combined radiotherapy and radical cystectomy compared with radical radiotherapy for invasive bladder cancer: are these data relevant to modern practice? Clin. Oncol., *16:* 166-171, 2004.

32. Shipley, W., Kaufman, D., Zehr, E., Heney, N., Lane, S., Thakral, H., Althausen, A., and Zietman, A. Selective bladder preservation by combined modality protocol treatment: long-term outcomes of 190 patients with invasive bladder cancer. Urology, *60:* 62-67, 2002.
33. Zietman, A., Sacco, D., Skowronski, U., Gomery, P., Kaufman, D., Clark, J., Talcott, J., and Shipley, W. Organ conservation in invasive bladder cancer by transurethral resection, chemotherapy and radiation: results of a urodynamic and quality of life study on long-term survivors. J. Urol., *170:* 1772-1776, 2003.
34. Coppin, C., Gospodarowicz, M., James, K., Tannock, I. F., Zee, B., Carson, J., Pater, J., and Sullivan, L. The NCI-Canada trial of concurrent cisplatin and radiotherapy for muscle invasive bladder cancer. J. Clin. Oncol., *14:* 2901-2907, 1996.
35. Farah, R., Chodak, G. W., Vogelzang, N. J., Awan, A. M., Quiet, C. A., Moormeier, J., Schoenberg, H., and Weichselbaum, R. R. Curative radiotherapy following chemotherapy for invasive bladder carcinoma (a preliminary report). Int. J. Radiat. Oncol. Biol. Phys., *20:* 413-417, 1991.
36. Tester, W., Caplan, R., Heaney, J., Venner, P., Whittington, R., Byhardt, R., True, L., and Shipley, W. Neoadjuvant combined modality program with selective organ preservation for invasive bladder cancer: results of Radiation Therapy Oncology Group phase II trial 8802. J. Clin. Oncol., *14:* 119-126, 1996.
37. Wajsman, Z., Marino, R., Parsons, J., Oblon, D., and McCarley, D. Bladder-sparing approach in the treatment of invasive bladder cancer. Sem. Urol., *8*, 1990.
38. Ghersi, D., Stewart, L. A., Parmar, M. K. B., Coppin, C., Martinez-Pineiro, J., Raghavan, D., and Wallace, M. A. Neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: a randomised controlled trial. Lancet, *354:* 533-540, 1999.
39. Collaboration, A. B. C. A. M.-a. Neoadjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis. Lancet, *361:* 1927-1934, 2003.
40. Hayter, C. R. R., Paszat, L. F., Groome, P. A., Schulze, K., Math, M., and MacKillop, W. J. A population-based study of the use and outcome of radical radiotherapy for invasive bladder cancer. Int. J. Radiat. Oncol. Biol. Phys., *45:* 1239-1245, 1999.
41. Scrimger, R., Murtha, A., Parliament, M., Venner, P., Hanson, J., Houle, G., and Chetner, M. Muscle-invasive transitional cell carcinoma of the urinary bladder: a population-based study of patterns of care and prognostic factors. Int. J. Radiat. Oncol. Biol. Phys., *51:* 23-30, 2001.
42. Mameghan, H., Fisher, R., Mameghan, J., and Brook, S. Analysis of failure following definitive radiotherapy for invasive transitional cell carcinoma of the bladder. Int. J. Radiat. Oncol. Biol. Phys., *31:* 247-254, 1995.
43. Moonen, L., Voet, H. v., Nijs, R. d., Horenblas, S., Hart, A., and Bartelink., H. Muscle-invasive bladder cancer treated with external beam radiation: influence of total dose, overall treatment time, and treatment interruption on local control. Int J Radiat Oncol Biol Phys, *42:* 525-530, 1998.
44. Quilty, P. M. and Duncan, W. Treatment of superficial (T1) tumours of the bladder by radical radiotherapy. Br. J. Urol., *58:* 147-152, 1986.
45. Rodel, C., Dunst, J., Grabenbauer, G., Kuhn, R., Papadopoulos, T., Schrott, K. M., and Sauer, R. Radiotherapy is an effective treatment for high-risk T1-bladder cancer. Strahlenther. Onkol., *177:* 82-88, 2001.
46. Shipley, W. U., Rose, M. A., Perrone, T. L., Mannix, C. M., Heney, N. M., and Prout, G. R. Full-dose irradiation for patients with invasive bladder carcinoma: clinical and histological factors prognostic of improved survival. J. Urol., *134:* 679-683, 1985.
47. Shipley, W. U., Prout, G. R., Kaufman, S. D., and Perrone, T. L. Invasive bladder carcinoma. The importance of initial transurethral surgery and other significant prognostic factors for improved survival with full-dose irradiation. Cancer, *60:* 514-520, 1987.
48. Timmer, P. R., Harlief, H. A., and Hooijkaas, J. A. Bladder cancer: Pattern of recurrence in 142 patients. Int. J. Radiat. Oncol. Biol. Phys., *11:* 899-905, 1985.
49. Pollack, A., Wu, C. S., Czerniak, B., Zagars, G. K., Benedict, W. F., and McDonnell, T. J. Abnormal bcl-2 and pRb expression are independent correlates of radiation response in muscle-invasive bladder cancer. Clin. Cancer Res., *3:* 1823-1829, 1997.
50. Pollack, A., Czerniak, B., Zagars, G. K., Hu, S. X., Wu, C. S., Dinney, C. P., Chyle, V., and Benedict, W. F. Retinoblastoma protein expression and radiation response in muscle-invasive bladder cancer. Int. J. Radiat. Oncol. Biol. Phys., *39:* 687-695, 1997.
51. Moonen, L., Ong, F., Gallee, M., Verheij, M., Horenblas S, Hart, A., and Bartelink, H. Apoptosis, proliferation and p53, cyclin D1, and retinoblastoma gene expression in relation to radiation response in transitional cell carcinoma of the bladder. Int. J. Radiat. Oncol. Biol. Phys., *49:* 1305-1310, 2001.
52. Chyle, V., Pollack, A., Czerniak, B., Stephens, L. C., Zagars, G. K., Terry, N. H., and Meyn, R. E. Apoptosis and downstaging after preoperative radiotherapy for muscle-invasive bladder cancer. Int. J. Radiat. Oncol. Biol. Phys., *35:* 281-287, 1996.
53. Rodel, C., Grabenbauer, G. G., Rodel, F., Birkenhake, S., Kuhn, R., Martus, P., Zorcher, T., Fursich, D., Papadopoulos, T., Dunst, J., Schrott, K. M., and Sauer, R. Apoptosis, p53, bcl-2, and KI-67 in invasive bladder carcinoma: possible predictors for response to radiochemotherapy and successful bladder preservation. Int. J. Radiat. Oncol. Biol. Phys., *46:* 1213-1221, 2000.
54. Fung, C. Y., Shipley, W. U., Young, R. H., Griffin, P. P., Convery, K. M., Kaufman, D. S., Althausen, A. F., Heney, N. M., and Prout, G. R., Jr Prognostic factors in invasive bladder carcinoma in a prospective trial of preoperative adjuvant chemotherapy and radiotherapy. J. Clin. Oncol., *9:* 1533-1542, 1991.
55. Wolf, H., Olsen, P. R., and Hojgaard, K. Urothelial dysplasia concomitant with bladder tumours: A determinant for future new occurrences in patients treated by full-course radiotherapy. Lancet 1005-1008, 1985.
56. Zietman, A., Grocela, J., Zehr, E., Kaufman, D., Young, R., Althausen, A., Heney, N., and Shipley, W. Selective bladder conservation using transurethral resection, chemotherapy, and radiation: management and consequences of Ta, T1, and Tis recurrence within the retained bladder. Urology, *58:* 380-385, 2001.
57. Davidson, S. E., Symonds, R. P., Snee, M. P., Upadhyay, S., Habeshaw, T., and Robertson, A. G. Assessment of factors influencing the outcome of radiotherapy for bladder cancer. Br. J. Urol., *66:* 288-293, 1990.
58. Goffinet, D. R., Schneider, M. J., Glatstein, E. J., Ludwig, H., Ray, G. R., Dunnick, N. R., and Bagshaw, M. A. Bladder cancer: results of radiation therapy in 384 patients. Radiology, *117:* 149-153, 1975.
59. Yu, W. S., Sagerman, R. H., Chung, C. T., Dalal, P. S., and King, G. A. Bladder carcinoma. Experience with radical and preoperative radiotherapy in 421 patients. Cancer, *56:* 1293-1299, 1985.
60. Goodman, G. B., Hislop, T. G., Elwood, J. M., and Balfour, J. Conservation of bladder function in patients with invasive bladder cancer treated by definitive irradiation and selective cystectomy. Int. J. Radiat. Oncol. Biol. Phys., *7:* 569-573, 1981.
61. Quilty, P. M. and Duncan, W. The influence of hemoglobin level on the regression and long term control of transitional cell carcinoma of the bladder following photon irradiation. Int. J. Radiat. Oncol. Biol. Phys., *12:* 1735-1742, 1986.

62. Subarsky, P. and Hill, R. The hypoxic tumour microenvironment and metastatic progression. Clin. Exp. Metastasis, *20:* 237-250, 2003.

63. Hoskin, P., Sibtain, A., Daley, F., and Wilson, G. GLUT1 and CAIX as intrinsic markers of hypoxia in bladder cancer: relationship with vascularity and proliferation as predictors of outcome of ARCON. Br. J. Cancer, *89:* 1290-1297, 2003.

64. Fyles, A., Milosevic, M., Hedley, D., Pintilie, M., Levin, W., Manchul, L., and Hill, R. P. Tumor hypoxia is an independent predictor of outcome in patients with node negative cervix cancer. J. Clin. Oncol., 2002.

65. Brizel, D. M., Scully, S. P., Harrelson, J. M., Layfield, L. J., Bean, J. M., Prosnitz, L. R., and Dewhirst, M. W. Tumor oxygenation predicts for likelihood of distant metastases in human soft tissue sarcoma. Cancer Res., *56:* 941-943, 1996.

66. Roy, C., Bras, Y. L., Mangold, L., Saussine, C., Tuchmann, C., Pfleger, D., and Jacqmin, D. Small pelvic lymph node metastases: evaluation with MR imaging. Clin. Radiol., *52:* 437-440, 1997.

67. Barentsz, J. O., Witjes, J. A., and Ruijs, J. H. What is new in bladder cancer imaging. Urol. Clin. North Am., *24:* 583-602, 1997.

68. Heicappell, R., Muller-Mattheis, V., Reinhardt, M., Vosberg, H., Gerharz, C. D., Muller-Gartner, H., and Ackermann, R. Staging of pelvic lymph nodes in neoplasms of the bladder and prostate by positron emission tomography with 2-[(18)F].-2-deoxy-D-glucose. Eur Urol, *36:* 582-587., 1999.

69. Milosevic, M., Gospodarowicz, M., Jewett, M., Bristow, R., and Haycocks, T. Intensity-modulated radiation therapy (IMRT) for lymph node metastases in bladder cancer. *In:* V. Gregoire, P. Scalliet, and K. Ang (eds.), Clinical target volumes in conformal and intensity modulated radiation therapy, pp. 157-169. New York: Springer-Verlag, 2003.

70. Agranovich, A., Czaykowski, P., Hui, D., Pickles, T., and Kwan, W. Radiotherapy for muscle-invasive urinary bladder cancer in elderly patients. Can. J. Urol., *10:* 2056-2061, 2003.

71. Borgaonkar, S., Jain, A., Bollina, P., McLaren, D., Tulloch, D., Kerr, G., and Howard, G. Radical radiotherapy and salvage cystectomy as the primary management of transitional cell carcinoma of the bladder. Results following the introduction of a CT planning technique. Clin. Oncol., *14:* 141-147.

72. Larsen, L. E. and Engelholm, S. A. The value of three-dimensional radiotherapy planning in advanced carcinoma of the urinary bladder based on computed tomography. Acta Oncol., *33:* 655-659, 1994.

73. Bentzen, S. M., Jessen, K. A., Jorgensen, J., and Sell, A. Impact of CT-based treatment planning on radiation therapy of carcinoma of the bladder. Acta Radiol. Oncol., *23:* 199-203, 1984.

74. Rothwell, R. I., Ash, D. V., and Jones, W. G. Radiation treatment planning for bladder cancer: a comparison of cystogram localisation with computed tomography. Clin. Radiol., *34:* 103-111, 1983.

75. Logue, J. P., Sharrock, C. L., Cowan, R. A., Read, G., Marrs, J., and Mott, D. Clinical variability of target volume description in conformal radiotherapy planning. Int J Radiat Oncol Biol Phys, *41:* 929-931, 1998.

76. Meijer, G., Rasch, C., Remeijer, P., and Lebesque, J. Three-dimensional analysis of delineation errors, setup errors, and organ motion during radiotherapy of bladder cancer. Int. J. Radiat. Oncol. Biol. Phys., *55:* 1277-1287, 2003.

77. Cowan, R., McBain, C., Ryder, W., Wylie, J., Logue, J., Turner, S., Voet, J. V. d., Collins, C., Khoo, V., and Read, G. Radiotherapy for muscle-invasive carcinoma of the bladder: results of a randomized trial comparing conventional whole bladder with dose-escalated partial bladder radiotherapy. Int. J. Radiat. Oncol. Biol. Phys., *59:* 197-207, 2004.

78. Turner, S. L., Swindell, S. L., Bowl, N., Marrs, J., Brookes, B., Read, G., and Cowan, R. A. Bladder movement during radiation therapy for bladder cancer: implications for treatment planning. Int. J. Radiat. Oncol. Biol. Phys., *39:* 355-360, 1997.

79. Muren, L., Smaaland, R., and Dahl, O. Organ motion, set-up variation and treatment margins in radical radiotherapy of urinary bladder cancer. Radiother. Oncol., *69:* 291-304, 2003.

80. Muren, L., Redpath, A., and McLaren, D. Treatment margins and treatment fractionation in conformal radiotherapy of muscle-invading urinary bladder cancer. Radiother. Oncol., *71:* 65-71, 2004.

81. Turner, W. H., Markwalder, R., Perrig, S., and Studer, U. E. Meticulous pelvic lymphadenectomy in surgical treatment of the invasive bladder cancer: an option or a must? Eur. Urol., *33 (Suppl 4):* 21-22, 1998.

82. Vieweg, J., Gschwend, J. E., Herr, H. W., and Fair, W. R. Pelvic lymph node dissection can be curative in patients with node positive bladder cancer. J. Urol., *161:* 449-454, 1999.

83. Stein, J. P., Lieskovsky, G., Cote, R., Groshen, S., Feng, A. C., Boyd, S., Skinner, E., Bochner, B., Thangathurai, D., Mikhail, M., Raghavan, D., and Skinner, D. G. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. J. Clin. Oncol., *19:* 666-675., 2001.

84. Smith, J. A. and Whitmore, W. F. Regional lymph node metastases from bladder cancer. J. Urol., *126:* 591-593, 1981.

85. Zincke, H., Patterson, D. E., Utz, D. C., and Benson, R. C. Pelvic lymphadenectomy and radical cystectomy for transitional cell carcinoma of the bladder with pelvic lymph node disease. Br. J. Urol., *57:* 156-159, 1985.

86. Poulson, A. L., Horn, T., and Steven, K. Radical cystectomy: extending the limits of pelvic lymph node dissection improves survival for patients with bladder cancer confined to the bladder wall. J. Urol., 1998.

87. Bretheau, D. and Ponthieu, A. Results of radical cystectomy and pelvic lymphadenectomy for bladder cancer with pelvic node metastases. Urol. Int., *57:* 27-31, 1996.

88. Quilty, P. M., Kerr, G. R., and Duncan, W. Prognostic indices for bladder cancer: An analysis of patients with transitional cell carcinoma of the bladder primarily treated by radical megavoltage x-ray therapy. Radiother. Oncol., *7:* 311-321, 1986.

89. Sell, A., Jakobsen, A., Nerstrom, B., Sorensen, B., Steven, K., and Barlebo, H. Treatment of advanced bladder cancer category T2, T3 and T4a. Scand. J. Urol. Nephrol., *138:* 193-201, 1991.

90. Naslund, I., Nilsson, B., and Littbrand, B. Hyperfractionated radiotherapy of bladder cancer. A ten-year follow-up of a randomized clinical trial. Acta Oncol., *33:* 397-402, 1994.

91. Goldobenko, G., Matveev, B., Shipilov, V., Klimakov, B., and Tkachev, S. Radiation treatment of bladder cancer using different fractionation regimens. Med. Radiol. (Mosk.), *36:* 14-16, 1991.

92. Stuschke, M. and Thames, H. D. Hyperfractionated radiotherapy of human tumors: overview of the randomized clinical trials. Int. J. Radiat. Oncol. Biol. Phys., *37:* 259-267, 1997.

93. Thames, H. D. and Hendry, J. H. Fractionation in radiotherapy, p. 297. London: Taylor and Francis Inc., 1987.

94. Trott, K. R. and Kummermehr, J. What is known about tumour proliferation rates to choose between accelerated fractionation or hyperfractionation. Radiother. Oncol., *3:* 1-9, 1985.

95. Hainau, B. and Dombernowsky, P. Histology and cell proliferation in human bladder tumors. Cancer, *33:* 115-126, 1974.

96. Rew, D. A., Thomas, D. J., Coptcoat, M., and Wilson, G. D. Measurement of in vivo urological tumour cell kinetics using multiplanar flow cytometry. Preliminary study. Br. J. Urol., *68:* 44-48, 1991.

97. Maciejewski, B. and Majewski, S. Dose fractionation and tumour repopulation in radiotherapy for bladder cancer. Radiother. Oncol., *21:* 163-170, 1991.

98. Neve, W. D., Lybeert, M., Goor, C., Crommelin, M., and Ribot, J. Radiotherapy for T2 and T3 carcinoma of the bladder: the influence of overall treatment time. Radiother. Oncol., *36:* 183-188, 1995.

99. Cole, D. J., Durrant, K. R., Roberts, J. T., Dawes, P. J., Yosef, H., and Hopewell, J. W. A pilot study of accelerated fractionation in the radiotherapy of invasive carcinoma of the bladder. Br. J. Radiol., *65:* 792-798, 1992.

100. Pos, F., Tienhoven, G. v., Hulshof, M., Koedooder, K., and Gonzalez, D. G. Concomitant boost radiotherapy for muscle invasive bladder cancer. Radiother. Oncol., *68:* 75-80, 2003.

101. Yavuz, A., Yavuz, M., Ozgur, G., Colak, F., Ozyavuz, R., Cimsitoglu, E., and Ilis, E. Accelerated superfractionated radiotherapy with concomitant boost for invasive bladder cancer. Int. J. Radiat. Oncol. Biol. Phys., *56:* 734-745, 2003.

102. Zouhair, A., Ozsahin, M., Schneider, D., Bauer, J., Jichlinski, P., Roth, A., Douglas, P., and Miralbell, R. Invasive bladder carcinoma: a pilot study of conservative treatment with accelerated radiotherapy and concomitant cisplatin. Int. J. Cancer, *96:* 350-355, 2001.

103. Moonen, L., van der Voet, H., Horenblas, S., and Bartelink, H. A feasibility study of accelerated fractionation in radiotherapy of carcinoma of the urinary bladder. Int J Radiat Oncol Biol Phys, *37:* 537-542, 1997.

104. Plataniotis, G., Michalopoulos, E., Kouvaris, J., Vlahos, L., and Papavasiliou, C. A feasibility study of partially accelerated radiotherapy for invasive bladder cancer. Radiotherapy & Oncology, *33:* 84-87, 1994.

105. Horwich, A., Dearnaley, D., Huddart, R., Graham, J., Bessel, E., Mason, M., and Meyer, L. A trial of accelerated fractionation (AF) in T2/3 bladder cancer (Abstract). Eur J Cancer, *35 (Supp 4):* S342, 1999.

106. Kob, D., Arndt, J., Kriester, A., Schwenk, M., and Kloetzer, K. Results of percutaneous radiotherapy of bladder cancer using 1 and 2 series of irradiation. Strahlentherapie, *161:* 673-677, 1985.

107. Rostom, A., Tahir, S., Gershuny, A., Kandil, A., Folkes, A., and White, W. Once weekly irradiation for carcinoma of the bladder. Int. J. Radiat. Oncol. Biol. Phys., *35:* 289-292, 1996.

108. McLaren, D. B., Morrey, D., and Mason, M. D. Hypofractionated radiotherapy for muscle invasive bladder cancer in the elderly. Radiother Oncol, *43:* 171-174, 1997.

109. Salminen, E. Unconventional fractionation for palliative radiotherapy of urinary bladder cancer. A retrospective review of 94 patients. Acta Oncol., *31:* 449-454, 1992.

110. Scholten, A. N., Leer, J. W., Collins, C. D., Wondergem, J., Hermans, J., and Timothy, A. Hypofractionated radiotherapy for invasive bladder cancer. Radiother. Oncol., *43:* 163-169, 1997.

111. Pisters, L. L., Tykochinsky, G., and Wajsman, Z. Intravesical bacillus Calmette-Guerin or mitomycin C in the treatment of carcinoma in situ of the bladder following prior pelvic radiation therapy. J Urol, *146:* 1514-1517, 1991.

112. Palou, J., Sanchez-Martin, F. M., Rosales, A., Salvador, J., Algaba, F., and Vicente, J. Intravesical bacille Calmette-Guerin in the treatment of carcinoma in situ or high-grade superficial bladder carcinoma after radiotherapy for bladder carcinoma. BJU Int, *83:* 429-431, 1999.

113. Bloom, H. J., Hendry, W. F., Wallace, D. M., and Skeet, R. G. Treatment of T3 bladder cancer: controlled trial of pre-operative radiotherapy and radical cystectomy versus radical radiotherapy. Br. J. Urol., *54:* 136-151, 1982.

114. Abratt, R. P., Wilson, J. A., Pontin, A. R., and Barnes, R. D. Salvage cystectomy after radical irradiation for bladder cancer-prognostic factors and complications. Br. J. Urol., *72:* 756-760, 1993.

115. Blandy, J. P., England, H. R., Evans, S. J., Hope-Stone, H. F., Mair, G. M., Mantell, B. S., Oliver, R. T., Paris, A. M., and Risdon, R. A. T3 bladder cancer—the case for salvage cystectomy. Br. J. Urol., *52:* 506-510, 1980.

116. Crawford, E. D. and Skinner, D. G. Salvage cystectomy after irradiation failure. J. Urol., *123:* 32-34, 1980.

117. Konnak, J. W. and Grossman, H. B. Salvage cystectomy following failed definitive radiation therapy for transitional cell carcinoma of bladder. Urology, *26:* 550-553, 1985.

118. Nurmi, M., Valavaara, R., Puntala, P., and Ekfors, T. Single-stage salvage cystectomy: results and complications in 20 patients. Eur. Urol., *16:* 89-91, 1989.

119. Smith, J. A. and Whitmore, W. F. Salvage cystectomy for bladder cancer after failure of definitive irradiation. J. Urol., *125:* 643-645, 1981.

120. Swanson, D. A., Eschenbach, A. C. v., Bracken, R. B., and Johnson, D. E. Salvage cystectomy for bladder carcinoma. Cancer, *1;47:* 2275-2279, 1981.

121. Osborn, D. E., Honan, R. P., Palmer, M. K., Barnard, R. J., McIntyre, D., and Pointon, R. S. Factors influencing salvage cystectomy results. Br. J. Urol., *54:* 122-125, 1982.

122. Bochner, B. H., Figueroa, A. J., Skinner, E. C., Lieskovsky, G., Petrovich, Z., Boyd, S. D., and Skinner, D. G. Salvage radical cystoprostatectomy and orthotopic urinary diversion following radiation failure. J Urol, *160:* 29-33, 1998.

123. Mannel, R. S., Manetta, A., Buller, R. E., Braly, P. S., Walker, J. L., and Archer, J. S. Use of ileocecal continent urinary reservoir in patients with previous pelvic irradiation. Gynecol Oncol, *59:* 376-378, 1995.

124. Richards, B., Bastable, J. R. G., Freedman, L., Glashan, R. W., Harris, G., Newling, D. W. W., Robinson, M. R. G., Smith, P. H., and Group, a. T. Y. U. C. R. Adjuvant chemotherapy with doxorubicin (Adriamycin) and 5-fluorouracil in T3, NX, MO bladder cancer treated with radiotherapy. Br. J. Urol., *55:* 386-391, 1982.

125. Skinner, D. G., Daniels, J. R., Russell, C. A., Lieskovsky, G., Boyd, S. D., Nichols, P., Kern, W., Sakamoto, J., Krailo, M., and Groshen, S. The role of adjuvant chemotherapy following cystectomy for invasive bladder cancer: a prospective comparative trial. J. Urol., *145:* 459-464, 1991.

126. Freiha, F., Reese, J., and Torti, F. M. A randomized trial of radical cystectomy versus radical cystectomy plus cisplatin, vinblastine and methotrexate chemotherapy for muscle invasive bladder cancer. J. Urol., *155:* 495-499, 1996.

127. Stockle, M., Meyenburg, W., Wellek, S., Voges, G. E., Rossmann, M., Gertenbach, U., Thuroff, J. W., Huber, C., and Hohenfellner, R. Adjuvant polychemotherapy of nonorgan-confined bladder cancer after radical cystectomy revisited: long-term results of a controlled prospective study and further clinical experience. J. Urol., *153:* 47-52, 1995.

128. Studer, U. E., Bacchi, M., Biedermann, C., Jaeger, P., Kraft, R., Mazzucchelli, L., Markwalder, R., Senn, E., and Sonntag, R. W. Adjuvant cisplatin chemotherapy following cystectomy for bladder cancer: results of a prospective randomized trial. J. Urol., *152:* 81-84, 1994.

129. Maase, H. v. d., Hansen, S. W., Roberts, J. T., Dogliotti, L., Oliver, T., Moore, M. J., Bodrogi, I., Albers, P., Knuth, A., Lippert, C. M., Kerbrat, P., Rovira, P. S., Wersall, P., Cleall, S. P., Roychowdhury, D. F., Tomlin, I., Visseren-Grul, C. M., and Conte, P. F. Gencitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. J. Clin. Oncol., *18:* 3068-3077, 2000.

Committee 11

Non-urothelial Cancer of the Bladder

Chair

H. Abol-Enein (Egypt)

Members

B.R. Kava (USA)

A.J.K. Carmack (USA)

CONTENTS

Non-urothelial Cancer of the Bladder

H. Abol-Enein

B.R. Kava, A.J.K. Carmack

Worldwide, urothelial (formerly known as transitional cell) carcinoma is the most prevalent histologic type of bladder tumor. Both superficial and invasive disease have been extensively studied. However, at the other end of the bladder tumor spectrum are squamous cell carcinoma, adenocarcinoma, and other uncommon tumors. The latter includes small cell carcinoma, sarcoma, carcinosarcoma and sarcomatoid tumors, paraganglioma, lymphoma, melanoma, and pseudotumors. Other epithelial abnormalities can mimic tumors and biopsy is frequently indicated for proper diagnosis.

I. SQUAMOUS CELL CARCINOMA

Squamous cell carcinoma (SCC) occurs in both bladders infected with and those free of bilharziasis. The incidence, epidemiology, and the natural history of the 2 subpopulations are different.

1. Squamous Cell Carcinoma Not Associated With Bilharziasis

a) Epidemiology

While bilharziasis is the leading cause of SCC worldwide, schistosomal infections are rare in western countries. Primary squamous cell carcinoma in the non-bilharzial bladder is uncommon. It represents the second most common bladder malignancy in western countries, comprising 2% to 5% in most contemporary cystectomy series [1-5]. The tumors are most often diagnosed in the seventh decade of life.

Using data obtained from the Surveillance, Epidemiology, and End Results (SEER) program between 1973-1997, Porter et al. determined that black Americans were twice as likely to develop SCC of the bladder than white Americans with an overall annual incidence of 1.2/100,000 person-years (95% CI 0.4 to 1.37) in the former versus 0.6/100,000 person-years (95% CI 0.57 to 0.64) in the latter [6]. This racial variability was present in men and women for all age groups beyond 45 years, and, despite a slight decline in the annual incidence over the 3 decades studied, remained relatively constant.

In the United States, although the incidence of urothelial carcinoma in men is at least 3 times that in women, there is less of a male predominance in SCC. Compiling the data from 915 patients in 10 series of SCC, Johansson and Cohen reported that the ratio of males to females was 1.4:1, which is consistent with other reports [1-3,7]. Similarly to urothelial carcinoma, women are more likely to present with more advanced disease than men [8]. Analyzing data from the Netherlands Cancer Registry, Mungan et al. confirmed the higher incidence of T3 and T4 non-urothelial bladder cancer in women (21.7% vs. 14.5% in T3 and 14.5% vs. 8.4% in T4) [9].

1. Spinal Cord Injury

In the US, patients with spinal cord injuries constitute the largest group of patients affected by SCC. This is thought to be due to inflammation from chronic urinary tract irritation; SCC also is likelier to occur in patients with chronic inflammatory disorders of the bladder, persistent calculi, chronic cystitis, and bladder diverticuli [10].

It has been estimated that 10% of cases of SCC of the bladder occur in patients with a catheter indwelling for at least 10 years [11]. Other studies have documented a 16- to 28-fold increased risk for SCC of the bladder in paraplegics. Patients who perform clean intermittent self-catheterization are less likely to develop the disease [12,13].

The incidence of bladder cancer in patients with spinal cord injuries was initially thought to be 2.3% to 10%, with the majority representing SCC [11,14,15]. A recent review of admission data from 33 560 patients with spinal cord injuries in the US Department of Veterans Affairs found only 130 patients with bladder cancer for an overall incidence of 0.39% [16]. Forty-two patient records were available for review, including 23 (55%) with urothelial carcinoma, 14 (33%) with SCC, and 4 (10%) with adenocarcinoma. It is noteworthy that in 26 patients with indwelling catheters, the incidences of SCC and urothelial carcinoma were equal, implicating chronic inflammation from an indwelling foreign body in the pathogenesis of SCC. The higher prevalence of urothelial carcinoma in this population may also reflect the higher prevalence of cigarette smoking in the US veteran population.

In another study from Bickel et al., 8 patients with bladder cancer were diagnosed among 2 900 patients with spinal cord injuries from 3 Louisiana medical centers, for an overall incidence of 0.32% [17]. Only 2 of 8 (25%) were found to have SCC, neither of whom had an indwelling catheter. Finally, in the largest study to date from Pannek et al., 43 561 patients with spinal cord injuries from Eastern Europe were evaluated by a questionnaire sent to all urologic departments involved in the management of spinal cord injury centers [18]. Forty-eight patients with bladder cancer were identified for an overall incidence of 0.11%. Interestingly, the number of patients in this series with indwelling catheters was 7%, and only 19% of the 48 patients had SCC. The authors concluded that the declining percentage of SCC and the declining incidence of bladder cancer may be a consequence of the reduced use of indwelling catheters.

Guidelines cannot be made on surveillance of patients with spinal cord injuries for SCC. The initial reports in which a high percentage of patients with spinal cord injuries developed SCC are subject to a number of flaws, primarily as a result of the retrospective manner in which data was obtained. While the true incidence of SCC in the spinal cord injured population appears to be less than 1%, it is recommended that these patients be monitored, particularly if they have indwelling catheters. Any history of hematuria should be evaluated. The frequency of surveillance and the extent of diagnostic evaluations cannot be determined based upon the literature to date.

2. SMOKING

The relationship between SCC and cigarette smoking is not clear cut. Johansson and Cohen found a higher incidence of SCC in smokers [7]. SEER data support a direct correlation between quantity of cigarettes smoked and the relative risk of development of SCC [19]. Indirect evidence from the Swedish Cancer Registry, however, does not support an association of SCC with smoking. A review of this database, which plotted incidence trends in bladder cancer in Sweden between 1960 and 1993, found that despite a rising incidence of urothelial carcinoma in Swedish women, which correlated with an increased prevalence of smoking during those years, there was a relatively constant incidence of SCC [20].

b) Etiology

Because urinary tract infection is more common in women, a relation between squamous metaplasia, leukoplakia, and the development of squamous cell carcinoma was proposed by Connery and Holly and Mellinger [21,22]. In a series of 20 patients with long-standing leukoplakia, O'Flynn and Mullaney observed the development of 5 cases of squamous cell carcinoma [23]. SCC is also often associated with squamous metaplasia, although in and of itself this is not considered to be a premalignant lesion [10]. In fact, studies have confirmed the high prevalence of squamous metaplasia in the general population [24].

A few case reports have documented the association between cyclophosphamide, BCG, human papilloma virus, and the development of SCC of the urinary bladder [25,26]. Recently, some studies have revealed possible genetic and chromosomal changes in relation to SCC. Abnormalities of chromosomes 3, 8, 10, 13, and 17 have been detected in SCC [27]. Studies on uroplakin II gene expression found a significant difference of expression between urothelial carcinoma and SCC, with the expression being greater in SCC. Uroplakins are the major differentiation products of the urothelium that control the different pathways of urothelial differentiation [5].

c) Clinical and Pathologic Features

Hematuria is the main clinical presentation in 63-100% of patients. Irritative bladder symptoms are seen in two-thirds of patients, while weight loss, back or pelvic pain, or frank obstructive symptoms are less common and are suggestive of advanced disease [2-4,28]. A urinary tract infection is present in

30% to 93% of patients at the time of diagnosis [2-4,29,30]. Symptoms are often present for a protracted period of time before the patient is diagnosed [2,3,5,29]. The majority of patients present with no previous history of urologic tumors. Superficial SCC of the bladder is rare, and the majority of tumors are muscle-invasive at presentation (**Figure 1**).

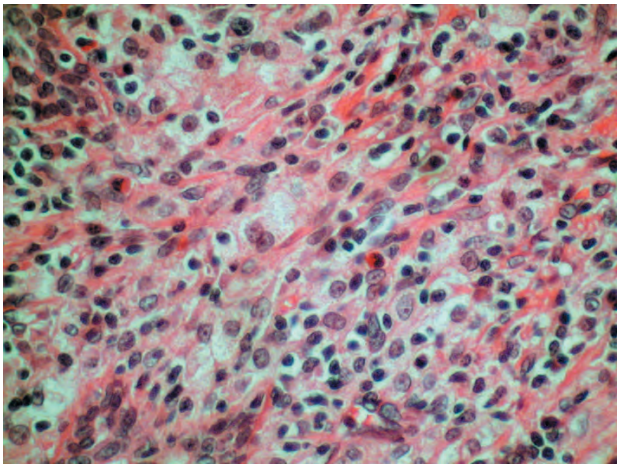


Figure 1. Squamous Cell Carcinoma Invading the Bladder Wall (Courtesy of Dr. Miguel Gonzalez)

Pure squamous cell carcinoma of the bladder must be distinguished from urothelial carcinoma with squamous differentiation. Relative to the number of series addressing treatment in patients with urothelial carcinoma, there are relatively few series that have addressed pure squamous cell carcinoma in western countries. The majority of these are more than 10 years old and lack the current staging and grading systems in use.

Superficial tumors are almost never seen; patients are usually diagnosed at an advanced stage. The majority of patients have a large, solitary tumor that extensively involves the bladder wall. The tumors appear as sessile lesions, often with ulceration and areas of squamous metaplasia adjacent to the primary tumor. There is a predilection for the trigone, but SCC can arise anywhere within the bladder. It may extend locally into the ureters and urethra. It may occupy a bladder diverticulum and also has been described in association with bladder calculi [31].

Debbagh et al., reported that 10 of 14 patients had palpable tumors on rectal examination and 11 had upper urinary tract obstruction [32]. Pretreatment imaging studies demonstrate hydronephrosis in 33% to 59% of cases [2,3,5]. Ninety-two percent of 114 cases of SCC of the bladder had T2 to T4 disease at the time of diagnosis, and most of the tumors were of high grade [3]. Similarly to urothelial carcinoma, clinical understaging is seen in as many as 73% of patients [3,33].

d) Treatment

Pure SCC of the bladder has a very poor prognosis, with the majority of patients dying within 1 to 3 years of diagnosis. Despite a variety of treatment regimens including radiation, chemotherapy, and surgery, in a series of 120 patients from the Royal Marsden Hospital, the overall 5-year survival rate was 16%, with only 8% of patients developing metastatic disease [29]. Therefore, failure to provide locoregional control appears to be the problem in managing these tumors.

1. Radiation

The reported results after treatment by definitive external irradiation are uniformly poor [3,28]. Radiation therapy alone in patients with SCC has been used as primary treatment or as an adjunct to surgery in the neoadjuvant setting. In a report by Quilty et al., 51 patients were treated with radical radiotherapy delivered with a 3-field beam-directed technique, covering the entire bladder, to a prescribed dose of 55 Gy given in 20 fractions over 4 weeks [30]. Patients were treated prone, immediately after emptying the bladder. Only 4 of the patients had T2 cancer and the overall survival was 26.9% at 3 years with a median survival of 14.3 months. Of 48 patients treated with radiation therapy by Rundle et al., the 5-year survival rates for patients with T2 and T3 disease were 16.7% and 4.8% respectively, while no patient with T4 disease survived beyond 11 months [3]. Similarly, in a series of 17 patients with T2 and T3 tumors treated with radiation therapy alone, Johnson et al. reported a 20% 5-year survival, which was not statistically less than the 34.6% 5-year survival seen in 7 patients in which preoperative radiation was followed by radical cystectomy [2].

2. Radical Cystectomy

Surgical treatment appears to provide a better therapeutic yield. Richie and associates reported a 5-year survival rate of 48% of 25 patients treated by radical cystectomy [33]. The authors believed this to compare favorably with the results in patients with urothelial carcinoma, however, they did not include in the analysis 3 patients (9%) who died in the perioperative period and an additional 5 patients in whom insufficient pathology or follow-up data was obtained. After adjusting for these cases, the 5-year survival is significantly less than reported. They identified tumor stage as the most important predictor of outcome.

Serrata et al. reported on 19 patients with pure SCC of the bladder [5]. All cases had a solitary locally advanced tumor and were treated by radical cystectomy. Sixty-three percent of the treated patients died of locally recurrent bladder cancer during a mean follow-up period of 52 months. Distant metastases were observed in only 1 patient.

Johnson and coworkers employed integrated preoperative radiation therapy followed by cystectomy and reported a 5-year survival of 34% [2]. Swanson and colleagues reported their results using the same approach [34]. Patients with T2 disease showed the highest survival figures. Furthermore, the results were better in patients whose tumors were downstaged by preoperative irradiation than for those who showed no downstaging. However, no conclusions can be drawn about the efficacy of preoperative irradiation plus cystectomy for non-bilharzial SCC, because too few patients treated in this way have been reported [35]. Because the tumor is uncommon, only a few cases are available for studies. It would be extremely difficult to obtain well-controlled prospective studies to achieve objective conclusions.

In another more contemporary series with a mean follow-up of 42 months, 9 of 14 patients (37%) with SCC who underwent radical cystectomy were still alive. Only 1 of the patients undergoing cystectomy received preoperative radiation therapy and 4 received neoadjuvant chemotherapy (M-VAC), with no objective responses noted. In this series of 19 patients, 12 died of locoregional disease, with only 1 of these patients dying with documented metastases. All of the 3 patients with ileal neobladders developed recurrence at the anastomosis between the neobladder and urethra. It is not specified whether frozen section biopsies of the bladder neck or urethra were performed intraoperatively. This contrasts with no anastomotic recurrences in 5 female patients with SCC who underwent orthotopic urinary diversion in a series by Stenzl et al [36]. Negative intraoperative frozen section biopsies of the bladder neck were obtained prior to orthotopic reconstruction in this series.

Several large contemporary cystectomy series in the literature have compared the results in patients with urothelial carcinoma and non-urothelial bladder cancer. In a large series from Japan, there was no significant difference in the 5-year post-cystectomy survival for patients with urothelial carcinoma (68.0%, n =1042) and with non-urothelial carcinoma (60.8%, n =89) [37]. Multivariate analysis did not find non-urothelial carcinoma as an independent prognostic factor in survival.

3. Chemotherapy

The role of neoadjuvant or adjuvant chemotherapy for pure SCC of the bladder is uncertain. Chemotherapy is usually not recommended due to the low chemosensitivity of SCC of the bladder. SCC is considerably less responsive to the standard chemotherapy regimens used for urothelial carcinoma [38,39]; neoadjuvant MVAC has been tried without any objective response [40]. An effective chemotherapy protocol against this disease has not yet been found, though newer combination regimens consisting of agents such as gemcitabine, paclitaxel, and docetaxel, when combined with a platinum compound, may yield sustained disease remissions in up to 50% of cases and hold promise for the future [41].

Interestingly, SCC has a low incidence of distant metastasis, ranging from 8% to 10% [42]. Still, the prognosis of SCC of the bladder is dismal. Most of the patients die of locoregional failure within 3 years. Distant metastasis is more often the cause of death in patients with urothelial carcinoma than in those with SCC. Therefore, pelvic control for SCC is more important and adds incentive to attempt methods of treatments to reduce the incidence of pelvic recurrence [43].

e) Prevention and Early Detection

Several screening protocols have been advocated in an attempt to diagnose those tumors earlier and to improve the outcome. Broecker et al. recommended annual cystoscopy and urine cytology in patients with long-term paraplegia [44]. Others suggested routine random bladder biopsies every 1 or 2 years. Navon et al. do not routinely use urine cytology or random biopsies except in patients with spinal cord injuries for more than 10 years and in patients with recurrent or chronic urinary tract infections [45]. Celis et al. showed that psoriasin (a calcium-binding protein expressed by squamous epithelia) is a potential marker of SCC [46]. Other biomarkers, such as SCC antigen, bcl-2, and p53 oncoproteins, may have a possible role in early diagnosis [47]. However, the exact role of these new markers requires further studies for validation in the early detection and follow-up of bladder SCC.

Summary

Non-bilharzial SCC is an uncommon form of bladder cancer. It has a very poor prognosis, with death most often secondary to locoregional failure, not metastasis. The current, limited, literature supports cystectomy as the treatment of choice (Grade B).

2. Squamous Cell Carcinoma in the Bilharzial Bladder

a) Epidemiology

This type of cancer is prevalent where urinary bilharziasis is endemic. The highest incidence of SCC of the bilharzial bladder is in Egypt. In a recent report by Ghoneim et al., SCC constituted 59% of 1 026 cystectomy specimens [48]. A high incidence of SCC is also found in Iraq, the Jizan region in southern Saudi Arabia, Yemen, and Sudan. In Africa, the disease has been reported in the Gold Coast and South Africa. However, the incidence in these countries is less, because bilharziasis is less endemic and less severe [49]. The mean age of the patients is 10 to 20 years lower than that in non-bilharzial cancer [43]. The median age is 46 years. Eighty percent of the cancer specimens showed histologic evidence of bilharzial infestation [48]. There is a lag period of approximately 30 years between bilharzial infection and the subsequent development of the disease. The male-to-female ratio is 5:1 [50]. The male predominance is thought to be related to the increased exposure to bilharzial infestation, as men work more in the fields and stay in contact with water contaminated with the infective parasite longer.

b) Etiology

There is good evidence from animal models that the biogenesis of bladder cancer is a multistage process. It involves initiation by carcinogens followed by promotion of tumor growth [51]. Bilharzial bladder cancer may be initiated by exposure to an environmentally- or locally-produced chemical carcinogen that is excreted in urine. This reacts with the mucosal surface of the bladder to produce irreversible and potentially carcinogenic changes in the DNA of some urothelial cells. Chronic bacterial infection, commonly complicating urinary bilharziasis, has been implicated in the production of nitrosamines, which are well-known potent carcinogens derived from precursors in the urine, and the secretion of ß-glucuronidase enzyme, which may split the conjugated carcinogens to yield free carcinogenic products [52,53]. The possibility of carcinogenic products of parasitic origin is not supported by recent investigation [49]. However, local mechanical irritation by schistosoma eggs appears to be an important promoting factor [53]. Vitamin A deficiency may explain the high frequency of squamous metaplasia of the bladder epithelium and the predominance of SCC in patients with bilharziasis.

c) Clinical and Pathologic Features

Patients usually present with symptoms of cystitis, including painful micturition, frequency, and hematuria. An extensive irregular filling defect is usually detected on cystogram. CT scanning or MRI is helpful for diagnosis and staging. The diagnosis depends on cystoscopy, biopsy, and careful bimanual examination under anesthesia [35]. Urine cytology is also a valuable diagnostic tool for SCC in bilharzial patients [54]. Cytokeratin shedding in urine has been used as a biological marker for the early detection of SCC [55].

Most patients present for treatment at an advanced stage, and 25% of cases are inoperable when first seen [43]. This is because of the overlap of symptoms of simple bilharzial cystitis with early malignant cystitis. When clinical staging was compared to the pathological findings, a clinical error of 37% was found with a tendency of understaging [56]. In a study of 608 patients with SCC of bilharzial bladders, pT1 disease was found in 2.6%, pT2 in 10.5%, pT3 in 80.0%, and pT4 in 6.9% [48]. The grading of the tumor in the same study showed grade I in 49.7%, grade II in 33.2%, and grade III in 17.1%. Lymph nodes were involved in only 18.7% of the cystectomy specimens. The prevalence of low grade disease and the intensive mural fibrosis associated with bilharziasis may explain the low incidence of lymph node positivity [35].

Grossly, the tumors are generally of the nodular fungating type and located in the dome or posterior or lateral walls of the bladder. Five gross types are recognized: nodular (60%), ulcerative (23%), verrucous (7%), papillary (7%), and diffuse (3%) [49]. A variety of atypical changes in the bladder mucosa including metaplasia, dysplasia, and, rarely, carcinoma in situ may be associated with the disease [57].

d) Treatment

1. Endoscopic Resection

In view of the tumor bulk and its advanced stage, transurethral resection appears to be unfeasible for definitive treatment and there are no reports on

results with the procedure in bilharzial bladder malignancy. Endoscopic resection should only be used for obtaining a biopsy for histopathological diagnosis.

2. Segmental Resection (Partial Cystectomy)

Segmental resection is an attractive alternative to circumvent the physiologic and social inconveniences of urinary diversion and possible loss of sexual potency, but local resection is only feasible in select conditions. They must be solitary tumors not involving the trigone and of a size allowing resection with an adequate safety margin, and the rest of the bladder mucosa must be free of any associated precancerous lesions. These strict criteria are found in a minority of cases. El-Hammady et al. found resectable bladder cancer in only 19 of 190 (10%) patients [58]. Augmentation cystoplasty was required in 5 patients to increase the residual bladder capacity. Five-year survival was 26.5%. Patients with low grade tumors had roughly twice the survival rate of those with high grade disease. On the other hand, less favorable results were reported by Omar in a series of 22 cases [59]. All patients but 1 developed tumor recurrence within 2 years. This different outcome may be related to the wide variability of selection criteria.

3. Radical Cystectomy

In view of the clinical and pathologic characteristics and the natural history of the disease, radical cystectomy with urinary diversion provides a logical treatment approach for patients with resectable tumors [60,61]. In men, the operation entails removal of the bladder, perivesical fat, peritoneal covering, prostate, seminal vesicles, and the endopelvic lymph nodes. In women, the bladder, urethra (if is not used for orthotopic bladder substitution), uterus, upper vagina with the pelvic fatty tissue, and the aforementioned lymph nodes are removed.

In a series of 138 cases, Ghoneim and associates reported a high postoperative mortality of 13.7%. This was due to peritonitis, adhesive intestinal obstruction, and hepatic failure. Cardiopulmonary complications were uncommon among this relatively young group of patients. In this old series, the overall 5-year survival was 32.6%. It was 43% in pT1 and pT2 and 30% in pT3 and pT4. Low grade tumors showed 46% survival, while in high grade disease it was 21%. Lymph node involvement reduced the 5-year survival to 20% [61]. In a recent report of the results in 1 026 cystectomy patients from an endemic area of schistosomiasis, 59% of the tumors were SCC. Bilharzial ova were identifiable in 88% of the specimens. Extravesical extension was not significantly different among patients with SCC or urothelial carcinoma (13.5% and 14.9%, respectively). The overall 5-year survival rate of patients with SCC was 50.3%. Only tumor stage, grade, and lymph node involvement had independent significant effects on survival. The latter halved the survival rate [48].

These clinical trials provide evidence that cystectomy alone, despite being radical, is inadequate to deal with the extent of local pathology. An adjuvant treatment directed to the pelvis might improve survival. Preoperative radiation therapy has been proposed as adjuvant therapy.

4. Radiation

The growth characteristics of carcinoma of the bilharzial bladder have been studied to evaluate its potential radioresponsiveness [62]. Two growth features were demonstrated: (1) high cell mitotic rate with a potential doubling time of 6 days and (2) an extensive cell loss factor. Tumors with such growth characteristics were expected to exhibit a radiation response [63]. Nevertheless, early experiences with external beam radiation therapy for definitive control of these tumors were disappointing [64]. The factors which interfered with the efficiency of radiation treatment in these cases included the coexisting bilharzial urologic lesions, which interfere with local tissue tolerance, and the considerable tumor bulk, which reduced local tumor control. Furthermore, the presence of radioresistant hypoxic tumor cells is suspected in light of the capillary vascular pattern of this cancer [65].

5. Neoadjuvant Radiation

The aim of preoperative radiation is to eradicate smaller cell burdens in the deep infiltrating parts of the tumor as well as the micro-extensions into the perivesical tissues and lymphatics. These small tumor foci are expected to have a better radiation response because they are oxygenated and composed of a relatively small number of cells with high mitotic indices. These biological factors and the pattern of the treatment failures due to local pelvic recurrence have justified the use of preoperative radiotherapy.

Awaad and associates compared the results of cystectomy after the preoperative administration of 40 Gy with a control group treated by cystectomy only [66]. The reported 2-year survival rates were significantly improved in the irradiated group. Ghoneim and colleagues compared the results of cystectomy

after preoperative irradiation using 20 Gy with those of cystectomy alone [67].

They treated 92 patients, divided among the 2 groups, and followed them for 60 months. Although patients who received preoperative radiation had better survival rates, this improvement did not approach statistical significance. In low stage tumors, regardless of the grade, survival was not influenced by preoperative irradiation as it was for high stage tumors.

The presence of a large proportion of hypoxic cells in the bulky tumors could explain the modest improvement after this regimen. To enhance the therapeutic value of irradiation, misonidazole, a hypoxic cell sensitizer, was given before the delivery of the radiation regimen. The trial was conducted with 3 arms: cystectomy only, 20 Gy of preoperative radiation followed by cystectomy, and preoperative radiation followed by cystectomy with misonidazole added as a radiosenitizer. The addition of misonidazole did not provide any additional survival benefit to the patients receiving preoperative radiotherapy (*Level 1*, [67]) .

6. Chemotherapy

Several chemotherapeutic agents have been tried in the management of unresectable SCC of the bilharzial bladder by Gad-el-Mawla et al. in the National Cancer Institute of Cairo University. All were phase II studies using a single agent. The most promising results were obtained with epirubicin [69]. Neoadjuvant and adjuvant epirubicin chemotherapy were used in a prospective randomized study including 71 patients with invasive cancer in bilharzial bladders. Two-thirds of the treated patients had SCC. The disease-free survival rates were 73.5% and 37.9%, favoring the chemotherapy group [70]. Further long-term follow-up results have not been published.

In a recent multicenter study including 120 patients treated with neoadjuvant cisplatin and gemcitabine, patients with SCC did not show a survival benefit over those undergoing cystectomy alone [71].

e) Prevention and Early Detection

Bilharzial bladder cancer is a preventable malignant disease. Primary prevention entails control of bilharziasis through snail control (the intermediate host of the parasite) and mass treatment of the rural population with oral antibilharzial drugs such as praziquantel [49]. Secondary prevention includes early detection using urine cytology and selective screening of the population at risk. The yield of 1 screening study done in a rural area in Egypt was 2 per 1000 individuals [54]. Such a detection rate would not justify regular screening.

Summary

Bilharzial SCC is the most common form of bladder cancer in endemic areas. It most often presents at an advanced stage but with low grade cells. Cystectomy is the standard treatment, but the long-term survival remains disappointing (*Grade B*). Limited evidence supports a potential role of neoadjuvant chemotherapy and radiation therapy, but is not sufficient to make a recommendation.

II. ADENOCARCINOMA

Adenocarcinoma of the bladder is the third most common histologic type of bladder carcinoma. It comprises 0.5% to 2.0% of all bladder tumors [72,73]. Adenocarcinoma has the unique distinction as the most common tumor arising in the bladder of patients with exstrophy. These patients carry a 4% lifetime risk of developing adenocarcinoma [74]. Adenocarcinoma of the bladder may also occur in association with schistosomiasis, endometriosis, bladder augmentations, and other irritative conditions of the urinary bladder [75,76].

One study from the United States used SEER data and identified only 32 patients (0.7%) with adenocarcinoma from 4 045 patients with newly diagnosed bladder cancer over a 1 year period from 1977-1978 [19].

Similarly to urothelial carcinoma, adenocarcinoma shows a male predominance. In a total of 11 series comprising 247 patients, the sex ratio between males and females was 2.7:1 [7].

Adenocarcinoma of the urinary bladder is classified based upon its site of origin as either primary adenocarcinoma, urachal adenocarcinoma, or secondary (metastatic) adenocarcinoma representing the local extension of a primary colon, prostate, or ovarian cancer [77]. Primary, urachal, exstrophy-associated, and metastatic adenocarcinoma will be discussed separately.

1. Primary Adenocarcinoma

a) Epidemiology

El-Bolkainy and associates reported an incidence of 8.1% in a series of 229 cases of bladder cancer [43]. Between 1970 and 1995, 1 870 cystectomies were carried out in the Urology and Nephrology Center of Mansoura. Of these, 185 cases proved to be primary non-urachal adenocarcinoma of the bladder on histopathologic examination (9.9%, [78]).

b) Clinical Features

Primary adenocarcinoma of the bladder presents with hematuria in most patients, which may be associated with irritative voiding symptoms and, occasionally, mucus passage in the urine [71,72,78-81]. Cystoscopically, the tumor is usually sessile, but can be papillary [80]. It can arise anywhere along the lateral walls, trigone, dome, and anterior wall of the bladder [71,78,80-82]. Multiple tumors are present approximately 50% of the time [71,78]. Adenocarcinoma is virtually always invasive with only 1 series documenting 2 tumors, of which 27 were Ta or T1 [82]. Interestingly, both patients were alive at 51 and 61 months following TUR alone.

Primary adenocarcinoma of the bladder has a very poor prognosis regardless of the modalities used for treatment. Five-year survival varies from 0% to 31%; the small number of patients in each series precludes individual comparisons based upon treatment undertaken. In a retrospective series of 48 patients treated for primary adenocarcinoma of the bladder, stage was the only factor that was highly predictive of outcome.

c) Pathologic Features (Figure 2)

In order for a diagnosis of primary adenocarcinoma of the bladder to be made, it must be distinguished from urothelial carcinoma with areas of glandular metaplasia. The pathogenesis of primary non-urachal adenocarcinoma is based on the ability of the urothelium to undergo metaplastic changes [83]. Mostofi proposed that the metaplastic potential of the urothelium has 2 distinct patterns [84]. Progressive invagination of hyperplastic epithelial buds into the lamina propria (von Brunn's nests) leads to the formation of cystitis cystica. Subsequently, metaplasia of the urothelial lining of these cysts to columnar mucin-producing cells results in the production of cystitis glandularis, which is a premalignant lesion. Follow-up is necessary [85]. Alternatively, cuboidal or columnar metaplasia of the surface epithelium can occur with no downward invagination. Chronic vesical irritation and infection are the predisposing factors for these changes [83,86]. This explains, at least partly, the higher incidence of these tumors among patients with bilharzial cystitis.

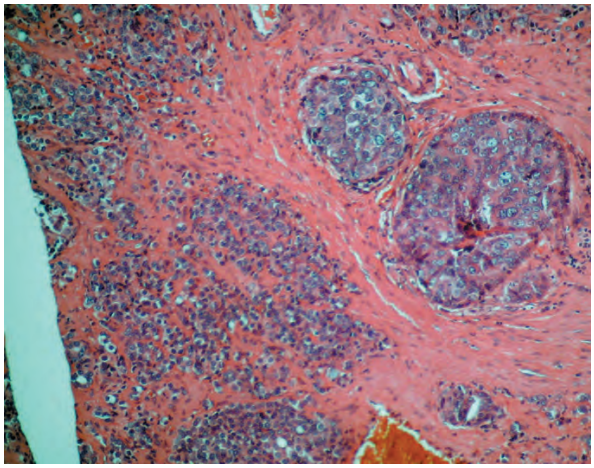


Figure 2. Adenocarcinoma Invading the Bladder Wall (Courtesy of Dr. Miguel Gonzalez)

Histologically, adenocarcinoma may be non-mucin-producing or mucin-producing. Most of these tumors are mucin-secreting but the passage of mucus during micturition is uncommon [87]. In a large series published from Egypt, two-thirds of the tumors were mucin-secreting, in most of which the site of deposition was extracellular (interstitial). Less commonly, mucin is secreted within the lumen of the acini and, infrequently, excessive intracellular mucin displaces the nucleus to a peripheral crescent, giving the cells a signet ring appearance. It is generally believed that this variety has a poor prognosis [88,89].

No uniformly accepted grading system for adenocarcinoma of the bladder exists. On the basis of histopathological findings, Anderstrom et al. classified vesical adenocarcinoma into 5 patterns: glandular with columnar, sometimes enteric–appearing cells; colloid carcinoma; papillary adenocarcinoma; signet ring cell carcinoma; and clear cell carcinoma [75]. Several other histologic subtypes have been described including mucinous, enteric (colonic) type, signet ring cell, adenocarcinoma not otherwise specified (NOS), clear cell, hepatoid, and mixed type [81]. Unfortunately, no clear data exist on whether these different varieties have an impact on survival or indicate prognosis, though signet ring cell carcinoma appears to impart a very rapid course resulting in death in the majority of patients within 6 months of diagnosis [82].

d) Treatment

Several treatment modalities have been used in the management of primary adenocarcinoma of the bladder. The therapeutic yield after transurethral resection with or without radiotherapy has been shown to be poor; Kramer et al. reported a 5-year survival of 19% [78].

Partial cystectomy for localized disease in the mobile parts of the bladder has been used by several authors. Analysis of the published data indicates that the results after this procedure are dismal [72,90-92]. On the other hand, Anderstrom et al. reported a 5-year survival of 54% among 15 patients treated by partial cystectomy [75].

Adenocarcinoma is not a radioresponsive disease. The reported 5-year survival is less than 20% of patients treated by external irradiation alone. The addition of preoperative irradiation did not improve the survival in 2 studies of 34 and 25 patients [75,90]. The experience of using chemotherapy in the treatment of bladder adenocarcinoma is limited. From the results with gastrointestinal adenocarcinoma, combination chemotherapy based on 5-fluorouracil has been attempted by several investigators. Most of the published series are of small numbers and the response is universally unsatisfactory [93-95].

Radical cystectomy with or without adjuvant therapy has been reported by several authors. Most of the published reports are based on few patients and usually of short-term follow-up. The reported 5-year disease-free survival ranges from 0 to 80% [75,90-92,96,97].

In an Egyptian series, the 5-year survival following cystectomy was 55%, and there was no difference from those of urothelial or squamous cell origin [47,98]. The Cox regression analysis proved that stage, grade, and lymph node involvement were the independent prognostic factors. None of the histologic varieties including cell type or the site of mucin deposition were shown to be independent prognostic factors [77].

2. URACHAL ADENOCARCINOMA

a) Epidemiology

Urachal carcinoma is extremely rare and represents about 1 in 1400 bladder tumors [99]. In a retrospective series of 48 primary adenocarcinomas of the bladder reported by Dandekar et al., urachal adenocarcinoma occurred in a younger age group than nonurachal adenocarcinoma (mean age 49 years urachal vs. 58 years nonurachal) and the male to female ratio was less pronounced (4:3 urachal vs. 23:4 nonurachal) [82].

b) Clinical and Pathologic Features

Urachal adenocarcinoma is an uncommon tumor that typically displays a histologic appearance that is indistinguishable from enteric type adenocarcinoma. It may occur as a mucinous or signet ring variety and rarely presents with classic symptoms of urachal disease such as abdominal pain, umbilical discharge, and dysuria.

What distinguishes urachal from other adenocarcinomas is its location, predominantly growing as an extravesical mass with a smaller endovesical component that invades the dome of the urinary bladder. There should be a sharp demarcation between the tumor and the surface urothelium and the absence of an additional adenocarcinoma elsewhere within or outside of the urinary bladder with secondary spread to the urachus or dome of the bladder [100]. The presence of concomitant cystitis glandularis or urothelial dysplasia would not support the diagnosis of urachal carcinoma.

According to Begg [101], this type of tumor results from abnormalities in the closure of the allantois, resulting in the formation of urachal cysts and rests. The tumor must be located at the apex or anterior wall of the bladder or in the supravesical space. The adjacent mucosa must be normal. The bladder mucosa may cover the surface of the tumor or, if there is ulceration, there is an abrupt change from normal mucosa to tumor [86].

Sheldon et al. initially described the staging system that is still widely used for urachal carcinoma [102]:

- Stage I - tumor in the urachal mucosa,
- Stage II - local invasion confined to the urachus,
- Stage III - local extension to the bladder, abdominal wall, peritoneum or local viscera, and
- Stage IV - regional lymph node involvement or distant metastases.

c) Treatment

For urachal tumors, results of treatment by partial cystectomy with excision of the umbilicus are modest. In a series of 10 patients with urachal carcinoma reported by Gill et al., there were 3 local recurrences following partial cystectomy with excision of the

umbilicus [80]. This was believed to be the result of inadequate excision of the tumor, and, as a result, they recommended frozen sections of the margins be taken [80]. Whitehead and Tessler reported a 25% 5-year survival rate with partial cystectomy and en bloc excision of the umbilicus [103]. Others reported better survival in patients treated with extended radical cystectomy with en bloc excision of the umbilicus [104].

The literature supports wide excision of the umbilicus, urachus, posterior rectus fascia, and peritoneal reflection as well as partial cystectomy for treatment of urachal carcinoma. In a series of 12 patients treated at Memorial Sloan Kettering Cancer Center from 1979-1993, 10 of 12 patients were cured with wide local excision and partial cystectomy, with follow up ranging from 1 to 13 years [105]. Recurrences occurred in a patient with lymph node metastases at the time of resection and in another patient found to have liver metastases at the time of surgery.

In another series by the MD Anderson Cancer Center, 42 patients with urachal carcinoma were retrospectively reviewed [106]. Thirty-five patients had undergone initial surgery for the tumor, the majority of these surgeries being performed at outside institutions. Of note, only 19 of 35 patients had en bloc resection of the urachal ligament and umbilicus. It was speculated that the majority of patients had been thought to have urothelial cancer and, as a result, the urachal ligament was not carefully controlled. Although en bloc resection was not statistically associated with survival, 13 of the 16 long-term survivors were in the group treated with en bloc resection of the urachus and umbilicus with partial cystectomy.

The median survival in the MD Anderson series was 46 months, with 40% of patients alive at 5 years. Survival was not statistically associated with age, gender, race, or histological grade of the tumor. Interestingly, it was also not associated with the degree of local extension and whether partial or radical cystectomy was performed. Survival was significantly less in patients with either lymph node metastases or positive surgical margins.

Of 20 patients receiving chemotherapy for metastatic disease, there were only 4 patients with significant objective responses, usually after a regimen of 5-fluorouracil and cisplatin. There was only 1 long-term survivor in this group. Adjuvant chemotherapy in patients with margin-positive or lymph node-positive disease in the absence of distant metastases did not appear to alter the outcome.

3. Adenocarcinoma In Bladder Exstrophy

a) Epidemiology

Adenocarcinoma is the most common cancer involving the bladder in patients with bladder exstrophy. Exstrophy patients have a reported 4% lifetime risk of developing this type of malignancy [73]. In a review of 40 patients with untreated bladder exstrophy, McIntosh and Worley (1955) found that 33 cases were adenocarcinoma, the mean age at diagnosis was 44 years, and two-thirds of the patients were male [107]. Even with the advent of urinary diversion surgery, the risk of developing carcinoma in the bladder remnant is significant. Smeulders et al. reported on a series of 102 patients born with bladder exstrophy who were followed for a minimum of 35 years [73].

There were 4 cases of bladder cancer, which was calculated to be 694 times greater than the risk in the normal adult population. Three of the 4 patients had undergone a simple cystectomy before the age of 5, and all were males. This implies that there was retention of a portion of the bladder in these individuals, which in the presence of sperm or secretions from the male genitourinary tract may have contributed to the development of these malignancies.

b) Pathologic Features

The histopathology of the bladder in exstrophy patients has been well-described [108]. The development of adenocarcinoma of these bladder remnants is thought to arise from either metaplasia of the urothelium, which is exposed to inflammatory stimuli, or as a result of the displacement of ectopic colonic or rectal epithelium that occurs during division of the cloaca.

The fact that the majority of the bladder malignancies occur during the fifth and sixth decades of life and that adenocarcinoma has been found to arise in other conditions resulting in defunctionalized bladders and after augmentation enteroplasty favors the “metaplasia theory [109-111]”. The prognosis of these tumors is poor as a result of late presentation. As a result, all patients with exstrophy who have retained their bladders should be followed closely, although no specific follow-up regimen can be recommended based upon the existing literature.

4. Secondary (Metastatic) Bladder Adenocarcinoma

Secondary bladder tumors can be classified as those tumors that invade the bladder through direct extension from adjacent organs, through lymphohematogeneous dissemination to the bladder, and from lymphomas and leukemias. A retrospective review of surgical and postmortem pathology from 1907-1997 showed that secondary tumors comprised 2.3% of the surgical and 20% of the postmortem cases [113]. The most common sites of tumor origin were the colon (59/282), prostate (54/282), rectum (34/282) and the cervix (32/282).

Adenocarcinomas comprised 117 of 215 secondary tumors in which histology was reviewed. While some of these adenocarcinomas are histologically quite distinctive, in some cases (such as prostate and colorectal tumors), they may present the clinician with a challenge to determine from which organ the tumor originates.

Approximately 10% of colorectal adenocarcinomas will be attached to adjacent structures, with the urinary bladder being 1 of the most common organs involved [114,115]. Talamonti et al. reported on a series of 70 patients undergoing en bloc bladder resection for colorectal carcinoma [116]. There were 58 primary and 12 recurrent tumors in the series. Median survival was 34 months in patients with negative surgical margins and 11 months for patients with positive margins. There were no 5-year survivors.

A more recent series by Carne et al., retrospectively evaluated 53 patients who had secondary involvement of the bladder with a colorectal cancer over a 15-year period [117]. The most common site of the primary tumor was the sigmoid colon (46/53), with the remainder invading from the rectum (2/53), the right colon (4/53), and the transverse colon (1/53). All 4 patients undergoing blunt dissection of the bladder from the tumor without resection of the bladder portion developed local recurrences and subsequently died of their disease. There were no local recurrences in 4 patients undergoing total cystectomy and 3 of the 4 patients with follow-up were alive, 2 without and 1 with disease. Finally, in the 45 patients who underwent partial cystectomy, there were a total of 8 (19%) local recurrences. They emphasized the importance of obtaining frozen sections on the margins at the time of partial cystectomy. However, whether frozen sections were taken in the patients who had local recurrences was not reported.

Summary

The treatment of adenocarcinoma depends on the subclassification. Primary adenocarcinoma is poorly responsive to radiation and chemotherapy and should be treated with radical cystectomy (*Grade B*). Urachal adenocarcinoma should be treated with en bloc resection of the urachus and umbilicus with partial cystectomy (*Grade B*). The incidence of adenocarcinoma is much higher in exstrophy patients. Any patient with bladder exstrophy who has retained his or her bladder should be closely followed, though an exact regimen cannot be defined based on currently-available evidence (*Grade C*). In patients with metastatic adenocarcinoma involving the bladder, patients should undergo complete resection of the involved portion of the bladder, either with partial cystectomy with verified negative margins or radical cystectomy (*Grade B*).

III. SMALL CELL CARCINOMA

1. Epidemiology

Small cell carcinoma is a neuroendocrine tumor that most commonly arises in the lungs. Extrapulmonary small cell carcinoma can occur in multiple locations, including the urinary bladder. Primary small cell carcinoma of the urinary bladder is exceedingly rare, with only 286 cases reported in the English-language literature [118]. Evidence is quite limited, and is primarily in the form of small case series and case reports.

Two prior reviews have shown that small cell carcinoma accounts for 0.48% to 0.7% of all cases of primary bladder tumors [119-122]. One review of 243 cases of small cell carcinoma of the bladder revealed that 62% were pure small cell carcinoma and 38% were combined carcinomas, most frequently with urothelial carcinoma, adenocarcinoma, or squamous cell carcinoma [123]. Interestingly, the reverse was seen in a recent multi-institutional review by Cheng et al. (32% pure small cell carcinoma, 68% with other histologic types) [124].

2. Clinical Features

An analysis of the characteristics of 238 patients with small cell carcinoma of the bladder has been

reported by Sved et al [118]. The mean age was 67.8 with a range of 20 to 91 years, and 80% of the patients were male. Similarly, the review of 64 patients by Cheng et al. showed a male-to-female ratio of 3.3:1 and a mean age of 66 years (range 36 to 85). Hematuria was the presenting complaint in 88% to 90% of patients in the 2 reviews. Rarely, paraneoplastic syndromes herald the diagnosis [123,125]. The initial work-up is the same as that for any patient with hematuria and a suspected bladder tumor. Small cell carcinoma cannot be distinguished from urothelial carcinoma on cystoscopy, but when a pathologist identifies this lesion, the patient should undergo a full metastatic work-up [121]. The vast majority of patients present with muscle-invasive disease (94% of the 183 patients on whom this information is available). Metastatic disease is reported in 67% of cases, most commonly to lymph nodes, liver, bone, lung, and brain [118].

3. Pathologic Features

The tumor is composed of a population of relatively uniform cells with scant cytoplasm and hyperchromatic nuclei (**Figures 3A, 3B**). Frequent mitotic figures and extensive necrosis are common [126]. The origin of small cell carcinoma is uncertain. It may be derived from neuroendocrine cells or multipotent stem cells of the bladder [121]. Diagnosis is usually made by hematoxylin and eosin, however, special stains to confirm the neuroendocrine origin may be required [127].

A retrospective analysis of 29 urine specimens from patients diagnosed with small cell carcinoma showed that 56% could be diagnosed by urinary cytopathology. The other cases were interpreted as high grade urothelial carcinoma. Five patients had both small cell carcinoma and urothelial carcinoma, and 3 of these were identified as small cell carcinoma on cytologic examination [128].

4. Treatment

The most common site for small cell carcinoma is the lung. High quality studies have been performed and treatment regimens are well-defined for primary lung small cell carcinoma. Small cell carcinoma of the lung is treated as a systemic disease, because, similarly to primary small cell carcinoma of the bladder, less than one-third of patients present with organ-confined disease. Chemotherapy is the mainstay of management. Patients with early-stage small cell carcinoma of the lung are most commonly treated with cisplatin plus etoposide or alternating with cyclophosphamide, doxorubicin, and vincristine [129]. The median survival of these patients is 10 to 14 months [130]. Radiation confers an additional survival advantage in early-stage disease, but is not helpful in patients with advanced disease [131]. Surgical resection has not been shown to be beneficial [129]. Patients with advanced disease have a uniformly poor prognosis.

The small number of reports on patients with small cell carcinoma of the bladder suggest that it behaves similarly to small cell carcinoma of the lung. Overall, local treatment yields very poor survival rates, while systemic therapy does provide improvement. In the review by Sved et al., 7 patients who underwent cystectomy alone all died from 1 to 25 months after surgery [118]. The dismal prognosis of patients

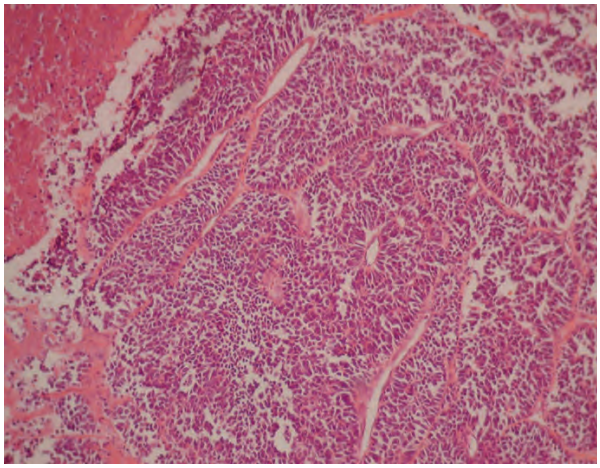


Figure 3. A - Small Cell Carcinoma of the Bladder, Low Power

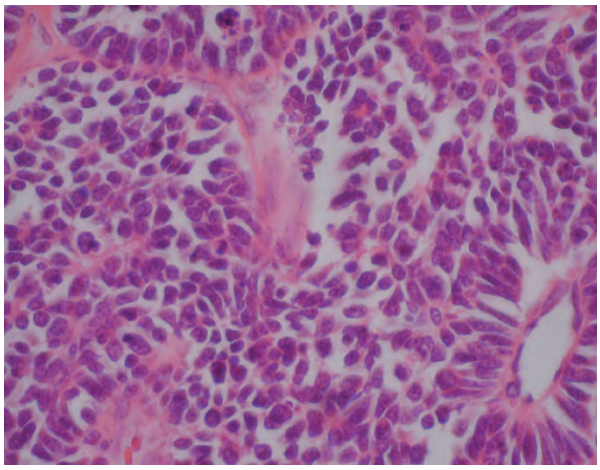


Figure 3. B - High Power

treated by radical surgery invited the use of neoadjuvant and adjuvant chemotherapy regimens.

Adding chemotherapy to the regimen appears to increase survival. In 5 small series reviewed by Sved et al., 13 of 18 patients who had cystectomy plus chemotherapy were alive at a mean of 27 months [118,132-135]. In addition, Walther reported favorable response rates in 7 patients treated with systemic etoposide and cisplatin in neoadjuvant and adjuvant protocols [119].

Similarly, in a recent retrospective review from M.D. Anderson Cancer Center, median survival and 5-year disease-free survival were significantly improved in patients who received preoperative chemotherapy [136]. Of 25 patients who underwent cystectomy with or without postoperative chemotherapy, the median cancer-specific survival was 23 months and the 5-year disease-free survival was only 36%. Conversely, of the 21 patients who received preoperative chemotherapy, the median cancer-specific survival had not yet been reached at the time of the report and the 5-year disease-free survival was 78%. Only 4 cancer-related deaths occurred in these 21 patients, and all occurred before 2 years. Additionally, the preoperative chemotherapy regimen determined response; only 2 of 12 patients who received a regimen directed toward small cell carcinoma (etoposide and cisplatin or ifosfamide and doxorubicin) had residual small cell tumors in their cystectomy specimen. Of those who received a regimen directed toward urothelial carcinoma (MVAC or taxol, methotrexate, and cisplatin), 6 of 9 had residual small cell carcinoma on cystectomy [136].

Reports of probable cures do exist; 1 patient with small cell carcinoma metastatic to the pelvic lymph nodes who received M-VAC before undergoing radical cystoprostatectomy was alive at 9 years [135]. Another patient treated with neoadjuvant M-VAC before radical cystoprostatectomy had no evidence of disease in the specimen and remained disease-free 3 years after surgery [137].

Radiation therapy alone has not been successful for treating small cell carcinoma, with a mean survival of less than 8 months in 40 reported cases, but long-term survival has been reported in patients treated with radiation therapy and chemotherapy. Of 5 patients who had complete remission after receiving chemotherapy and radiation, all were alive at greater than 4 years and only 1 required cystectomy for local recurrence [118].

Three of 12 patients who received partial cystectomy with chemotherapy or radiation therapy remained alive at the time of reporting, with a median survival of 34.9 months. Management with TURBT alone has resulted in uniformly poor results, with a mean survival of less than 8 months in most small series [118].

Summary

Small cell carcinoma of the bladder is an aggressive disease that often presents in advanced stages. Because of the rarity of this lesion, evidence is limited. Cure is most likely with aggressive multimodal therapy and a combined local and systemic approach.

IV. OTHER BLADDER TUMORS

1. Bladder Sarcoma

Malignant soft tissue tumors represent the most common histological type of the non-epithelial bladder tumors. Half of bladder sarcomas are leiomyosarcoma, 20% are rhabdomyosarcoma, and the remainder are angio-, osteo-, and carcinosarcoma [138]. The histological pattern of leiomyosarcoma is characterized by interwoven bundles of spindle-shaped cells. The incidence is higher in patients with previous local radiation treatment or systemic chemotherapy [139]. Most patients present with hematuria, and the diagnosis is made early. The majority of the tumors are of high grade. Tumor grade is established on the basis of mitotic rate and proliferation indices rather than nuclear atypia [139]. The preferred treatment for localized disease is radical cystectomy with negative margin resection. The 5-year survival rate is 80%. Metastatic sarcomas are treated with multimodality protocols. Doxorubicin and ifosfamide are the most active single agents available [140].

2. Carcinosarcoma and Sarcomatoid Tumors

In the purest sense of the term, *collision tumor* refers to 2 coexistent but cytogenetically distinct tumors, one of epithelial and the other of mesenchymal origin. There has been no consensus in the literature regarding the nomenclature of these tumors, which have been categorized as either carcinosarcoma or sarcomatoid carcinoma. Carcinosarcoma is a rare type of primary tumor composed of an admixture of

malignant epithelial (carcinoma) and malignant soft tissue elements (sarcoma). This biphasic tumor contains an epithelial malignant component that stains positive for a variety of epithelial markers. These tumors also contain a sarcomatous component that does not stain for epithelial markers, and may further differentiate into osteosarcoma, chondrosarcoma, leiomyosarcoma, or rhabdomyosarcoma. The term *sarcomatoid* has been used to describe a malignant spindle cell tumor with epithelial differentiation [142]. In a series of 41 patients, Lopez-Beltran reported that both carcinosarcoma and sarcomatoid tumors had similar presentations [142]. The most common epithelial component was urothelial in both types.

Carcinosarcomas must be differentiated from urothelial carcinomas with osseous or cartilaginous metaplasia, and with other sarcomas of the urinary bladder [142].

Sarcomatoid carcinomas consist of predominantly malignant spindle cells that stain for epithelial markers, differentiating them from pure sarcomas. In addition, the cytological atypia present in sarcomatoid carcinomas distinguishes these lesions from postoperative spindle cell nodules and inflammatory pseudotumors [143]. Recent work using comparative genomic hybridization techniques has demonstrated a large overlap of chromosomal aberrations in carcinosarcoma and sarcomatoid carcinomas, strongly suggesting a monoclonal origin for both of these tumors [144].

Carcinosarcomas and sarcomatoid carcinomas are extremely rare, and appear in the literature as isolated case reports or as single small series. In the largest series reported from the Mayo clinic over a 60-year period, the majority of tumors occurred in patients in the sixth decade [142]. As with other bladder neoplasms, they usually presented with hematuria and occurred more frequently in men than women (2:1 for carcinosarcoma and 4:1 for sarcomatoid carcinoma). Four of 15 (27%) patients with carcinosarcoma had previously received cyclophosphamide treatment for lymphoma or recurrent urothelial carcinoma and 2 patients (13%) had received pelvic radiation for an antecedent pelvic malignancy. Four patients of the 26 (15%) in the sarcomatoid carcinoma cohort had an antecedent history of urothelial carcinoma.

Regardless of the histopathologic features of the tumor, the majority of patients with either carcinosarcoma or sarcomatoid carcinoma present with advanced disease. As in other bladder malignancies, stage is predictive of survival. In the Mayo clinic series, despite the majority of patients undergoing aggressive surgical treatment, the mean survival was less than 18 months. Treatment failure occurs within 1 to 2 years following treatment [142]. A favorable response to combination cisplatin and gemcitabine has recently been reported in a single case report, but further study is needed to validate this in the neoadjuvant and adjuvant settings [143]. Multimodality treatment is recommended in the treatment of these rare tumors.

3. Pheochromocytoma (Paraganglioma)

Bladder pheochromocytoma may be hormonally active and presents with attacks of paroxysmal hypertension, headaches, palpitations, blurred vision, and sweating associated with the act of micturition [145]. If the disease is suspected, cystoscopy should be performed under adrenergic blockade in the operating theater. The gross appearance is often a solitary submucosal or intramural nodule. Biopsy should be avoided. The diagnosis depends on CT scan or MRI for anatomical location and the extent of the lesion. Isotopic scanning using ^{131}iodine metaiodinebenzylguinidine (MIBG) is the study of choice for localizing small pheochromocytomas with more than 90% specificity [146]. Positron emission tomography was recently used with high sensitivity as well [145].

The standard treatment is local excision via partial cystectomy combined with pelvic lymph node dissection. The surgery is employed under the same precautions as in adrenal pheochromocytoma with controlled adrenergic blockade [146].

It may be difficult to distinguish benign and malignant lesions if the disease is localized. Lifelong follow-up is important as the malignant pheochromocytoma may show local recurrence with or without metachronous metastases.

4. Pseudotumors

Bladder pseudotumors are rare and may resemble malignancy. The etiology and histogenesis remain unclear. Some of these lesions present as “postoperative spindle-cell tumors.” It may be difficult to distinguish them from leiomyosarcoma on a histopathological basis [147]. However, absence of significant nuclear atypia, less than 3 mitotic figures per high power field, and presence of spindle cells with myxoid degeneration and eosinophilic cytoplasm favor pseudotumor. Some tumors may show a fascicular

growth pattern with deposition of interstitial collagen [148]. Local recurrence or distant metastases are rare following tumor excision. If the diagnosis is clear, transurethral resection or partial cystectomy is sufficient. Radical cystectomy may be required if the diagnosis is difficult to distinguish from bladder sarcoma.

5. MELANOMA

Primary bladder melanoma is very rare. It affects the urethra more than the bladder. Secondary melanoma of the bladder was found in patients with widespread metastatic melanoma of the skin [139,149]. The patient's history and careful examination of the skin is essential to confirm the primary nature of the tumor. The histological picture of bladder melanoma is similar to other melanomas. It is composed of large malignant cells arranged in nests with variable amounts of pigments [126]. The cell origin of bladder melanoma is undefined. Treatment of primary bladder melanoma is radical surgery. The prognosis is poor [150,151].

6. LYMPHOMA

Bladder lymphoma is usually a part of metastatic spread of systemic disease. Primary lymphoma is very rare. Microscopic analysis shows diffuse infiltration of lymphoid cells into the normal structures of the bladder [3]. Primary lymphoma is more common in women. It is mostly localized and of low grade with good prognosis. Local irradiation is the recommended treatment with a high recurrence-free survival [152,153].

Table. Optimal Treatment of Miscellaneous Bladder Tumors

Disease	Optimal Treatment	Grade of Recommendation
Squamous Cell Carcinoma	Radical cystectomy	B
Primary Adenocarcinoma	Radical cystectomy	B
Urachal Adenocarcinoma	En bloc excision of urachus and umbilicus with partial cystectomy	B
Metastatic Adenocarcinoma Involving the Bladder	Complete resection of involved portion of bladder, either partial cystectomy with negative margins or radical cystectomy	B
Small Cell Carcinoma	Local treatment and chemotherapy	B
Bladder Sarcoma	Radical cystectomy	C
Carcinosarcoma, Sarcomatoid Tumors	Multimodality therapy	C
Paraganglioma and Pheochromocytoma	Partial cystectomy with pelvic lymph node dissection, perioperative adrenergic blockade	C
Pseudotumors	Transurethral resection or partial cystectomy	C
Melanoma, Primary of Bladder	Radical cystectomy	C
Lymphoma, Primary	Local irradiation	C

RECOMMENDATIONS

I. SQUAMOUS CELL CARCINOMA

1. A surveillance schedule for squamous cell carcinoma in patients with spinal cord injuries cannot be determined from the currently available evidence (*Grade D*).
2. Cystectomy is the best primary therapy for squamous cell carcinoma, whether bilharzial or non-bilharzial (*Grade B*).

II. ADENOCARCINOMA

1. Patients with bladder exstrophy who have retained their bladders should be closely followed, but no particular regimen can be recommended based on currently-available evidence (*Grade D.*)
2. Primary adenocarcinoma should be treated with radical cystectomy (*Grade B*).
3. Urachal adenocarcinoma should be treated with en bloc excision of the urachus and umbilicus with partial cystectomy (*Grade B*).
4. In patients with metastatic adenocarcinoma involving the bladder, patients should undergo complete resection of the involved portion of the bladder, either with partial cystectomy with verified negative margins or radical cystectomy (*Grade B*).

III. SMALL CELL CARCINOMA

1. When small cell carcinoma is identified on a TURBT specimen, the patient should undergo a full metastatic work-up including a CT of the abdomen and pelvis, a bone scan, a chest x-ray, and a neurologic examination (*Grade C*).
2. Patients with small cell carcinoma of the urinary bladder require aggressive combination therapy to achieve cures, such as combined chemotherapy and radical cystectomy or chemotherapy and radiation therapy (*Grade B*).

IV. BLADDER SARCOMA

1. Bladder sarcoma should be treated with radical cystectomy with negative margin resections (*Grade C*).
2. Metastatic sarcoma should be treated with a multimodality protocol (*Grade C*).

V. CARCINOSARCOMA AND SARCOMATOID TUMORS

- Carcinosarcoma and sarcomatoid tumors have a poor prognosis and surgical management is inadequate. Multimodality therapy is recommended (*Grade C*).

VI. PARAGANGLIOMA AND PHEOCHROMOCYTOMA

- The standard treatment of paraganglioma and pheochromocytoma is partial cystectomy with pelvic lymph node dissection, using the same precautions as for any other pheochromocytoma with adrenergic blockade (*Grade C*).

VII. BLADDER PSEUDOTUMORS

- When the diagnosis of a bladder pseudotumor is clear, transurethral resection or partial cystectomy is appropriate treatment. If necessary to exclude sarcoma, radical cystectomy may be performed (*Grade C*).

VIII. MELANOMA

- Primary bladder melanoma should be treated with radical surgery, but the prognosis remains poor (*Grade C*).

IX. LYMPHOMA

- Primary lymphoma of the bladder should be treated with local irradiation (*Grade C*).

V. REFERENCES

1. Miller A, Mitchell JP, Brown NN. The Bristol bladder tumor registry. Br J Urol 1969;41 (Supp.):1-64.
2. Johnson DE, Schoenwald MB, Ayala AG, Miller LS. Squamous cell carcinoma of the bladder. J Urol 1976;115:542-544.
3. Rundle JSH, Hart AJL, McGeorge A, Smith JS, Malcolm AJ, Smith PM. Squamous cell carcinoma of the bladder: a review of 114 patients. Br J Urol 1982;54:522-526.
4. Lopez JI, Angulo Cuesta J, Flores Corral N, Toledo JD. Squamous cell carcinoma of the urinary bladder. Clinico-pathologic study of 7 cases. Arch Esp Urol 1994;47:756-760.
5. Serretta V, Pomara G, Piazza F, Gange E. Pure squamous cell carcinoma of the bladder in western countries. Eur Urol 2000;37:85-89.
6. Porter MP, Voigt LF, Penson DF, Weiss NS. Racial variation in the incidence of squamous cell carcinoma of the bladder in the United States. J Urol 2002;168:1960-1963.
7. Johansson SL and Cohen SM. Epidemiology and etiology of bladder cancer. Sem Surg Oncol 1997;13:291-298.
8. Fleshner N, Herr HW, Stewart AK, Murphy GP, Mettlin C, Menck HR. The national cancer data base report on bladder carcinoma. Cancer 1996;78(7):1505-1513.
9. Mungan NA, Kiemeney LA, van Dijck JA, van der Poel HG, Witjes JA. Gender differences in stage distribution of bladder cancer. Urology 2000;55:368-371.
10. Cohen SM, Shirai R, Steineck G. Epidemiology and etiology of premalignant and malignant urothelial changes. Scand J Nephrol Suppl 2000;205:105-115.
11. Locke JR, Hill DE, Walzer Y. Incidence of squamous cell carcinoma in patients with long term catheter drainage. J Urol 1985;133:1034-1035.
12. Sene AP, Massey JA, McMahon RTF, Carroll BNP. Squamous cell carcinoma in a patient on clean intermittent self catheterization. Br J Urol 1990;65:213-214.
13. Zaidi SZ, Theaker JM, Smart CJ. Squamous cell carcinoma in a patient on clean intermittent self catheterization (case report). Br J Urol 1997;80:352-353.
14. Bejany DE, Lockhart JL, Rhamy RK. Malignant vesical tumors following spinal cord injury. J Urol 1987;138:1390-1392.
15. Kaufman JM, Fam B, Jacobs SC, Gabilondo F, Yalla S, Kane JP, Rossier AB. Bladder cancer and squamous metaplasia in spinal cord injury patients. J Urol 1977;118:967.
16. West DA, Cummings JM, Longo WE Virgo KS, Johnson FE, Parra RO. Role of chronic catheterization in the development of bladder cancer in patients with spinal cord injury. Urology 1999;53:292-297.
17. Bickel A, Culkin DJ, Wheeler JS Jr. Bladder cancer in spinal cord injury patients. J Urol 1991;146:1240-1242.
18. Pannek J. Transitional cell carcinoma in patients with spinal cord injury: a high risk malignancy? Urology 2002;59:240-244.
19. Kantor AF, Hartge P, Hoover RN, Fraumeni JF Jr. Epidemiological characteristics of squamous cell carcinoma and adenocarcinoma of the bladder. Cancer Res 1988;48:3853-3855.
20. Thorn M, Bergstrom R, Johansson AM, Ramstrom L, Persson I, Malmstrom PU. Trends in urinary bladder cancer incidence in Sweden 1960-93 with special reference to histopathology, time period birth cohort, and smoking. Cancer Causes and Control 1997;8:560-567.
21. Connery DB. Leukoplakia in the urinary bladder and its association with carcinoma. J Urol 1953;69:121.
22. Holly PS and Mellinger GT. Leukoplakia of the bladder and carcinoma. J Urol 1961;86:235.
23. O'Flynn JD and Mullaney J. Vesical leukoplakia progressing to carcinoma. Br J Urol 1974;46:31.
24. Wiener DP, Koss LG, Sablay B, Freed SZ. The prevalence and significance of Brunn's nests, cystitis cystica, and squamous metaplasia in normal bladders. J Urol 1979;122:317-321.
25. Westenend PJ, Stoop JA, Hendriks JGH. Human papillomaviruses 6/11, 16/18 and 31/33/51 are not associated with squamous cell carcinoma of the urinary bladder. BJU Int 2001; 88:198-201.
26. Tatsura H, Ishiguro Y, Okamuro T, Kohri K. Bladder squamous cell carcinoma with human papilloma virus type 6 (HPV 6). Int J Urol 1995;2:347-349.
27. Fadl-Elmula I, Gorunova L, Lundgren R, Mandahl N, Forsby N, Mitelman F, Heim S. Chromosomal abnormalities in 2 bladder carcinomas with secondary squamous cell differentiation. Cancer Genet Cytogenet 1998;102:125-130.
28. Bessett Pl, Abell MR, Herwig KR. A clinicopathologic study of squamous cell carcinoma of the bladder. J Urol 1974;112:66-67.
29. Jones MA, Bloom HJG, Williams G, Trott PA, Wallace DM. The management of squamous cell carcinoma of the bladder. J Urol 1980;52:511-514.
30. Quilty PM and Duncan W. Radiotherapy for squamous cell carcinoma of the urinary bladder. Int J Radiation Oncology Biol Phys 1986;12:861-865.
31. Costello AJ, Tiptaft RC, England HR, Blandy JP. Squamous cell carcinoma of bladder. Urology 1984;23(3):234-236.
32. Debbagh A, Bennani S, Hafiani M, el Mrini M, Benjelloun S. Epidermoid carcinoma of the bladder. A report of 14 cases. Ann Urol (Paris) 1997;31:199-203.
33. Richie JP, Waisman J, Skinner DG, Dretler SP. Squamous carcinoma of the bladder: treatment by radical cystectomy. J Urol 1976;115:670-671.
34. Swanson DA, Liles A, Zagars GK. Pre-operative irradiation and radical cystectomy for stages T_2 and T_3 squamous cell carcinoma of the bladder. J Urol 1990;143:37-40.
35. Ghoneim MA. Nontransitional cell bladder cancer. In Krane RJ, Siroky MB, Fitzpatrick JM eds. Clinical Urology. Chap 47. Philadelphia: Lippincott Co, 1994:679-687.
36. Stenzl A, Jarolim L, Coloby P, Golia S, Bartsch G, Babjuk M, Kakizoe T, Robertson C. Urethra-sparing cystectomy and orthotopic urinary diversion in women with malignant pelvic tumors. Cancer 2001;92(7):1864-1871.
37. Nishiyama H, Habuchi T, Watanabe J, Teramukai S, Tada H, Ono Y, Ohshima S, Fujimoto K, Hirao Y, Fukushima M, Ogawa O. Clinical outcome of a large-scale multi-institutional retrospective study for locally advanced bladder cancer: a survey including 1131 patients treated during 1990-2000 in Japan. Eur Urol 2004;45:176-181.
38. Khaled HM, Hamza MR, Mansour O, Gaafar R, Zaghloul MS. A phase II study of gemcitabine plus cisplatin chemotherapy in advanced bilharzial bladder carcinoma. Eur J Cancer 2000;36:S34-S37.
39. Loehrer Sr. PJ, Einhorn LH, Elson PJ, Crawford ED, Kuebler P, Tannock I, Raghavan D, Stuart-Harris RS, Sarosdy MF, Lowe BA, Blumenstein B, Trump D. A randomized comparison of cisplatin alone or in combination with methotrexate, vinblastine, and doxorubicin in patients with metastatic urothelial carcinoma: a cooperative group study. J Clin Oncol 1992;10(7):1066-1073.
40. Sternberg CN, Yagoda A, Scher HI, Watson RC, Ahmed T, Weiselberg LR, Geller N, Hollander PS, Herr HW, Sogani PC, et al. Preliminary results of M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) for transitional cell carcinoma of the urothelium. J Urol 1985;133:403-407.
41. Raghavan D. Progress in the chemotherapy of metastatic cancer of the urinary tract. Cancer 2003;97(Suppl 8):2050-2055.

42. Wishnow KI and Dmochowski R. Pelvic recurrence after radical cystectomy without preoperative radiation. J Urol 1988;140:42-43.
43. El-Bolkainy MN, Ghoneim MA, Mansour MA. Carcinoma of the bilharzial bladder in Egypt: Clinical and pathological features. Br J Urol 1972;44:561.
44. Broecker BH, Klein FA, Hackler RH. Cancer of the bladder in spinal cord injury patients. J Urol 1981;125:196-197.
45. Navon JD, Soliman H, Khonsari F, Ahlering T. Screening cystoscopy and survival of spinal cord injured patients with squamous cell cancer of the bladder. J Urol 1997;157:2109-2111.
46. Celis JE, Rasmussen HH, Vorum H, Madsen P, Honore B, Wolf H, Orntoft TF. Bladder squamous cell carcinoma express psoriasin and externalize it to the urine. J Urol 1996;155:2105-2112.
47. Tsukamoto T, Kumamoto Y, Ohmura K, Miyao N, Nammbu A, Takagi Y, Itoh N. Squamous cell carcinoma associated antigen in uro-epithelial carcinoma. Urology 1992;40:477-483.
48. Ghoneim MA, El-Mekresh MH, El-Baz MA, El-Attar IA, Ashamallah A. Radical cystectomy for carcinoma of the bladder: Critical evaluation of the results in 1026 cases. J Urol 1997;158:393-399.
49. El-Bolkainy MN. Topographic pathology of cancer. Cairo University: The National Cancer Institute, 1998:59-63.
50. El-Sebai l, Sherif M, El-Bolkainy MN, Mansour MA, Ghoneim MA. Verrucose squamous carcinoma of bladder. Urology 1974;4:407-410.
51. Hicks RM. Multistage carcinogenesis in the urinary bladder. Br Med Bull 1980;36:39.
52. Hicks RM, Walters CL, El-Sebai I, El-Aaser AA, El-Merzabni MM, Gough TA. Demonstration of nitrosamines in human urine: Preliminary observations on a possible aetiology for bladder cancer in association with chronic urinary tract infections. Proc R Soc Med 1977;70:413.
53. El-Merzabani MM and El-Aaser AA. Etiological factors of bilharzial bladder cancer in Egypt: Nitrosamines and their precursors in urine. Eur J Cancer 1979;15:287.
54. El-Bolkainy MN, Ghoneim MA, El-Morsey BA, Nasr SM. Carcinoma of bilharzial bladder: diagnostic value of urine cytology. Urology 1974;3:319-323.
55. Basta MT, Attallah AM, Seddek MN, el-Mohamady H, Al-Hilaly ES, Atwaan N, Ghoneim M. Cytokeratin shedding in urine: a biological marker for bladder cancer? Br J Urol 1988;61:116-121.
56. Ghoneim MA, Mansour MA, El-Bolkainy MN. Staging of carcinoma of bilharzial bladder. Urology 1974;3:40-42.
57. Kafagy MM, El-Bolkainy MN, Mansour MA. Carcinoma of the bilharzial urinary bladder: a study of the associated lesions in 86 cases. Cancer 1972;30:150.
58. El-Hammady SM, Ghoneim MA, Hussein ES, Ashamallah AG, El-Bolkainy MN. Segmental resection for carcinoma of the bladder. Mansoura Med Bull 1975;3:191.
59. Omar SM. Segmental resection for carcinoma of the bladder. Egypt Med Assoc 1969;52:975.
60. Ghoneim MA and Awaad HK. Results of treatment in carcinoma of the bilharzial bladder. J Urol 1980;123:850-852.
61. Ghoneim MA, Ashamallah AG, Hammady S, Gaballah MA, Soliman HS. Cystectomy for carcinoma of the bilharzial bladder: 138 cases 5-year later. Br J Urol 1979;51:541-544.
62. Awaad HK, Hegazy M, Ezzat S, El-Bolkainy MN, Burgers MV. Cell proliferation of carcinoma in bilharzial bladder: An autoradiology study. Cell Tissue Kinet. 1979;12:513-520.
63. Denekamp J. The relationship between the cell loss factor and the immediate response to radiation in animal tumors. Eur J Cancer 1972;8:335-340.
64. Awaad HK. Radiation therapy in bladder cancer. Alex Med J Cancer 1958;4:118.
65. Omar AH, Shalaby MA, Ibrahim AH. On the capillary vascular bed in carcinoma of the urinary bladder. East Afr Med J 1975;51:34.
66. Awaad HK, Abdel Baki H, El-Bolkainy N, Burgers M, El-Badawy S, Mansour M, Soliman O, Omar S, Khafagy M. Preoperative irradiation of T3 carcinoma in bilharzial bladder. Int J Radiat Oncol Biol Phys 1979;5:787-794.
67. Ghoneim MA, Ashamallah AK, Awaad HK, Whitmore WE. Randomized trial of cystectomy with or without pre-operative radiotherapy for carcinoma of the bilharzial bladder. J Urol 1985;134:266-268.
68. Denekamp J, McNally NJ, Fowler JF, Joiner MC. Misonidazole in fractionated radiotherapy: Are many small fractions best? Br J Radiol 1980;53:981-990.
69. Gad-el-Mawla N, Hamza MR, Zikri ZK, el-Serafi M, el-Khodary A, Khaled H, Abdel-Ware A. Chemotherapy in invasive carcinoma of the bladder: A review of phase II trials in Egypt. Acta Oncol 1989:28:73-76.
70. Gad-el-Mawla N, Mansour MA, Eissa S, Ali NM, Elattar, I., Hamza MR, Khaled H, Habboubi N, Magrath I, El-Sebai I. A randomized pilot study of high-dose epirubicin as neoadjuvant chemotherapy in the treatment of cancer of bilharzial bladder. Ann Oncol 1991;2:137-140.
71. Khalid H, Zaghloul M, Ghoneim M, Sabr R, Manie M, Abol-Enein H, Mageed H, Mansour O, Sherbiny M, Mahran T. Gemcitabine and cisplatin as a neoadjuvant chemotherapy for invasive bladder cancer: Effect on bladder preservation and survival. Proc Am Soc Clin Oncol 22: page 411, 2003 (abstr 1652).
72. Jacobo E, Loening S, Schmidt JD, Culp DA. Primary adenocarcinoma of the bladder. J Urol 1977;17:54-56.
73. Bennett JK, Wheatley JK, Walton KN. 10-year experience with adenocarcinoma of the bladder. J Urol 1984;131:262-263.
74. Smeulders N and Woodhouse CR. Neoplasia in adult exstrophy patients. BJU Int 2001;87(7):623-628.
75. Makar N. Some observations on pseudoglandular proliferation in the bilharzial bladder. Acta Union Internationalis Contra Cancrum 1962;18:599.
76. Anderstrom C, Johansson SL, von Schultz L. Primary adenocarcinoma of the urinary bladder. A clinicopathologic and prognostic study. Cancer 1983;52:1273-1280.
77. Wheeler JD and Hill WT. Adenocarcinoma involving the urinary bladder. Cancer 1954;7:119-135.
78. El-Mekresh M, El-Baz M, Abol-Enein H, Ghoneim M. Primary adenocarcinoma of the urinary bladder: a report of 185 cases. Br J Urol 1998;82:206-212.
79. Kramer S, Bredael J, Croker B, Paulson D, Glenn J. Primary non-urachal adenocarcinoma of the bladder. J Urol 1979;121:278-281.
80. Dandekar NP, Dalal AV, Tongaonkar HB, Kamat MR. Adenocarcinoma of bladder. Eur J Surg Oncol 1997;23:157-160.
81. Gill HS, Dhillon HK, Woodhouse CRJ. Adenocarcinoma of the urinary bladder. Br J Urol 1989;64:138-142.
82. Grignon DJ, Ro JY, Ayala AG, Johnson DE, Ordonez NG. Primary adenocarcinoma of the urinary bladder: a clinicopathologic analysis of 72 cases. Cancer 1991;67(8):2165-2172.
83. Choi H, Lamb S, Pintar K, Jacobs SC. Primary signet ring cell carcinoma of the urinary bladder. Cancer 1984;53:1985-1990.
84. Allen TD and Henderson BW. Adenocarcinoma of the bladder. J Urol 1965;93:50-56.
85. Mostafi FK. Potentialities of bladder epithelium. J Urol 1954;71:705-714.
86. Kittredge WE, Coliett AJ, Morgan C. Adenocarcinoma of the

bladder associated with cystitis glandularis. A case report. J Urol 1964;91:145-150.

87. Mostofi FK, Thompson RV, Dean AL. Mucous adenocarcinoma of the bladder. Cancer 1955;18:599.
88. El-Sebai I. Cancer of the bladder in Egypt. Kasr El-Aini J Surg 1961;2:183-241.
89. Blute ML, Engen DE, Treavis WD, Kvols LK. Primary signet ring cell adenocarcinoma of the bladder. J Urol 1989;141:17-21.
90. Fiter L, Gimeno F, Martin L, Gimeno F, Martin L, Comez Te Jeda L. Signet-ring adenocarcinoma of the bladder. Urology 1993;41:30-33.
91. Thomas DG, Ward AM, Williams JL. A study of 52 cases of adenocarcinoma of the bladder. Br J Urol 1971;43:4-15.
92. Abenoza P, Monivel C, Fraley E. Primary adenocarcinoma of the urinary bladder. A clinico-pathologic study of 16 cases. Urology 1987;31:9-14.
93. Nocks B, Heney N, Daly J. Primary adenocarcinoma of urinary bladder. Urology 1983;21:26-29.
94. Nevin JE, Melnick I, Baggerly. JT, Easley CA, Landes R. Advanced carcinoma of the bladder: Treatment using hypogastric artery infusion with 5-fluorouracil, either as a single agent or in combination with bleomycin or adriamycin and supervoltage radiation. J Urol 1974;112:752-758.
95. Logothetis CJ, Samuels ML, Ogden S. Chemotherapy for adenocarcinoma of bladder and urachal origin. 5-Fluorouracil, doxorubicin and mitomycin-C. Urology 1985;26:252-255.
96. Hatch RR and Fuchs EF. Intra-arterial infusion of 5-fluorouracil for recurrent adenocarcinoma of bladder. Urology 1989;33:311-312.
97. Burrett AL, Epstein JI, Marshall FF. Adenocarcinoma of urinary bladder: classification and management. Urology 1991;67:315-321.
98. Raitanen MP, Hellstrom PA, Kyllonen AP, Leisti EL, Kontturi MJ. Diagnostic and therapeutic aspects of adenocarcinoma of the urinary bladder. Ann Chir Gyn 1993;82:43-49.
99. Skinner DG and Leiskovsky G. Contemporary cystectomy with pelvic node dissection compared to preoperative radiation therapy plus cystectomy in management of invasive bladder cancer. J Urol 1984;131:1069-1073.
100. Beck AD, Gaudin HJ, Bonham DG. Carcinoma of the urachus. Br J Urol 1970;42:555.
101. Johnson DE, Hodge GB, Abdul-Karim FW, Ayala AG. Urachal carcinoma. Urology 1985;26:218.
102. Begg RC. The urachus, its anatomy, histology and development. J Anat 1930;64:170.
103. Sheldon CA, Clayman RV, Gonzalez R, Williams RD, Faley EE. Malignant urachal lesions. J Urol 1984;131:1.
104. Whitehead DE and Tessler AN. Carcinoma of the urachus. Br J Urol 1971;43:468.
105. Kakizoe T, Matsumoto K, Andoh M, Nishio Y, Kishi K. Adenocarcinoma of the urachus. Urology 1983;21:360.
106. Herr HW. Urachal carcinoma: the case for extended partial cystectomy. J Urol 1994 Feb;151(2):365-366.
107. Siefker-Radtke AO, Gee J, Shen Y, Wen S, Daliani D, Millikan RE, Pisters LL. Multimodality management of urachal carcinoma: the M. D. Anderson Cancer Center experience. J Urol 2003 Apr;169(4):1295-1298.
108. McIntosh JF and Worley G Jr. Adenocarcinoma arising in exstrophy of the bladder: report of two cases and review of the literature. J Urol 1955;73:820-829.
109. Williams DI. Epispadias and exstrophy. In Eckstein HB, Hohenfellner R, Williams DI eds, Surgical Paediatric Urology. Stuttgart: Georg Thieme, 1997:298-312.
110. Yap RL, Weiser A, Ozer O, Pazona J, Schaeffer A. Adenocarcinoma arising from a defunctionalized bladder. J Urol 2002;167:1782-1783.
111. Witters S and Baert-Van Damme L. Bladder exstrophy complicated by adenocarcinoma. Eur Urol 1987;13:415-416.
112. Barrington JW, Fulford S, Griffiths D, Stephenson TP. Tumors in bladder remnant after augmentation enterocystoplasy. J Urol 1997;157:482-486.
113. Bates AW and Baithun SI. Secondary neoplasms of the bladder are histological mimics of nontransitional cell primary tumours: clinicopathological and histological features of 282 cases. Histopathology 2000;36:32-40.
114. Gall FP, Tonak J, Altendorf A. Multivisceral resections in colorectal cancer. Dis Colon Rectum 1987;30:337-341.
115. Lopez MJ and Monafo WM. Role of extended resection in the initial treatment of locally advanced colorectal carcinoma. Surgery 1993;113:365-372.
116. Talamonti MS, Shumate CR, Carlson GW, Curley SA. Locally advanced carcinoma of the colon and rectum involving the urinary bladder. Surg Gynecol Obstet 1993;177:481-487.
117. Carne PWG, Frye JNR, Kennedy-Smith A, Keating J, Merrie A, Dennett E, Frizelle FA. Local invasion of the bladder with colorectal cancer: surgical management and patterns of local recurrence. Dis Colon Rectum 2004;47:44-47.
118. Sved P, Gomez P, Manoharan M, Civantos F, Soloway MS. Small cell carcinoma of the bladder. BJU Int 2004;94(1):12-17. (*Level 3*)
119. Walther PJ. Adjuvant/neoadjuvant etoposide/cisplatin and cystectomy for management of invasive small cell carcinoma. J Urol 2002;167(4):285 [Abstract 1124]..
120. Trias I, Algaba F, Condom E, Espanol I, Segui J, Orsola I, Villavicencio H, Garcia Del Muro X. Small cell carcinoma of the urinary bladder. Presentation of 23 cases and review of 134 published cases. Eur Urol 2001;39(1):85-90.
121. Blomjour CE, Vos W, De Voogt HJ, Van der Valk P, Meijer CJ. Small cell carcinoma of the urinary bladder. A clinicopathologic, morphologic, immunohistochemical, and ultrastructural study of 18 cases. Cancer 1989;64(6):1347-1357.
122. Holmang S, Borghede G, Johansson SL. Primary small cell carcinoma of the bladder: a report of 25 cases. J Urol 1995;153:1820-1822.
123. Abbas F, Civantos F, Benedetto P, Soloway MS. Small cell carcinoma of the bladder and prostate. Urology 1995;46:617-630.
124. Cheng L, Pan CX, Yang XJ, Lopez-Beltran A, MacLennan GT, Lin H, Kuzel TM, Papavero V, Tretiakova M, Nigro K, Koch MO, Eble JN. Small cell carcinoma of the urinary bladder. Cancer. 2004 Sep 1;101(5):957-962.
125. Kanat O, Evrensel T, Filiz G, Usta M, Baskan E, Dilek K, Manavoglu O. Systemic AA amyloidosis and nephritic syndrome associated with small cell carcinoma of the bladder. Nephrol Dial Transplant. 2003 Nov;18(11):2453-2454.
126. Grignon DJ. Neoplasms of the urinary bladder. In: Bostwick DG, Eble JN, editors. Urologic surgical pathology. St. Louis (MO): Mosby-Year Book, Inc; 1997. p. 216-305.
127. Helpap B. Morphology and therapeutic strategies for neuroendocrine tumors of the genitourinary tract. Cancer 2002;95(7):1415-1420.
128. Van Hoeven KH and Artymyshyn RL. Cytology of small cell carcinoma of the urinary bladder. Diag Cytopathol 1996;14:292-297.
129. Sandler AB. Chemotherapy for small cell lung cancer. Semin Oncol 2003;30:9-25.
130. Ihde DC. Chemotherapy of lung cancer. N Eng J Med 1992;327:1434-1441.

131. Erridge SC and Murray N. Thoracic radiotherapy for limited-stage small cell lung cancer. Issues of timing, volumes, dose and fractionation. Semin Oncol 2003;30:26-37.

132. Grignon DJ, Ro JY, Ayala AG, Shum DT, Ordonez NG, Logothetis CJ, Johnson DE, Mackay B. Small cell carcinoma of the urinary bladder. A clinicopathologic analysis of 22 cases. Cancer 1992:69:527-536.

133. Oesterling JE, Brendler CB, Burgers JK, Marshall FF, Epstein JL. Advanced small cell carcinoma of the bladder. Successful treatment with combined radical cystoprostatectomy and adjuvant methotrexate, vinblastine, doxorubicin and cisplatin chemotherapy. Cancer 1990:65:1928-1936.

134. Nejat RJ, Purohit R, Goluboff ET, Petrylak D, Rubin MA, Benson MC. Cure of undifferentiated small cell carcinoma of the urinary bladder with M-VAC chemotherapy. Urol Oncol 2001;6:53-55.

135. Cheng D, Unger P, Forscher CA, Fine E. Successful treatment of metastatic small cell carcinoma of the bladder with methotrexate, vinblastine, doxorubicin, and cisplatin therapy. J Urol 1995;153:417-419.

136. Siefker-Radtke AO, Dinney CP, Abrahams NA, Moran C, Shen Y, Pisters LL, Grossman, HB, Swanson DA, Millikan RE. Evidence supporting preoperative chemotherapy for small cell carcinoma of the bladder: a retrospective review of the M. D. Anderson cancer experience. J Urol 2004 Aug;172(2):481-484.

137. Bastus R, Caballero JM, Gonzalez G, Borrat P, Casalotos J, Gomez de Segura G, Marti LI, Ristol J, Cirera L. Small cell carcinoma of the urinary bladder treated with chemotherapy and radiotherapy: results in 5 cases. Eur Urol 1999;35:323-326.

138. Parekh DJ, Jung C, O'Conner J, Dutta S, Smith Jr ER. Leiomyosarcoma in urinary bladder after cyclophosphamide therapy for retinoblastoma and review of bladder sarcomas. Urology 2002;60(1):164.

139. Helpap B. Nonepithelial neoplasms of the urinary bladder. Virchows Arch 2001;439(4):497-503.

140. Russo P, Brady MS, Conlon K, Hajdu SI, Fair WR, Herr HW, Brennan MF. Adult urological sarcoma. J Urol 1992;147(4):1032-1036 [Discussion 1036-1037]..

141. Lopez-Beltran A, Sauter G, Gasser T, et al.: Infiltrating urothelial carcinoma in Pathology and Genetics of Tumours of the Urinary System and Male Genital Organs. World Health Organization Classification of Tumours. IARC Press 2004, p 102.

142. Lopez-Beltran A, Pacelli A, Rothenberg HJ, Wollan PC, Zincke H, Blute ML, Bostwick DG. Carcinosarcoma and sarcomatoid carcinoma of the bladder: clinicopathological study of 41 cases. J Urol 1998;159(5):1497-1503.

143. Froehner M, Gaertner HJ, Maseck A, Wirth MP. Durable complete remission of metastatic sarcomatoid carcinoma of the bladder with cisplatin and gemcitabine in an 80-year-old man. Urology 2001;58(5):799.

144. Torenbeek R, Hermsen MAJA, Meijer GA, Baak JPA, Meijer CJLM. Analysis by comparative genomic hybridization of epithelial and spindle cell components in sarcomatoid carcinoma and carcinosarcoma: histogenetic aspects. J Pathol 1999;189: 338-343.

145. Hwang JJ, Uchio EM, Patel SV, Linehan WM, Walther MM, Pacak K. Diagnostic localization of malignant bladder pheochromocytoma using 6-18F fluorodopamine positron emission tomography. J Urol 2003;169(1):274-275.

146. Klingler HC, Klingler PJ, Martin Jr JK, Smallridge RC, Smith SL, Hinder RA. Pheochromocytoma. Urology 2001;57(6):1025-1032.

147. Iczkowski KA, Shanks JH, Gadaleanu V, Cheng L, Jones EC, Neumann R, Nascimento AG, Bostwick DG. Inflammatory pseudotumor and sarcoma of urinary bladder: differential diagnosis and outcome in thirty-eight spindle cell neoplasms. Mod Pathol 2001;14(10):1043-1051.

148. Jones EC, Clement PB, Young RH. Inflammatory pseudotumor of the urinary bladder. A clinicopathological, immunohistochemical, ultrastructural, and flow cytometric study of 13 cases. Am J Surg Pathol 1993;17(3):264-274.

149. Tainio HM, Kylmala TM, Haapasalo HK. Primary malignant melanoma of the urinary bladder associated with widespread metastases. Scand J Urol Nephrol 1999;33(6):406-407.

150. De Torres I, Fortuno MA, Raventos A, Tarragona J, Banus JM, Vidal MT. Primary malignant melanoma of the bladder: immunohistochemical study of a new case and review of the literature. J Urol 1995;154(2 Pt 1):525-527.

151. Ito K, Matsuo Y, Takahashi O, Yajima H, Yamanaka H, Ito H. Synchronous malignant melanoma of the male bulbar urethra and transitional cell carcinoma of the bladder. BJU Int 1999;84(7):877-878.

152. Al-Maghrabi J, Kamel-Reid S, Jewett M, Gospodarowicz M, Wells W, Banerjee D. Primary low-grade B-cell lymphoma of mucosa associated lymphoid tissue type arising in the urinary bladder: report of 4 cases with molecular genetic analysis. Arch Pathol Lab Med 2001;125(3):332-336.

153. Kempton CL, Kurtin PJ, Inwards DJ, Wollan P, Bostwick DG. Malignant lymphoma of the bladder: evidence from 36 cases that low-grade lymphoma of the MALT- type is the most common primary bladder lymphoma. Am J Surg Pathol 1997;21(11):1324-1333.