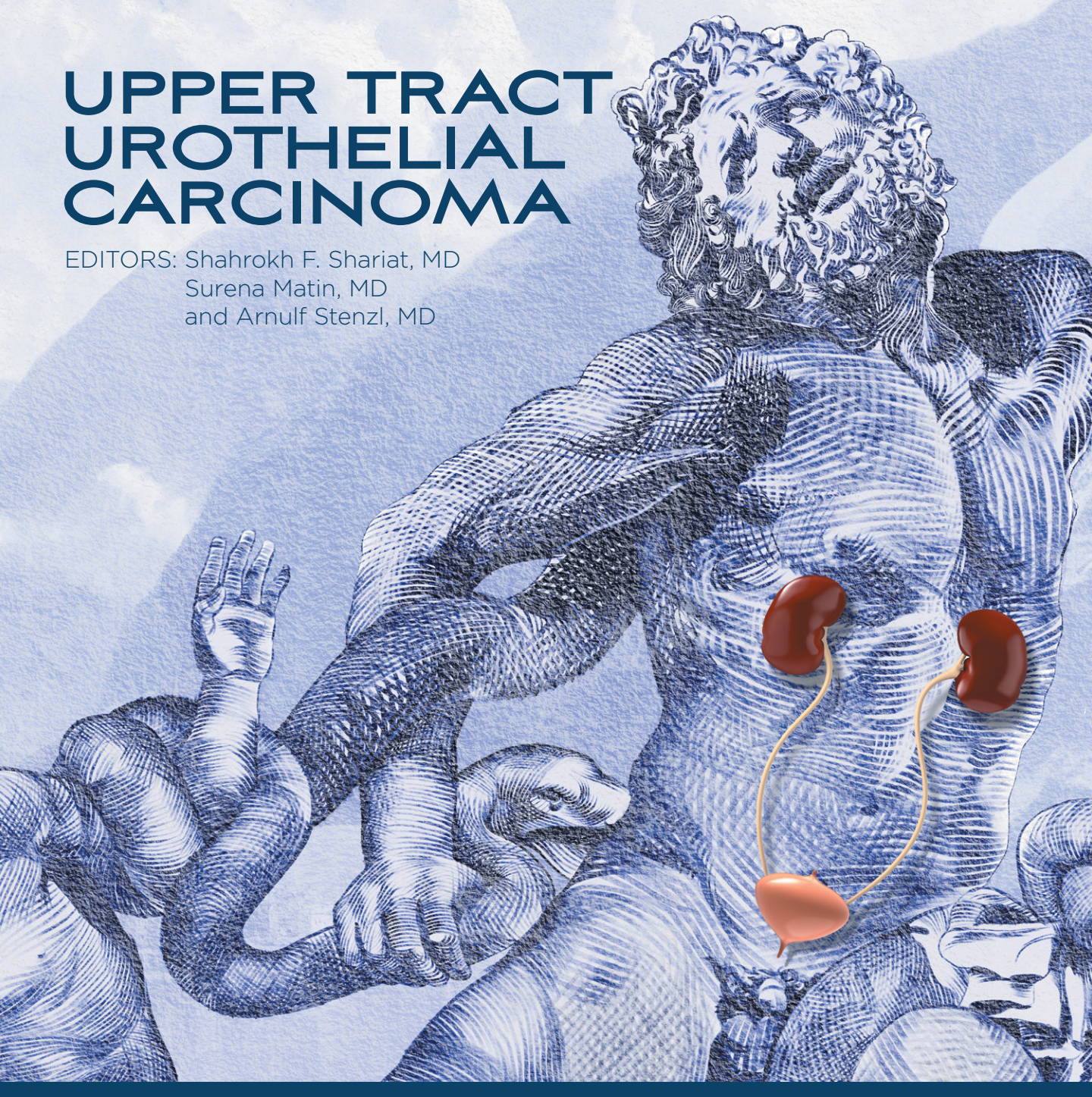
UPPER TRACT UROTHELIAL CARCINOMA

EDITORS: Shahrokh F. Shariat, MD
Surena Matin, MD
and Arnulf Stenzl, MD



A Joint SIU-ICUD International Consultation

Vancouver, Canada, September 8-12, 2013

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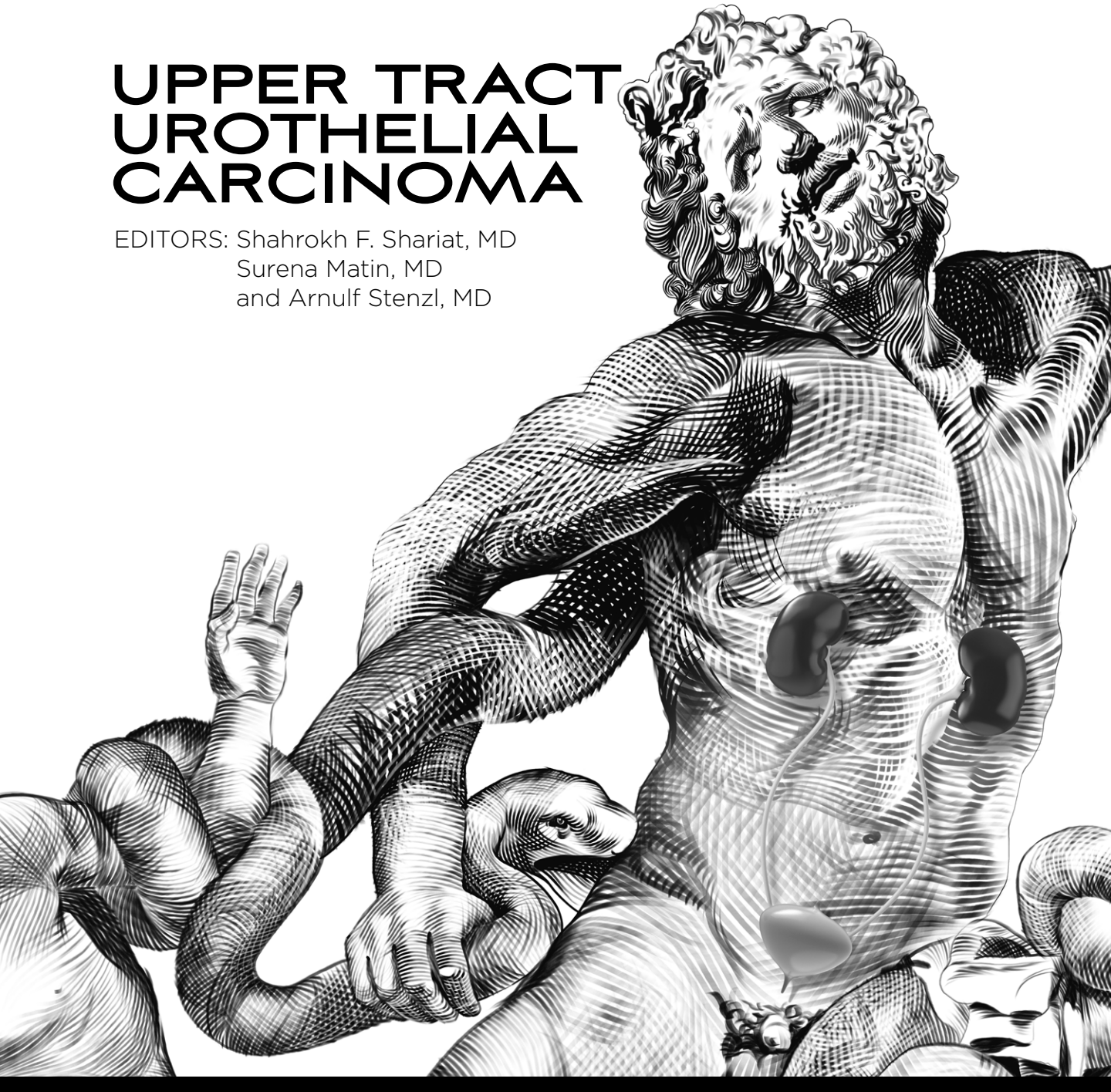

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For information and orders:
SIU Central Office
1155 University Street
Suite 1012
Montréal (QC)
Canada H3B 3A7
T: +1 514 875-5665
F: +1 514 875-0205
E-mail: communications@siu-urology.org
Website: www.siu-urology.org

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Medical Editing: Areti Malapetsas, Doris Vincent, Namita Kumar, and Nicole Palmer.
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Accurate indications, adverse reactions, and dosage schedules for drugs are provided in this book, but it is possible that these may change after publication. The reader is urged to review the product information (i.e., product monograph, package insert or leaflet, prescribing information) published by the manufacturers of the medications mentioned.

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Abbreviations Used in the Text

AJCC	American Joint Committee on Cancer
ASA	American Society of Anesthesiologists
ASCO	American Society of Clinical Oncology
AUM	asymmetric unit membrane
BCG	bacillus Calmette-Guérin
BEN	Balkan endemic nephropathy
BMI	body mass index
BR	bladder recurrence
CA125	cancer antigen 125
CAM	anti-cytokeratin
CD31	cluster of differentiation 31
CDX	caudal type homeobox
CEA	carcinoembryonic antigen
CI	confidence interval
CIS	carcinoma in situ
CK20	Cytokeratin 20
CKD	chronic kidney disease
COX	Cyclooxygenase
CR	complete response
CRP	C-reactive protein
CSM	cancer-specific mortality
CSS	cancer-specific survival
CT	computed tomography
DFS	disease-free survival
DNA	deoxyribonucleic acid
DR	disease recurrence
DSM	disease-specific mortality
DSS	disease-specific survival
DWI	diffusion-weighted imaging

EAU	European Association of Urology
EBER	Epstein–Barr virus-encoded small RNA
EBV	Epstein–Barr virus
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
EMA	epithelial membrane antigen
EMT	epithelial-mesenchymal transition
ENDO	endoscopic
EORTC	European Organisation for Research and Treatment of Cancer
FISH	fluorescence in situ hybridization
FS	frozen section
FU	fluorouracil
FVIIIR-Ag	factor VIII related–antigen
GATA	globin transcription factor
GFR	glomerular filtration rate
GI	gastrointestinal
GIA	trademark; add TM symbol to instance
GOR	grade of recommendation
HD	high definition
HIF	hypoxia-inducible factor
HIF-1α	hypoxia-inducible factor 1-alpha
HNPCC	hereditary non-polyposis colon cancer
HMW	high molecular weight
HMW-CK	high molecular weight cytokeratin
HPV	human papillomavirus
HR	hazard ratio
ICCI	confidence interval
IFN	interferon
IFS	intraoperative frozen section
IHC	immunohistochemistry
INI	integrase interactor

ISUP	International Society of Urological Pathology
IUNLMP	inverted urothelial neoplasm of low malignant potential
IVP	intravenous urography
IVR	intravesical recurrence
KL	Krebs Von den Lungen
KPR	kidney preserving rates
KSS	kidney-sparing surgery
LCA	leukocyte common antigen
LEV	level of evidence
LN	lymph node
LND	lymph node dissection
LNI	lymph node invasion
LNU	laparoscopic nephroureterectomy
LOE	level of evidence
LN	lymph node
LOH	loss of heterozygosity
LR	local recurrence
LVI	lymphovascular invasion
MFS	metastatic-free survival
MIB1	mindbomb E3 ubiquitin protein ligase 1
MPC	micropapillary carcinoma
MMR	mismatch repair
MR	magnetic resonance
MRI	magnetic resonance imaging
MSI	microsatellite instability
MUC1	Mucin1
MVAC	methotrexate, vinblastine, doxorubicin, and cisplatin
NAT	N-acetyltransferase
NBI	narrow band imaging
NCCN	National Comprehensive Cancer Network
NED	no evidence of disease
NF	nuclear factor
NMIBC	non-muscle invasive bladder cancer

NOC	non-organ confined
NPV	negative predictive value
NR	no response
NSE	neuron-specific enolase
NU	nephrouterectomy
NUC	nested variant of urothelial carcinoma
NX	no node dissection
ODMIT	One Dose Mitomycin
ODMIT-c	One Dose Mitomycin C
OM	overall mortality
ONU	open RNU
OR	odds ratio
OS	overall survival
p53	tumour protein 53
p63	tumour protein 63
pan-CK	Pan-cytokeratin
PAS	periodic acid Schiff
PCN	percutaneous nephroscopy
PCR	polymerase chain reaction
PDD	photodynamic diagnostic
PET	positron emission tomography
PFS	progression-free survival
PPV	positive predictive value
PS	performance status
PSA	prostate-specific antigen
PSM	positive surgical margin
PSMA	prostate-specific membrane antigen
pT	Primary tumour
pT1	tumour invades subepithelial connective tissue
pT2	Invasion of tumour into the muscularis propria
pT3	For renal pelvis: tumour invades beyond the muscularis propria into peripelvic fat or renal parenchyma
pT4	Tumour invades adjacent organs or though the renal parenchyma into perinephric fat

pTa	papillary non-invasive carcinoma
PUNLMP	papillary urothelial neoplasm of low malignant potential
PUNUMP	papillary urothelial neoplasm of uncertain malignant potential
RCC	renal cell carcinoma
RFS	recurrence-free survival
RNA	ribonucleic acid
RNU	radical nephroureterectomy
RP	retrograde pyelography
RU	renal unit
SCC	squamous cell carcinoma
SEER	Surveillance, Epidemiology and End Results
SU	segmental ureterectomy
TCC	transitional cell carcinoma
TIMP	tissue inhibitor of metalloproteinase
TNM	tumor node metastasis
TTF-1	thyroid transcription factor 1
TURBT	transurethral resection of bladder tumor
UC	urothelial carcinoma
UCB	urothelial carcinoma of the bladder
UCC	urothelial cell carcinoma
UCUUT	urothelial carcinoma of the upper urinary tract
UICC	International Union Against Cancer
URS	ureteroscopy
UT	upper tract
UTTCC	upper tract transitional cell carcinoma
UTUC	upper tract urothelial carcinoma
UUT	upper urinary tract
VAC	vinblastine, adriamycin and cisplatin
VUR	vesicoureteral reflux
WHO	World Health Organization
YAG	yttrium aluminum garnet

Preface

Shahrokh F. Shariat, MD
Professor & Chairman of Urology, Medical University Vienna, Austria

Surena Matin, MD
Professor of Urology, University of Texas M. D. Anderson Cancer Center, Houston, TX

Arnulf Stenzl, MD
Professor of Urology, Germany

The initial spark for this book originated from a 90-minute telephone conversation between Shahrokh Shariat and Surena Matin, during which time the great challenges facing those who treat upper tract urothelial carcinoma (UTUC), and the great strides being made, were discussed. Subsequently, over several teleconferences and one sunny afternoon, Arnulf Stenzl, Surena Matin, and Shahrokh Shariat developed the plans and outline for the product that you are now viewing. The subsequent real work emanated from a tremendous international collaboration of over 50 urologists, medical oncologists, and pathologists from four continents serving on five committees, chaired by George Thalmann, Shahrokh Shariat, Surena Matin, Arnulf Stenzl, and Matthew Milowsky. A summary of the findings was presented at the Société Internationale d'Urologie meeting in Vancouver in 2013. We are so grateful to Dr. Paul Abrams and the SIU leadership for allowing this unique venture involving three editors and such a large international cast for an oft overlooked disease.

This ICUD represents a remarkable milestone in the history of upper tract urothelial carcinoma. Frequently overlooked at international meetings, often ignored in teaching conferences, and generally misunderstood by most practitioners, upper tract urothelial carcinoma still garners incredible interest from the urologic community on advancing the science and treatment of this disease. In 2012, the first ever symposium on UTUC was held in conjunction with the Society of Urologic Oncology meeting, and the large conference room was filled with a standing room–only crowd. We, our collaborators, and you, our reader, appreciate the critically important and interesting aspects we have learned so recently on its causes, risk factors, genetics, and treatments, especially when we have felt the repeated frustration of helping a patient when little solid evidence exists to help them.

One of the most important elements is for us to have a common language, which forms the foundation for all subsequent learning and research. The terminology of UTUC as established in this book is one of those critically important elements. The older terminology of "transitional cell" is not only outdated, but confusing to patients and even some providers. It also helps establish this disease as the unique entity that it is, given differences from bladder cancer in molecular, genetic, clinical, and epidemiologic aspects.

Great strides are being made in our understanding of and treatments against this disease. Much is yet to be done. The substantial work covered in this book is state-of-the-art and one of the few major works currently published that highlight the growing momentum of interest in this disease.

Evidence-Based Medicine Overview of the Main Steps for Developing and Grading Guideline Recommendations

P. Abrams, S. Khoury, A. Grant

Introduction

The International Consultation on Urological Diseases (ICUD) is a non-governmental organization registered with the World Health Organisation (WHO). In the last ten years, consultations have been organized on BPH, prostate cancer, urinary stone disease, nosocomial infections, erectile dysfunction and urinary incontinence. These consultations have looked at published evidence and produced recommendations at four levels: highly recommended, recommended, optional and not recommended. This method has been useful but the ICUD believes that there should be more explicit statements of the levels of evidence that generate the subsequent grades of recommendations.

The Agency for Health Care Policy and Research (AHCPR) have used specified evidence levels to justify recommendations for the investigation and treatment of a variety of conditions. The Oxford Centre for Evidence-Based Medicine have produced a widely accepted adaptation of the work of AHCPR. (June 5th 2001, www.cebm.net).

The ICUD has examined the Oxford guidelines and discussed with the Oxford group their applicability to the consultations organized by ICUD. It is highly desirable that the recommendations made by the consultations follow an accepted grading system supported by explicit levels of evidence.

The ICUD proposes that future consultations should use a modified version of the Oxford system which can be directly "mapped" onto the Oxford system.

1. First Step

Define the specific questions or statements that the recommendations are supposed to address.

2. Second Step

Analyze and rate (level of evidence) the relevant papers published in the literature.

The analysis of the literature is an important step in preparing recommendations and their guarantee of quality.

2.1 What papers should be included in the analysis?

- Papers published, or accepted for publication in the peer-reviewed issues of journals.
- The committee should do its best to search for papers accepted for publication by the peer-reviewed journals in the relevant field but not yet published.
- Abstracts published in peer-reviewed journals should be identified. If of sufficient interest, the author(s) should be asked for full details of methodology and results. The relevant committee members can then "peer review" the data, and if the data confirms the details in the abstract, then that abstract may be included, with an explanatory footnote. This is a complex issue – it may actually increase publication bias as "uninteresting" abstracts commonly do not progress to full publication.
- Papers published in non-peer-reviewed supplements will not be included. An exhaustive list should be obtained through:
  - I. The major databases covering the last ten years (e.g. Medline, Embase, Cochrane Library, Biosis, Science Citation Index).
  - II. The table of contents of the major journals of urology and other relevant journals, for the last three months, to take into account the possible delay in the indexation of the published papers in the databases.

It is expected that the highly experienced and expert committee members provide additional assurance that no important study would be missed using this review process.

2.2 How are papers analyzed?

Papers published in peer-reviewed journals have differing quality and level of evidence. Each committee will rate the included papers according to levels of evidence (see below).

The level (strength) of evidence provided by an individual study depends on the ability of the study design to minimize the possibility of bias and to maximize attribution.

It is influenced by:

The type of study, whose hierarchy is outlined below:

- Systematic reviews and meta-analysis of randomized controlled trials
- Randomized controlled trials
- Non-randomized cohort studies
- Case-control studies
- Case series
- Expert opinion

How well the study was designed and carried out

Failure to give due attention to key aspects of study methodology increases the risk of bias or confounding factors, and thus reduces the study's reliability.

The use of **standard checklists** is recommended to insure that all relevant aspects are considered and that a consistent approach is used in the methodological assessment of the evidence.

The objective of the checklist is to give a quality rating for individual studies.

How well the study was reported

The ICUD has adopted the CONSORT statement and its widely accepted checklist. The CONSORT statement and the checklist are available at www.consort-statement.org.

2.3 How are papers rated?

Papers are rated following a level of evidence scale.

ICUD has modified the Oxford Centre for Evidence-Based Medicine levels of evidence.

The levels of evidence scales vary between types of studies (i.e. therapy, diagnosis, differential diagnosis/ symptom prevalence study) the Oxford Centre for Evidence-Based Medicine Website: www.cebm.net.

3. Third Step: Synthesis of the Evidence

After the selection of the papers and the rating of the level of evidence of each study, the next step is to compile a summary of the individual studies and the overall direction of the evidence in an **Evidence Table**.

4. Fourth Step: Considered Judgment (Integration of Individual Clinical Expertise)

Having completed a rigorous and objective synthesis of the evidence base, the committee must then make a judgment as to the grade of the recommendation on the basis of this evidence. This requires the exercise of judgment based on clinical experience as well as knowledge of the evidence and the methods used to generate it. Evidence-based medicine requires the integration of individual clinical expertise with the best available external clinical evidence from systematic research. Without the former, practice quickly becomes tyrannized by evidence, for even excellent external evidence may be inapplicable to, or inappropriate for, an individual patient. On the other hand, without current best evidence, practice quickly becomes out of date. Although it is not practical to lay our "rules" for exercising judgment, guideline development groups are asked to consider the evidence in terms of quantity, quality, and consistency, as well as applicability, generalizability and clinical impact.

5. Fifth Step: Final Grading

The grading of the recommendation is intended to strike an appropriate balance between incorporating the complexity of type and quality of the evidence, and maintaining clarity for guideline users.

The recommendations for grading follow the Oxford Centre for Evidence-Based Medicine. The levels of evidence shown below have again been modified in the light of previous consultations. There are now four levels of evidence instead of five.

The grades of recommendation have not been reduced and a "no recommendation possible" grade has been added.

6. Levels of Evidence and Grades of Recommendation for Therapeutic Interventions

All interventions should be judged by the body of evidence for their efficacy, tolerability, safety, clinical effectiveness and cost-effectiveness. It is accepted that, at present, little data exists on cost-effectiveness for most interventions.

6.1 Levels of evidence

Firstly, it should be stated that any level of evidence may be positive (the therapy works) or negative (the therapy doesn't work). A level of evidence is given to each individual study.

Level of Evidence	Criteria
I	▪ Incorporates Oxford 1a, 1b ▪ Usually involves: ▪ meta-analysis of trials (randomized controlled trials [RCTs]) or, ▪ a good-quality RCT or, ▪ "all or none" studies in which treatment is not an option (e.g. in vesicovaginal fistula)
II	▪ Incorporates Oxford 2a, 2b and 2c ▪ Includes: ▪ ***low-quality RCT*** (e.g. <80% follow-up), ▪ ***meta-analysis*** (with homogeneity) of ***good-quality prospective cohort studies*** ▪ May include a single group when individuals who develop the condition are compared with others from within the original cohort group. ▪ There can be parallel cohorts, where those with the condition in the first group are compared with those in the second group
III	▪ Incorporates Oxford 3a, 3b and 4 ▪ Includes: ▪ ***good-quality retrospective case-control studies***, where a group of patients who have a condition are matched appropriately (e.g. for age, sex, etc.) with control individuals who do not have the condition ▪ ***good-quality case series,*** where a complete group of patients, all with the same condition, disease or therapeutic intervention, are described without a comparison control group
IV	▪ Incorporates Oxford 4 ▪ Includes ***expert opinion***, where the opinion is based not on evidence but on "first principles" (e.g. physiological or anatomical) or bench research. ▪ The ***Delphi process*** can be used to give expert opinion greater authority: ▪ involves a series of questions posed to a panel ▪ answers are collected into a series of "options" ▪ these "options" are serially ranked; if a 75% agreement is reached, then a Delphi consensus statement can be made

6.2 Grades of recommendation

The ICUD will use the four grades from the Oxford system. As with levels of evidence, the grades of evidence may apply either positively (procedure is recommended) or negatively (procedure is not recommended). Where there is disparity of evidence, for example if there were three well-conducted RCTs indicating that Drug A was superior to placebo, but one RCT whose results show no difference, then there has to be an individual judgment as to the grade of recommendation given and the rationale explained.

Grade A recommendation usually depends on consistent level I evidence and often means that the recommendation is effectively mandatory and placed within a clinical-care pathway. However, there will be occasions where excellent evidence (level I) does not lead to a Grade A recommendation, for example, if the therapy is prohibitively expensive, dangerous or unethical. Grade A recommendation can follow from Level II evidence. However, a Grade A recommendation needs a greater body of evidence if based on anything except Level I evidence.

Grade B recommendation usually depends on consistent level 2/3 studies, or "majority evidence" from RCTs.

Grade C recommendation usually depends on level 4 studies or "majority evidence" from level 2/3 studies or Delphi processed expert opinion.

Grade D "No recommendation possible" would be used where the evidence is inadequate or conflicting and when expert opinion is delivered without a formal analytical process, such as by Delphi.

7. Levels of Evidence and Grades of Recommendation for Methods of Assessment and Investigation

From initial discussions with the Oxford group, it is clear that application of levels of evidence/grades of recommendation for diagnostic techniques is much more complex than for interventions. The ICUD recommends that, as a minimum, any test should be subjected to three questions:

1. Does the test have good technical performance? For example, do three aliquots of the same urine sample give the same result when subjected to dipstick testing?
2. Does the test have good diagnostic performance, ideally against a "gold standard" measure?
3. Does the test have good therapeutic performance, that is, does the use of the test alter clinical management? Does the use of the test improve outcome?

For the third component (therapeutic performance) the same approach can be used as for section 6.

8. Levels of Evidence and Grades of Recommendation for Basic Science and Epidemiology Studies

The proposed ICUD system does not easily fit into these areas of science. Further research needs to be carried out in order to develop explicit levels of evidence that can lead to recommendations as to the soundness of data in these important aspects of medicine.

Conclusion

The ICUD believes that its consultations should follow the ICUD system of levels of evidence and grades of recommendation, where possible. This system can be mapped to the Oxford system.

There are aspects to the ICUD system that require further research and development, particularly diagnostic performance and cost-effectiveness, and also factors such as patient preference.

Summary of the International Consultation on Urological Disease Modified Oxford Centre for Evidence-Based Medicine Grading System for Guideline Recommendations

Levels of Evidence	Description
I	Meta-analysis of RCTs or high-quality RCT
II	Low-quality RCT or good-quality prospective cohort study
III	Good-quality retrospective case-control study or cohort study
IV	Expert opinion

Abbreviation: RCT=randomized controlled trial

Summary of the International Consultation on Urological Disease Modified Oxford Centre for Evidence-Based Medicine Grading System for Guideline Recommendations

Grades of Recommendation	Description
A	Usually consistent with level I evidence
B	Consistent level II or III evidence or "majority evidence" from RCTs
C	Level IV evidence or "majority evidence" from level II or III studies
D	No recommendation possible because of inadequate or conflicting evidence

RCT=randomized controlled trial

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Committee 1

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Epidemiology, Diagnosis, and Evaluation

Committee 1

1.1 Gender and Race

1.1.2 Overview

Upper tract urothelial carcinoma (UTUC) is a rare but potentially lethal disease. In general, urothelial carcinoma is the sixth most common malignancy among all cancers in both genders. It is the second leading urological malignancy after prostate cancer.[1] Upper tract urothelial carcinoma, however, which comprises urothelial malignancies of the pelvicalyceal cavities and ureters, only accounts for 5% of all urothelial cancers and less than 10% of renal tumours.[1–4] Determination of the true and exact UTUC incidence is difficult because renal pelvicalyceal tumours are often combined with other renal tumours (e.g., renal cell carcinoma) as one group.

The estimated annual incidence of UTUC in the Western world is about 1 to 2 new cases per 100,000 inhabitants.[3,4] Population-based studies found that incidence rates increased up to 10 fold, according to data from the 1940s to the mid-1990s.[3,5] Renal pelvicalyceal tumours are about twice as common as ureteral tumours.[6] Raman *et al.*[7] analyzed the epidemiological UTUC patterns over the past 30 years in a large population-based cohort from the United States. The incidence of renal pelvicalyceal tumours remained almost unchanged, with a minimal reduction from 1.19 to 1.15 cases per 100,000 person-years; the incidence of ureter tumours increased from 0.69 to 0.91 cases per 100,000 person-years, and the total incidence of UTUC increased from 1.88 to 2.06 cases per 100,000 person-years.[7] The peak incidence of UTUC is between age 70 and 80 years, with men twice as likely to develop UTUC as women.[2,4,8] In the past 30 years, the mean age at diagnosis increased from 68 to 73 years. In addition, the incidence rate of women with a UTUC diagnosis increased from 35.9% to 38.7%.[7]

As with most cancers, the extent of disease, particularly the disease stage at the time of diagnosis, is directly associated with UTUC outcomes.[6,9] At the time of diagnosis, 40% to 50% of patients have *in situ* (pTa to pT1) disease, 50% to 60% of patients have invasive or advanced disease (p≥T2), and about a quarter of patients already have regional metastasis.[2,6,8] The proportion of *in situ* tumours increased significantly from 7% to 31% over the past 30 years, while the proportion of local tumours declined (50% to 24%, $p<0.001$). Interestingly, the incidence of regional disease increased by 2.6%, whereas the incidence of distant disease (8%–9%) did not change over time.[7]

At time of diagnosis or treatment with radical nephroureterectomy (RNU), a quarter of UTUC patients previously had non-muscle–invasive bladder cancer[2,8,10]; concurrent bladder cancer was present in 8% to 13% of cases.[4] The prevalence of UTUC development in patients treated with radical cystectomy for bladder cancer is 0.75% to 6.4% during long-term follow-up.[11–14] More than 70% of UTUC cases develop within 5 years of bladder cancer diagnosis/treatment, and only 6% of UTUC cases develop after 10 years of bladder cancer diagnosis/treatment.[14] A total of 15% to 50% of UTUC patients experience bladder cancer after radical nephroureterectomy.[15,16] Incidence rates for metachronous UTUC in the contralateral upper tract, after treatment on curative intent, are observed in 0.8% to 6% of patients.[17–19] (Further details and risk factors will be discussed in section 1.3, "Relation to Urothelial Cancer of the Bladder").

Various factors likely played important roles in the changes observed in UTUC incidence rates and epidemiological disease patterns over the past half-century. Significant improvements in cross-sectional imaging strategies and techniques probably led to earlier and better detection of more tumours, especially smaller tumours in the upper urinary tract. Axial imaging (e.g., computed tomography or magnetic resonance imaging) tremendously outperforms intravenous pyelography used in the past in diagnostic accuracy.[20,21] In addition, refinements in the endoscopic therapeutic strategies and approaches (e.g., introduction of flexible and digital ureteroscopes) enabled easier and better detection as well as histological confirmation of early-stage tumours.[22] Finally, improvements in bladder cancer treatments resulted in increased survival from the cancer, and certainly conveyed an increased UTUC incidence, revealing the natural history of UTUC.

1.1.3 Gender

Population-based and multi-institutional studies have shown that men are approximately twice as likely as women to develop UTUC (female-to-male ratio: 1.5–2.3:1; Level of Evidence [LOE] 3).[2,8,23–25] In contrast to urothelial carcinoma of the bladder, gender is not a predictor of prognosis in UTUC (LOE 3). Two large, retrospective, multi-institutional studies found no association between gender and pathologic features, disease recurrence, or cancer-specific mortality in UTUC patients treated with RNU.[23,25] A population-based study addressed one of the potential limitations of studying the influence of gender on mortality by using competing risks regression analysis.[24] In this study, women were more likely to present with more locally advanced stages (pT3) than men. However, when adjusting for standard clinico-pathologic features in the multivariable competing risk model, gender did not affect cancer-specific survival (LOE 3).[24] While one recently published study from Japan found female gender to be associated with intravesical bladder cancer recurrence,[26] a large multi-institutional study from Europe and the United States, in contrast, did not find this association.[10]

1.1.4 Race

The majority of UTUC patients are caucasians (80%–90%; LOE 3).[7,14,27–29] In multi-institutional and population-based studies, UTUC prevalence decreased from caucasians to Asian or other ethnicities to black non-Hispanic ethnicities (LOE 3).[7,27,28] While the UTUC incidence rate among caucasians significantly decreased in the past 30 years (92.6% to 88.3%, $p<0.001$), the incidence rate increased in black patients (3.4% to 4.3%, $p=0.4$) and other ethnicities (4.0% to 7.5%, $p<0.001$).[7] More frequent health care access with better early detection in non-caucasian ethnicities may be a reason for this trend. A recent, large population-based study found significantly poorer all-cause mortality in black non-Hispanic patients compared with all other racial groups (LOE 3).[7] In contrast, a large multi-institutional study in European and Japanese patients did not find any difference in survival outcomes between both ethnicities.[28] In summary, there are differences in clinico-pathologic characteristics between different ethnicities, but race does not seem to be an independent predictor for survival (LOE 3).[4]

1.2 Etiology and Risk Factors

The mechanism of carcinogenesis in UTUC is similar in many aspects to urothelial carcinoma of the lower urinary tract, but it can differ to some extent. Both hereditary and environmental factors can contribute to the development of UTUC.

1.2.1 Environmental factors

Tobacco exposure is presently considered the most important risk factor for urothelial carcinoma. It increases the relative risk of developing UTUC from 2.5% to 7% (LOE 2).[30–32]

The effect of smoking on the prognosis of UTUC was analyzed only in small studies. In one cohort study of 105 cases, it was shown that the disease-related survival period was significantly shorter in cigarette smokers compared to those who had never smoked.[33] In another study of 288 patients, the substantial risk for death in patients with UTUC was higher in active smokers compared to patients who had never smoked (LOE 3).[34]

It was confirmed that the occupational exposure to certain aromatic amines influences the risk for urothelial carcinoma (LOE 2).[31,32,35] Several chemicals such as benzidine, β-naphtylamine, 4-aminobiphenyl, 4-nitrobiphenyl, polycyclic aromatic hydrocarbons, diesel exhausts, and paint substances have been identified as responsible for urothelial cancer development. Exposure to these substances may occur through inhalation or absorption through the skin. These substances have been used in many industries (e.g., dyes, textiles, rubber, chemicals, petrochemicals, and coal). Although the use of benzidine, β-naphtylamine, and 4-aminobiphenyl is prohibited and strictly controlled in developed countries, the occupational etiology remains important because exposure to some potential carcinogens, for instance, in diesel exhausts or paint substances, still exists.[31,32] Tumours in the upper urinary tract are less common than in the bladder and, in most cases, are secondary after bladder cancer.[31,32] The average duration of exposure needed to develop UTUC is approximately 7 years, with a latency period of about 20 years following the termination of exposure.[32] The estimated risk, also called the odds ratio (OR), of developing urothelial carcinoma after exposure to aromatic amines is 8.3 (LOE 2).[36]

The cases of UTUC related to overconsumption of phenacetin, which is used in various analgesic compounds, were initially reported in the 1960s in Sweden.[32] It is expected that phenacetin indirectly causes carcinogenesis by inducing nephrotoxicity through papillary necrosis (LOE 3).[32,37] Because the use of phenacetin was abandoned in the 1980s, the number of cases is decreasing.[32]

A high incidence rate of chronic nephropathy and UTUC in some endemic areas, due to herbs with powerful nephrotoxic and carcinogenic impact, was observed (LOE 3).

Balkan endemic nephropathy, a chronic tubulo-interstitial disease with a slow progression to terminal renal failure, affects people living in some rural areas of the Balkans along the Danube River. A typical feature of this condition is a strong association with UTUC. In endemic areas of the

disease, the incidence of UTUC is significantly higher, by as much as 100 times, than in non-endemic regions.[38] This connection was first described in the 1950s. Fortunately, a strong reduction in the number of cases has been observed during the past 20 years.[32]

A similar association was observed between Chinese herbal products and end-stage renal failure with high risk for UTUC.[32] Nephropathy and urothelial carcinoma related to the use of herbs was initially reported in Belgium in the 1990s, but many cases appeared in China and Taiwan (LOE 2).[39–41]

It was confirmed that both Balkan endemic nephropathy and Chinese herbs nephropathy were associated with aristolochic acid contained in *Aristolochia fangchi* and *Aristolochia clamatis*. Aristolochic acid, a constituent of all Aristolochia plants, is a powerful nephrotoxin and human carcinogen associated with chronic kidney disease and UTUC. This acid contains a set of highly toxic nitrophenolate derivatives that exhibit a powerful mutagenic action due to their ability to make covalent links with cell DNA. The aristolochic acid derivative d-aristolactam causes a specific mutation in the p53 gene at codon 139. This mutation is very rare in the non-exposed population and is predominant in patients with nephropathy due to Chinese herbs or Balkan endemic nephropathy who present with UTUC (LOE 2).[31,32,39]

The high incidence of UTUC in some areas of Taiwan can be explained by association with blackfoot disease (endemic vasculitis) or exposure to arsenic (LOE 3).[39,42–44]

1.2.2 Genetic susceptibility

It is generally accepted that bladder carcinogenesis develops from the interaction of environmental exposure and genetic susceptibility. It is well known that some genetic polymorphisms are associated with an increased risk for urothelial cancer or faster disease progression. Genetic polymorphism with different enzyme expression can alter the metabolism of carcinogenic substances, like aromatic amines, and explain different individual susceptibility to various risk factors. The typical example observed in bladder urothelial tumours is the enzyme N-acetyltransferase (NAT), which transforms aromatic amine compounds into either less reactive metabolites or into another detoxification enzyme, glutathione S-transferase M1 (GSTM1). Certain levels of similarity between urothelial carcinoma of the lower and upper urinary tract is expected.[31]

Two polymorphisms specific to UTUC have also been reported.[31,32] It was shown that variant allele SULT1A1*2, which reduces sulfotransferase activity, and a polymorphism located at the T allele of rs9642880 on chromosome 8q24 enhance the risk of developing UTUC (LOE 2).[45,46]

1.2.3 Hereditary factors

Familial cases of UTUC linked to hereditary nonpolyposis colorectal carcinoma (HNPCC) were confirmed (LOE 2).[31,47,48] The disease, also known as Lynch syndrome, is caused by mutations in mismatch repair genes.[31,47,48] There is a suspicion of hereditary UTUC if the patient is <60 years of age, and/or has a personal history of an HNPCC-associated cancer, and/or is a first-degree relative of someone <50 years of age with HNPCC-associated cancer, and/or has two first-degree relatives with an HNPCC-associated cancer (LOE 2).[49]

1.3 Relation to Urothelial Cancer of the Bladder

Urothelial cancers are inherently multifocal and have a high propensity for recurrence after initial ablative treatment. These characteristics create challenging clinical scenarios. They include multiple synchronous and/or metachronous tumours in different areas of the urothelium, in the upper urinary tracts, bladder, and urethra. It is difficult to determine whether these lesions represent seeding sites of shedding tumour cells that originated from the same primary tumour or whether these are true second primary *de novo* lesions. There is evidence supporting both the field effect and the monoclonality theories.[50] However, the majority of the studies using histopathologic, molecular, and genomic mapping analyses favour the monoclonality hypothesis: exfoliated tumour cells are spread intraluminally to other parts of the urothelium, especially in the presence of invasive primary tumours.[51–54] Most likely, both mechanisms may be present simultaneously, explaining the multiple variations in presentation of synchronous and metachronous tumours affecting both the lower and upper urinary tract; many times these tumours also affect the contralateral upper tract unit.[55]

1.3.1 Synchronous tumours

The reported incidence rate of concurrent upper urothelial urinary tract and bladder tumours is between 8% and 13% of cases.[15,31,56–58] Recurrence in the contralateral upper urinary tract is reported to be around 2% to 6%; one-third of these tumours in the upper urinary tract are multifocal at diagnosis.[57,59,60] In a Swedish population, synchronous bilateral upper urinary tract tumours were also rare and were preceded by bladder cancer in 80% of patients (LOE 2).[61]

1.3.2 Metachronous tumours, primary in the bladder

The risk of being diagnosed with upper urinary tract tumour was believed to be approximately 0.7% to 1.7% in a median of 4.1 years of follow-up in patients with bladder cancer.[62,63] More recent studies have shown rates of upper urinary tract tumours after radical cystectomy as high as 4.9% at 5 years.[13,64]

Most contemporary series show that after radical cystectomy, about 3% to 5% of all patients will develop a metachronous tumour in the upper urinary tract. The median reported time from cystectomy to the diagnosis of the metachronous upper urinary urothelial tumours is 43 months (range: 25–62 months), with isolated reports of very late occurrences up to 9 years after cystectomy (LOE 2).[65–70]

There are basically two forms of oncologic relapse after radical cystectomy, and they are distinct in terms of presentation and timing. True tumour relapses typically occur early (within 2 to 3 years after surgery) and manifest as local recurrence in the pelvis (bony metastasis), viscera (most commonly liver and lungs), or lymph nodes in the pelvis or retroperitoneum. This form of recurrence accounts for more than 80% of all tumour recurrences after radical cystectomy, and they are located outside of the urothelium.[68,69] The other form of relapse occurs in the retained urothelium. There is controversy

about the nomenclature because authors consider them (or at least the great majority of them) to be second primary or *de novo* tumours. These tumours typically occur later, after radical cystectomy; they are more often identified after development of tumour-related symptoms (e.g., hematuria and flank pain), rather than by routine surveillance findings (e.g., positive cytology or abnormal imaging) (LOE 3).[67–69,71] Tumour recurrence in the ureteral anastomosis (distal ureters) and proximal urethra often is associated with the presence of carcinoma *in situ* (CIS) in the bladder's primary tumour and/or in the positive margins; it is usually considered recurrent disease, and not a second primary lesion, by the majority of the authors and experts. These cases tend to relapse sooner after radical cystectomy.[67,71,72]

Based on the 3% to 5% risk of having an upper urinary tract tumour after a primary bladder cancer, clinical practice guidelines recommend surveillance of the upper urinary tracts by urinary cytology, endoscopy, and axial imaging.[12,31,73] The objective of surveillance protocols after radical cystectomy is to detect both types of relapses described above. For the early recurrences occurring outside of the urothelium, the goal is to detect tumour relapse at an early phase, so systemic therapy can be started as early as possible. For the urothelial relapses or second primary tumours, early detection is important for radical treatment with curative intent before the disease becomes systemic and widespread. There is no consensus about the ideal surveillance regimen; the method, interval, and duration vary in the literature (LOE 3).[66–71]

The series with long-term follow-up shows that the overall prevalence of upper urinary tract tumour development after radical cystectomy for bladder cancer is 0.75% to 6.4%.[11–14] The long-term surveillance is considered necessary for at least 5 to 10 years because the majority of patients (>70%) will develop upper tract tumours within 5 years of bladder cancer management; another 6% of cancers occur after 10 years of follow-up.[14] The need for long-term surveillance is further supported by results of one of the largest single-centre series reported. Using a landmark time analysis, investigators found 3- and 5-year cumulative upper urinary tract recurrence rates after radical cystectomy of 4% and 7%, respectively; this showed a continuous 3-year risk for upper urinary tract recurrence of 4% to 6% at any point of follow-up, up to 4 years.[64] Moreover, the presence of CIS in the bladder raised the risk for upper urinary tract tumours to 25% in patients treated with Bacillus Calmette-Guérin (BCG) at 10 years of follow-up.[74]

In a recent review of the literature, metachronous upper urinary tract tumours after radical cystectomy were most often identified in symptomatic (hematuria in 60% to 80%, flank pain, pyelonephritis, and weight loss) versus asymptomatic patients (62% versus 38%).[12] With the fast progress of imaging technologies and future advances in biomarker development, we should be able to detect these lesions at early phases and stages, while the patient is still asymptomatic. While cytology remains a main tool for surveillance of the urinary tract after cystectomy, imaging tests such as intravenous pyelogram (IVP) and computed tomography (CT) urogram are also important; they detect up to 55% of the metachronous UTUC relapses.[65–68,70,71] Computed tomography urogram is usually the preferred method for offering the capability of monitoring the other areas in the abdomen and pelvis outside of the urinary tract. It has been reported that the location of the tumour in the upper urinary tract may significantly affect the detection rates of the CT scan. This method is able to provide 78% to 94% detection of renal pelvis lesions versus 19% to 53% of ureteral lesions; these rates are especially limited with lesions smaller than 2 cm (LOE 2).[75–77]

There is debate about the risk factors associated with relapse. Pathological T-stage is a risk factor for development of true tumour relapse, which occurs early in the follow-up. Higher-stage disease in the bladder is not independently associated with the occurrence of metachronous upper tract lesions because of the shorter overall survival interval. For this reason, the development of second primary tumours in the upper urinary tracts is more commonly associated with organ-confined disease in the bladder (≤pT2pN0).[12,65–71]

The presence of positive ureteral margins during cystectomy has been shown to be predictive of metachronous upper urinary tract tumours, but not necessarily in the anastomotic area (LOE 3).[78,79] Therefore, it has been an accepted concept that sequential resection of the distal ureteral margins to achieve negative margins, in case of CIS, does not eliminate the risk for upper urinary tract tumour occurrence during the surveillance period.

It has been reported that greater than 75% of metachronous upper urinary tract tumours identified in patients with previous radical cystectomy are invasive and high grade, in comparison with 30% of primary lesions; thus they are associated with poorer survival rates.[65–67,71,79–82] Moreover, the tumour location in the upper tract may also affect survival, with non-anastomotic metachronous UTUC having longer disease-free survival after radical cystectomy.[72]

A history of bladder cancer has been shown to be an important risk factor. At the time of diagnosis or treatment with RNU, a quarter of the patients with upper urinary tract tumour had a history of bladder cancer (LOE 3).[91–93]

1.3.3 Metachronous tumours, primary in the upper urinary tract

Incidence rates for metachronous upper urinary tract urothelial tumours in the contralateral side after treatment on curative intent are observed in 0.8% to 6% of cases.[2,8,10]

Differently than the previous situation, metachronous bladder tumours occurring after a primary urothelial cancer in the upper tract can be considered a recurrent or relapsed disease, based on the monoclonality theory. However, this is not always the case. Data also shows that many times there are pathological and molecular differences between these lesions. For the purposes of this section, we will consider them all recurrent lesions.

The bladder is the most common site of recurrence after treatment of UTUC. Approximately 15% to 50% of patients also develop bladder cancer after having an upper urinary tract primary tumour.[15,18,60,82,84,85]

In terms of timing, most studies show that 80% to 90% of the metachronous bladder tumours occur within 2 years of treatment of the primary upper urinary tract lesion (LOE 3).[62,89,95,99–101] Additionally, more than 50% of the bladder cancer recurrences are observed after the first year of surveillance, following a primary upper tract lesion (LOE 3).[84,86,88]

Despite the low level of evidence provided by small, single-centre, retrospective case series, the type of approach (open versus laparoscopic) apparently does not seem to influence the risk for bladder recurrence.[85,89–92]

Multiple techniques exist for resection of the distal ureter. The existing published data does not support one technique over another, but the oncologic principles seem to be universally accepted. The distal ureter needs to be completely resected *en bloc* with a 1-cm bladder cuff, while avoiding tumour spillage in the pelvis and retroperitoneum. These principles should always be applied to either nephroureterectomy or distal segmental ureterectomy. The reported rates of bladder recurrence after a nephroureterectomy, including different methods of distal ureter resection, vary between 6.7% and 50% (LOE 3).[56,88,93–95] Further discussion of the advantages and risks involved with each technique will be discussed later in this document.

Bladder recurrence rates are also similar in those lesions treated endoscopically, ranging from 17% to 47% in the main series.[86,91,96–100] There has been no reported difference in the bladder recurrence rates after endoscopic management and partial or segmental ureterectomy (LOE 3).[101]

Of the most commonly studied risk factors for development of metachronous bladder lesions after treatment for UTUC, the most significant reported factors are multifocality, tumour stage and grade, site of the primary tumour, and the volume of the disease.[60,18,84,88,92]

Most clinical guidelines recommend routine bladder surveillance, by cystoscopy and urinary cytology, after the initial treatment for UTUC. The specific surveillance schedule varies slightly among the guidelines. It is dependent on the presence of bladder tumour at diagnosis and stage and grade of the primary upper tract tumour. As most of the recurrences (80% to 90%) occur within the first 2 years of follow-up, surveillance duration is recommended more frequently for the first 2 years, lasting for at least 5 years (LOE 3).[18,31,102,103]

1.4 Diagnosis: Clinical Symptoms and Evaluation

1.4.1 Clinical symptoms

Gross or microscopic hematuria is the most common presenting symptom of patients with UTUC (70% to 80%; LOE 3).[104] Importantly, this percentage might even be higher, due to the more frequent use of anticoagulants in recent years.[105] Flank pain is the second most common symptom, occuring in approximately one-third of patients (20% to 40%).[56,106,107] This may be be related to a gradual onset of obstruction or hydronephrotic distension. Acute renal colic has also been related to the passage of clots.[106,108] A lumbar mass is present in only 10% to 20% of patients.[56,107] Upper urinary tract urothelial cell carcinoma is rarely incidentally found on radiographic examination and a minority (15%) of patients are asymptomatic at diagnosis. Consequently, nearly all UTUC cases are diagnosed during the patient's life and are infrequently found in autopsies.[109]

Hydronephrosis, diagnosed by ultrasound and/or CT scan, can be detected in 37% to 80% of patients. This finding is of clinical relevance because of its relation to adverse prognosis.[110–113] In case of the presence of systemic symptoms (weight loss, fatigue, fever, night sweats) and concomitant diagnosis of UTUC, a search for distant metastasis and evaluation of peri-operative chemotherapy regimens is recommended.[113]

1.4.2 Clinical evaluation

The initial clinical evaluation of patients suspected of having UTUC should contain clinical status with examination of the abdomen. Flank pain or palpable lumbar mass are findings that should be noticed. Further evaluations include examination of the urine, both to detect a hematuria and to examine cytology in the urine. By ultrasound, hydronephrosis or renal mass can be found, and more diagnostic steps like CT scan, cystoscopy, or ureteroscopy can be initiated.

1.4.3 Levels of evidence

Studies about clinical symptoms have been primarily retrospective. Therefore, the level of evidence is low for all symptoms. There is a lack of validation. At present there are neither randomized trials nor meta-analyses. Thus, studies that evaluated hematuria or the relation between hydronephrosis and ureter tumours and prognosis are retrospective and not validated. Therefore, the level of evidence is 3.

1.5 Molecular Biology of UTUC and the Role of Biomarkers for Prognosis

1.5.1 Introduction

There have been significant strides over the last decade in the elucidation of the molecular pathways and carcinogenesis of urothelial carcinoma of the bladder (UCB). This is due in large part to advancements in the technological methods of molecular biology. Microarrays, proteomics, and high-throughput molecular profiling have led to a basic understanding of the major pathways involved in UCB that ultimately result in the complex heterogeneity of this type of cancer. Although similar molecular methods have been applied to the study of UTUC, progress in the pathogenesis of this disease has been limited. This is due in part to the fact that the prevalence of UTUC is significantly less than that of UCB, accounting for only 5% to 10% of all urothelial carcinomas, with an estimated annual incidence of approximately 2 new cases per 100,000 in Western countries.[114] In addition, the use of various animal models for characterization of the normal development and embryogenesis of bladder urothelium has created a sustainable methodology for ultimately studying the process of tumourigenesis, the equivalent of which has been lacking in UTUC.[115] It is argued that the basic mechanisms of carcinogenesis among UCB and UTUC are likely similar. However, the epidemiological, etiological, and molecular differences that exist between these conditions create significant

divergence in the clinical approach to each. This makes these two disease processes quite distinct. Even though both entities are considered to be synchronous or metachronous multifocal diseases with similar risk factors, there are certain acquired etiologies that are associated more with UTUC than with UCB. For example, aristolochic acid–induced nephropathies, caused by either Chinese herbal medication or Balkan-endemic nephropathy, have a close to 200-fold increased risk for UTUC compared to UCB.[116] Similarly, chronic ingestion of phenacetin leads to a 6-fold higher chance of UTUC in comparison to UCB.[116] There is also strong evidence to suggest significant genetic differences, namely from the increased disposition to UTUC of patients with hereditary nonpolyposis colon cancer. This is due to mutations in genes related to the DNA mismatch repair (DNA MMR) system, which is ultimately manifested by increased microsatellite instability (MSI). While MSI is rarely encountered in UCB, it has been shown to occur in almost 15% of sporadic cases of UTUC.[47] In addition, DNA hypermethylation, which is a mechanism for gene regulation prevalent in many cancers, has emerged as another potential diagnostic factor distinguishing UTUC from UCB on the epigenetic level.[117] These key differences lend support to the fact that UTUC should be considered a separate morphologic and pathologic entity with a similar but diverging molecular biology. Further understanding of the molecular pathways of UCB will undoubtedly continue to shed light on the similar processes involved in pathogenesis of UTUC, but the key to comprehending this disease on the molecular level will be to understand its differences.

1.5.2 Molecular biology of UTUC

To date, little is known of the molecular pathways involved in the tumour initiation, progression, and spread of UTUC. As both UTUC and UCB originate in the urothelium, it can be inferred that at least some of the major molecular pathways will be common among the two. There are two distinct models for pathogenesis that lead to bladder tumour initiation. The first model is characterized by mutations in the fibroblast growth factor receptor 3 (FGFR3), human RAS (hRAS), and PI3 kinase that cause upregulation of the receptor tyrosine kinase and RAS second messengers, ultimately leading to low-grade, non-muscle–invasive papillary tumours. The second model comprises loss of function of tumour suppressor genes, namely p53, pRb, and pTEN, initiating *in situ* tumour growth followed by multiple chromosomal deletions at various sites that lead to progression and muscle invasion.[118] It is speculated that invasive UTUC may undergo a similar stepwise progression; however, given the extent of microsatellite instability seen in sporadic cases of UTUC, the loss of function of one or more genes of the DNA MMR system will likely play a pivotal role in driving the oncogenic development of this cancer.[119] There is also evidence pointing to activation of the PI3K/AKT/mTOR pathway in the development of urothelial carcinomas of the renal pelvis.[120] This may be through direct effect of activating mutations in the FGFR3 receptor or other tyrosine kinase receptors. Upregulation of the mTOR pathway may in turn promote cell growth and differentiation through a myriad of second messengers and the influence of other mitogenic pathways.[121] In addition, similar to UCB, FGFR3 receptor mutations have been also linked to lower-grade UTUC and better prognosis. Van Oers *et al.*[122] compared 117 bladder tumours with 163 UTUC tumours and found that FGFR3 mutations were more frequently associated with low-grade UCB and UTUC, and higher cancer-specific survival rates compared to wild-type genes in invasive tumours. The role of loss of function of tumour suppressor genes such as p53 in the carcinogenesis of UTUC is not clear, although it may be likely that p53 will play a similar role as seen in UCB.

1.5.3 Challenges in using biomarkers for UTUC

Biomarkers in UTUC are cell-associated molecules that are distinctively produced by the tumour and are measurable through a reproducible, valid molecular diagnostic technique in tissue, blood, or urine specimens. The primary use of biomarkers is to further diagnose, prognosticate, or detect recurrences in a readily available and non-invasive assay. In recent years, there has been a significant amount of research in detection and development of biomarkers for UCB, and more recently UTUC, mostly for the purpose of improved diagnosis or risk stratification. As is well recognized in UTUC, one of the main problems is a lack of adequate risk stratification between patients with aggressive disease and those with relatively indolent disease, with low chance for progression. As the treatment for each of these groups is vastly dichotomous and can lead to significant morbidity, there is a need for improved risk assessment using a biomarker panel. Despite this, there is no single biomarker to date that is in routine clinical use for this purpose. There are multiple barriers to the development and design of biomarkers for routine use in any cancer, which can be analytic or regulatory.[123] Given that most biomarker research is done outside the context of standard clinical trials, the reproducibility of the study results is severely limited.[124] In addition, the majority of research studies focus on using various biomarkers as independent predictors of survival or prognosis, either alone or with multiple other clinicopathologic factors in a multivariate analysis. However, small sample size and poor methodology make such conclusions difficult to achieve. The problem is compounded with regard to biomarker development for UTUC, as it is already a rare disease with limited tissue availability compared with UCB.[125] In addition, there is a lack of incorporation of the existing molecular markers shown to be significant in prognosis of UTUC into the current risk-stratification paradigms. This is likely due to a lack of consistent results and reproducibility. In order for a molecular marker to be clinically useful, one must show that adding it to an existing model, based on the most important clinical and pathologic factors, substantively improves the predictive accuracy (discrimination and calibration) of the model. As it is rare for a molecular marker to provide sufficient information to be used in and of itself, independent of other clinico-pathologic factors, further trials must begin to incorporate biomarker data into the risk-stratification schema in order to ultimately provide a clinically applicable, individualized approach to patients with UTUC.

1.5.4 Potential molecular marker categories

1.5.4.1 Mismatch repair markers

Genomic instability refers to the significant increase in a cell's mutation rate above the level of normal somatic cells. It is the main mechanism for carcinogenesis along with resistance to apoptosis. Instability can occur both at the chromosomal level or the base pair level, instigating the uncontrolled cell proliferation that leads to malignancy. A genomic defect at this level can be detected by microsatellite instability. Microsatellites are regions of DNA consisting of short repetitions in base pairs, ranging from 1 to 5 nucleotides. They are usually present in introns or other non-coding DNA sequences and can be used as markers of genetic instability.[47] Due to their often long tandem repetitive sequences, microsatellites can be quite prone to mutations as a result of various mechanisms of DNA base pair mismatch, such as slipped DNA strand mispairing.[126] The MMR system consists of the proteins hMLH1, hPMS1, hPMS2, hMSH2, hMLH3, and hMSH6, all of which act to preserve base pair sequence fidelity.[47] Loss of function of any of these proteins can result in a defective DNA MMR system that leads to multiple mutations. This can result in what is called microsatellite instability

within the coding region of target genes. The resulting frameshift mutations could render these gene products either non-functional or hyperfunctional and contribute to the cascade of uncontrolled cell growth. Such is the mechanism for HNPCC, which is the most common monogenetic predisposition form of hereditary colon cancer. It is caused by germline mutations in the hMSH2 (60% frequency), hMLH1 (30%), and hMSH6 (10%) DNA repair proteins.[127] The most common extracolonic manifestations of HNPCC include endometrial or ovarian cancer; however, UTUC occurs at a rate of 6% among these patients.[128]

Microsatellite instability, which has been identified as a surrogate marker for MMR gene mutations, has been used as a prognostic genetic biomarker in UTUC. Rouprêt *et al.*[129] showed that patients with invasive UTUC with high levels of microsatellite instability (defined as two or more loci with MSI after a polymerase chain reaction) have significantly better cancer-specific survival compared with those with low or stable microsatellite instability (defined as either one marker or no MSI, respectively). In addition, Blaszyk *et al.*[127] studied a consecutive group of 114 patients who underwent radical nephroureterectomy and found a 31.3% rate of tumours that exhibited microsatellite instability. These patients were also more prone to having additional non-urologic tumours such as colon cancer. However, in this study, only stage and grade and not microsatellite instability were independent predictors of cancer-specific survival, likely due to a small cohort. Also, another study by Rouprêt *et al.*[47] described that a number of other urologic cancers may be associated with microsatellite instability and HNPCC, including prostate and testicular cancers. This emphasizes the need for detailed family histories in cancer patients, especially those presenting at a younger age, in order to identify the small but critical subset of patients with hereditary cancers that can not only affect the index patient, but also the patient's relatives.

Recently, Ho *et al.*[130] proposed a urine microsatellite marker profile specific to UTUC using high-throughput molecular analysis. Loss of heterozygosity of primary tumours and their matched urine DNA samples were analyzed in 30 patients with UTUC, and then marker specificity was confirmed by comparing them to a cohort of 22 patients with renal cell carcinoma. A total of 83.3% (25 of 30) patients were detected using 13 different urine microsatellite markers, which were shown to be distinctly different from urine markers used to detect renal cell carcinoma. Similar high-throughput urine-based markers may be used to help positively confirm the presence of UTUC with high enough specificity and perhaps help the clinician distinguish it from renal cell cancers in difficult cases.

1.5.4.2 Cell Membrane–Associated Markers

1.5.4.2.1 Epithelial cadherin

Epithelial cadherin (E-cadherin) is the most commonly studied member of the cadherin superfamily. Epithelial cadherin is a transmembranous cell adhesion receptor and can be detected by immunohistochemistry (IHC). The protein is coded by the CDH1 gene, and its loss of function has been associated with invasion and metastasis characteristics in multiple different types of tumours.[131] Nakanishi *et al.*[132] did a preliminary study of the association of E-cadherin expression in UTUC and found that lower expression was correlated with higher tumour stage and grade in univariate analysis. In a larger study by Fromont *et al.*,[133] multiple potential biomarkers, including Ki-67, p53, p27, Survivin, MSH2, and E-cadherin were analyzed using tissue microarray in 62 patients with UTUC treated over 12 years. On multivariate analysis, lower expression of E-cadherin along with age and stage were found to be independent factors for prognosis and recurrence. The study also suggests that using

E-cadherin expression for invasive UTUC may be of little advantage, as this is already associated with a poor prognosis, but may alternatively be used as a biomarker to identify the subset of non-invasive UTUCs that are likely to recur and/or invade in a more aggressive manner.

1.5.4.2.2 L-type amino acid transporter1

L-type amino acid transporter1 (LAT1) is a family of transmembranous sodium-independent cell membrane proteins responsible for the transport of neutral amino acids. It provides cells with essential amino acids for cell growth and cellular responses. It requires covalent association with the heavy chain of 4F2 (4F2hc) for its functional form, which is a cell surface antigen associated with multiple transmembrane proteins.[134] In a study examining the expressions of LAT1 and 4F2hc in 124 cases of UTUC using IHC, positive expressions were recognized in 79.8% and 89.5% of tumour samples.[135] In all tumours, a cooperative expression of LAT1 protein and 4F2hc protein was significantly correlated with both overall and disease-free survival rates in the univariate analysis, but not in the multivariate analysis. The authors concluded that the detection of the active form of LAT1 protein would appear to be of value in informing the risk for progression in UTUC.[135] Clearly, further studies on the utilization of this cell membrane protein need to be done.

1.5.4.2.3 Uroplakins

Uroplakins (UP) are a family of four cell-surface receptor proteins, consisting of UP Ia, Ib, II, and III. They are ubiquitous in urothelial cells. In normal mammalian urothelium, uroplakins are expressed in the superficial umbrella cells with a very large extracellular domain that spans intraluminally.[136] Although the function is not fully understood, uroplakins are thought to be a structural component of the asymmetric unit membrane (AUM). It is a highly specialized biomembrane elaborated by terminally differentiated urothelial cells that contribute to the permeability barrier function of the urothelial apical surface. Uroplakins aggregate on the apical surface of cells to form plaques under electron microscopy, and they may also play an important role in regulating the assembly of the AUM.[137] Wu *et al.*[138] reported on the expression of UPII in UCB and found that 39.5% expressed UPII, whereas squamous cell carcinoma of the bladder expressed this membrane protein. Additonal studies have found that expression of the uroplakin gene in urothelium that has undergone malignant transformation is severely reduced or absent.[139] These studies suggest that not only uroplakin may be used as a cytodifferential marker, but also loss of uroplakin may indicate malignant transformation potential of urothelial cells. To further characterize this in UTUC, 71 patients who had undergone radical nephroureterectomy, with a mean follow-up of 61 months, were evaluated by IHC for expression of UPIII.[137] Expression was found in 75% of patients with pT1 staging or less and in 65% or grade 1 through 2 tumours or less. Conversely, patients with higher stage or grade (pT2 or greater, grade 3) had only 40% and 33% UPIII expression. The cancer-specific survival of patients with loss of UPIII expression was significantly worse than those with positive expression. This study is interesting in that previous studies of UPIII expression in UCB showed no association with survival,[140] which may provide insight into a molecular link that explains the more aggressive nature of UTUC compared to UCB. Uroplakin III marker could potentially be used for differentiation and designation of more aggressive forms of UTUC in the future.

1.5.5 Angiogenetic factors

1.5.5.1 Hypoxia-inducible factor 1α

Hypoxia-inducible factor 1α (HIF-1α) is the alpha subunit of a highly conserved heterodimer nuclear transcription factor that plays a role in many different types of cancers, including urothelial malignancies. In normal oxygen level conditions, the alpha subunit of HIF-1 protein is hydroxylated, which allows the binding of the vHL protein to this complex.[141] However, in hypoxic conditions, HIF-1α binds to its β subunit and translocates into the nucleus where it acts as a transcription factor to upregulate a multitude of angiogenetic factors, including vascular endothelial growth factor (VEGF). As many malignancies often progress in a setting of tumour hypoxia, HIF-1α has been implicated as the primary driver of angiogenesis, including UTUC. In a study of 127 patients with UTUC testing for the expression of messenger RNA and protein, HIF-1α expression was found in 55.1% and was undetectable in normal urothelium.[141] It was also found to be an independent predictor of tumour grade, cancer-specific survival, and overall survival, but not stage.[141] A similar study of 98 patients also confirmed overexpression of HIF-1α to be an independent predictor of lower disease-free and cancer-specific survival.[142]

1.5.6 Cell cycle–associated markers

The cell cycle is a series of regulated steps that governs cellular proliferation. Progression through the cell cycle is mediated in part by the buildup of cyclins, proteins that activate cyclin-dependent kinases (cdks). Cyclin-dependent kinases can phosphorylate a number of tumour suppressor genes that allow for the cell to enter S phase of DNA replication. Cyclin-dependent kinase inhibitors such as p21 and p27 act as brakes on cell cycle progression, and the p53 protein serves as the "guardian of the genome" by inducing multiple mechanisms of cell cycle arrest after cell stress.[143] Mutations of cell cycle regulatory genes are the most common genetic alterations found in human cancer, including UTUC.

1.5.6.1 Cyclin-dependent kinase inhibitor p27

Cyclin-dependent kinase inhibitor p27 operates mostly during the G1 cell cycle arrest phase and acts to halt progression to the synthesis phase in the event of cellular stress. Kamai *et al.*[144] evaluated the prognostic significance of p27 in 37 patients by IHC and found lower levels of expression to be associated with poorer disease-free survival. However, other studies have grouped p27 with multiple other cell cycle– and apoptosis-related biomarkers in tissue microarray studies and found no significant prognostic value.[133] As with many of these biomarker studies, different methodologies and molecular techniques, in addition to small sample sizes, undoubtedly influence outcomes.

1.5.6.2 Antigen Ki-67

Antigen Ki-67 is a cellular marker of proliferation. Although its precise function is not known, it is present in all phases of the cell cycle (G1, S, G2), but not in the senescent phase (G0). There have been multiple studies investigating the prognostic association of Ki-67 in UTUC. Jeon *et al.*[145] showed that Ki-67 overexpression predicted advanced tumour stage and grade, and was found to be an independent predictor of progression-free and disease-specific survival. Two other single-centre studies were unable to demonstrate the independent significance of altered Ki-67.[133,146]

Interestingly, Ki-67 was also found to be a predictor of synchronous and metachronous UCB in patients diagnosed with UTUC, although the cohort studied consisted of only 38 patients.[147]

1.5.6.3 Tumour suppressor gene p53

Tumour suppressor gene p53 is the most common tumour suppressor gene found to be mutated in human cancers. Its main function is to regulate cell cycle progression through a myriad of pathways by halting the cycle at the G1/S regulating point, induce expression of DNA repair mechanisms, and ultimately induce apoptosis.[143] There have been many studies demonstrating loss of heterozygosity in UCB; a meta-analysis of the role of p53 in bladder cancer found 117 studies including 10,026 patients, with sample sizes ranging from 12 to 270 patients.[148] Two systematic reviews of the role of p53 in UTUC were conducted. The first was a meta-analysis of the published literature that investigated p53 expression and its effects on UTUC prognosis. Among seven papers that met criteria for review, a total of 514 patients with a mean number of 73.4 patients per study were included. When only unadjusted survival data were analyzed among the studies, p53 overexpression appeared to be a significant prognostic factor, although the assays and thresholds for overexpression that were used varied widely among the studies.[149] Another paper reviewing all available publications regarding p53 expression in UTUC in a less rigorous fashion noted 24 studies on the subject. Among these, expression of p53 was a significant univariate prognostic marker in 12 publications; however, multivariate analysis demonstrated that p53 expression is of independent prognostic significance in only five studies, all of which contain potential statistical bias according to the review.[150] It is clear that larger, prospective, multi-institutional studies are necessary to definitively ascertain the role of p53 as a prognostic biomarker in UTUC.

1.5.7 Epigenetic mechanisms

There has been significant recent interest in the epigenetic mechanisms involved in carcinogenesis. Epigenetics refers to gene modifications that occur without alteration of the genetic sequence, and include chromatin ultrastructure modification, gene splicing, and DNA methylation. The latter process and its potential for prognostication as a biomarker has been studied in urothelial cancers. This epigenetic mechanism occurs widely through cancerous cells and always affects the same promoters. When a promoter is methylated, the gene is silenced. If promoters of tumour suppressor genes are hypermethylated, it can result in aberrant cell activity that can promote carcinogenesis.[116] Although this mechanism has been studied to some degree in UCB, very few studies have demonstrated its role in UTUC. Catto *et al.*[117] found that promoter hypermethylation was present in 86% of UTUC samples studied and occurs more extensively compared to UCB. Methylation was also associated with advanced tumour stage and grade, and higher tumour progression and tumour-specific mortality compared to unmethylated UTUCs. Many of the similar foci of promoter methylation in UTUC compared with UCB were studied, including death-associated protein kinase, human mutL homolog 1, E-cadherin, p16, and methylated in tumor loci 31 genes. Larger-scale screening of abnormal epigenetic events are needed to identify the epigenetic fingerprints specific to all types of urothelial carcinomas.

1.5.7.1 Cytogenetic markers

Fluorescence *in situ* hybridization (FISH) has been widely used to detect and monitor UCB. Similar studies with UTUC have demonstrated that the FISH assay on chromosomes 3, 7, 9, and 17 improves the sensitivity of urine cytology in the diagnosis of UTUC, while maintaining a similar specificity.[151]

However, it is unclear as to whether a positive FISH for the detection of UTUC can lead to less invasive diagnostic methods such as ureteroscopy, especially as this modality allows for detection and sampling of the upper tract lesion with high sensitivity and specificity. Recently, a cohort of 33 patients with UTUC were investigated with hyperploidy at chromosomes 3, 7, and 17, and loss of 9p21 loci and stratified according to grade, stage, and other clinicopathologic characteristics.[152] Seven tumours were low grade, and the remaining were high grade. There was a statistically significant relationship between an increase in the percentage of hyperploidy and higher grade in the tumour specimen for each chromosome. There was no significant association with stage. Based on these studies, it remains to be seen whether there will be a significant role for FISH in not only the diagnosis but also the prognosis and risk stratification of UTUC.

1.5.8 Levels of evidence

At this time, studies in molecular markers have been primarily single-centre, retrospective studies. The ICUD has published a review on grading guideline recommendations and levels of evidence after discussions with the Oxford Group. They noted that application of levels of evidence/grades of recommendation for diagnostic techniques is much more complex than for interventions. "The ICUD recommend that, as a minimum, any test should be subjected to three questions: (1) Does the test have good technical performance, for example, do three aliquots of the same urine sample give the same result when subjected to "stix" testing? (2) Does the test have good diagnostic performance, ideally against a "gold standard" measure? (3) Does the test have good therapeutic performance, that is, does the use of the test alter clinical management, does the use of the test improve outcome?

As one can discern from the discussion above, most markers have been studied in small cohorts and have not been validated, and there are few meta-analyses.

Only p53 has been studied relatively extensively, with two systematic reviews conducted on the role of p53 in UTUC.[149,150] There is level 3 evidence that p53 overexpression appears to be a significant prognostic factor, although the assays and thresholds for overexpression used varied widely among the studies.[149] The other review included 24 studies on role of p53 in UTUC, but p53 expression had independent prognostic significance in only five studies, all of which contained potential statistical bias according to the review.[150] Other markers were not studied sufficiently to justify any level of evidence, and overall, no recommendation can be made for using markers at this time for management of UTUC.

Prior to application of markers for clinical use, there needs to be prospective studies that demonstrate a clinical benefit.

1.5.9 Conclusion

Upper tract urothelial carcinoma, like UCB, is a heterogeneous and highly complex disease, the study of which is made significantly more challenging due to its rarity. The advent of improved techniques in molecular biology will lead to a more central role for molecular biomarkers in the detection, prognosis, risk stratification, and potential treatment options for this disease. However, this field is in its infancy. Using high-throughput molecular techniques, further large, multicentre trials are necessary

to not only ascertain use of a panel of biomarkers for prognostication, but also to incorporate these panels into current diagnosis and treatment algorithms in a meaningful way. Upper tract urothelial carcinoma remains a deadly disease, and a significant amount of work is needed to use the currently identified molecular targets and turn them into true biomarkers that can impact the survival of patients with this disease.

1.6 Tumour Location and Distribution

1.6.1 Diagnosis

Upper tract urothelial carcinoma represents only about 5% of all urothelial tumours. Upper tract tumours can occur as primary tumours and can also develop in patients with bladder cancer that has been treated either locally or radically. The scarcity of this disease and the near absence of randomized controlled trials in this field render any level of evidence presented 2 at best.

Accurate determination of tumour location, including renal pelvis or upper, mid, or lower ureter, as well as accurate determination of tumour laterality and multifocality are important for several reasons. Any impact of tumour location on survival may influence decisions on peri-operative chemotherapy in patients with UTUC. In addition, tumour location and laterality play an important role in how patients with upper tract tumours are followed up, and this is particularly true in patients that undergo conservative endoscopic treatment.

1.6.2 Tumour location: frequency and laterality

It is estimated from several large retrospective cohorts assessing oncologic outcomes after RNU, as well as studies specifically looking at the impact of tumour location on oncologic outcomes after RNU, that the frequency of renal pelvic tumours is about 1.5 to 2 times that of ureteral tumours (LOE 3). In a large study by Munoz and Ellison[3] on 9,072 cases of UTUC from the Surveillance, Epidemiology and End Results (SEER) registry, 59.5% were renal pelvic tumours and 40.5% were ureteric tumours. More recently, Lughezzani *et al.*[153] reported on 2,299 patients from the SEER registry that underwent RNU or segmental ureterectomy for UTUC, with 61.9% having renal pelvic tumours and 38.1% having ureteric tumours. In a multi-institutional series, Margulis *et al.*[2] reported on the outcomes of 1,363 patients that underwent RNU at 12 institutions, with 64.4% of patients having renal pelvic tumours and 35.6% of patients having ureteric tumours. Other large series studying outcomes after RNU report similar results, with the incidence rate of renal pelvic tumours between 65.1% and 65.9%, versus the incidence rate of ureteric tumours between 34.1% and 34.9% (LOE 3).[154,155]

On the other hand, some studies also report on tumour multifocality in addition to location. Walton *et al.*[29] reported on 773 patients, with 53.1% having renal pelvic tumours, 30.5% having ureteric tumours, and 6.2% having both renal pelvic and ureteral tumours. Similarly, Ariane *et al.*[156] found that among 609 patients, 52% had tumours in the renal pelvis, 30.4% in the ureter, and 17.6% had both. Yafi *et al.*[157] reported on 673 patients, with 59% of tumours renal pelvic, 34% ureteric, and 7%

multifocal (LOE 3). Finally, in the only prospective randomized trial comparing laparoscopic to open RNU, Simone *et al.*[158] reported on 80 patients, with 36.3% having renal pelvic tumours, 40% having ureteric tumours, and 23.8% having both (LOE 2).

Several studies have also reported on the laterality of UTUC, with data suggesting an almost equal distribution of right-sided versus left-sided tumours (LOE 3). In the study by Simone *et al.*,[158] 51.2% of patients had right-sided tumours and 48.8% had left-sided tumours. In a study by Secin *et al.*,[159] evaluating lymph node dissection in 252 patients with UTUC, 52.4% of patients had right-sided tumours whereas 47.6% of patients had left-sided tumours. Similarly, other studies have shown the incidence of right- versus left-sided tumours ranging from 48.8% to 49.4% versus 50.6% to 51.2%, respectively (LOE 3).[160,161]

In addition to reporting on tumour location, multifocality, and laterality, some authors have also reported on the distribution of UTUC within the ureter in patients with ureteral tumours. Li *et al.*[161] reported on 127 patients with ureteral tumours, with 31.5% having tumours in the proximal ureter, 31.5% in the mid-ureter, and 37% in the distal ureter. Similarly, Raman *et al.*[86] also showed that the incidence of ureteral tumours may be higher than those of the distal ureter. Of 103 patients in that study, 51 had ureteral tumours, with 21.6% in the upper third, 19.6% in the mid third, and 58.8% in the lower third of the ureter.[86] Others have reported a distal ureteral tumour rate as high as 67.7% in patients with ureteral tumours.[60] Albeit with a small number of patients, several studies investigating the ureteroscopic and percutaneous management of UTUC also reveal the preponderance of distal ureteral tumours.[162,163] Recently, Cutress *et al.*[184] reported on 73 patients, with 50 having ureteral tumours. Of those, 82% were distal, with the remaining 12% equally distributed between upper and mid-ureter (LOE 3).[163] These studies invariably select patients with comorbidities and favourable tumour characteristics and may not be reflective of the distribution over the entire UTUC patient population (LOE 3).

1.6.3 Tumour location: prognosis

Early, retrospective, single-institutional studies reported that ureteric tumours have a worse prognosis than renal pelvic tumours.[59,60,164] Zigeuner *et al.*[165] also showed that patients with ureteral tumours have a higher chance of subsequently developing bladder cancer (risk ratio: 2.0, p=0.02). In addition, Cosentino *et al.*[166] recently demonstrated that tumour location is also a predictor for concomitant bladder cancer. Park *et al.*[167] demonstrated the prognostic significance of ureteral tumour location in patients with pathologic T3 disease, suggesting a protective role for renal parenchyma in this subgroup of patients. Furthermore, two recent large, retrospective, multi-institutional studies have also demonstrated worse survival in patients with ureteral tumours.[157,168] In contrast, conflicting evidence from several other large multi-institutional series suggests that tumour location loses its prognostic impact after adjusting for tumour stage. [58,169,170,171–174] In spite of this, the European Association of Urology (EAU) guidelines recently identified that tumour location remains a prognostic factor in patients with UTUC.[175] Taken all together, definitive prognostic impact of tumour location (renal pelvis versus ureter) on patients with UTUC remains controversial (LOE 3). Whether multifocality within the ureter or renal pelvis is the main driver of outcome requires further evaluation and may explain the conflicting results on the impact of tumour location in the literature.

1.6.4 Tumour multifocality: prognosis

Multifocal tumours are those that arise in at least two distinctive locations within the upper urinary tract. Pathologic tumour multifocality can be reported in up to 50% of patients.[16] Brown *et al.*[176] and Novara *et al.*[160] initially demonstrated the prognostic significance of tumour multifocality in patients with UTUC, with the latter revealing a higher risk for cancer-specific mortality in patients with multifocal tumours. This was further validated by several more recent multi-institutional studies.[157,168,170,177,178] Furthermore, Xylinas *et al.*[16] recently reported tumour multifocality as an independent predictor for subsequent intravesical recurrence. This data strongly suggests that tumour multifocality is associated with worse outcomes in patients with UTUC and that it should be routinely reported by pathologists (LOE 3). Interestingly, none of the studies evaluated the extent of multifocality on outcome.

1.6.5 Concomitant CIS: prognosis

There is considerable variability in the reported incidence of concomitant carcinoma *in situ* (CIS) in patients with UTUC, ranging from as low as 5.9% up to 35.4%, in part due to pathologic reporting inconsistencies.[2,16,179] Pieras *et al.*[179] demonstrated that patients with pathologic concomitant CIS had a higher rate of subsequent bladder recurrences. More recently, both Otto *et al.*[180] and Wheat *et al.*[181] reported on the prognostic impact of pathologic concomitant CIS, demonstrating higher recurrence rates and cancer-specific mortality in patients with concomitant CIS. Therefore, the presence of concomitant CIS should be reported, as it may be associated with higher recurrence rates, necessitating more diligent surveillance (LOE 3).

On the other hand, pure CIS of the upper tract is a rare entity. Some studies group pathologic CIS with non-muscle–invasive disease.[154–156,168,174] Others report no incidence of pathologic pure CIS.[153,158,169,172] In a series of 1,363 patients, the incidence of pure pathologic CIS was 2.1%,[2,182] with 65% in the ureter and 35% in the renal pelvis. Walton *et al.*[29] reported the incidence of pure pathologic CIS in their cohort of 773 patients at 1.2%. Yafi *et al.*[157] reported a pure pathologic CIS rate of 1.2% in their cohort of 637 patients. Both do not comment on CIS location. Other studies have reported pure CIS rates ranging from 1.9% to 4% (LOE 3).[58,60,171]

1.6.6 Location, multifocality, and bladder recurrences

The reported incidence of bladder recurrences following treatment for UTUC varies considerably in the literature, ranging from 10% to 50%.[16,18,60,82,87,184,185] In fact, a recent study from the SEER registry by Kates *et al.*[185] identified a bladder recurrence rate as low as 4.6%. Although some studies revealed a correlation between tumour location and intravesical recurrence,[165,184] others found no association.[86,88,90,186] On the other hand, UTUC multifocality has has been shown in several studies to be prognostic of intravesical recurrence, and it is the most commonly reported risk factor associated with bladder recurrences following treatment for UTUC (LOE 3).[15,16,18,86,88]

1.6.7 Tumour histology

Urothelial carcinomas make up 90% to 95% of upper tract tumours, with other non-urothelial subtypes including squamous cell carcinoma (7%–10%), adenocarcinoma (1%), small cell carcinoma (<1%), and sarcoma (<1%).[175] In addition to non-urothelial subtypes, a variety of histologic variants of UTUC have been reported, and in fact, all histologic variants described in the upper tract have also been noted in the bladder. These histologic variants of the upper tract are more common than non-urothelial tumours of the upper tract and are usually associated with high-grade tumours.[175,187] In a recent multicentre study by Rink *et al.*[187] looking at 1,648 patients that underwent RNU, 25% were found to have variant histology, with 100% of those having high-grade disease. In a clinicopathologic study of 108 patients with UTUC by Perez-Montiel *et al.*,[188] up to 40% of cases were found to harbour variant histology. Histologic variants of UTUC that have been described include squamous cell, glandular, sarcomatoid, micropapillary, small cell, and plasmacytoid cancers, and patients may also present with multiple variants. The most common variants are squamous cell then glandular cancer.[213,214] In their study on 1,648 patients, Rink *et al.*[187] found no difference in survival on multivariate analysis for patients with variant histology compared to those with pure urothelial pathology. Studies assessing survival in patients with non-urothelial pathology reveal a poor prognosis for patients with non-urothelial carcinoma, usually owing to advanced stage at diagnosis. However, stage for stage, prognosis does not seem to be different between patients with urothelial versus non-urothelial pathology (LOE 3).[189,190]

1.6.8 Summary

- In patients with UTUC, renal pelvic tumours are almost twice as common as ureteral tumours. There is an equal distribution of right-sided versus left-sided tumours.
- In patients with ureteral tumours, distal tumours are more common.
- Although ureteral tumours appear to have a worse prognosis, definitive prognostic impact of tumour location remains controversial; however, tumour multifocality is prognostic and also associated with higher intravesical recurrences.
- Several variants of UTUC exist. Non-urothelial upper tract pathology is rare.

1.7 Progression and Metastasis

1.7.1 Diagnosis

From a large population-based database including 13,800 patients from the SEER registry diagnosed with UTUC between 1973 and 2005, Raman *et al.*[7] concluded that throughout the study period, there was an increase in the overall incidence of UTUC from 1.88 to 2.06 cases per 100,000 person-years. This was associated with an increase in the incidence of ureteral disease (0.69 to 0.91) and a slight decrease in the incidence of renal pelvic disease (1.19 to 1.15). In this study, the percentage of *in situ* tumours (Ta/Tis) increased from 7.2% in the first 10 years to 31.0% in the last 10 years of the study period. This was associated with a significant reduction in T1/T2 tumours from 50.4% in the first 10 years to 23.6% in the last 10 years ($p<0.001$). This data indicates a relative stability in the

incidence of organ-confined disease (*in situ* and local). Although small, there was a statistically significant increase in the proportion of regional disease (T3/T4) diagnosed throughout the study period (33.7% to 36.3%, p=0.003). Despite these changes, however, there was no significant difference in the percentage of patients presenting with distant metastasis, with the proportion of patients with distant disease ranging from 8.0% to 9.2% over the three decades (LOE 3).[7] Similarly, in a recent study by David *et al.*[191] on 25,228 patients from the National Cancer Data Base diagnosed with UTUC, the authors investigated trends in stage and grade migration from 1993 to 2005. They report that there was an increase in the proportion of early-stage tumours (Tis/Ta/T1) throughout the study period (renal pelvis 44% to 48%, p=0.06; ureteral 52% to 57%, p=0.08). This was accounted for by an increase in Ta renal pelvic tumours from 10.5% to 23.2% (p<0.001) and a concomitant decrease in T2 tumours from 18.7% to 8.7% (p<0.001). The increase in early-stage ureteral tumours was also accounted for by an increase in Ta tumours from 12.7% to 30.7% (p<0.01) and a decrease in T2 tumours from 21.9% to 16.1% (p<0.01). Notably, the proportion of T1 tumours in both the renal pelvis and ureter decreased from 1993 to 2005. Furthermore, there was also an increase in the proportion of high-grade disease throughout the study period, with the incidence of high-grade renal pelvic tumours increasing from 38.2% to 49.6% (p<0.001) and the incidence of high-grade ureteric tumours increasing from 44.5% to 53.0% (p<0.001) (LOE 3).[191]

Only two other recent population-based studies were identified in the literature that described trends in the incidence of UTUC. Munoz and Ellison[3] previously studied 9,072 patients from the SEER registry diagnosed with UTUC between 1973 and 1996, and revealed an increase in the incidence of ureteral tumours (0.69 to 0.73 per 100,000 person-years) as well as an increase in the proportion of *in situ* tumours (7.2% to 23.1%) throughout the study period. Again, no change was noted in the incidence of distant disease (8.5% to 8.0%). A population-based study out of Denmark by Mellemgaard *et al.*,[5] covering epidemiological trends over 45 years, revealed a 10-fold increase in the incidence of UTUC, although the absolute incidence of disease was lower than what was observed from SEER (LOE 3).

Multiple surgical studies have shown that at least 50% of patients with UTUC present with muscle-invasive disease. Lughezzani *et al.*[153] reported on 2,299 patients from the SEER registry treated with nephroureterectomy or segmental ureterectomy, with 67.3% having muscle-invasive disease. Several multi-institutional series studying oncologic outcomes after RNU also report on the proportion of pathologic muscle-invasive disease, with the incidence rate ranging from 49.6% to 55.9%.[2,29,154–156] In the only randomized controlled trial comparing laparoscopic to open RNU, Simone *et al.*[158] reported on the oncologic outcomes of 80 patients, with 60% having pathologic muscle-invasive disease (LOE 2). This is, however, in stark contrast to urothelial carcinoma of the bladder, where the reported incidence of patients presenting with muscle-invasive disease is between 15% and 25%.[192] Importantly, unlike population-based studies, this aforementioned data is skewed toward the surgical patient population of UTUC; as such, it does not cover the whole spectrum of UTUC, as neither patients treated with conservative management nor patients presenting with metastatic disease and treated with chemotherapy are included.

Upper tract tumours can spread via hematogenous and lymphatic routes, as well as by direct extension to adjacent structures. Due to the scarcity of UTUC, only one recent study was identified in the literature looking at pathologically confirmed metastatic UTUC following definitive therapy. In

2011, Shinigare *et al.*[193] reported on 52 patients with pathologic stage T2 to T4 UTUC and identified the lymph nodes as the most common site of metastasis (75%). This was followed by lung (65%), liver (54%), bone (39%), and peritoneum (19%). Furthermore, abdominal lymphadenopathy was the most common lymph node metastatic site (69%), followed by mediastinal (35%) and then pelvic lymphadenopathy (21%). In this study, the median time from diagnosis to pathologically proven metastasis was 7 months (LOE 3).[193] In their single-centre study, Brown *et al.*[176] looked at recurrence of tumour in 184 patients who underwent RNU. The most common metastatic sites in 20 patients who did experience distant metastasis were the liver (40%), followed by lung (29%) and then bone (23%).[176] In addition, in a prospective study on 80 patients undergoing laparoscopic versus open RNU, Simone *et al.*[158] reported on the metastatic pattern of 17 patients in whom disease did recur. The most common site of metastasis was bone (41%), followed by lymph nodes (24%), lung (18%), and liver (12%). Furthermore, in their study on 252 patients that underwent RNU, Secin *et al.*[159] reported a difference in the lymph node metastatic sites between right-sided and left-sided tumours. The most common lymph node metastatic sites among patients with right-sided UTUC were paracaval (33.3%), then retrocaval (25%), followed by precaval, hilar, interaortocaval, retroperitoneal, and peri-ureteral (8.3% each). On the other hand, the most common lymph node metastatic sites for left-sided UTUC were paraaortic (52.4%), then hilar (28.6%), followed by mesenteric (9.5%), and interaortocaval and pelvic (4.8% each) (LOE 3).[159]

1.7.1.1 Outcomes of urothelial carcinoma of upper tract versus bladder

There is limited data comparing outcomes of patients with upper versus lower UTUCs, with studies revealing conflicting results. In the largest multicentre study to date, Rink *et al.*[6] retrospectively assessed the outcomes of 4,335 patients with urothelial carcinoma of the bladder, 1,615 patients with renal pelvic urothelial carcinoma, and 877 patients with ureteral urothelial carcinoma, all of whom underwent radical surgery. Patients with bladder urothelial carcinoma were found to have worse pathologic features. For patients with non-muscle invasive disease, bladder cancer patients had worse outcomes compared to patients from both the ureteral and renal pelvic tumour groups. For patients with T2 and T3 disease, there was no difference among all groups. For patients with T4 disease, those with upper tract tumours had worse outcomes (LOE 3).[6] In a smaller single-centre, retrospective review of 280 patients, Moussa *et al.*[194] also revealed that bladder cancer patients had worse pathologic features. However, when stratifying patients by stage, outcomes were similar between patients with bladder versus upper tract urothelial carcinoma (LOE 3). Catto *et al.*[195] revealed similar outcomes when stratifying patients by stage; however, in their retrospective review of 425 patients, those with upper tract tumours had worse pathologic features (LOE 3). Potential differences in stage-specific outcomes between patients with upper versus lower UTUCs may highlight the need for individualized treatment for all patient groups.

1.7.2 Summary

- Population-based studies reveal an increase in the incidence of low-stage tumours (Ta and Tis).
- The most common sites of distant metastasis are lymph nodes, liver, lung, and bone.
  - This observation is affected by whether a lymphadenectomy is performed.
- Right-sided tumours have different sites of lymph node metastasis than left-sided tumours.

1.8 Evaluation and Staging

1.8.1 Radiological evaluation

The majority of upper urinary tract tumours are detected primarily by radiologic procedures, such as retrograde pyelography, excretory urography, CT urography, and MR urography. Probably the first retrograde attempt for a visualization of the upper urinary tract was undertaken by Tuffier in 1897. Schmidt and Kolischer published the first pyelographic images in 1901.[197] Fritz Voelcker and Alexander von Lichtenberg incidentally performed the first complete outline of the ureter and renal pelvis in a radiogram in 1905.[198] While making radiographs of the bladder using colloidal silver, they noticed that the silver solution had entered the ureter and renal pelvis. One year later they succeeded in their first deliberate attempt to produce a retrograde pyelography with the help of a ureteral catheter. They noticed that "since it is not possible even with the highest pressures to force a fluid from the bladder into the ureters and the renal pelvis, it is necessary to force a path into the renal pelvis by means of the insertion of a ureteral catheter." The basic technique was born, but the instillation agent changed several times from then on: oxygen and carbon dioxide as negative contrast, silver oxide, and silver iodide.[199] Finally, in 1918, iodide salts were selected due to their property of selectively absorbing x-rays in combination with their similar osmotic pressure to concentrated urine. Furthermore, it was the least hypertonic agent of all the various tested substances.

Although retrograde pyelography permitted an accurate examination of the urinary tract, the procedures themselves were still invasive and painful. In 1923, Osborne and Rowntree initially published on the principles of excretory pyelography.[200] They used sodium iodide, both orally and intravenously. From this point onward, excretory urography (EU) became the most widely used technique for examining the upper urinary tract.

The EU is a radiographic examination of the urinary tract using intravenous water-soluble iodinated contrast media in conjunction with plain radiographic and possibly tomographic images. Typically, it includes an abdominal radiograph before intravenous administration of the contrast media, followed by sequential radiographs. The goal of EU is to detect anatomical and physiological abnormalities of the urinary tract. The following are accepted indications for EU, as delineated by the American College of Radiology guidelines published in 2010[201]:

- To evaluate the presence or continuing presence of suspected or known ureteral obstruction.
- To assess the integrity of the urinary tract status post-trauma (including iatrogenic interventions), particularly in situations in which cross-sectional imaging is unavailable or inappropriate.
- To assess the urinary tract for suspected congenital anomalies, particularly in situations in which cross-sectional imaging is unavailable or inappropriate.
- To assess the urinary tract for lesions that may explain hematuria or infection. In particular, EU may be used to evaluate for an underlying parenchymal mass or may be used to evaluate for a lesion of the urothelial tract in settings in which cross-sectional imaging is unavailable or inappropriate.

The appearance of upper tract lesions on EU has been well described. The patterns of abnormalities include the following[202]:

1. Filling defects in the renal collecting system (single or multiple, smooth or irregular, and sometimes stippled, which may be due to contrast medium caught in the tumour's papillary fronds).
2. Filling defects in a distended calyx secondary to obstruction when there is a tumour in the infundibulum; calyceal amputation is seen when this obstruction is complete.
3. Filling defects in the ureter with or without proximal hydroureteronephrosis.

For several decades, intravenous EU remained the standard for exploring the upper urinary tract. Due to the procedure's inability to facilitate further staging, EU has been increasingly replaced by advanced examination techniques, such as CT and MR urography (LOE 3). Computed tomography urography is defined as a diagnostic examination optimized for imaging the kidneys, ureters, and bladder that involves the use of multidetector CT with thin-slice imaging, intravenous administration of a contrast medium, and imaging in the excretory phase.[203] The indications for CT urography include the investigation of hematuria, complex urinary tract infections, hydronephrosis, chronic symptomatic urolithiasis, traumatic and iatrogenic ureteral injury, and patients at increased risk for UTUC. Multislice-Detector Computed Tomography (MDCT) urography became the new gold standard for tumour detection, as it enables near-isotropic high-quality multiplanar image reconstruction (LOE 3).[204] Prior to the advent of helical CT and MDCT, the performance of CT urography was suboptimal, with a sensitivity of only 50%.[108] Polypoid lesions smaller than 3 mm are detected with a sensitivity of 40%, lesions between 3–5 mm with 89%, and lesions between 5–10 mm with 89% and a specificity of 99%. The main early difficulty was the identification of flat lesions, which remained undetectable until they developed into massive infiltrations. Multislice-Detector Computed Tomography urography can also detect the thickening of the wall of the renal pelvis or ureter as a sign of UTUC, and also enables the assessment of peri-ureteric and renal parenchymal tissue, as well as regional nodal status. However, despite meta-analyses of published literature on pooled sensitivities and specificities on both measures, no randomized prospective data comparing CT urography with EU have been published until now. Furthermore, any x-ray examination should be performed with the minimum radiation dose, according to the "as low as reasonably achievable" principle. For this reason, the diagnostic quality of CT urography still does not preclude the application of EU.

Magnetic resonance imaging (MRI) urography is an evolving technique. It is indicated in patients who cannot be subjected to an MDCT urography or excretory urography, because of renal dysfunction, for example (LOE 3).[205] However, it remains contraindicated in selected patients with severe renal impairment (<30 mL/min creatinine clearance) due to the risk for nephrogenic systemic fibrosis. The detection rate with MRI is 75% after contrast injection for tumours <2 cm.[206] Magnetic resonance imaging without contrast is less helpful compared to MDCT urography in diagnosing upper urinary tract tumours, due to lower diagnostic accuracy, higher cost, and lower patient acceptance

(LOE 4). Magnetic resonance imaging urography suffers from the limitation of poorer spatial resolution than CT urography. Furthermore, it is known that there are various artifacts, including motion artifacts from breathing and peristalsis, which limit the current clinical importance of MRI.

The use of positron emission tomography (PET)/CT in this context is not established, and mainly case reports have been published (LOE 4).

1.9 Endoscopic Evaluation

1.9.1 Background and objective

Flexible ureteroscopy (URS) allows exploration of the ureter and entire intrarenal collecting system in 78% to 95% of patients (LOE 3).[207] By these means, it has become a valuable tool for assessing the tumour by direct inspection and concomitant biopsy.

The main goal of endoscopic evaluation in UTUC is to optimize diagnosis and staging. The latter is especially relevant when considering an organ-preserving approach in the context of an increasing trend for reducing treatment invasiveness and morbidity in appropriately selected patients and not limited to those with solitary kidneys.

1.9.2 Role as diagnostic and staging tool

In addition to providing diagnostic confirmation, direct tumour visualization also allows for assessment of tumour morphology and size. Therefore, endoscopic evaluation is especially relevant when there is diagnostic uncertainty, which is frequently the case with filling defects <5 mm on CT urography. However, correlation of morphology with tumour stage and grade is less accurate. Williams *et al.*[208] found a correlation of only 41% of ureteroscopic appearance in predicting invasive disease in a single-centre series of 46 patients (LOE 3). Meanwhile, another small series by El-Hakim *et al.*[209] showed that simple inspection was able to predict 71% of low-grade tumours and 80% of high-grade tumours (LOE 3). This raises the need for further staging tools, such as selective cytology and histological examination, as an adjunct to URS. Ureteroscopy also serves as an adjunct to performance of a retrograde pyelogram. However, correlation of its findings with UTUC stage and grade is poor. Thus, it is currently not recommended as part of the upper tract tumour workup (LOE 3).[208]

Cytology is less sensitive for UTUC than for bladder cancer, even for high-grade tumours.[210,211] Although selective cytology has been shown to improve diagnostic accuracy of UTUC when compared to that obtained by voided urine, with sensitivity of up to 71% for high-grade disease and 78% for muscle-invasive tumours in a large multicentric study, it has limited accuracy for staging and grading of UTUC on its own (LOE 3).[212]

Determination of UTUC histological grade and tumour stage is probably the most relevant information when deciding therapy, due to their well-established role as prognostic factors. Therefore, several retrospective studies have looked at the correlation of ureteroscopic biopsies with final diagnosis

at nephroureterectomy (NU), with conflicting results. In 1997, Keeley *et al.*[213] reported a concordance of 90.4% for tumour grade, with equal upgrading and downgrading (LOE 3). More recently, Williams *et al.*[208] reported an accuracy of 75% in predicting tumour grade in 28 patients, and Wang *et al.*[214] found significant amounts of upgrading for grade I (96%) and grade II (40%) tumours (LOE 3). Meanwhile, Smith and colleagues[215] reported a change in grade and stage in 37% and 38% of patients from URS to NU, respectively. The authors concluded that ureteroscopic biopsy carried a significant risk of underestimating the aggressiveness of disease, reflected by 43% of patients being reclassified from low-grade, non-invasive disease to high-grade and/or invasive disease in their series (LOE 3). Similarly, Straub *et al.*[211] reported a 15% of upgrading, with only 68% accuracy in predicting high-grade cancer on final pathology when combined with selective cytology (LOE 3). The largest series published so far, by Clements *et al.*,[216] found a good correlation of high-grade at ureteroscopic biopsy being significantly associated with high-grade (hazard ratio [HR] 16.6; 95% confidence interval [CI]: 7.0–39.5, $p<0.001$) and muscle-invasive stage (HR: 3.6; 95% CI: 2.1–6.8, $p<0.001$) at NU on multivariate analysis in 230 patients (LOE 3). However, the predictive accuracy of low-grade ureteroscopic biopsies was limited; 44% had high-grade disease at NU and 29% were muscle invasive. Similarly, ureteroscopic tumour stage was not a reliable predictor for final pathologic outcomes. In the same line, Vashistha *et al.*[217] reported a 87.1% agreement in terms of grade, with only a 60% agreement in terms of stage, in a single centre of 118 patients (LOE 3). Confirming this, grade and stage concordance were 92.6% and 43%, respectively, in a recent study by Rojas *et al.*[218] (LOE 3). Overall, it can be concluded that histological examination after sampling by URS appears to be a good predictor for tumour grade (LOE 3). However, it is not accurate enough in terms of staging, which is not surprising since current devices are unable to obtain deep tissue samples. This underscores the importance of a judicious indication of endoscopic treatment in patients with UTUC.

The low accuracy of single diagnostic and staging modalities in UTUC has led to the idea that a combination of different modalities may improve the ability to predict grade or stage in the pre-operative setting. A large multicentric study by Brien and coworkers[219] designed a model by combining the presence of hydronephrosis, ureteroscopic tumour grade, and urinary cytology to predict advanced UTUC (pT2-T4 or non-organ confined at NU). Abnormality of all three variables had a positive predictive value (PPV) of 89% for muscle-invasive and 73% for non-organ confined UTUC. Notably, when all tests were normal, the negative predictive value (NPV) was 100% (LOE 3).[110] A similar multicentric study looking at predictors of non-organ confined UTUC developed a prognostic model including ureteroscopic tumour grade, tumour architecture, and tumour location, achieving 76.6% accuracy.[27] Both of these models constitute valuable pre-operative tools, eventually impacting surgery choice and extent (LOE 3). It is important to note that almost all of the pre-operative variables are dependent on the performance of a diagnostic URS, underscoring its potential role as a standard step in the management of UTUC.

1.9.3 Technical aspects of URS in UTUC

Endoscopic visualization of upper tract tumours may be limited with conventional white light ureteroscopy. Narrow-band imaging (NBI) takes advantage of altered vasculature morphology of urothelial mucosa, optimizing the detection and assessment of urothelial tumours. Traxer *et al.*[207] reported a promising 27% improvement of tumour detection rate with NBI in a small single-centre

series, providing also a detailed description of their limits and blood vessel architecture (LOE 3). However, further studies are necessary to validate this technology before inclusion in routine management of UTUC.

Tissue sampling is still critical and limited despite technologic developments in recent years, especially in the presence of flat lesions. There are several forcipes available for biopsy sampling, some of them allowing for acquisition of large tissue samples. Ritter *et al.*[219] compared five different devices in an *ex-vivo* study, reporting different sample qualities for each of them, as well as different impacts on irrigation flow, deflection, and field of view of three different flexible ureteroscopes (LOE 3). Further tools to improve sampling include the use of ureteral access sheaths (UAS) during URS. Placement of a UAS may facilitate procurement of multiple biopsy specimens, therefore optimizing the diagnostic yield. Gorin *et al.*[220] reported a high tumour grade concordance between URS and NU in 64 patients undergoing procedure with UAS (LOE 3). However, there was no control group, making further evaluation necessary.

Small-size samples may lead to increased difficulties when analyzing specimens in the context of tissue compression or denudation, eventually resulting in diagnostic misinterpretation and therefore underestimating the extent of disease. In fact, Vashistha and colleagues[217] reported higher accuracy for tumour grading in the presence of larger tissue samples. However, it did not impact prediction of tumour stage (LOE 3). Meanwhile, biopsy volume did not affect agreement between biopsy and final pathology in terms of grading or staging in two single-centre studies (LOE 3).[215,218] This is in line with further findings of the *ex-vivo* study by Ritter and coworkers,[219] where no significant reduction of tissue artifacts with larger samples was observed (LOE 3). This underscores the need for better tools to achieve a good quality ureteroscopic biopsy, including clinical validations, since *ex-vivo* conditions are far from clinical practice.

1.9.4 Impact of endoscopic evaluation on UTUC prognosis

Performing a URS before NU involves a potential delay to definitive surgical treatment, eventually resulting in worse clinical outcomes. However, no significant differences were found between patients undergoing NU and those undergoing ureteroscopic biopsy before NU in terms of post-operative disease status (p=0.16) and recurrence-free status (p=0.18) after a mean follow-up of 38.7 months in a single-centre series (LOE 3).[221] These observations were confirmed by two recent multicentric studies, in which intravesical recurrence and cancer-specific survival were not affected by the performance of a diagnostic ureteroscopy, even for muscle-invasive tumours (LOE 3).[222,223] Therefore, UTUC staging by pre-operative URS appears to be reasonable without affecting oncologic outcomes.

1.9.5 Current recommendations

The current recommendation for diagnostic URS according to evidence is grade C. There is consensus that, if available, URS with biopsy should be considered in the pre-operative assessment of every UTUC patient. Information obtained (tumour grade, urinary cytology, tumour architecture) in combination with clinical findings (hydronephrosis, tumour location) are valuable tools and may significantly impact the decision on definitive surgical treatment.

1.10 Evaluation and Staging

1.10.1 Staging

1.10.1.1 TNM staging

Upper tract urothelial carcinoma clinical staging is based on the TNM staging system. According to the TNM system, patients can be categorized into six prognostic groups, as proposed by the American Joint Committee on Cancer (AJCC). **Tables 1-1** and **1-2** list the current 2009 TNM staging system with the corresponding AJCC prognostic groups.[224]

TABLE 1-1 2009 TNM Staging

T Category (Primary Tumour)	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma *in situ*
T1	Tumour invades sub-epithelial connective tissue
T2	Tumour invades muscularis
T3	(Renal pelvis) Tumour invades beyond muscularis into peri-pelvic fat or renal parenchyma; (Ureter) Tumour invades beyond muscularis into peri-ureteric fat
T4	Tumour invades adjacent organs or through the kidney into peri-nephric fat
N Category (regional lymph nodes)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node 2 cm or less in greater dimension
N2	Metastasis in a single lymph node more than 2 cm but not more than 5 cm in greatest dimension, or multiple lymph nodes, none more than 5 cm in greater dimension
N3	Metastasis in a lymph node more than 5 cm in greater dimension
M Category (distant metastasis)	
M0	No distant metastasis
M1	Distant metastasis

TABLE 1-2 AJCC Stages of UTUC

Stage 0a	Ta	N0	M0
Stage 0is	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
Stage IV	T4 Any T Any T	N0 N1, -2, -3 Any N	M0 M0 M1

1.10.1.2 Staging by radiographic evaluation and ureteroscopic findings

Conventional imaging methods such as intravenous pyelography (IVP) and retrograde pyelography (RP) cannot demonstrate extension into peri-pelvic or peri-ureteric fat or metastasis. Cross-sectional imaging with CT and/or MRI is routinely employed in the staging of UTUC patients. These techniques can demonstrate intrarenal and extrarenal local extension of a tumour and the presence of nodal or distant metastases simultaneously. Ureteroscopic evaluation and biopsy are also used in conjunction with these imaging techniques for UTUC staging.

Sonography has a very limited role in the staging of UTUC. New developments in endoluminal ultrasound might make it available for use in staging; however, validation of the technique on UTUC staging accuracy should be further investigated (LOE 3).[225]

1.10.1.2.1 Staging by CT scan

Early work has demonstrated the limitations of conventional CT scans for accurate clinical staging of UTUC. In 2000, Scolieri *et al.*[77] reported on 37 UTUC patients and found that the overall accuracy of conventional CT scanning for the prediction of pathological TNM stage was only 59.5%. Recent advances with MDCT have greatly improved the diagnostic accuracy for pre-operative staging of UTUC (LOE 3).[226,227] Fritz *et al.*[227] compared pre-operative MDCT findings with the final histopathology and reported that 28 of 29 tumours (96.6%) and 8 of 12 tumours (66.7%) were correctly diagnosed as organ-confined tumours (Ta-T2) and as locally invasive tumours (T3/4), respectively (LOE 3). The overall accuracy of MDCT in the prediction of staging in their study was 87.8%. Understaging was observed in 4 of 41 tumours (9.8%), due to being undetectable for microscopic invasion, and overstaging in 1 of 41 tumours (2.4%), due to additional inflammatory changes.

1.10.1.3 Staging by MRI

Magnetic resonance urography suffers from significant limitations due to poorer spatial resolution compared to MDCT, as well as various artifacts, including motion artifacts from breathing and peristalsis. Currently, MR urography has limited clinical applications, such as when a patient is allergic to iodine-based contrast agents. However, some investigators have presented promising results for diffusion-weighted imaging (DWI) for UTUC staging (LOE 3).[228,229] In a study of 40 patients, Akita *et al.*[228] investigated the diagnostic performance of DWI for pre-operative staging of renal pelvic tumours. They reported that the diagnostic accuracy of T2-weighted single-shot fast spin-echo imaging (SSFSE) with DWI for identifying T3b (macroscopic invasion, 5 mm or greater invasion into the renal parenchyma) tumours was 93%, which was significantly higher than that of SSFSE alone (75%) and similar to that of SSFSE plus contrast-enhanced imaging (83%). They concluded that DWI could be used for pre-operative T categorization of renal pelvic tumours without contrast material (LOE 3).

1.10.1.4 Staging by endoscopic biopsy stage

Ureteroscopic biopsy under the present instrumentation cannot reliably provide full-thickness samples to accurately diagnose muscle-invasive disease because of the relatively thin ureteral wall and the associated risks for perforation if deep biopsies or resections are attempted. In fact, pathological stage diagnosed by endoscopic biopsy is often inaccurate owing to understaging. Vashistha *et al.*[217] reported that only 59.6% (17 of 29 tumours) of their surgical resections had concordance on pT stage with initial biopsies, and 12 biopsies had a lower pT stage than the resected specimen (LOE 3). Similar results were observed in another study, which found that 10 (45%) of the 22 Ta cases diagnosed by ureteroscopic biopsy were pathologically upstaged to pT1 or greater disease.[80] Improved tumour sampling as a consequence of advances in endoscopic tools might enhance staging accuracy in future investigations.

1.10.2 Prediction of UTUC pathological stage

The ability to accurately predict low-volume, low-grade, and low-stage tumours is paramount for the accurate selection of patients to be treated with nephron sparing management.

Patients with UTUC had significantly higher local recurrence and distant metastasis rates, especially those with higher pT stages. This means that effective strategies for peri-operative systemic therapy are needed to improve survival in patients at high risk for local recurrence and distant metastasis. Neoadjuvant cisplatin-based chemotherapy is a reasonable option, especially for UTUC, as compared to an adjuvant setting because renal function decreases significantly after RNU (LOE 3).[231] Accurate pre-operative diagnosis of a muscle-invasive or non-organ confined UTUC tumour results in the proper identification of candidates for lymph node dissection (LND) or neoadjuvant chemotherapy.

Lymph node dissection during RNU is now believed to be an important step, because LND can provide more accurate diagnostic information and might have a therapeutic role for higher-staged UTUC. In fact, nodal status (pNx, pN0, and pN+) in RNU specimens is a strong predictor for cancer specific survival in UTUC patients,[232] and the extension of LND (the number of lymph nodes removed) in pN0 UTUC patients seems to be associated with patient survival (LOE 3).[233] The questions are who should be treated by LND and how candidates for LND can be identified pre-operatively among UTUC patients treated with RNU.

The accurate prediction of pathological stage allows precise decision making with respect to the management of UTUC patients; however, it is not easy to properly diagnose pre-operative UTUC staging. Radiographic and/or endoscopic evaluation with or without cytology findings could be utilized for the prediction of disease staging to guide the therapeutic options.

1.10.2.1 IVP and RP appearance for the prediction of UTUC pathological stage

Intravenous pyelogram has been frequently used as the primary initial examination for upper-tract urothelial lesions, and RP is performed to further characterize any abnormality in the upper urinary tract. To assess the predictive value of IVP and/or RP and/or antegrade pyelography on staging, Lee *et al.*[234] evaluated the association between the filling defect pattern of the urographic findings and pathological stage (LOE 3). In their study, the filling defects on urography in 126 ureters were divided into four patterns according to their shape: ovoid (22.2%), polypoid (33.3%), infiltrating (29.4%), or plaque-like (15.1%). They demonstrated that infiltrating or plaque-like filling defects were significantly associated with muscle-invasive or advanced disease and concluded that the filling defect patterns of ureteral tumours may provide pre-operative staging information. However, another study did not support this finding. Williams *et al.*[208] reported that ovoid/polypoid defects and infiltrating/plaque-like appearance were observed in 16 (53.3%) and 13 (43.3%) of 30 patients, respectively, in their series (LOE 3). They showed that an infiltrating/plaque-like appearance had only 31% predictive value for muscle-invasive disease.

1.10.2.2 Urinary cytology for the prediction of UTUC pathological stage

Messer *et al.*[212] used a large series of data from 326 UTUC patients and evaluated the predictive value of urinary cytology obtained from either bladder or selective ureteral catheterization on final pathological stage (LOE 3). Overall, 153 (47%) had pT2-T4 UTUC on the final pathological specimens, and cytology data were positive in 40% of patients, atypical in 40%, and negative in 20%. From the results showing that 53% of patients with a negative cytology had muscle-invasive UTUC on final pathology, they concluded that urinary cytology in isolation was suboptimal for pre-operative identification of invasive UTUC, and this was true even when restricting the analysis to selective ureteral catheterization.

1.10.2.3 Endoscopic biopsy grade for the prediction of UTUC pathological stage

Some investigators have shown that the clinical grade determined by pre-operative diagnostic biopsy can be used to predict the pathological stage (LOE 3).[208,213,216,235] Brown *et al.*[235] studied 119 patients who underwent ureteroscopic biopsy and were subsequently treated by RNU, and reported those with clinical grade 3 had a 66.2% risk of having pT2 or greater disease and a 42.3% risk of having pT3 or greater disease (LOE 3). Clements *et al.*[216] accumulated a large series of 238 patients from five medical centres in the United States and evaluated the relationship between the pre-operative ureteroscopic biopsy data and final pathological disease characteristics (LOE 3). In their series, on ureteroscopic biopsy, 140 (59%) and 98 (41%) were found to be low-grade and high-grade, respectively, and 140 (59%) and 98 (41%) non-muscle–invasive tumours and muscle invasive tumours, respectively, on surgical extirpated specimen. They found that 1) the PPV of a high grade in ureteroscopic biopsy for a muscle-invasive tumour was 60%, and a high grade in ureteroscopic biopsy was independently associated with a muscle-invasive tumour in the final pathology; and 2) a low grade in ureteroscopic

biopsy had only a PPV of 71% for non-muscle–invasive UTUC. On the other hand, Guarnizo *et al.*[80] reported that only 3 (27%) of 8 patients with clinical grade 3 tumours on ureteroscopic biopsy had pT2 or greater disease.

1.10.2.4 Presence of hydronephrosis on radiographic evaluation for the prediction of UTUC pathological stage

The presence of hydronephrosis is thought be associated with a higher stage because hydronephrosis can be attributed to one of several factors, including luminal obstruction, intramural invasion, and extrinsic compression. Ng and colleagues[113] evaluated the association between the presence of hydronephrosis on pre-operative CT scan and the final pathological stage in 106 UTUC patients. They observed hydronephrosis in 39 patients (37%) and showed that the presence of pre-operative hydronephrosis independently predicted non-organ confined disease. Other investigators have evaluated whether hydronephrosis grading could pre-operatively predict a worse pathological outcome (LOE 3).[111,112] Ito *et al.*[112] identified 91 patients who were evaluated by CT and/or MRI images and reported that 73.6% had ipsilateral hydronephrosis pre-operatively. In their study, ipsilateral hydronephrosis was graded in five stages (0 to 4). In their pre-operative multivariate analysis controlling for patient age, gender, tumour site, hydronephrosis grade, clinical stage, urine cytology, and tumour length, a higher hydronephrosis grade (grade 2–4 hydronephrosis versus the 0/1 hydronephrosis) independently predicted pathological T stage (T3 or greater) (LOE 3).

1.10.2.5 Pre-operative multivariable model for the prediction of muscle-invasive and non-organ confined disease

Radiological evaluation, endoscopic findings, and cytological findings in isolation are insufficient to predict final pathological staging. Recently, several groups have combined these tests to improve the pre-operative prediction of UTUC staging. Brien *et al.*[110] described the importance of combining pre-operative variables such as hydronephrosis on imaging, ureteroscopic grade, and urinary cytology for identifying patients at risk for locally advanced disease. They found an abnormality with all three features had 89% PPV for muscle-invasive UTUC, 73% PPV for non-organ confined disease, and normality for all these tests had 100% NPV for both muscle-invasive and non-organ confined disease (LOE 3). In a study of 274 patients at Memorial Sloan-Kettering Cancer Center, Favaretto *et al.*[236] attempted to develop a pre-operative multivariable model to accurately identify patients who are at risk for pT2 or greater and non-organ confined disease (pT3/4 or pN+). In their results, local invasion on pre-operative imaging by CT scan or MRI and high-grade disease on ureteroscopic evaluation were independent predictors for advanced pathological stage (LOE 3). A patient with high-grade UTUC on ureteroscopy and the presence of local invasion on imaging has an 82% probability for pT2 or greater disease and 75% probability for non-organ confined disease. Margulis *et al.*[27] used 659 patients from the database of a large international, multicentre UTUC collaborative group and created a nomogram for the pre-operative prediction of non-organ confined UTUC based upon the three variables of tumour grade (high versus low), architecture (sessile versus papillary), and location (ureter versus renal pelvis). The pre-operative nomogram achieved 76.6% accuracy for predicting non-organ confined UTUC (LOE 3).

Further improvement is still needed to establish more accurate and reliable pre-operative prediction tools for identifying muscle-invasive and non-organ confined UTUC. Modern imaging modalities and novel biomarkers might provide such improvement in future investigations.

1.10.3 Recommendations

Cross-sectional imaging with CT and/or MRI is utilized as a gold standard modality for the staging of UTUC patients (LOE 3, Grade of Recommendation [GOR] B).

The ability to predict primary tumour stage using pre-operative imaging, endoscopic evaluation, or cytology findings in isolation is limited (LOE 3, GOR B).

Combination of radiological, endoscopic, and cytology findings might improve the predictive accuracy of locally advanced disease (LOE 3, GOR C).

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C2

Prognostic Factors and Predictive Tools in Upper Tract Urothelial Carcinoma

CHAIR

Morgan Rouprêt, France

CO-CHAIR

Shahrokh F. Shariat, Austria

MEMBERS

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Nathan Lawrentschuk, Australia
Giacomo Novara, Italy
Jay Raman, United States
Christian Schwentner, Austria
Christian Seitz, Germany
Evanguelos Xylinas, France

Committee 2

CONTENTS

Prognostic Factors and Predictive Tools in Upper Tract Urothelial Carcinoma

2.1 Introduction

Upper tract urothelial carcinoma (UTUC) is an uncommon malignancy accounting for only 5% of urothelial carcinomas (UCs).[1] The outcomes of patients with UTUC are heterogeneous, and therefore, difficult to predict. Given the low incidence of the disease, data regarding clinicopathological predictors of outcomes are sparse. The absence of randomized trials in patients with UTUC makes decisions complex. Until recently, there was little high-quality data to guide physicians and patients in the management of UTUC. This is largely due to the low incidence of this disease, resulting in single-centre, small-study cohorts. Multi-institutional collaborative studies have identified several potential outcome predictors following radical nephroureterectomy (RNU) for UTUC, thereby improving upon traditional pathologic staging systems.[2–9] Accurate estimation of treatment success, complications, and long-term morbidity are essential for patients to make informed medical decisions regarding the management of their disease. Pre-operatively, the correct identification of patients harbouring low-risk UTUC versus more aggressive disease is critical in counseling patients with UTUC. This, together with the heterogeneity of UTUC biology and prognosis, as well as the presence of different treatment options, makes the decision-making process extremely challenging. As a result, researchers have developed prognostic tools based on statistical models to obtain the most accurate and reliable predictions. These tools can provide predictions that are both evidence based and individualized. Among the available decision tools, nomograms are currently the most accurate and widely used tools for prediction of outcomes in patients with cancer.[10] Nomograms have been adopted in oncologic disciplines such as breast, colon, prostate, kidney, and bladder cancers.[11]

Our aim was to provide an overview of the currently available prognostic factors for UTUC, focusing on clinical and pathologic characteristics, molecular markers, and available predictive tools.

2.2 Patient-related Factors

2.2.1 Age

Several population-based and multicentre studies have reported that advanced patient age is an independent predictor of cancer-specific mortality (CSM) after RNU[12–14] (see **Table 2-1**). The mean age at diagnosis is around 70 years. Changes in the biologic potential of the tumour, with UTUC being more aggressive in elderly patients, and differences in care patterns (e.g. greater reluctance to perform radical surgery, use of peri-operative chemotherapy regimens, and baseline kidney function) could explain these observations. However, based on the available evidence, age alone should not be an exclusion criterion for RNU, as the complications of this procedure in the elderly are not excessive or much different from those in their younger counterparts.

TABLE 2-1 Prognostic factors of UTUC related to the patient

Characteristics	Comment	Reference
Age	Advanced chronological age is an independent predictor of DR, CSM, and OM.	Lughezzani *et al.*[12] Shariat *et al.*[13] Chromecki *et al.*[14]
Gender	No impact of gender on outcomes.	Lughezzani *et al.*[15]
Race	African-American race is an independent predictor of CSM.	Matsumoto *et al.*[16] Raman *et al.*[17]
Comorbidities	▪ ECOG-PS ≥1 is an independent predictor of OM. ▪ ASA score is an independent predictor of CSM.	Chromecki *et al.*[14] Martinez-Salamanca *et al.*[18] Berod *et al.*[19]
Obesity	Body mass index ≥30 is an independent predictor of DR, CSM, and OS.	Ehdaie *et al.*[2]
Smoking exposure	Smoking status and cumulative exposure are associated with DR, CSM, and OM.	McLaughlin *et al.*[20] Rink *et al.*[21]

ASA: American Society of Anesthesiologists; CSM: cancer-specific mortality; DR: disease recurrence; ECOG-PS: Eastern Cooperative Oncology Group performance status; OM: overall mortality; UTUC: upper tract urothelial carcinoma.

2.2.2 Gender

Upper tract urothelial carcinoma is more common in men than in women.[1] Unlike in lower tract UC, female gender is not associated with features of aggressive disease[6] or inferior oncologic outcomes after RNU.[15] Therefore, gender should not be considered as a predictor of survival in patients with UTUC.

2.2.3 Ethnicity

The incidence of UTUC appears to be increasing in most racial groups, mostly owing to earlier detection. Although a multicentre study originating from academic centres did not show any difference between races,[16] population-based studies have indicated that black (African-American) patients have worse outcomes compared to other racial groups.[17] As with many diseases, whether this is due to differences in biological processes or, more likely, differences in health attitudes and access to care, remains to be evaluated.

2.2.4 Comorbidity indexes

Eastern Cooperative Oncology Group (ECOG) performance status (PS; ECOG-PS) has been shown to be independently associated with higher peri-operative mortality and overall mortality (OM) after RNU, but not disease recurrence (DR) or cancer-specific mortality (CSM).[18] Conversely, the French Collaborative Group reported an association between American Society of Anesthesiologists (ASA) scores and CSM after RNU.[19] In a recent study, the addition of ECOG-PS to a multivariable model that included standard clinicopathologic features was significantly associated with DR and CSM.[14] These findings require further investigation and validation.

2.2.5 Obesity

The prognostic role of obesity has been demonstrated in several malignancies, such as renal cell and prostate cancer. A recent multi-institutional study examined the relationship between body mass index and oncologic outcomes in patients with UTUC.[2] The authors reported that a body mass index ≥30% was associated with poorer DR, CSM, and OM. Further studies are needed to investigate the biological basis for such findings, and whether these risks can be modified.

2.2.6 Tobacco consumption

Smoking is an established risk factor for the development of UC.[20] A recent multicentre study investigated the relationship between smoking exposure and prognosis for patients with UTUC.[21] The authors showed that smoking status (current versus never) and cumulative exposure (heavy long-term smokers who smoked >20 cigarettes per day for >20 years) were associated with adverse DR and CSM.[21] Interestingly, smoking cessation for more than 10 years mitigated these detrimental effects.[21] The authors concluded that smoking cessation programs should be integral parts of the cancer care administrated to patients with UTUC.

Conclusions	LOE
Advanced age, African-American race, comorbidity profile (assessed by validated indexes), obese body habitus, and smoking exposure are the main patient-related prognostic factors associated with worse outcomes in UTUC.	3

2.3 Tumour-related Factors

2.3.1 Hydronephrosis

Several studies have explored the relationship between the presence of hydronephrosis on pre-operative imaging, pathologic stage, and cancer-specific survival (CSS) in patients with UTUC (see **Table 2-2**). The presence of hydronephrosis has been associated with more advanced disease stage[22–24] and CSS.[25]

TABLE 2-2 Prognostic factors of UTUC related to the disease

Characteristics	Comment	Reference
Hydronephrosis	Presence of hydronephrosis is associated with higher stage, DR, and CSM.	Cho *et al.*[22] Ito *et al.*[23] Brien *et al.*[24] Ng *et al.*[25]
Symptoms	Systemic symptoms are associated with metastatic disease.	Raman *et al.*[26] Inman *et al.*[27]

CSM: cancer-specific mortality; DR: disease recurrence; IVR: intravesical recurrence; UTUC: upper tract urothelial carcinoma.

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TABLE 2-2 Prognostic factors of UTUC related to the disease, *Cont'd*

Characteristics	Comment	Reference
Tumour location	The impact of tumour location on outcomes results in contradictory findings.	Park *et al.*[28] Zigeuner *et al.*[29] Favaretto *et al.*[30]
Tumor multifocality	Presence of multifocal tumours is an independent predictor of CSM.	Ouzzane *et al.*[8] Chromecki *et al.*[31] Yafi *et al.*[32]
Tumour size	Tumor size >3 cm is an independent predictor of DR and CSM.	Simone *et al.*[33] Pieras *et al.*[34]
Previous/Synchronous bladder cancer	Presence of a previous or synchronous bladder cancer is an independent predictor of IVR.	*Mullerad et al.*[37] *Xylinas et al.*[38] *Novara et al.*[39]

CSM: cancer-specific mortality; DR: disease recurrence; IVR: intravesical recurrence; UTUC: upper tract urothelial carcinoma.

2.3.2 Symptoms

The presence of systemic symptoms, such as pain and weight loss, has been associated with higher-stage and higher-grade UTUC[26] and OM, in patients treated with RNU for UTUC.[27] Further multi-institutional efforts are needed to validate this predictor. It is hypothesized that such systemic symptoms are suggestive of micro-metastatic disease. Therefore, with more advanced imaging studies, most of the patients with systemic symptoms likely will be identified as metastatic at presentation.

2.3.3 Location within upper urinary tract

The impact of tumour location (in the renal pelvicalyceal system versus ureter) on the prognosis of patients with UTUC is controversial. Several single-institutional studies initially reported that ureteral location was associated with worse outcomes.[28,29] A recent multi-institutional French study confirmed this finding.[8] However, other population-based, multi-institutional studies have failed to find an association between tumour location and oncologic outcomes after RNU, once adjusted for tumour stage.[5,30] To conclude, the currently available retrospective studies do not permit a definitive conclusion regarding the impact of tumour location on UTUC prognosis. However, although there is a differential impact of tumour location on tumour stage, lymph node (LN) status and tumour stage are more powerful drivers of tumour biology and clinical behaviour.

2.3.4 Multifocality

Multifocal tumours are defined as tumours with two or more distinct locations within the urinary tract. In retrospective studies, tumour multifocality (occurring in at least 30% of patients) has been shown to be an independent predictor of CSM.[8,31] Tumour presence in both the renal pelvicalyceal system and ureter is worse than when in either location alone, with regard to cancer-specific outcomes.[32] Based on the current literature evidence, tumour multifocality should be routinely determined by clinicians, with adequate sampling and reporting by pathologists.

2.3.5 Tumour size

Tumour size is an established predictor of cancer-related outcomes in several malignancies. Cut-off tumour diametres of 3 cm and 4 cm have been associated with occurrence of metastasis[33] and intravesical recurrence (IVR) after RNU,[34] respectively. However, both of these studies need validation by studies with larger cohorts. From clinical experience, Ta tumours can reach a large size and have a low risk of becoming invasive. Whether tumour size is an accurate predictor of the biological behaviour of an individual tumour remains to be determined.

2.3.6 Clinical tumour grade and stage

Endoscopic evaluation (±biopsy) establishes the definitive diagnosis of UTUC and helps risk-stratify patients toward conservative or radical management. Biopsy grade is accurate and can help predict pathologic grade and stage.[24] Unlike with lower tract UC, the clinical staging of UTUC is difficult because biopsies that include underlying muscle are generally not possible.[35] Imaging studies can help improve clinical staging based on the presence of hydronephrosis (see above) and invasion in soft tissue.[36]

2.3.7 History of bladder cancer

Upper tract urothelial carcinoma is considered part of a panurothelial phenomenon that can yield multifocal tumours including lower tract UC. Previous history of bladder cancer has been associated with intravesical recurrence,[37,38] DR, and CSM after RNU.[37,39]

Conclusions	LOE
The presence of hydronephrosis on pre-operative imaging, the presence of symptoms (pain, weight loss), ureteral tumour location, multifocality, tumour size of >3 cm, biopsy tumour grade and stage, and a previous history of bladder cancer are the main disease-related prognostic factors associated with worse outcomes in UTUC.	3

2.4 Surgery-related Factors

2.4.1 Delayed surgery

In lower tract UC, a delay between diagnosis and radical cystectomy (≥3 months) is considered to have a negative impact on prognosis (see **Table 2-3**). A multi-institutional study investigated the prognostic impact of the time interval between diagnosis and RNU on oncologic outcomes in patients with UTUC.[40] The study showed that a longer interval (≥3 months) was also associated with advanced pathologic stage, DR, and CSM in patients with invasive disease.[40] This data, together with that from the lower tract, suggests that once a tumour becomes invasive, which is difficult to assess clinically in UTUC, one should proceed to definite therapy in a time-sensitive fashion.

TABLE 2-3 Prognostic factors of UTUC related to the surgery

Characteristics	Comment	Reference
Delay of treatment	A delay ≥3 months is associated with higher stages in invasive UTUC.	Waldert *et al.*[40]
Surgical approach	Outcomes between open and laparoscopic RNU are not different.	Ni *et al.*[41] Hanna *et al.*[42] Simone *et al.*[43]
Distal ureter management	▪ Lack of complete bladder-cuff removal is associated with DR and CSM. ▪ Endoscopic distal ureter management is associated with IVR.	Xylinas *et al.*[9] Lughezzani *et al.*[44]

CSM: cancer-specific mortality; DR: disease recurrence; IVR: intravesical recurrence; RNU: radical nephroureterectomy; UTUC: upper tract urothelial carcinoma.

2.4.2 Surgical approach

Open RNU (ONU) with excision of a bladder cuff is considered the gold standard in treatment for invasive or high-risk non-invasive UTUC regardless of the location of the tumour in the urinary tract.[1] Laparoscopic RNU (LNU) and robotic RNU have emerged as minimally invasive alternatives to ONU, with advantages in terms of less blood loss, shorter length of hospital stay, and shorter convalescence.[41,42] To date, only one prospective randomized trial has shown no difference in terms of DR and CSM between LNU and ONU.[43] In non–organ-confined tumours, LNU was inferior to ONU. This difference could be attributed to surgeon experience and other factors such as the differential use of lymph node dissection (LND) between the two groups. A population-based study (with a propensity score–matched analysis) and a meta-analysis of retrospective studies confirmed the safety of LNU with regard to oncologic outcomes compared with ONU.[41,42] Provided the surgeon adheres to sound oncologic principles, there should be no difference between the approaches.

2.4.3 Distal ureter management

Excision of the bladder cuff is mandatory in invasive or high-risk non-invasive UTUC.[1] Moreover, the procedure must comply with oncologic principles, which consist of preventing tumour seeding by avoiding entry into the urinary tract during tumour resection. Resection of the distal ureter and its orifice is performed because these areas are part of the urinary tract and present a considerable risk for tumour recurrence. After removal of the proximal section, it is nearly impossible to image during follow-up. Recent publications on survival after RNU have concluded that removal of the distal ureter (bladder cuff) improves prognosis after RNU.[44] Moreover, endoscopic distal ureter management has been associated with a higher risk of IVR.[9] Although a variety of techniques have been described for the management of the bladder cuff, it is imperative that complete removal is performed. Therefore, techniques such as ureteral stripping lead to incomplete surgery and should be avoided.[1]

2.4.4 Lymph node dissection

Lymph node dissection during RNU allows for optimal staging of the disease and may have a therapeutic role.[45] However, the anatomical sites of LND have not been clearly defined yet. Specific LND templates are likely to have a greater impact on patient survival than the number of LNs removed.[45,46] The cumulative data from the literature on this subject suggests that LND should be performed during RNU or distal ureterectomy for invasive UTUC.[1,45] The templates for LND need to be defined through large multicentre template studies. As with lower tract urothelial carcinoma of the bladder (UCB), a pathologic nodal staging score has been proposed to predict the probability of a patient staged as pN0 being truly node negative.[47] However, all data are retrospective; consequently, underreporting of the true rate of node-positive disease is likely.

Conclusions	LOE
A delay between ureteroscopic biopsy and RNU (≥3 months) may impact the oncologic outcomes after RNU.	3
No difference in terms of DR and CSM has been reported between LNU and ONU.	2
Laparoscopic RNU and endoscopic distal ureter management have been associated with higher risks of IVR after RNU.	3
The LND during RNU provides optimal staging and may have a therapeutic benefit, as extrapolated from the bladder cancer literature.	3

Recommendations	GOR
Open radical nephroureterectomy is the standard of treatment for high-grade or clinically infiltrating UTUC.	B
In experienced hands, laparoscopic radical nephroureterectomy is an alternative to the open procedure.	C

2.5 Pathologic Factors

2.5.1 Stage

Pathologic tumour stage is the best-established predictor of survival in patients with UTUC and should always be considered in the pre-operative and post-operative counseling of these patients, specifically in the determination of the intensity of post-operative surveillance and the decision-making regarding adjuvant therapies and trials[39,48] (see **Table 2-4**). The 5-year CSS rate decreased from >90% in patients with pTa/pT1 disease to <20% in patients with pT4 UTUC.

TABLE 2-4 Prognostic factors of UTUC related to pathologic features

Characteristics	Comment	Reference
Pathologic tumour stage	Advanced pT stage is an independent predictor of DR and CSM.	Novara *et al.*[39] Margulis *et al.*[48]
Pathologic tumour grade	▪ Higher tumour grade is an independent predictor of DR and CSM. ▪ Both the 1973 and the 2004 WHO classifications of tumour grade independently predict cancer-control outcomes.	Margulis *et al.*[48] Lopez-Beltran *et al.*[49]
Concomitant CIS	Concomitant CIS is associated with advanced tumour stage and grade, and is an independent predictor of IVR, DR, and CSM.	Lopez-Beltran *et al.*[50] Otto *et al.*[51] Xylinas *et al.*[52]
LVI	Presence of LVI is associated with advanced tumour stage and grade, DR, and CSM, specifically in pN0 patients.	Kikuchi *et al.*[4] Novara *et al.*[54]
Tumour architecture	Sessile tumour is associated with DR and CSM.	Margulis *et al.*[48] Remzi *et al.*[55] Fritsche *et al.*[56]
Tumour necrosis	Controversial impact on oncologic outcomes.	Zigeuner *et al.*[57] Seitz *et al.*[58]
LNI	Presence of LNI is associated with DR and CSM.	Roscigno *et al.*[45] Margulis *et al.*[48] Bolenz *et al.*[53]

CIS: carcinoma *in situ*; CSM: cancer-specific mortality; DR: disease recurrence; IVR: intravesical recurrence; LNI: lymph node involvement; LVI: lymphovascular invasion; UTUC: upper tract urothelial carcinoma; WHO: World Health Organization.

2.5.2 Grade

Tumour grade is another well-established predictor of cancer-related outcomes in patients with UTUC because it is strongly related to single-cell behaviour and tumour stage. Both the 1973 and 2004 World Health Organization (WHO) classifications are predictive of outcomes.[48,49] Tumour grade should always be taken into account in the pre-operative and post-operative counseling of these patients. Specifically, in the pre-operative setting, tumour grade can help guide decision regarding RNU versus endoscopic management.

2.5.3 Concomitant carcinoma *in situ*

Concomitant carcinoma *in situ* (CIS) of the upper urinary tract is a rare entity that appears to be associated with DR and CSM in patients with organ-confined disease.[50] Moreover, the presence of concomitant CIS is associated with IVR after RNU.[51,52] Therefore, the presence of concomitant CIS should always be evaluated in patients with UTUC because patients with CIS require more aggressive surveillance regimens and strategies using topical therapies.

2.5.4 Lymph node invasion

The presence of lymph node invasion (LNI) is considered an important prognostic factor, indicating the metastatic spread of a tumour to the patient's lymph nodes (LNs).[45,48] In patients with LNI, lymph node density (≥30%) may help risk-stratify patients with regard to DR and CSM.[53] Extranodal extension appears to be a powerful predictor of clinical outcomes in patients with LNI.[3,53] Lymph node invasion is an important prognostic factor in patients with UTUC. Efforts are still needed to standardize the indications and LND templates.

2.5.5 Lymphovascular invasion

In retrospective studies, lymphovascular invasion (LVI) is present in approximately 20% of patients with UTUC, and it represents an independent predictor of DR and CSS; specifically adding information in patients with LN-negative UTUC.[4,54] Lymphovascular invasion status should be reported in the pathologic report of all UTUC specimens.[4,54] A consensus regarding the pathologic definition of LVI needs to be reached.

2.5.6 Tumour architecture

Several studies have investigated the prognostic impact of tumour architecture (sessile compared with papillary) on the survival of patients with UTUC. Three multi-institutional studies found that a sessile/infiltrative growth pattern was associated with features of aggressive disease, DR, and CSM[48,55,56] These findings suggest that tumour architecture should always be mentioned during the endoscopic evaluation of UTUC, as well as in the gross description of the pathologic reports.

2.5.7 Tumour necrosis

Extensive tumour necrosis (defined as >10% of the tumour area) has been implicated an independent predictor of oncologic outcomes in patients after RNU.[57] However, a recent multicentre international study failed to confirm these findings.[58] Therefore, the prognostic role of tumour necrosis in patients with UTUC requires further confirmation in larger, well-designed, multi-institutional studies.

2.5.8 Positive surgical margins

The presence of positive surgical margins is reported in ≤8.5% of RNU cases. The presence of positive surgical margins has been associated with higher rates of DR and CSM.[59] However, it is necessary to differentiate between ureteral-positive margin and soft tissue–positive margin. Although both negatively impact outcomes for the patient, soft tissue–positive margins are often associated with a dismal prognosis.[59]

2.5.9 Histological variants

In retrospective studies, nearly 25% of patients with UTUC treated with RNU harbour histological variants.[60] Variant histology has been associated with features of aggressive disease,[60] but not with oncologic outcomes when adjusted for the effects of standard clinicopathological features.[60] Moreover, variant histology does not appear to affect response to adjuvant systemic chemotherapy in patients treated with RNU.[61] Future studies may allow for the stratification of outcomes between different types of variant histology.

Conclusions	LOE
A higher tumour stage and grade, concomitant CIS or LVI, LN metastasis, sessile tumour architecture, extensive tumour necrosis (>10%), positive surgical margins, and histologic variants are the main pathological features associated with worse outcomes in UTUC.	3

2.6 Molecular Markers

2.6.1 Tissue-based markers

Several research groups are working on UTUC oncogenesis and progression pathways. Tissue-based markers, such as cell-cycle regulators (p53),[62] cell proliferation (Ki67),[63] angiogenesis (EGFR and HIF1a),[64,65] cell-adhesion (E-cadherin),[66,67] and apoptosis (Bcl-2 and survivin)[68,69] have been tested with promising prognostic value (see **Table 2-5**). The main limitations shared by these studies are their retrospective nature and small sample size; thus, these findings require further validation before inclusion in clinical decision-making for the management of UTUC. Even more than in bladder UC, reliable biomarkers are essential to improving upon the limitations of the current clinical staging of UTUC.

TABLE 2-5 Summary of the molecular markers in patients with UTUC

Markers	Function	Method	Comment	Reference
Tissue-based				
P53	Cell-cycle regulation	Immunohistochemistry	Overexpression is associated with advanced T stage and higher tumour grade	Ku *et al.*[62]
Ki-67	Cell proliferation	Immunohistochemistry	Overexpression is associated with advanced T stage and higher tumour grade. It is an independent predictor of synchronous/ metachronous bladder cancer.	Jeon *et al.*[63]
EGFR	Cell proliferation and differentiation	Immunohistochemistry	Overexpression is associated with advanced disease and metaplastic differentiation.	Leibl *et al.*[64]
HIF-1α	Angiogenesis	Immunohistochemistry	Overexpression is an independent marker for DR and OM.	Nakanishi *et al.*[65]
E-cadherin	Cell adhesion	Immunohistochemistry	Lower levels are associated with advanced disease and are an independent predictor of DR and CSM.	Inoue *et al.*[66] Fromont *et al.*[67]
Bcl-2	Apoptosis	Immunohistochemistry	Overexpression is associated with advanced T stage and higher tumour grade.	Nakanishi *et al.*[68]
Survivin	Apoptosis	Immunohistochemistry	Overexpression is associated with advanced T stage and higher tumour grade. It is an independent predictor of CSM.	Jeong *et al.*[69]
Blood-based				
C-reactive protein	Inflammatory response	ELISA	Elevated levels are independently associated with DR and CSM.	Saito *et al.*[70] Lehmann *et al.*[71] Tanaka *et al.*[72] Stein *et al.*[73]
Leukocytes	Inflammatory response	Cytometry	Elevated levels are independently associated with DR and CSM.	Lehmann *et al.*[71]
Genetic				
Microsatellite instability	Defect in DNA repair process	PCR	Microsatellite instability is an independent marker of CSM.	Roupret (*et al.*[74] Rouprêt *et al.*[75]

CSM: cancer-specific mortality; DR: disease recurrence; EGFR: epidermal growth factor receptor; ELISA: enzyme-linked immunosorbent assay; OM: overall mortality; PCR: polymerase chain reaction; UTUC: upper tract urothelial carcinoma.

2.6.2 Blood-based markers

Only a few blood-based markers have been investigated in patients with UTUC. Increased levels of C-reactive protein and leukocytes have been associated with DR and CSM.[70–73] However, to date, there is a paucity of evidence to support the role of blood-based markers as predictors of outcomes in patients with UTUC.

2.6.3 Genetic markers

Microsatellite instability (MSI) is defined as the presence of ubiquitous mutations in microsatellite DNA sequences and has been found to be associated with hereditary non-polyposis colorectal cancer, as well as with many sporadic human cancers. The presence of MSI has also been demonstrated in patients with UTUC.[74] Moreover, MSI is associated with prognosis.[75]

To date, no marker has fulfilled the clinical and statistical criteria necessary to support its introduction into daily clinical decision-making.[76]

2.7 Predictive Tools

Nomograms have been proposed in the pre- and post-operative settings to predict various endpoints in order to improve patient counseling, post-operative surveillance regimens, identification of the best patient for conservative management, LND, chemotherapy administration, and risk stratification for inclusion in clinical trials (see **Table 2-6**). The variety of variables incorporated into nomograms has expanded from standard clinical and pathological features to imaging techniques.[36]

TABLE 2-6 Available Predictive Models in UTUC

Reference	Prediction form	Setting	Endpoint	Number of patients	Variables	Accuracy	Validation
Margulis *et al.*[80]	Probability nomogram	Pre-operative	Prediction of NOC disease after RNU	659	Tumour location, grade, and architecture	76.6%	Internal
Favaretto *et al.*[36]	Risk grouping	Pre-operative	Predictors of pathological stage at the time of RNU	274	High-grade on ureteroscopy biopsies, tumour location, local invasion, and hydronephrosis on imaging	71% for muscle-invasive UTUC and 70% for NOC	Not performed

CIS: carcinoma in situ; CSS: cancer-specific survival, LN: lymph node; LVI: lymphovascular invasion; NOC; non-organ confined; RFS: recurrence-free survival; RNU: radical nephroureterectomy; UTUC: upper tract urothelial carcinoma.

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TABLE 2-6 Available Predictive Models in UTUC, *Cont'd*

Reference	Prediction form	Setting	Endpoint	Number of patients	Variables	Accuracy	Validation
Jeldres *et al.*[83]	Probability nomogram	Post-operative	5-year CSS	5,918	Age, T stage, LN status, grade	75.4%	Internal
Yates *et al.*[84]	Probability nomogram	Post-operative	3-, 5-year CSS	667	Age, T stage, LN status, grade, tumour location	78%	Internal
Cha *et al.*[85]	Probability nomogram	Post-operative	2-, 5-year RFS and CSS	2,244	Age, T stage, LN status, grade, LVI, architecture, and concomitant CIS	80.7% for RFS and 82% for CSS	Internal
Rouprêt *et al.*[86]	Probability nomogram	Post-operative	5-year CSS	3,387	Age, T stage, LN stage, architecture, and LVI	79%	Internal

CIS: carcinoma in situ; CSS: cancer-specific survival, LN: lymph node; LVI: lymphovascular invasion; NOC; non-organ confined; RFS: recurrence-free survival; RNU: radical nephroureterectomy; UTUC: upper tract urothelial carcinoma.

2.7.1 Pre-operative prediction of pathologic features of radical nephroureterectomy

With the improvement of endoscopic tools, many patients with UTUC now can be managed conservatively. Tumour staging is notoriously difficult in the pre-operative setting. Predictive tools can help identify which patients have T2 and higher-stage UTUC and therefore can benefit from RNU. Improved understanding of the extent of LND and thoughtful integration of systemic therapy with surgical resection may also help improve treatment outcomes of patients with advanced UTUC.[45] Neoadjuvant chemotherapy may be particularly beneficial in UTUC[77] because the loss of renal function after RNU[78] may render a patient ineligible for treatment with cisplatin-based combination chemotherapy. Unfortunately, chemotherapy and more aggressive surgery may expose patients to increased morbidity, with possible over-treatment. Several studies have shown that patients with muscle-invasive UTUC benefit from LND and neoadjuvant chemotherapy, specifically patients with non-organ confined (NOC) UTUC.[7,45,77] Thus, the accurate prediction of muscle-invasive and/or NOC UTUC can guide appropriate patient selection for these treatments as well as for inclusion in relevant clinical trials. To date, only three models have been described in the pre-operative setting.[36,79,80]

Margulis *et al.* developed a multivariable model for the prediction of NOC UTUC, based on pre-operative clinical and pathologic features (n=659).[80] Their predictive tool, based on tumour location, architecture, and grade, enabled the prediction of NOC disease at RNU with an accuracy of 76.6%.

Brien *et al.* relied on data from 172 patients who underwent RNU for UTUC at five referral centres.[24] They found that the presence of pre-operative hydronephrosis, high-grade ureteroscopic biopsy, and positive urinary cytology was associated with advanced-stage UTUC. The authors concluded that these readily available components of the diagnostic evaluation may improve pre-operative

risk stratification for patients with UTUC, thereby guiding the use of conservative management versus extirpative surgery as well as the need for neoadjuvant chemotherapy regimens. Messer *et al.* confirmed these findings in a larger series of 408 patients.[79]

Favaretto *et al.* also combined results from imaging and ureteroscopy[36] and confirmed that invasion and hydronephrosis on pre-operative imaging and high-grade tumour at ureteroscopy or cytology were significantly associated with muscle-invasive UTUC on RNU specimen. The combination of these three reached an accuracy of 71% for predicting NOC UTUC.

Further research is needed to determine whether the use of these prediction models could help in patient counseling and decision-making regarding conservative management versus RNU, administration of neoadjuvant chemotherapy, and/or the performance of extended LND. The incorporation of novel biomarkers or modern imaging modalities could probably increase the accuracy of these models.[81] There is no doubt that pre-operative prediction is crucial for risk stratification and therefore the appropriate patient-specific management of UTUC.

2.7.2 Prediction of oncologic outcomes after radical nephroureterectomy

The rationale for post-operative assessment relies on the ability to propose adjuvant systemic therapy to patients at the highest risk of experiencing DR and ultimately death from UTUC. Moreover, it allows evidence-based follow-up scheduling. Several post-operative prognostic risk factors have been identified to help in this clinical decision-making process. Currently, decisions are made based on individual attribution of risk to pathologic stage,[48] tumour grade,[48] LVI,[4] LNI,[45,48,82] and extent of lymphadenectomy.[82] Several nomograms have integrated most of these features to predict DR and CSM after RNU for patients with UTUC.[83–85]

Jeldres *et al.* proposed the first nomogram for UTUC in the post-operative setting.[83] Within the Surveillance, Epidemiology, and End Results (SEER) database, the authors identified 5,918 patients who had been treated with RNU for UTUC and randomly split them into a development (n=2,959) and an external validation (n=2,959) cohort. Their model, which was based on age, tumour stage, tumour grade, and LN status, predicted 5-year CSS with an accuracy of 75.4%. It was significantly more accurate (p<0.01) than the 2002 American Joint Committee on Cancer–International Union Against Cancer (AJCC/UICC) TNM classification, at 64.8%. However, the tumour grading system they used was a historical classification.[1]

Recently, three new nomograms were proposed, one from the French Collaborative Group,[84] one from the International UTUC Collaboration,[85] and one combining the two datasets of patients.[86] Yates *et al.* combined clinical and pathologic variables to give accurate predictions regarding 5-year CSS.[84] Their cohort included 667 patients from 21 French institutions who underwent RNU for UTUC. Using five variables (age, tumour location, tumour grade, T stage, and LN status), this nomogram had a predictive accuracy of 78%.

The International UTUC Collaboration nomogram study[85] combined several more novel prognostic factors than the previous nomograms: age, T stage, tumour grade, LN status, LVI, architecture of the tumour, and concomitant CIS. Cha *et al.*[85] included 2,244 patients treated with RNU without neoadjuvant or adjuvant therapy at 23 international institutions. Their nomograms predicted DR and CSM with 76.8% and 81.5% accuracy, respectively. These models offer improvements in calibration over AJCC-stage grouping.

Finally, the combined nomogram study included 3,387 patients treated with RNU.[86] The merged study population was randomly split into a development (n=2,371) and a validation (n=1,016) cohort. Decision curve analyses were used to select the most performant model, which included age, T stage, LN status, tumour architecture, and LVI. The discrimination of the nomogram was 79%, and it was well calibrated. Although these predictive tools offer an approach toward evidence-based integration of complex data, their clinical utility remains to be proven.

2.8 Limitations

2.8.1 Study design

The major limitations of all the data discussed above are the retrospective and multicentre design of the studies.[1,36,79,80,83–85] The low incidence of UTUC only allows such an approach in the first phase. To create a large cohort, national or international studies are needed, with multiple institutions and surgeons. Moreover, specific model criteria, such as inclusion and exclusion criteria, do not allow the use of models for patients with different characteristics, or for those who have been exposed to different treatment modalities.

2.8.2 Suboptimal predictive accuracy

No prediction model developed to date is perfect. This might be due to the lack of consideration of all potential risk factors and the inability to assemble all known prognostic factors optimally. Urothelial carcinomas have heterogeneous biological behaviour. Therefore, novel biomarkers and imaging tools are needed to capture the complex biological potential of UTUC, and thereby enhance the predictive accuracy of current tools.

2.8.3 Validation

These nomograms were satisfactorily accurate (discrimination between patients with or without the outcome of interest) and well calibrated (accuracy of a prediction for an individual patient). However, before these predictive tools are put into widespread use, they must be externally validated in populations other than the population used for their development.[87] Indeed, differences in disease and population characteristics, as well as in treatment protocols and expertise, may undermine the accuracy and calibration of predictive tools when they are applied to a different population. For example,

predictive tools that were developed using high-volume–centre databases may not be applicable to community practice. Only one single nomogram has been validated externally so far.[84] It is therefore necessary to externally validate all other predictive tools.[89]

Conclusions	LOE
Several predictive tools have been proposed in UTUC, both in the pre-operative and post-operative settings. To date, none has been externally validated.	3

2.9 Conclusions

Five years ago, there were no predictive tools to help us in the management of UTUC, and the strategy was mostly defined in parallel with bladder cancer. The drastic increase in the quality and quantity of UTUC research based on the power of international collaborative networks (i.e. the UTUC Collaboration and the French database) has allowed for the development of sophisticated mathematical modeling to accurately predict outcomes for each individual patient. Despite the significant added value of this information for our patients with UTUC, some limitations persist. In the future, prospective registry studies and clinical trials are necessary to advance our understanding and improve the care delivered to patients with UTUC. With the arrival of comparative effectiveness research combined with the power of personalized medicine tools such as tumour sequencing, a new era has begun, flattening the hurdles in the management of patients with UTUC. More than ever before, multiple specialties must come together to improve care for patients with UTUC through comprehensive collaborative research and tumour boards.[88]

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C3

Pathology

CHAIR

Brian D. Robinson, United States

MEMBERS

Eva Compérat, France

Donna E. Hansel, United States

Rodolfo Montironi, Italy

Committee 3

CONTENTS

Pathology

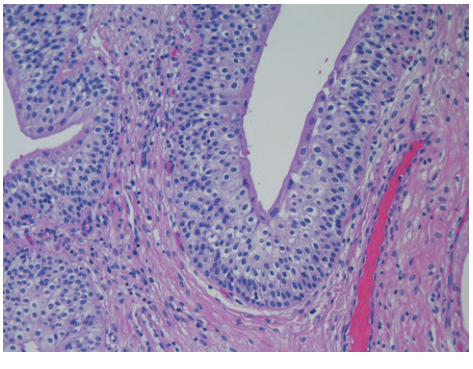
3.1 Introduction

With few exceptions, the pathology of upper tract urothelial carcinoma (UTUC) has been presumed to be the same as that of urothelial carcinoma of the bladder (UCB). While this assumption seems reasonable given that the histologic features of UTUC and UCB are virtually identical under the microscope, a growing body of evidence has begun to suggest that differences between these two cancers do exist. Nevertheless, studies specific to the pathology of UTUC remain rare and much of what we know about UTUC continues to be derived from studies of UCB. To that end, we owe a great deal of thanks to our colleagues from the 2nd International Consultation on Bladder Cancer in 2012 who provided us with an excellent review of UCB and the framework upon which to build these guidelines for UTUC. In the following pages, we review the pathologic features of urothelial carcinoma (UC) and provide information specific to UTUC, where data is available.

3.2 Non-Neoplastic and Pre-Neoplastic Changes in the Urothelial Mucosa

Normal urothelium is a multi-layered epithelium composed of basal, intermediate, and superficial cells (**Figure 3-1**). The number of cell layers in the upper urinary tract varies by location, with the renal pelvis having a slightly thinner urothelial layer (3–5 cells) compared with the ureter (4–7 cells)[1] The thickness of the urothelium may also vary due to tissue orientation and tangential sectioning, factors that must be kept in mind when assessing for hyperplasia.[2]

FIGURE 3-1
Normal urothelium of the renal pelvis.

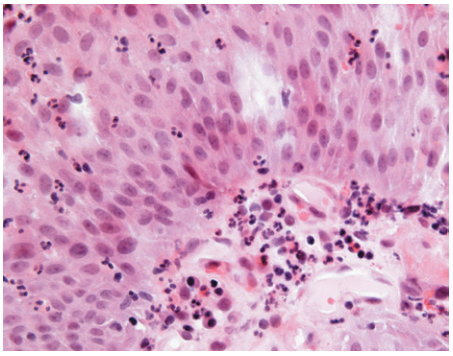


3.2.1 Reactive epithelial changes

Calculi, stents, acute and/or chronic inflammation, infection, radiation therapy, and chemotherapy are just some of the factors that may lead to reactive epithelial changes (**Figure 3-2**). Clinical history and close examination are key to preventing misdiagnosis as either dysplasia or carcinoma *in situ* (CIS). Reactive urothelium maintains relatively normal nuclear polarity without much disorganization. The nuclei are generally uniform in size and show only slight enlargement compared with normal urothelial cells. There is no hyperchromasia and little to no nuclear membrane irregularity.

Nucleoli may be present, including multiple nucleoli in a single nucleus, but they are generally small. Immunohistochemistry (IHC) may be helpful in distinguishing reactive changes from CIS (See section "3.9 – Immunohistochemistry and Molecular Markers").

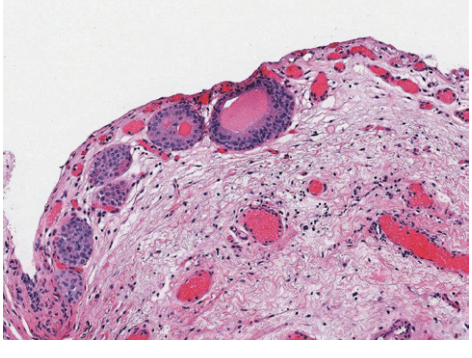
FIGURE 3-2
Reactive epithelial changes.



3.2.2 Urothelial denudation

Instrumentation, inflammation, and the presence of calculi or stents are benign conditions that may lead to denudation of the urothelium. However, the presence of extensive or complete denudation in a biopsy should raise suspicion of CIS, particularly in a patient with a prior history of carcinoma (**Figure 3-3**). In a study by Levi *et al.*, CIS was subsequently diagnosed in 31% of all patients with denuded biopsies, but this number increased to 75% in patients who had denuded biopsies as well as a history of CIS.[3] In another study, 54% of patients with denuded biopsies had concurrent positive urine cytology, reinforcing the need to send urine for cytologic examination in these patients.[4] Denudation in papillary neoplasms should also raise the pathologist's suspicion of high-grade carcinoma, as 79% of denuded papillary tumours were associated with high-grade papillary urothelial carcinomas, in one study.[5] Pathologists should scrutinize denuded biopsies for the presence of residual high-grade cells in order to allow for accurate diagnosis. The presence of extensive or complete denudation should be reported.

FIGURE 3-3
Denuded urothelial mucosa. Another area of this same biopsy showed residual carcinoma cells clinging to the surface.



3.2.3 Squamous metaplasia

Squamous metaplasia is usually due to chronic irritation of the urothelium, such as with stent placement, renal or ureteral calculi, and ureteritis or pyelonephritis. Non-keratinizing squamous metaplasia is considered a benign condition with no malignant potential. However, keratinizing squamous metaplasia has been associated with the development of invasive and *in situ* carcinomas that have squamous differentiation. It is a proposed precursor of squamous cell carcinoma.[6] Pathologists should report the presence of squamous metaplasia in biopsies and indicate whether it is keratinizing or non-keratinizing.

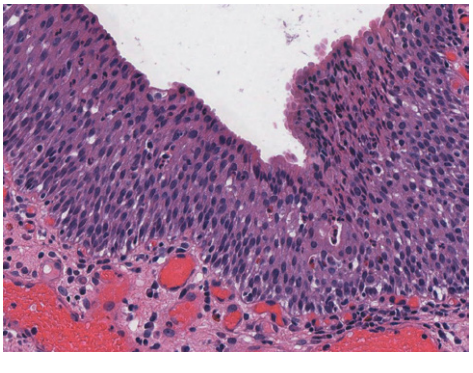
3.2.4 Proliferative ureteritis and pyelitis

Proliferation of von Brunn nests, ureteropyelitis cystica, and ureteropyelitis glandularis represent a spectrum of proliferative changes that are histologically identical to those seen in the bladder. Although these lesions are inverted (endophytic), they may appear as a polypoid mass cystoscopically. Von Brunn nests refer to small groups of basal-like cells lying in the subepithelial connective tissue that have a connection to the overlying urothelium. However, this connection is not often evident in histologic sections. Ureteropyelitis cystica forms from cystic dilatation of von Brunn nests with acquisition of a luminal space. Ureteropyelitis glandularis has the architecture of ureteropyelitis cystica, but the cells of the luminal border have a cuboidal or columnar shape as opposed to the basal appearance in von Brunn nests and ureteropyelitis cystica. Occasionally, intestinal metaplasia may be seen within ureteropyelitis cystica et glandularis.

3.2.5 Flat urothelial hyperplasia

Flat urothelial hyperplasia is characterized by markedly thickened mucosa with an increase in the number of cell layers of usually 10 or more (**Figure 3-4**). The cells in urothelial hyperplasia do not show any significant cytologic abnormalities, although slight nuclear enlargement may be focally present. Morphologic evidence of maturation from base to surface is generally evident. Mitotic figures are rare. Urothelial compression artifact or tangential sectioning of mucosa with pseudopapillary growth (lacking a true vascular core) may resemble flat urothelial hyperplasia.[2,7,8]

FIGURE 3-4
Urothelial hyperplasia.

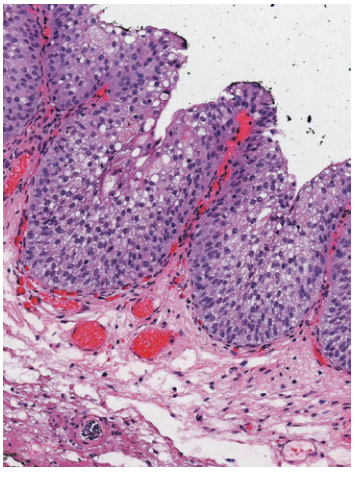


Flat urothelial hyperplasia has been observed in association with a variety of conditions including inflammatory disorders, urolithiasis, papillary urothelial hyperplasia, dysplasia, CIS, and low-grade papillary tumours. When seen as an isolated phenomenon, there is no evidence to suggest that urothelial hyperplasia has malignant potential. However, molecular analyses showing chromosome 9q deletions and mutations in the fibroblast growth factor receptor 3 gene in both urothelial hyperplasia and low-grade papillary neoplasia, suggest that this lesion may be clonally related to papillary tumours.[9] Flat urothelial hyperplasia has been considered by some authors to be the source of papillary neoplasia that is generally associated with low-grade tumours.[8,10]

3.2.6 Papillary urothelial hyperplasia

Papillary urothelial hyperplasia, another putative precursor of urothelial carcinoma, is characterized by undulating, thin, corrugated or pleat-like mucosal papillary folds that are non-branching. The folds may vary in height and are lined by multiple layers of cytologically normal urothelial cells that maintain normal nuclear polarity and are not accompanied by inflammation (**Figure 3-5**). Mitotic figures are rare. Although considered "hyperplastic," papillary hyperplasia may be surfaced by normal-appearing urothelium that are only 4 to 7 cells in thickness. There may be increased vascularity in the stroma at the base of the papillary folds.

FIGURE 3-5
Papillary urothelial hyperplasia.



Clinical studies of papillary hyperplasia are limited. Taylor *et al.* reported 16 cases of "typical" papillary hyperplasia occurring in patients with either a prior or concurrent low-grade papillary urothelial neoplasia.[11] The majority of their patients were men (11 men and 5 women) with a mean age of 67.5 years (range: 40—89 years). The lesion is considered by some to be the clonal precursor of papillary urothelial carcinoma based on associated genetic anomalies, but others contend that it actually represents early undiagnosed papillary carcinoma.[7,8]

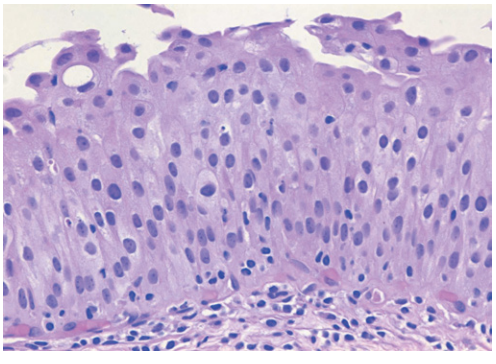
The primary differential diagnoses of papillary hyperplasia include papilloma, low-grade papillary carcinoma, and polypoid/papillary cystitis. In contrast to low-grade papillary neoplasms, papillary hyperplasia lacks well-defined central fibrovascular cores, arborization, and detached papillary fronds. Papillary hyperplasia also lacks the broad-based stalks and inflammation seen in polypoid/

papillary cystitis. Some cases of polypoid/papillary cystitis may have thin, non-branching, finger-like papillae, however papillary urothelial hyperplasia is not accompanied by abundant inflammation as seen in polypoid/papillary cystitis.[7,8]

3.2.7 Urothelial dysplasia

Urothelial dysplasia is a flat urothelial lesion with cytologic and architectural changes that raise concern for carcinoma *in situ* but do not m*eet all* of the criteria for an unequivocal diagnosis of CIS (**Figure 3-6**).[7,8,12] Overall, the urothelium in dysplasia is similar to that seen in low-grade papillary urothelial carcinoma. Cytologic abnormalities include cellular crowding, loss of orderly maturation, and loss of cellular polarity. However, these changes typically do not involve the full thickness of the urothelium, as most cellular abnormalities in dysplasia are restricted to the basal and intermediate cell layers. These alterations are not as pronounced as in CIS. Occasionally, there may be an increased number of cell layers. The superficial umbrella cells are usually present. Individual dysplastic cells show enlarged nuclei and nucleoli with irregular contours and coarsening of the chromatin. Multiple nucleoli and nuclear overlapping may be seen. Mitotic figures, when present, are generally basally located. The transition from normal to abnormal urothelium is subtle, and normal urothelial cells are often dispersed among the dysplastic cells.

FIGURE 3-6
Urothelial dysplasia.



It has proven difficult to create standardized nomenclature for intraurothelial cytologic abnormalities. Consequently, grading of urothelial dysplasia is not currently recommended. Therefore, the use of the term "atypia" as a synonym for either urothelial dysplasia or reactive epithelial changes is discouraged. Intraurothelial cytologic abnormalities that cannot be attributed to a reactive or reparative process and that lack sufficient abnormalities to be diagnosed as CIS, should be diagnosed as urothelial dysplasia, without qualifiers.

"Primary dysplasia" occurs in the absence of other urothelial tumours.[12–17] Its prevalence in the general population is unknown, due to the lack of large-scale screening studies. In an autopsy series of 313 patients without gross lesions, urothelial dysplasia was present in 6.8% of males and 5.7% of females. Dysplasia is not endoscopically visible, although occasionally the urothelium may appear raised and irregular or mildly erythematous. It is estimated that *de novo* (primary) dysplasia progresses to bladder neoplasia in 14 to 19% of cases. Using modern criteria for urothelial dysplasia, Cheng *et al.* found a 19% progression rate in 36 patients with isolated urothelial dysplasia during a mean follow-up of 8.2 years.[18] A similar progression rate (15%) was found in a different cohort of patients.[16,18]

"Secondary dysplasia" is seen in patients with a history of urothelial neoplasia. The incidence of dysplasia in these patients varies from 22% to 86%, approaching 100% in patients with invasive carcinoma. As many as 24% of random biopsies from patients with papillary non-invasive carcinoma (pTa) and lamina propria invasion (pT1) show epithelial abnormalities that include dysplasia and CIS. The presence of urothelial dysplasia indicates urothelial instability and is a harbinger of recurrence and progression. The recurrence rate was 73% in patients with superficial neoplasia and concomitant dysplasia, compared with 43% in those patients without coexisting dysplasia. Of the 30% of patients with superficial urothelial carcinoma of the bladder who developed muscle invasive cancer within 5 years after the initial diagnosis, most had dysplasia or CIS adjacent to the primary tumour. In the patients who also had dysplasia that was distant from the primary tumour, 36% eventually developed muscle invasive tumours, whereas only 7% of patients with normal urothelium in adjacent biopsies subsequently developed muscle invasive cancer.[12,15]

3.3 Classification and Grading of Urothelial Neoplasms

Ureteroscopic evaluation with biopsy is currently the gold standard for both visualizing and diagnosing tumours of the upper urinary tract. Unfortunately, the small diameter of the ureteral lumen limits the types of instruments that can be used to obtain an adequate biopsy. This may yield suboptimal tissue for accurately diagnosing, grading, and staging biopsy specimens taken from the upper urinary tract.[19–26]

Classification of upper tract urothelial carcinoma mirrors that of the urinary bladder, with all lesions of the bladder urothelium being possible in the upper tract and *vice versa*. The classification approach proposed by the World Health Organization (WHO) in 2004 is summarized in **Table 3-1**[27] There are three major groups of non-invasive urothelial neoplasms: flat, papillary, and inverted.[7,8] These three groups share a similar morphological spectrum of intraurothelial changes, ranging from hyperplasia to dysplasia to carcinoma *in situ*. However, they differ in terms of architectural growth patterns compared to the surrounding non-neoplastic mucosal surface. For example, they may remain confined within the thickness of the epithelium (flat), grow exophytically within the lumen of the organ (papillary), or grow endophytically in a non-infiltrative manner within the subepithelial connective tissue (inverted).[7] These groups do not represent three separate pathways of recurrence and/or progression. Different growth patterns of tumour may be seen synchronously or metachronously in a given patient.

TABLE 3-1 WHO/ISUP Classification of Tumours of the Urinary Tract (2004)

Urothelial tumours
Infiltrating urothelial carcinoma
▪ with squamous differentiation ▪ with glandular differentiation ▪ with trophoblastic differentiation ▪ Nested ▪ Microcystic ▪ Micropapillary ▪ Lymphoepithelioma-like ▪ Lymphoma-like ▪ Plasmacytoid ▪ Sarcomatoid ▪ Giant cell ▪ Undifferentiated
Non-invasive urothelial neoplasias
▪ Urothelial carcinoma in situ ▪ Non-invasive papillary urothelial carcinoma, high grade ▪ Non-invasive papillary urothelial carcinoma, low grade ▪ Non-invasive papillary urothelial neoplasm of low malignant potential ▪ Urothelial papilloma ▪ Inverted urothelial papilloma
Squamous neoplasms
▪ Squamous cell carcinoma ▪ Verrucous carcinoma ▪ Squamous cell papilloma
Glandular neoplasms

▪ Adenocarcinoma
  ▪ Enteric
  ▪ Mucinous
  ▪ Signet-ring cell
  ▪ Clear cell
▪ Villous adenoma

Neuroendocrine tumours
▪ Small cell carcinoma ▪ Carcinoid ▪ Paraganglioma
Melanocytic tumours
▪ Malignant melanoma ▪ Nevus

continued **on page 90**

TABLE 3-1 WHO/ISUP Classification of Tumors of the Urinary Tract (2004), *Cont'd*

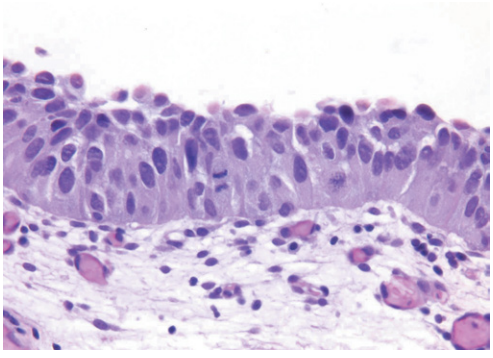
Mesenchymal tumours
▪ Rhabdomyosarcoma ▪ Leiomyosarcoma ▪ Angiosarcoma ▪ Osteosarcoma ▪ Malignant fibrous histiocytoma ▪ Leiomyoma ▪ Haemangioma ▪ Other
Haematopoietic and lymphoid tumours
▪ Lymphoma ▪ Plasmacytoma
Miscellaneous tumours
▪ Carcinoma of Skene, Cowper and Littre glands ▪ Metastatic tumours and tumours extending from other organs

3.3.1 Non-invasive flat urothelial neoplasms

3.3.1.1 Urothelial carcinoma in situ

Urothelial carcinoma *in situ* has been recognized for several decades as a precursor of invasive bladder cancer. It is characterized by a flat, disordered proliferation of urothelial cells with marked cytologic abnormalities (**Figure 3-7**). The morphological diagnosis of CIS requires severe cytological atypia, including large, irregular, and hyperchromatic nuclei that are typically greater than 5 to 6 times the size of normal lymphocytes. Full thickness involvement of the mucosa is not required, as CIS may be present as single cells clinging to the mucosal surface or as pagetoid spread within otherwise normal urothelium. Superficial umbrella cells may or may not be present. Marked disorganization of cells is characteristic, with loss of cellular polarity and decreased cellular cohesiveness. The tumour cells tend to be large and pleomorphic, with moderate to abundant cytoplasm. Nevertheless, the cells of CIS are sometimes small and have a high nuclear-to-cytoplasmic ratio. The chromatin tends to be coarse and clumped. Nucleoli may be multiple and they are often large and prominent in at least some of the cells. Mitotic figures, which are often atypical, are seen throughout the lesion, including in the uppermost layers of the urothelium. The adjacent mucosa often contains lesser degrees of cytologic abnormality. Tissue edema, vascular ectasia, and proliferation of small capillaries are frequently observed in the lamina propria.[7,8]

FIGURE 3-7
Urothelial carcinoma in situ.



The CIS cells are easily detached from the surface, facilitating their detection in exfoliative cytology specimens, but frequently resulting in a denuded appearance on biopsy tissue sections. This finding is designated "denuding cystitis" or "clinging CIS." Extensive or complete urothelial denudation should raise concern for the possibility of CIS, particularly when there is a history of treated carcinoma. Urine cytology or washings or brushings of the ureter or renal pelvis may be helpful in such a setting, since easily denuded malignant cells may be readily detected by that means[3]

Melamed *et al.* first described the natural history of urothelial carcinoma *in situ* of the bladder and found that 9 out of 25 patients (36%) developed invasive carcinoma within 5 years after the initial diagnosis.[28] Since then, studies have shown the actuarial progression-free survival, cancer-specific survival, and all-cause survival rates in bladder to be 63%, 79%, and 55%, respectively, at 10 years. Survival rates are 59%, 74%, and 40%, respectively, at 15 years.[29] Factors predictive of progression include multifocality, coexistent bladder neoplasia, DNA aneuploidy, cyclin D3 gene amplification, and recurrence after treatment.[9,12]

The natural history of CIS in the upper tract has not been established because these lesions are frequently treated by radical surgery upon initial diagnosis. Also, the prevalence of isolated CIS in the absence of other urothelial neoplasia is less common in the renal pelvis and ureter than in the lower tract.[30] However, the presence of concomitant CIS is a known poor prognostic factor in patients with organ confined UTUC after radical nephroureterectomy.[31] Endoscopically, CIS may appear as erythematous velvety or granular patches, although it may also be visually undetectable. Erythematous changes are often apparent at gross examination.

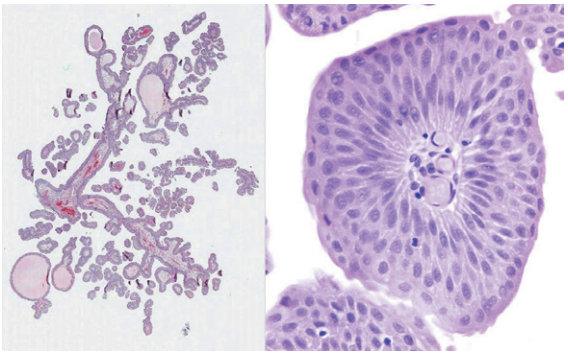
3.3.2 Non-invasive papillary urothelial neoplasms

According to the 2004 WHO classification, this group includes urothelial papilloma, papillary urothelial neoplasm of low malignant potential (PUNLMP), low-grade papillary urothelial carcinoma, and high-grade papillary urothelial carcinoma. Papillary urothelial neoplasm of low malignant potential, low-grade papillary carcinoma, and high-grade papillary carcinoma show a morphological spectrum that parallels that seen in flat hyperplasia, dysplasia, and CIS, respectively.

3.3.2.1 Urothelial papilloma

There has been a long-standing controversy regarding the nature of papillary lesions with minimal cytologic atypia (**Figure 3**-8). The application of this term by some experts to up to one-third of all papillary lesions was a major stimulant to the reevaluation of these lesions that began in 1997. The current classification retains the very restrictive traditional criteria. Histologically, papilloma is characterized by a few fine papillary fronds without fusion or complexity. Individual fronds are covered by an essentially normal urothelium without architectural or cytologic atypia. Papillomas meeting these restricted criteria occur at a younger age than other urothelial tumours and often present with only one or a few papillary processes. In the urinary bladder, these lesions have a low recurrence rate.[7,8,10] Urothelial papillomas in the upper urinary tract are, in our experience, even more uncommon than in the urinary bladder, and few studies that use the current 2004 WHO grading criteria have included urothelial papillomas in their cohorts, likely reflecting their rarity.[32]

FIGURE 3-8
Urothelial papilloma.

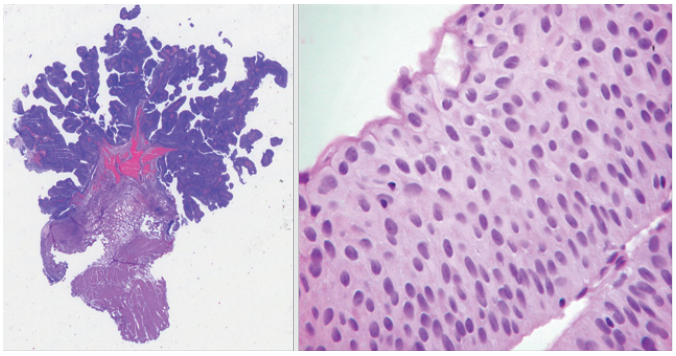


3.3.2.2 Papillary urothelial neoplasm of uncertain malignant potential

The creation of this category represented a compromise between the "papilloma" supporters and those insisting on the use of "carcinoma" for all papillary lesions. The 1998 consensus statement acknowledged that the lower grade papillary neoplasms were not intrinsically malignant but were associated with a significant risk for the development of new papillary tumours (i.e., recurrence). These lesions at the lower end of the spectrum were acknowledged to be clinically significant, with close clinical follow up necessary but further intravesical therapy not indicated.[15]

PUNLMP resembles urothelial papilloma but shows increased cellularity that exceeds the thickness of normal urothelium (**Figure 3-9**) and is morphologically similar to that of flat hyperplasia. PUNLMP largely, though not completely, corresponds to grade 1 papillary carcinomas in the 1973 WHO system. The tumour consists of delicate papillae with little or no fusion. The covering urothelium shows minimal architectural irregularity. Nuclei lack significant nuclear hyperchromasia or pleomorphism. The chromatin is fine and nucleoli are inconspicuous. Mitoses are infrequent and are basally located when present. These tumours have a significantly lower rate of recurrence than either low- or high-grade papillary carcinomas and a very low rate of grade and stage progression. In a review of published studies, Lopez-Beltran found the mean tumour recurrence rate to be 36% and the stage progression rate to be 3.7%.[33]

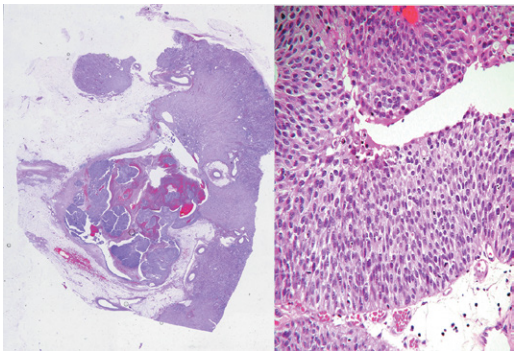
FIGURE 3-9
Papillary urothelial neoplasm of low malignant potential (PUNLMP).



3.3.2.3 Low-grade papillary urothelial carcinoma

The *low-grade papillary urothelial carcinoma* category contains the intermediate group of lesions. In the 1973 WHO system this group would include the lower half of grade 2 papillary carcinomas and the more atypical grade 1 carcinomas (**Figure 3-10**). Histologically, the papillae are largely delicate and separate but some fusion may be seen. At low magnification there is a generally ordered appearance of the cells within the epithelium. The nuclei tend to be uniformly enlarged but retain the elongated to oval shape of normal urothelial cells. The chromatin remains fine with small nucleoli. Scattered cells may show hyperchromasia but maintain a smooth and round nuclear contour. Mitoses may be present, but are few and remain basally located. Morphologically the epithelium in these tumours is similar to that seen in flat dysplasia.[7,8]

FIGURE 3-10
Non-invasive low grade papillary urothelial carcinoma.



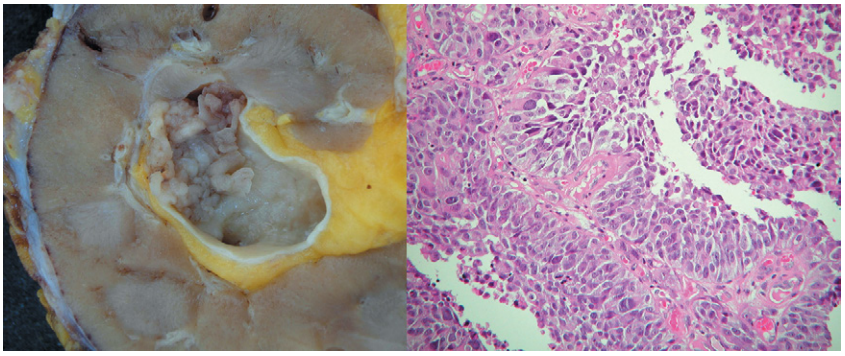
These tumours have a significantly higher recurrence rate than for PUNLMP, with rates comparable to those of high-grade papillary carcinomas. They also have a significantly higher rate of stage progression than PUNLMP, but progression rates are still much lower than for high-grade papillary carcinomas. A review of the literature revealed a mean recurrence rate of 50% and a mean stage progression rate of 10%.[8,10]

3.3.2.4 High-grade papillary urothelial carcinoma

The high-grade papillary urothelial carcinoma category contains all grade 3 carcinomas and the upper half of grade 2 papillary carcinomas in the former 1973 WHO system. Histologically, the papillae are frequently fused, forming apparent solid masses. The overall impression is one of disordered growth. The epithelium is of variable thickness. Individual cells are haphazardly arranged within the epithelium and have a generally discohesive nature. Nuclei are hyperchromatic and pleomorphic. The

chromatin is dense, irregularly distributed, and often clumped. Nucleoli may be single or multiple and are often prominent. Mitoses are generally frequent and may be seen at any level of the epithelium. The epithelial changes in this lesion correspond to those of flat CIS (**Figure 3-11**).[7,8,10]

FIGURE 3-11
Non-invasive high grade papillary urothelial carcinoma.



High-grade papillary urothelial carcinomas are often associated with invasive disease at the time of diagnosis.[34] These tumours not only have a risk of invasion but also have a significant risk of recurrence and progression. The overall progression rate to invasive carcinoma ranges from 15% to 40%. These tumours, even when non-invasive, should be treated aggressively. Heterogeneity of grade is recognized in papillary lesions and the consensus was that tumours should be graded on their worst part, although this needs further study.

3.3.2.5 Urothelial dysplasia and carcinoma in situ with "early papillary formation"

The basic architectural pattern is that of papillary urothelial hyperplasia. However, the features of the urothelium are those seen in flat dysplasia and CIS. These lesions are usually seen in follow-up biopsies of patients with a history of papillary urothelial lesions. Even though clinical studies on such lesions are still lacking, they are considered to represent the early phase of recurrence, with urothelial dysplasia and early papillary formation representing recurrence of a low-grade papillary urothelial carcinoma and CIS with early papillary formation representing recurrence of a high-grade papillary urothelial carcinoma.[35]

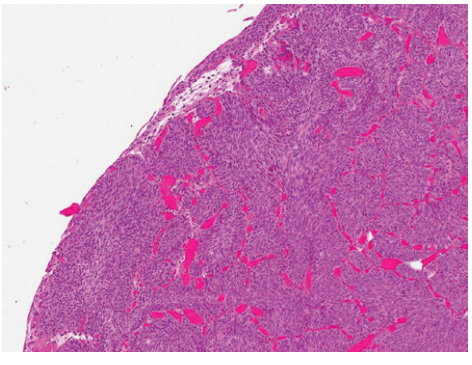
3.4 Non-Invasive Inverted Urothelial Neoplasms

Neoplasms of this group are characterized by non-infiltrative (non-invasive) growth downward into the subepithelial connective tissue as opposed to growth exophytically into the lumen. Endoscopically they often show a polypoid appearance.

3.4.1 Inverted urothelial papilloma

Included in the 2004 WHO classification, inverted urothelial papilloma has a polypoid appearance and consists of thin anastomosing trabeculae of urothelial cells within the subepithelial connective tissue. The surface of the lesion is covered by a normal or attenuated urothelium (**Figure 3-12**).[36,37] There is no nuclear pleomorphism and few mitoses can be seen. Inverted papilloma is associated with a low risk of recurrence (<5%). Cases of synchronous inverted papilloma and papillary carcinoma are known.

FIGURE 3-12
Inverted urothelial papilloma.



3.4.2 Morphologic spectrum of inverted urothelial neoplasms

Urothelial neoplasms with an inverted growth pattern (other than inverted urothelial papilloma) show a spectrum of architectural and cytological features with overall intraurothelial changes ranging from hyperplasia to CIS. Thus, classification of these lesions is similar to exophytic papillary neoplasms: inverted urothelial neoplasm of low malignant potential (IUNLMP), low-grade inverted urothelial carcinoma, and high-grade inverted urothelial carcinoma.

In comparison with inverted urothelial papilloma, the architectural features favoring a diagnosis of a urothelial neoplasm with an inverted growth pattern include thick columns with irregularity in their width and transition into more solid areas. The characteristic orderly maturation, spindling, and peripheral palisading seen in inverted papilloma are generally absent or inconspicuous. The histological appearance of urothelial neoplasms with a broad-front pattern is the pushing broad-front extension into the lamina propria. This is akin to cutaneous and mucosal verrucous carcinoma and reminiscent of the growth pattern of the von Brunn nests. The downward projection can be so pronounced that the base of the tumour lies on the muscularis propria.

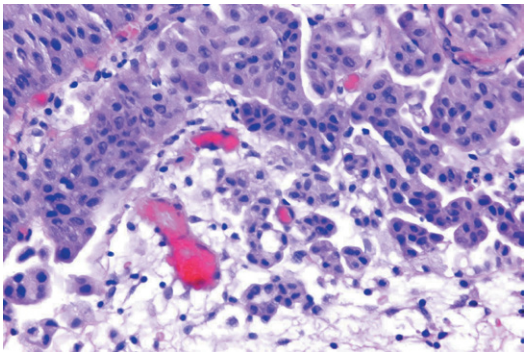
Non-invasive urothelial carcinomas with inverted growth patterns have been reported in the literature and mentioned in some recent books.[38–40] The endophytic growth pattern in this carcinoma has been described in two ways. It can comprise either as inter-anastomosing cords and columns of urothelium, often with a striking resemblance to inverted papilloma (inverted papilloma-like pattern), or as broad, pushing bulbous invaginations into the lamina propria (broad-front pattern). A diagnosis of invasion requires the unquestionable presence within the lamina propria of irregularly-shaped

nests or single cells that may have evoked a desmoplastic or inflammatory response. When a stromal response is absent, irregularity of the contours of the invasive nests, architectural complexity, and recognition of single-cell invasion are helpful.

3.5 Invasive Urothelial Carcinoma

Infiltrating urothelial carcinoma is defined by the WHO as a urothelial tumour that invades beyond the basement membrane. The 2002 tumour node metastasis (TNM) staging system defines pT1 tumours of the ureter and renal pelvis as those invading the lamina propria, but not the muscularis propria. The recognition of lamina propria invasion by urothelial carcinoma is one of the most challenging areas in surgical pathology and the pathologist should follow strict criteria in its assessment (**Figure 3-13**).[2,41]

FIGURE 3-13
Lamina propria invasion (pT1).



Most tumours present as a single, solid, polypoid mass with or without ulceration. They also may appear sessile and extensively infiltrate the bladder wall. Histologically, the neoplastic cells invade the bladder wall as nests, cords, trabeculae, small clusters, or single cells that are often separated by a desmoplastic stroma. The tumour sometimes grows in a more diffuse, sheet-like pattern, but even in these cases, focal nests and clusters are generally present. The cells show moderate to abundant amphophilic or eosinophilic cytoplasm and large hyperchromatic nuclei. In larger nests, palisading of nuclei may be seen at the edges of the nests. The nuclei are typically pleomorphic and have irregular contours with angular profiles. Nuclear grooves may be identified in some cells. Nucleoli are highly variable in number and appearance. Some cells contain single or multiple small nucleoli and others have large eosinophilic nucleoli. Foci of marked pleomorphism may be seen, with bizarre and multinuclear tumour cells present. Mitotic figures are common, including many abnormal forms. Invasive tumours are most commonly high grade, usually showing marked anaplasia with focal giant cell formation. Pathologic stage is most critical for assessing patient prognosis.

Unlike in non-invasive papillary urothelial neoplasms, the role of histologic grade in pT1 and higher-stage tumours has been suggested to be of only relative importance. The 1998 ISUP consensus proposed that invasive tumours should be graded as low-or high-grade similar to the scheme used for grading non-invasive lesions.

3.5.1 Histologic grade

3.5.1.1 Correlation between biopsy tumour grade and resection tumour grade

In a recent study, Vashistha *et al.* achieved a grade concordance of 87.1% between upper tract biopsies and the follow-up resection specimens, and almost all biopsies were able to be graded (97.5%).[42] Discordance was more frequently due to under-grading rather than over-grading (60.0% and 40.0%, respectively). Renal pelvic biopsies (91.7%) had a slightly higher grade concordance than those of the ureter (85.1%). These findings are in agreement with previous studies examining biopsy grade in UTUC, which demonstrated concordance rates ranging from 72% to 92.6%.[43] Therefore, in the vast majority of cases, the histologic grade assigned to the ureteroscopic biopsy sample predicts histologic grade in the resected specimen. Grading in ureteroscopic biopsies provides sufficient information for clinical decision making.

3.5.1.2 Relation of 1973 WHO to 2004 WHO classification

A major misconception is that there is a one-to-one translation between the 1973 and the 2004 WHO classifications. Only at the extremes of grades in the 1973 WHO classification system does this correlation hold true.[7,44] Lesions called papilloma in the 1973 WHO classification system would also be called papilloma in the 2004 WHO system. At the other end of the grading extreme, lesions called grade 3 in the 1973 WHO system are by definition high-grade carcinoma in the 2004 WHO system. However, for 1973 WHO grades 1 and 2, there is no direct translation to the 2004 WHO system. Some carcinomas classified as grade 1 in the 1973 system show no cytologic atypia and a merely thickened urothelium. These would be considered papillary urothelial neoplasms of low malignant potential in the 2004 system. However, other 1973-system grade 1 lesions showing slight cytologic atypia and scattered mitoses are diagnosed in the 2004 system as low-grade papillary urothelial carcinomas. Grade 2 in the 1973 system is a very broad category. It includes lesions that are relatively bland. In some places they are diagnosed as grade 1-2 under the 1973 system. However, in the 2004 system they would be called low-grade papillary urothelial carcinoma. In other cases, 1973-system grade 2 lesions border on higher grade lesions that many institutions identify as grade 2-3 under the same system. However, these same lesions would be called high-grade papillary urothelial carcinomas in the 2004 WHO classification system.[7,44]

3.5.2 Inter- and intra-observer reproducibility studies on grading

Most published observer variability studies showed that both the WHO 2004 and WHO 1973 grading systems for bladder urothelial neoplasm suffered from suboptimal observer agreement among pathologists, with most studies showing only moderate agreement.[45] The 2004 system showed relatively better reproducibility than the WHO 1973 system. Among the 2004 system grades, PUNLMP and papilloma had the lowest inter-observer reproducibility. Also, distinction between PUNLMP and low-grade papillary carcinoma appeared to be the most difficult. Condensing PUNLMP and low-grade papillary carcinoma improved grading reproducibility of the 2004 system. Evidence showed that education of pathologists might help improve inter-observer reproducibility of PUNLMP versus low-grade papillary carcinoma. For high-grade papillary carcinoma, a reason for inter-observer variability was tumour heterogeneity wherein a focus of high grade was not accounted for amidst a predominantly low-grade papillary tumour.

3.5.3 Grading papillary urothelial neoplasms with histologic heterogeneity

Papillary urothelial neoplasms encompass a spectrum of morphologic findings, including tumours that behave aggressively and tumours that are biologically benign. Attempting to differentiate biologic behavior based solely on subtle histopathological criteria poses significant challenges, especially considering the significant inter-observer variability that has been documented in numerous studies with all classification schemes. The system of the World Health Organization of 2004/International Society of Urological Pathology, hereafter called the WHO (2004)/ISUP, provides clearly defined histologic criteria for each of its diagnostic categories. However, urothelial neoplasms frequently demonstrate features of more than one grade. The grading of papillary urothelial tumours is typically based on the worst grade present.[15] However, cancer heterogeneity could have a significant impact on patient outcome. Cheng *et al.* examined 164 patients with stage pTa urothelial tumours and found that approximately one-third of tumours had morphologic tumour heterogeneity consistent with more than one histologic grade.[46] They graded both the primary and secondary patterns of tumour growth by the WHO (2004)/ISUP criteria with PUNLMP, low-grade carcinoma, and high-grade carcinoma patterns receiving scores of 1, 2, and 3, respectively. Each tumour was then evaluated by a combined scoring system on a scale of 2 to 6. With a median follow-up of 9.2 years, the prognosis of patients with a combined score of 6 (the entire tumour consisting of high-grade carcinoma) is considerably worse than those with a combined score of 5 (a tumour consisting of low- and high-grade carcinoma). The progression-free 10-year survival rates were 26% and 68%, respectively, p=0.02). The significant survival difference (42%) between score 5 and score 6 groups may suffice to warrant different management strategies in appropriate settings. Subsequent studies have also suggested that combined scoring systems may be useful in the grading of urothelial tumours.[47–49] Grading should take cancer heterogeneity into consideration, as prognostic accuracy was increased when the combined primary and secondary grades were applied.

Neither the WHO (2004)/ISUP system nor the WHO 1973 system takes tumour heterogeneity into account. However, the WHO 1973 system does allow a greater amount of diagnostic flexibility in that tumours are frequently classified as grade 1-2 or grade 2-3. This added flexibility may actually give a more accurate representation of the tumour histology than attempting to force a lesion into a single diagnostic category. It appears that prognostic accuracy is improved when heterogeneity is considered. Future investigations will be needed to fully address the impact of tumour heterogeneity on clinical outcome.

3.5.4 Grading invasive urothelial carcinomas

Both WHO (2004)/ISUP and the older WHO 1973 grading systems when applied to pT1 tumours are confronted by the fact that the vast majority of invasive tumours are high-grade. High-grade tumours are listed as such in the WHO (2004)/ISUP system and as grade 2 and grade 3 in the WHO 1973 system. Few tumours are classified as low grade. Because of the predominance of high-grade tumours, no study has shown the value of WHO (2004)/ISUP system in pure pT1 tumours (without including pTa tumours). The older 1973 system has shown the ability in some studies to provide grade dichotomy (or divisions) in the invasive pT1 tumours (i.e. grade 2 versus grade 3 or high-grade grade 2 versus high-grade grade 3). Such grade assignments are difficult in routine practice. Criteria

for grading in invasive settings or impact on management, based on grade, are not well defined. It is recommended therefore that when tumours are invasive, irrespective of depth, they should be considered high grade. This rule is also applicable to deceptively bland variants such as the nested or small tubular variants that histologically appear low grade but which tend to behave like invasive high-grade tumours of similar stage.[41]

3.6 Pathologic staging

Upper tract urothelial carcinoma typically presents as a solitary mass originating within the ureter or renal pelvis, although multifocal tumours are not rare. The tumours are generally solid lesions with a whitish color that may be polypoid, papillary, or sessile. Tumours may grossly appear friable, pedunculated, and non-invasive (**Figure 3-14**), or they may present as an ill-defined and infiltrative firm mass (**Figure 3-15**). Thorough sectioning of the base of the papillary tumour, the renal sinus and periureteral fat, and renal parenchyma is crucial to accurate staging, which continues to be one of the most important prognostic factors in UTUC.[50] A summary of staging definitions for UTUC is presented in **Table 3-2**.[51]

FIGURE 3-14
Non-invasive papillary urothelial carcinoma.

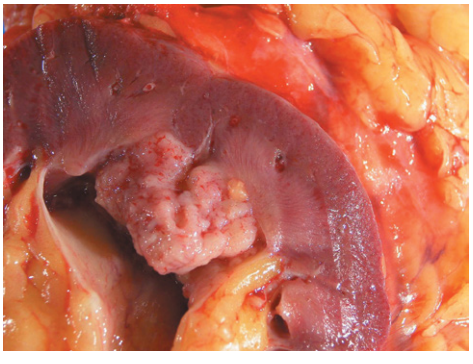


FIGURE 3-15
Invasive urothelial carcinoma.

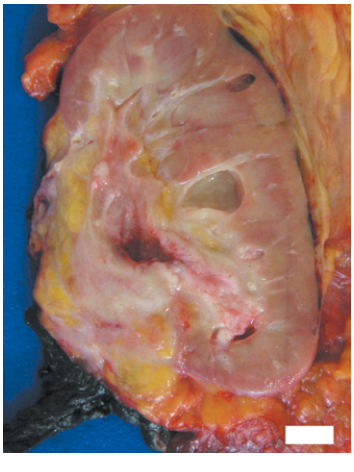


TABLE 3-2 Pathologic Staging of Tumours of the Renal Pelvis and Ureter

Primary Tumour (T)
pTx – Primary tumour cannot be assessed
pT0 – No evidence of primary tumour
pTa – Papillary non-invasive carcinoma
pTis – Carcinoma in situ
pT1 – Tumour invades subepithelial connective tissue (lamina propria)
pT2 – Tumour invades muscularis propria
pT3 – For renal pelvis only: Tumour invades beyond the musculars propria into peripelvic fat or renal parenchyma
pT3 – For ureter only: Tumour invades beyond the muscularis propria into periureteric fat
pT4 – Tumour invades adjacent organs or through the renal parenchyma into perinephric fat
Regional Lymph Nodes (N)
pNx – Regional lymph nodes cannot be assessed
pN0 – No regional lymph node metastasis
pN1 – Metastasis in a single lymph node, 2 cm or less in greatest dimension
pN2 – Metastasis in a single lymph node, more than 2 cm but not more than 5 cm in greatest dimension, or metastasis to multiple lymph nodes, none more than 5 cm in greatest dimension
pN3 – Metastasis in a lymph node more than 5 cm in greatest dimension
Distant Metastasis (M)
pMx – Distant metastasis cannot be assessed
pM0 – No distant metastasis
pM1 – Distant metastasis

3.6.1 Correlation between biopsy tumour stage and resection tumour stage

While grading of upper tract lesions on biopsy is relatively accurate, correctly staging upper tract tumours is fraught with difficulties, mainly due to the small size of the biopsy material available for diagnosis. Muscularis propria is rarely present in upper tract biopsies. Some biopsies may be so superficial that only epithelium is present, precluding assessment of invasion entirely. In the recent study by Vashistha *et al.*, they reported a primary tumour (pT) stage concordance of 60% for biopsies in which a stage was designated, however, a pT classification was not able to be assigned in 10.6% of cases.[42] The ureter (59.3%) and renal pelvis (62.5%) had similar pT stage concordance for biopsies that did have sufficient tissue for staging. If one includes unstaged biopsies in the analysis, though, pT stage concordance was only 52.5%, with a greater concordance for ureteral tumours (57.1%) compared to renal pelvis tumours (41.7%). In addition, almost all ureter biopsies were pT staged

(93.3%) as compared to biopsies taken from the renal pelvis (81%). The large number of unstaged renal pelvis biopsies and lower overall concordance rate may reflect the difficulty in extracting optimal tissue using the ureteroscope in the renal pelvis.

All stage discrepancies were due to under-staging, and one-third of biopsies initially diagnosed as non-invasive urothelial carcinoma ultimately showed invasive tumour upon follow-up pathology. Similar concordance rates (45.5%–68%) have been found in previous studies, although the percentage of unstaged biopsies (17.7%–32.5%) has varied or has not been specified.[20,23,26] Therefore, while tumour grading in biopsies is relatively accurate, particularly with larger tissue samples, tumour staging is unreliable.

3.6.2 Non-invasive carcinomas

Non-invasive carcinomas, whether low grade or high grade, are those tumours whose cells have not crossed the basement membrane, and thus are still physically separated from the subepithelial connective tissue. Non-invasive papillary urothelial carcinomas throughout the urinary system, including the ureter and renal pelvis, are considered pTa tumours according to the American Joint Commission on Cancer's tumour node metastasis staging system.[51] Urothelial carcinoma *in situ*, which is by definition a flat lesion, is considered separately and staged as pTis.

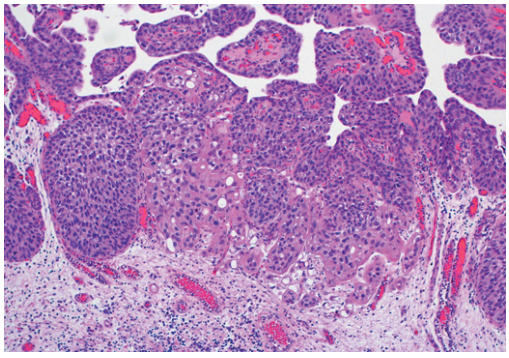
3.6.3 Invasive Carcinomas

Infiltrating urothelial carcinoma is defined by the WHO as a urothelial tumour that invades beyond the basement membrane. Neoplastic cells invade as nests, cords, trabeculae, small clusters, or single cells that are often separated by a desmoplastic stroma. Invasive tumours sometimes grow in a more diffuse, sheet-like pattern, but even in these cases focal nests and clusters are generally present. The cells show moderate to abundant amphophilic or eosinophilic cytoplasm and large hyperchromatic nuclei. In larger nests, palisading of nuclei may be seen at the edges of the nests. The nuclei are typically pleomorphic, hyperchromatic, and have irregular contours with angular profiles. Nuclear grooves may be identified in some cells. Nucleoli are highly variable in number and appearance. Some cells contain single or multiple small nucleoli and others have large eosinophilic nucleoli. Bizarre and multinucleated tumour cells may be present. Mitotic figures are common, including many abnormal forms.

3.6.3.1 Lamina propria invasion

The recognition of lamina propria invasion by urothelial carcinoma is one of the most challenging areas in surgical pathology, and the pathologist should follow strict criteria in its assessment.[2,41] Most commonly, tumours invade the underlying stroma as single cells or irregularly shaped nests of tumour cells. Sometimes finger-like extensions can be seen arising from the base of a papillary tumour. Frequently, the invading nests appear cytologically different from cells at the base of the non-invasive component. Invasive tumour cells often have more abundant cytoplasm and a higher degree of nuclear pleomorphism. In some cases, particularly in microinvasive disease, the invasive tumour cells may acquire abundant eosinophilic cytoplasm (**Figure 3-16**). At low to medium power magnification, these microinvasive cells seem to be more differentiated than the overlying non-invasive disease, a feature known as paradoxical differentiation.[41]

FIGURE 3-16
Superficial lamina propria invasion showing the irregular tongues and paradoxical differentiation (pink cytoplasm) of the invasive carcinoma cells.



Invasive carcinomas that are limited to the lamina propria (i.e. no involvement of the muscularis propria), whether focal or extensive, are considered pT1 tumours. In contrast to the urinary bladder, the ureter and renal pelvis generally lack muscularis mucosae, and there is no substaging of pT1 tumours in the upper urinary tract. Adipose tissue is also rarely present in the lamina propria of the ureter and renal pelvis.

3.6.3.2 Muscularis propria invasion

Invasion of tumour into the muscularis propria is considered stage pT2. Compared to the muscularis propria of the bladder, the renal pelvis and ureter muscularis propria is quite thin. In fact, in the pelvicalyceal system where urothelial mucosa directly overlies renal parenchyma, muscularis propria may be entirely absent, with only a thin layer of fibrous connective tissue between the urothelium and the kidney. The muscularis propria bundles are also relatively compact in the upper urinary tract. Adipose tissue is rarely present between the layers. The thinness of the muscularis propria in the upper urinary tract (UUT) may be one reason for the increased incidence of pT3 and pT4 tumours in the ureter and renal pelvis, as compared to the urinary bladder. Tumours in the renal pelvis that are staged pT3 invade beyond the muscularis propria into peripelvic fat or renal parenchyma. In the ureter, pT3 tumours invade beyond the muscularis propria into periureteric fat. Tumours that invade adjacent organs or invade through the renal parenchyma into perinephric fat are staged pT4.

3.6.3.3 Peripelvic/periureteral fat invasion

Invasion through the muscularis propria constitutes pT3 disease and most frequently manifests as sheets, nests, or single tumour cells infiltrating periuretereal or renal hilar (peripelvic) adipose tissue. Occasionally, though, tumour cells or nests of cells may clearly be beyond the muscularis propria layers but, due to a desmoplastic stromal response, do not intermingle directly with fat cells. These tumours should still be staged as pT3 tumours, based upon the TNM system of the American Joint Committee on Cancer (AJCC).

3.6.3.4 Renal parenchyma invasion (for renal pelvis tumours only)

For tumours of the renal pelvis, invasion through the basement membrane and into the renal parenchyma is staged as pT3 disease. Pathologists must be especially aware of the distinction between true renal parenchyma invasion and pagetoid spread of tumour within collecting ducts and renal tubules. In pagetoid spread of tumour within ducts and tubules, the tumour cells remain confined within the basement membrane and are, therefore, still *in situ* carcinoma cells. This is in spite of the fact that the cells appear to be "within" the kidney. Misdiagnosis of pagetoid spread as renal parenchyma invasion

can overstage a pTa/pTis tumour, which typically has an excellent outcome, as a pT3 tumour, which has a rather bleak prognosis. Even overstaging a muscle invasive (pT2) tumour with pagetoid spread into ducts and tubules as pT3 disease has potentially significant prognostic and therapeutic implications. A careful search for individual tumour cells or small clusters of tumour cells infiltrating between renal tubules can confirm the presence of renal parenchyma invasion. Large, irregular nests of tumour cells with an accompanying desmoplastic stromal response within the renal parenchyma also suggests pT3 disease.

3.6.3.5 Perinephric fat and adjacent organ invasion

Tumours of the renal pelvis that invade the renal parenchyma, extend through the cortex to the renal capsule, and then further infiltrate beyond the renal capsule into the perinephric fat, are pT4 tumours (**Figure 3-17**). It should be noted that invasion of renal parenchyma with concomitant invasion of the adjacent hilar/peripelvic adipose tissue does not indicate pT4 disease but rather is still pT3 disease, as the kidney and pelvicalyceal system merge seamlessly at the hilum without the presence of a capsule. Tumours of the renal pelvis that do not invade through the renal capsule into perinephric fat but do invade into other adjacent organs, such as vertebral bone or the adrenal gland, are also pT4 tumours.

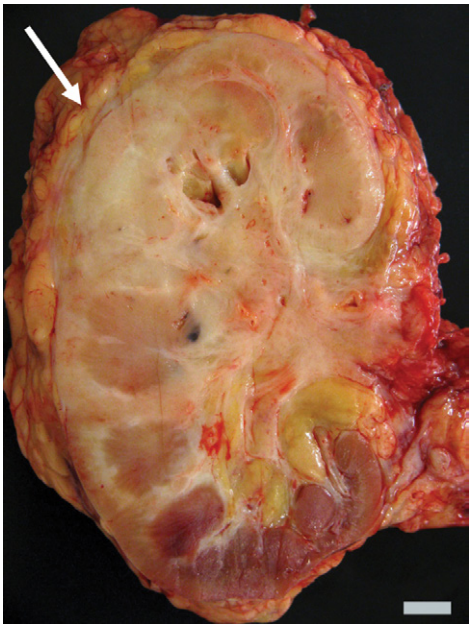


FIGURE 3-17
Invasive urothelial carcinoma extending from the renal pelvis through the kidney parenchyma and into perinephric fat (arrow) (stage pT4).

For tumours that are ureteral in origin, invasion into periureteral fat and through the renal capsule into renal parenchyma is considered pT4 disease. As with the renal pelvis, invasion of bone, adrenal gland, or other adjacent organs is also considered pT4 disease.

3.7 Histologic Variants

While the vast majority of tumours of the upper urinary tract are urothelial carcinomas, pure squamous cell carcinomas, adenocarcinomas, and neuroendocrine carcinomas, among others, do occur. More commonly seen, however, are foci of squamous differentiation and, less frequently, adenocarcinomatous/glandular differentiation within an otherwise usual urothelial carcinoma. Pure urothelial carcinomas also display a wide range of variant morphologies. Recognition of these morphologies is important for proper diagnosis, classification, and prognostication. This section highlights the various histologic patterns of urothelial carcinoma as well as other (non-urothelial) tumour types that have been described in the UTUC.

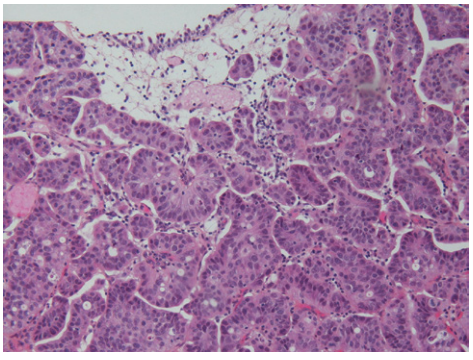
3.7.1 Micropapillary variant of urothelial carcinoma

Incidence: Micropapillary carcinoma (MPC) is a rare variant of urothelial carcinoma. Most studies have focused on the bladder, where the incidence is between 1 to 2.2% with a male predominance of 3:1. In the UUT this variant is exceedingly rare, accounting for less than 0.5% of tumours. The histological features correspond to those seen in the bladder.[52]

Gross appearance: There are no gross features to distinguish MPC from other types of urothelial carcinomas. Micropapillary carcinoma can be papillary with polypoid aspects as well as deeply infiltrating. Huge nodular whitish masses can exist but still do not allow differentiation from other infiltrating urothelial carcinomas. Furthermore, MPC might not occur in a pure (100%) form but may be mixed with common urothelial carcinoma.

Microscopic features: This carcinoma has a papillary architecture, similar to those seen in ovarian papillary serous neoplasms. The tumour is made of small irregular nests of tightly cohesive tumour cells without a fibrovascular core (**Figure 3-18**). MPC typically displays nuclear and cytoplasmic atypia with high-grade features, although MPC may sometimes have low-grade features. The nuclei are oriented at the periphery of the clusters, imparting an inverted appearance. The infiltrating tumour nests are surrounded by empty spaces (retraction artifact) and should not be misinterpreted as vascular invasion. These spaces may be lined by flattened spindle cells or may not have any lining. Staining for vascular markers can help exclude true angiolymphatic invasion. One of the characteristics of this tumour type is the lack of host response to the tumour cells. These patterns are also observed in metastatic sites. However, the lack of psammoma bodies, in contrast to metastatic ovarian carcinoma, and the presence of an *in situ* urothelial component can help to indicate a urothelial origin.

FIGURE 3-18
Micropapillary urothelial carcinoma.



A recent study from Sangoi *et al.* demonstrated that the consensus between "classic" and "non classic" MPC was only moderate (kappa 0.54).[53] Although agreement amongst the classic cases was high (93%), the diagnosis of a subset of 20 invasive UCs with extensive retraction and varying tumour nests surrounded by lacunar spaces was less consistent. Classic MPC features include multiple nests within the same lacunar space, intracytoplasmic vacuoles, epithelial ring forms, and micropapillae with elongated and slender nests with an average width <4.5 nuclei. Non-classical types displayed medium sized nests with >4.5 nuclei and nests with anastomosis, confluence, or branching.

Lymphovascular invasion (LVI) might be difficult to establish because of the hollow spaces around the nests, but LVI is common in MPC and contributes to its aggressiveness. The artificial empty spaces surrounding the MPC tumour nests lack vascular features such as endothelial lining and cellular constituents of blood. Immunohistochemical studies have failed to demonstrate endothelial components that line the retracted stroma.[52,54,55] These retraction spaces are thought to be an artifact of fixation and they are not seen on frozen sections.[56] Lymphovascular invasion can be confirmed easily by IHC, such as cluster of differentiation 31, CD34, D2-40, *Ulex europaeus* agglutinin I lectin, and factor VIII related-antigen.

Differential diagnosis: The main problem is distinguishing MPC of the urinary tract from micropapillary adenocarcinomas, such as carcinomas from the ovary, colon, pancreas, peritoneum, or breast. This distinction can be particularly challenging in metastatic sites, especially in female patients with a history of ovarian papillary serous carcinoma. Ductal carcinoma *in situ* of the breast may also exhibit micropapillary pattern, but distant metastasis to the ureter is unusual.[57] Immunohistochemistry may be of help, such as positivity of cytokeratin 7 (CK7), cytokeratin 20 (CK20), or Uroplakin III positivity. Tumour protein 63 (p63) is less useful in this type of tumour, because expression is lacking or weak. Imaging to exclude any distant primary is a key to confirm diagnosis.

Another issue is the minimum amount of MPC features that must be present to consider a UC as MPC. All these findings clearly suggest that more studies are needed to identify the pathologic features that may correlate with aggressive clinical outcome and lack of response to intravesical therapy.

Ancillary diagnostic tests: Micropapillary carcinoma expresses like other urothelial carcinoma pan-cytokeratins (pan-CK), which shows membranous and cytoplasmic staining in most cases. Cytokeratin 20 can be expressed more or less strongly, as with other high molecular weight cytokeratins. Epithelial membrane antigen (EMA) and p63 have been described to be positive, nevertheless

p63 expression can be lost or focal. Other markers such as thrombomodulin, cancer antigen 125 (CA125), B72.3, BerEP4 and placental alkaline phosphatase have been reported to be positive. A recent study could demonstrate mucin 1 (MUC1) expression around the membrane segment facing the stroma.[58] The authors described MUC1 expression as a typical feature of MPC that is also seen in tumours from other organs besides the bladder, with this particular architecture. Other relatively distinctive markers of MPC are expression of CA125, human epidermal growth factor receptor 2 (HER2/neu) and Krebs von de Lungen-6 (KL-6).[53] At present there are no specific markers for MPC and no published molecular comparative data to address this specific diagnostic issue, the diagnosis remains essentially based on morphology.

Some recent studies could show overexpression of tumour protein 53 (p53), mindbomb E3 ubiquitin protein ligase 1 (MIB1) and Aurora-A. However, no statistic difference could be made except with Aurora-A, a marker of early mitotic change, which might explain aggressiveness of MPC.[59] E-Cadherin has also reported being positive, on the contrary to plasmacytoid and signet ring differentiation.[60]

Prognosis: Correct identification of MPC variant is important, as most of these tumours are invasive at time of diagnosis. Perez-Montiel described 4 cases with pT2-3 stage, and all patients died from disease.[61] In another study, 5 cases of MPC of the urinary bladder were described with all patients dead of disease within 3 to 24 months.[62] Oh *et al.* described MPC in the ureter with a short survival.[55] In a relatively large study of 11 cases, aggressive behavior of micropapillary carcinoma in the upper urinary tract was again demonstrated, with LVI present in all cases and only two patients with pT2 disease demonstrating long-term survival.[56]

Amin did not specify in his first description a minimum amount of MPC features required to consider a tumour MPC. Several reports have since suggested different percentages as cut-offs.[52,59,63,64] Samaratunga and Comperat suggested diagnosing MPC even if the component is less than 10%. Similarly, Kamat *et al.* proposed rendering the diagnosis even when a minor component under 5% is present. Apparently, even a small focus of micropapillary pattern may be clinically and therapeutically significant, as increasing amounts of micropapillary components correlate to a worse prognosis.[56,59,63] Lymphovascular invasion and distant metastasis are frequent. Surgery still seems to be the best treatment and chemotherapy after nephroureterectomy also seems to be as effective as in traditional UTUC.[65]

3.7.2 Nested variant of urothelial carcinoma (NUC)

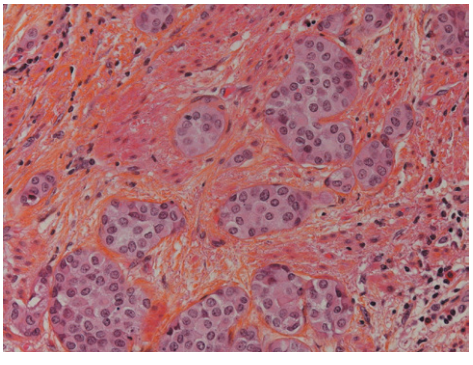
Definition: The nested variant of Urothelial Carcinoma (NUC) is an invasive urothelial carcinoma consisting of small, well-delimited nests with bland cytology. The nests are distributed in an irregular way, but may simulate benign processes such as hyperplasia of von Brunn nests.[66,67]

Incidence: The incidence in the bladder is only 0.3%, and it is even less frequent in the UUT[68] with only 2 case reports in the English literature.[69,70] Furthermore, it may be difficult to make the diagnosis when the tumour does not invade into the muscularis propria (pT2 stage). So some cases may, at least initially, go unrecognized.

Gross appearance: Once again, no macroscopic difference with other UC is seen. Most cases are described in the renal pelvis, nevertheless cases in the ureter exist. Tripodi *et al.* described whitish and thickened uneven mucosa in the renal pelvis calices and ureteropelvic junction.[70]

Microscopic features: The nested variant of UC consists of nests which are well-delimited by a thin layer of connective tissue (**Figure 3-19**). The nests do not display much atypia and appear relatively bland. They are irregularly distributed within the lamina propria and can invade the muscularis propria. An associated papillary tumour or carcinoma *in situ* is often absent, thus making diagnosis even more challenging. It can be difficult to make the diagnosis of an infiltrating tumour, especially in the absence of muscularis propria invasion.

FIGURE 3-19
Nested variant of urothelial carcinoma.



Different patterns can be observed in NUC. Either the tumour has the same aspect both in superficial and in the deeper layers of the ureteral/renal pelvis wall, with scattered, small, well-delimited nests. Alternatively, the superficial zone can show more tightly packed areas, which are haphazardly arranged and often confluent, with little intervening fibromuscular stroma. Abortive tubules can overlap with small tubules. In the deeper portions, tumour cells have a greater degree of cytologic atypia and the cytoplasm might be more eosinophilic. It is uncertain if the variant of urothelial carcinoma with small tubules should be considered as a sub-type of NUC. Some authors describe it as a microcystic variant of NUC, while others consider it completely separate. Nevertheless, the UC with small tubules might also have a deceptively bland aspect like the classic NUC. Admixtures with solid nests have been described.

Differential diagnosis: The main problem is to distinguish this tumour from florid proliferation of von Brunn nests.[71] If the tumour does not show clear infiltration of the underlying tissue or show cytologic atypia, it is impossible to differentiate from von Brunn nest hyperplasia. Normally, von Brunn nests have a close interface with the overlying normal urothelium and are at a uniform depth beneath the surface. The architecture and cytology of von Brunn nests is uniform.

3.7.3 Microcystic variant of urothelial carcinoma

Definition: In 1991, Young and Zukerberg reported 4 cases of UC in the urinary bladder with prominent microcystic pattern.[72] This variant is characterized by tubules which are dilated, forming microcysts. Some authors suggested at least 25% of the tumour should have microcystic changes to be considered as a microcystic urothelial carcinoma.[68]

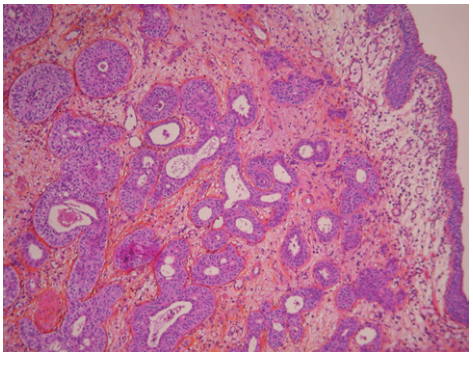
Incidence: Three cases of the UUT have been reported in the English literature. One of these cases was associated with neuroendocrine differentiation.

Gross appearance: One of these cases showed an ulcerated and ill-defined lesion of the renal pelvis, and another one presented as a friable exophytic tumour of the upper calyx. Both cases showed invasion into the renal parenchyma. The third case was a grayish white mass measuring 10 cm in diameter and deforming the renal surface. In some areas the tumour was predominantly cystic, and the walls contained whitish, friable papillary areas. Large areas of necrosis were present. This tumour also invaded the renal parenchyma and peripelvic fat.[73,74]

Microscopic features: The cases were described as proliferations of small tubules and numerous cysts in the lamina propria, muscularis propria, renal parenchyma, and peripelvic fat (**Figure 3-20**). The cysts were variable in size and shape but always measured less than 2 mm. They were lined by small cuboidal or flat cells with eosinophilic cytoplasm and round nuclei that typically lacked atypia. Mitotic activity was low, and no abnormal mitotic figures were described in the French series. Presence of necrosis was variable.

FIGURE 3-20
Microcystic variant of urothelial carcinoma.

(Photo courtesy of Dr. A. Vieillefond)



Differential diagnosis: Benign lesions such as nephrogenic adenoma and ureteropyelitis cystica et glandularis have to be considered. The glands of the ureteropyelitis cystica are often lined by cuboidal cells rather than urothelial cells. Nephrogenic adenomas might have a microcystic appearance, but usually displays other patterns also. Furthermore, nephrogenic adenoma is rare in the renal pelvis.

Ancillary studies: Positivity for Alcian blue and periodic acid-Schiff staining was reported. Like in other urothelial neoplasms, p63, high molecular weight cytokeratin (HMW-CK), and thrombomodulin have been reported to be positive.

Prognosis: Different outcomes have been reported, including disease recurrence and death from disease as well as good outcomes. As few cases are reported, the prognosis is difficult to establish.

3.7.4 Lymphoepithelioma-like carcinoma

Definition: This variant of urothelial carcinoma is composed of a dense inflammatory infiltrate surrounding nests of poorly differentiated carcinoma cells. These tumours bear a close resemblance to lymphoepitheliomas of the head and neck region.

Incidence: This variant was first described in the early nineties,[75] and fewer than 10 UUT cases have been reported in the English literature.[76–78] Most patients are in their seventies, and a male predilection exists. Gross hematuria and hydronephrosis have been described.[79] The stage of the disease is generally advanced.

Gross appearance: These tumours have a tendency to obstruct the ureter, but little information exists in the literature.[80]

Microscopic features: This is essentially an undifferentiated carcinoma that resembles lymphoepitheliomas in the nasopharynx. The carcinoma grows as sheets of tumour cells with large vesicular nuclei and prominent nucleoli. The stroma is densely infiltrated by lymphocytes. In rare cases, mixed cases with more conventional urothelial carcinoma, squamous cell carcinoma, and CIS have been reported (**Figure 3-21**).[77]

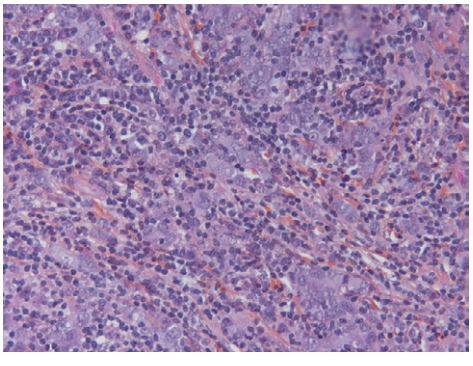


FIGURE 3-21
Lymphoepithelioma-like variant of urothelial carcinoma.

Differential diagnosis: If few epithelial cells are present, lymphoma may be highest on the differential, but immunohistochemistry for cytokeratins will highlight the carcinoma cells. One should also exclude a metastasis from a nasopharyngeal localization, in which case clinical history is most helpful.

Ancillary studies: Epstien-Barr virus-encoded small RNA (EBER) is not present in this type of tumour, in contrast to similar tumours of the nasopharyngeal region. This confirms that Epstien-Barr virus (EBV) is not a prerequisite for the development of this variant of UTUC. Some authors have suggested abnormalities in the p53 pathway are required for the development of this tumour,[75,81,82] and p53 is often overexpressed. The tumour cells typically express cytokeratin AE1/3, p63, and cytokeratin 15 (CK15), but CK7 and CK20 stains may be negative. The lymphoid cells show a mixture of T-cells (cluster of differentiation 3 positive) and B-cells (B-lymphocyte antigen CD20 positive).[78]

Prognosis: In the paper of Tamas, the authors noted a difference in prognosis between pure and mixed cases,[77] and other case reports seem to support the theory that pure forms have a more favorable outcome.

3.7.5 Clear cell (glycogen rich) variant of urothelial carcinoma

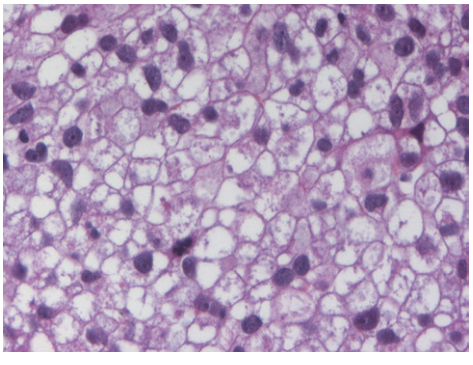
Definition: Upper Tract Urothelial Carcinoma in which there is a predominance of cells with clear cytoplasm.

Incidence: This variant is rare in the UUT, with fewer than 10 cases described in the English literature.[61,83] Gross hematuria is the most common presentation, and patients are usually between 40- and 60-years-old at diagnosis.

Gross appearance: No information is available about gross appearance.

Microscopic features: Tumours are high grade and may have papillary and/or solid growth patterns. Association with squamous differentiation has also been described.[61] Tumour cells have well-defined cell membranes and optically clear cytoplasm (**Figure 3-22**). Nuclei are centrally placed and pleomorphic. Most cases have some areas resembling classical UTUC and the clear cell areas can merge imperceptibly with conventional UTUC.

FIGURE 3-22
Clear cell variant of urothelial carcinoma.



Differential diagnosis: Other clear cell neoplasms should be considered, especially clear cell renal cell carcinoma involving the renal pelvis. Metastasis from a prostatic adenocarcinoma or paraganglioma should also be excluded.

Ancillary studies: This tumour exhibits positivity for HMW-CK, CK7, p63, transacting T-cell-specific transcription factor GATA-3 (GATA-3), thrombomodulin. Cytokeratin 20 staining is variable. Negative staining for renal markers (e.g. paired box gene 8), prostatic markers (e.g. prostate-specific antigen and prostate-specific membrane antigen), and neuroendocrine markers (e.g. synaptophysin and chromogranin A) can help to exclude the other tumours listed in the differential diagnosis.

Prognosis: These cases are frequently discovered at an advanced stage, and prognosis is thus generally poor.

3.7.6 Urothelial carcinoma with rhabdoid features

Definition: The rhabdoid variant of UTUC is a very rare and aggressive tumour. It is almost always seen with otherwise conventional, poorly differentiated UTUC.

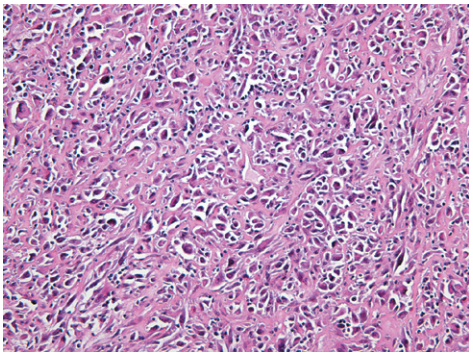
Incidence: This rare histologic variant occurs in less than 1% of UUT carcinomas.

Clinical: Typically this tumour is described in adults, with a male predominance. Age is usually between 50 and 70 years.[84] Gross hematuria is the most frequent presentation.

Gross appearance: Necrotic, obstructive, friable masses invading the renal parenchyma have been described. Solid whitish cysts with scattered necrotic foci in the pelvic wall have been reported.[84,85] Cases with polypoid aspects or multiple tumour nodules have also been described.

Microscopic features: There exists a striking resemblance to other skeletal muscle tumours. This tumour appears as a monotonous population of large, discohesive cells with distinct cell borders and abundant cytoplasm, with perinuclear eosinophilic inclusions (**Figure 3-23**). The nucleus is large. It is sometimes eccentrically located within the cell and the nucleoli are prominent. The tumour cells are either arranged singly, in small clusters, or as diffuse sheets. Inclusions in the cytoplasm are composed of whorls of intermediate filaments, based on findings from ultrastructural studies.

FIGURE 3-23
Rhabdoid variant of urothelial carcinoma.



Differential diagnosis: Given the localization one should first think of poorly differentiated UC. Distinction from a sarcomatoid carcinoma of the renal pelvis might be difficult. Of therapeutic importance is whether the tumour arises from the urothelium or renal parenchyma. Adrenal cortical carcinomas invading the kidney and involving the pelvis have to be excluded. Rhabdomyosarcoma and epithelioid angiomyolipoma may also be considered, as well as metastasis, such as from a hepatocellular carcinoma.

Ancillary studies: Rhabdoid tumours exhibit cytokeratin AE1/3, cytokeratin 8, vimentin, and integrase interactor 1 positivity, although some reported cases have been negative pan-cytokeratin, HMW-CK, and other common markers. Loss of heterozygosity (LOH) has been described at 5q, 8p, and 17p as well as allelic shift of one chromosomal focus in 6q.[85]

Prognosis: Upper Tract Urothelial Carcinoma with rhabdoid features is a highly aggressive tumour. Metastasis, especially to the liver and lung, at the time of diagnosis are not infrequent.[85] Patients typically die within a year, despite chemotherapy and surgery.

3.7.7 Plasmacytoid variant of urothelial carcinoma

Definition: This is a rare variant of urothelial carcinoma characterized by tumour cells that morphologically resemble plasma cells. Tumour cells are arranged as single cells within a loose stroma and, like plasma cells, have abundant eosinophilic cytoplasm and an eccentric nucleus. These tumours may show other features of UTUC, including sarcomatoid differentiation or conventional high-grade UTUC areas, but it quite frequently presents in its pure form.[86]

Incidence: The plasmacytoid variant is rare and, even in the bladder, published series are small. The estimated incidence in the bladder is less than 1%, and in the UUT only 1 case has been described in the English literature.[87]

Clinical: The majority of cases of plasmacytoid carcinoma of the bladder are in men, although the only case described in the UUT is a female patient. Age at diagnosis in the bladder is quite broad (46—89 years), with a mean age of around 65 years.[86,88] The only case report concerned a 72-year-old female patient. She presented recurrent urinary tract infection and intermittent gross and permanent microscopic hematuria.[87]

Gross appearance: No special findings have been described. In the above-mentioned case report in the UUT, the tumour had a white to yellow color with a knotty appearance that infiltrated the renal calices.

Microscopic features: The plasmacytoid variant has discohesive single cells with dense eosinophilic cytoplasm that can contain small vacuoles. The nuclei are hyperchromatic, round to oval, and eccentric (**Figure 3-24**). Pleomorphism is usually only moderate, and most of the time the cells display a relatively uniform appearance. Nucleoli can be present. The stroma is loose, edematous, and sometimes myxoid. Tumour cells can be arranged in small nests or cords, but they frequently form sheets diffusely infiltrating the underlying tissue. Mixture with other types of UTUC can be seen and the presence of CIS might be helpful in making the right diagnosis.[60]

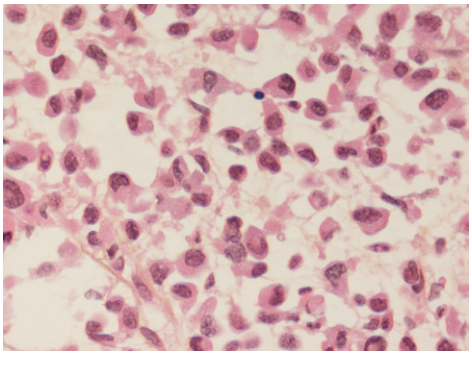


FIGURE 3-24
Plasmacytoid variant of urothelial carcinoma.

Differential diagnosis: The morphologic spectrum of this entity is broad, and if there is no concomitant classical type of UTUC or CIS, diagnosis might be difficult. Pathologists must be able distinguish between an epithelial lesion and a hematopoietic neoplasm, such as plasmacytoma. Malignant melanoma should be ruled out as well as different types of sarcomas, such as rhabdomyosarcoma. Neuroendocrine carcinomas and paragangliomas must be excluded. Pathologists must also consider metastatic adenocarcinomas from the gastrointestinal tract, such as gastric carcinoma and signet cell carcinoma from the stomach or colon. Lobular breast cancer merits consideration as well.

Ancillary diagnostic tests: Plasmacytoid carcinomas of the urothelium express pan-cytokeratins, CK7, CK20, and uroplakin III. In the above-mentioned case report, the carcinoma did not express CK20 or syndecan-1 (CD138), but CK7 and pan-CK were positive. In the bladder, plasmacytoid carcinomas positive for CD138 have been reported.[89–91] E-Cadherin can also be negative, and molecular studies seem to underline this finding.[60] Deletions on chromosome 9p21 seem to play a major role.

Prognosis: In the bladder, these tumours are known to be aggressive and the overall survival rate is poor.[2] Cases often present at an advanced staged. In the case report from Keck *et al.*, the patient had a pT3 carcinoma with lymph node metastasis and died after 20 months. Neoadjuvant and adjuvant chemotherapy do not seem to have a major impact on survival. Radical nephroureterectomy is often recommended.

3.7.8 Sarcomatoid carcinoma

Definition: Malignant urothelium-derived carcinoma that displays both spindle cell and epithelial elements.

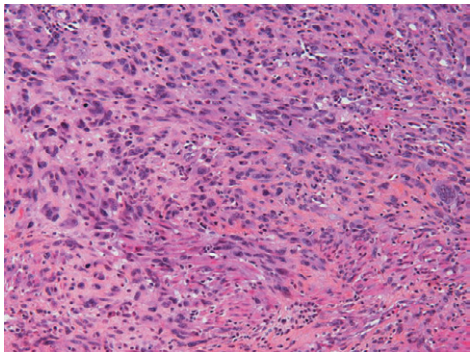
Incidence: Rare cases have been described in the UTUC, where the incidence is less than 1%. Perez-Montel reported one of the most important series with 6 cases.[61]

Clinical: The patients are middle-aged and between 50- and 75-years old. Hematuria and flank pain seem to be the most common clinical features.

Gross appearance: These tumours appear as large, solid, whitish masses that often invade the renal parenchyma.[93]

Microscopic features: These tumours display spindle cell features, comprised of atypical spindle cells arranged in short interlacing fascicles (**Figure 3-25**). The pattern might be vaguely storiform. They are high grade and may resemble malignant fibrous histiocytoma/pleomorphic sarcoma. Heterologous differentiation has been reported. Nuclei can show clumped chromatin and prominent, multiple nucleoli. The cytoplasm can be scant and eosinophilic. Mitotic figures are frequent and necrosis is often present.

FIGURE 3-25
Sarcomatoid variant of urothelial carcinoma.



Although the tumour resembles a sarcoma, the epithelial origin of this tumour is well established. Often the sarcomatoid component is admixed with more classical aspects of high-grade UTUC. Carcinoma *in situ* can be observed in the overlying or adjacent urothelium. Cases with pseudoangiosarcomatous and squamous differentiation have been described.[61]

Differential diagnosis: Pseudosarcomatous myofibroblastic proliferations (inflammatory myofibroblastic tumour, postoperative spindle cell nodule) can be difficult to differentiate from true sarcomatous lesions. This is especially true in patients with a clinical history of previous surgery, reinforcing the importance of clinical history in these cases. True sarcomas, such as leiomyosarcoma, might also be difficult to exclude.

Ancillary studies: These tumours express pan-cytokeratins, HMW-CK, cytokeratin 5/6, and p63, although positivity may be very focal and patchy in the sarcomatoid elements. Smooth-muscle actin is variably expressed, and anaplastic lymphoma kinase 1 is negative. Cells lining the vessel spaces have been reported to express CK7 while being cluster of differentiation 31 (CD31) negative. In the more conventional high-grade epithelial areas, conventional UTUC markers such as CK7, CK AE1/3, and EMA are often expressed, while actin and vimentin are usually negative in these areas. On the other hand, sarcomatoid areas may be positive for vimentin and actin and negative for epithelial markers. Both components are negative for CD31 and carcinoembryonic antigen (CEA).[84]

Prognosis: Outcome is poor as the stage at diagnosis is frequently advanced and few cases have reported lengthy survival. Relapse is frequent, and overall survival, even with chemotherapy, is short.[94]

3.7.9 Undifferentiated urothelial carcinoma with osteoclast-like giant cells

Definition: Upper Tract Urothelilial Carcinoma with osteoclast-like giant cells is a carcinoma that closely recapitulates the morphology of osteoclastic giant-cell tumours of bone and soft parts. Tumours are biphasic, composed of both mononuclear cells and osteoclast-like giant cells. These tumours are considered a variant of UTUC based on their association with conventional UTUC and ancillary studies.[95]

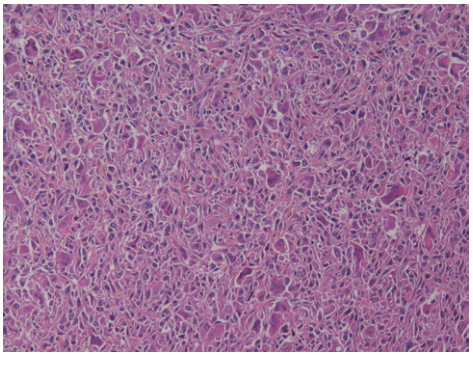
Incidence: Less than 20 cases have been described in the UUT. The first was described by Kimura *et al.* in 1983.[96] Fifty-percent of the cases occur in the renal pelvis.

Clinical: Patients range from 50- to 80- years-old at diagnosis. A slight male predominance exists. Symptoms are non-specific and include those typical for UTUC, including gross hematuria, flank pain, renal colic, and dysuria.

Gross appearance: Enlarged kidneys have been reported. The lesions can be solid nodular masses which largely invade and fill the renal pelvis with infiltration of renal parenchyma. Presence of these tumours in the distal ureter is exceptional. The tumours may be well-circumscribed focal hemorrhage and necrosis.[97]

Microscopic features: Osteoclast-like giant cell UTUC is composed of sheets and nodules of cells with a richly vascularized stroma and erythrocyte extravasation, sometimes forming blood-filled lakes (**Figure 3-26**). These carcinomas are fairly circumscribed and composed of a monotonous population of mononuclear cells with numerous interspersed giant cells. The mononuclear cells are characterized by round to oval shaped nuclei with vesicular chromatin and slight nuclear polymorphism. Nuclear grooves and irregular nuclear borders have been described. Nucleoli are frequently prominent. The cytoplasm can be amphophilic and vacuolated. Mitosis are present but not abundant.

FIGURE 3-26
Undifferentiated urothelial carcinoma with osteoclastic giant cells.



The osteoclast-like giant cells have multiple round to oval, bland-appearing nuclei, ranging from 5 to 40 nuclei per cell. The cytoplasm of these cells is eosinophilic with well-demarcated cell borders. The density of giant cells can be variable. Areas of hemorrhage with hemosiderin deposition and necrosis can be present. Chronic inflammation may be present in the background.

Associated conventional UTUC and CIS have been described. Lymphovascular invasion is common.[98]

Differential diagnosis: If a more conventional UTUC component is not present, the tumour may be misdiagnosed as a sarcoma of unknown primary.

Ancillary studies: Most cases demonstrate epithelial differentiation via focal positivity of cytokeratins or EMA. The multinucleated cells display positivity for CD68, LCA, CD51, and CD54, and they are negative for cytokeratins and EMA. Some of the mononuclear cells have a relatively high proliferation index, ranging from 20 to 50%. The mononuclear cells have also been reported to be positive for smooth muscle actin, desmin, S100, and CD68.[99]

Prognosis: Grim prognosis has been reported and stage at diagnosis is mostly advanced. Most patients die of metastatic disease within 18 months of diagnosis. Nevertheless, some patients without evidence of disease at 24 to 42 months after nephroureterectomy have been described.[100]

3.7.10 Squamous cell carcinoma

Definition: Primary malignancy of the renal pelvis and ureter comprised entirely keratin-forming squamous cells.

Incidence: While SCC accounts for 5% of bladder cancers, the incidence in the upper tract is even higher, approaching 10% in the literature.[93,101–104]

Clinical: Squamous cell carcinoma (SCC) is frequently associated with urolithiasis, hydronephrosis, and chronic inflammation.[105] Busby *et al.*, in their study of 12 patients, reported that 25% had previous stone disease.[104] Human papillomavirus (HPV) does not seem to play a role in the UUT. Mean age is 65 to 70 years. The sex ratio is almost 1:1. Some cases due to phenacetin abuse have been reported and several female patients had a history of external beam radiotherapy as treatment for gynecological tumours. Patients may have gross hematuria. Most tumours are pT3 or pT4 stage at diagnosis. Most SCC are located in the renal pelvis, and pure SCC in the ureter is rare.[103] Paraneoplastic syndromes, such as hypercalcemia, have been reported.

Gross appearance: These tumours often present as infiltrating, whitish, bulky masses with necrotic areas. Distinction between SCC and UC in gross examination is often difficult.

Microscopic features: SCC is characterized by sheets of cells with well-defined cell borders, eosinophilic cytoplasm, and oftentimes at least focal keratin pearl formation (**Figure 3-27**). Large nuclei with prominent nucleoli are common. An association between SCC and squamous metaplasia has been reported.[61] Focal clear cell changes admixed with SCC features has been described.

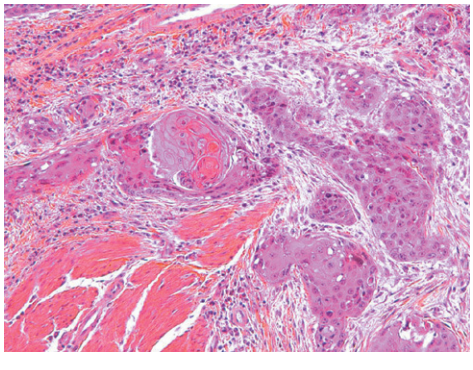


FIGURE 3-27
Squamous cell carcinoma of the renal pelvis.

Ancillary studies: Like SCC in other organs, these tumours are positive for p63, HMW-CK, and CK AE1/3.

Differential diagnosis: The primary differential diagnosis includes conventional UTUC with extensive squamous differentiation or metastasis of SCC from another site. Although direct invasion of the ureters by SCC of the cervix is theoretically possible, no report has been found in the literature.

Prognosis: Squamous cell carcinoma of the UUT has an unfavorable prognosis. In Perez-Montiel's study, all 14 patients had high-grade and high-stage disease (pT2-T4).[61] Rink *et al.* showed in a recent study that SCC had worse outcomes with advanced tumour stage and lymph node invasion ($p \leq 0.005$).[102] This group also demonstrated higher recurrence and cancer-specific mortality. Rausch *et al.* showed mean overall survival for SCC of the UUT to be 7.25 months, with a 5-year survival of 18%.[103] In the series of Busby *et al.*, the mean overall survival was 14.1 months and 1-year disease-specific survival was 57%.[104]

3.7.11 Verrucous carcinoma

Definition: Verrucous carcinoma is a rare subtype of SCC. In the bladder, cases linked to schistosomiasis have been described. This tumour is a well-differentiated SCC with broad, deep, pushing borders that does not demonstrate overt infiltration of the underlying stroma as in conventional UTUC.

Incidence: These tumours occur rarely, with only 3 cases involving the UUT in the English literature.[106–108]

Clinical: Etiology is unknown, although most of these lesions occur with chronic inflammation. Tumours reportedly occur in younger patients, with the described cases occurring in patients aged 33, 41, and 64. Patients may present with flank pain, recurrent pyelonephritis, abdominal pain, weight loss, and hematuria.

Gross appearance: Exophytic growth obliterates the pelvis and ureter lumen, resulting in hydronephrosis containing a brownish fluid. Other tumours are gray and plaque-like measuring several centimeters. One case displayed hundreds of papillary projections up to 3 cm.

Microscopic features: The tumour grows as an exophytic papillary mass with extensive keratinization. Acanthosis can be seen as well as a hyperplastic, papillomatous, wart-like architecture. Mitoses are generally lacking, and cellular atypia is mild. Tumours show pushing, rounded borders. A chronic inflammatory infiltrate surrounding the tumour can be present. Schistosomal eggs can be present. Although the WHO 2004 classification maintains that verrucous carcinomas should not be invasive, invasion of the underlying tissue was reported in each of the three cases mentioned here.

Ancillary studies: Some authors have suggested a link to HPV infection in the bladder. None of the 3 cases described in the UUT could prove a link with HPV infection.

Differential diagnosis: It can be difficult to diagnose verrucous carcinoma if deeper parts of the lesion are not sampled, as the underlying tissue is not evaluable and thus could appear simply as squamous metaplasia. Other differential diagnoses include squamous papilloma or conventional invasive SCC.

Prognosis: One patient was alive and well at a follow-up of 2 years, another patient had metastatic disease, and the last case was disease free at follow-up. Nevertheless, with only three reported cases the overall prognosis remains to be seen.

3.7.12 Adenocarcinoma

Definition: Primary malignancy of the ureter and renal pelvis with glandular differentiation, typically either features of enteric-type, mucinous, or signet ring cell carcinoma.

Incidence: Primary adenocarcinomas account for less than 1% of cancers of the UUT. Almost 100 cases have been described in the English literature. In a series from India, however, adenocarcinomas were reported in up to 21.5% of the tumours of the renal pelvis.[109] Perez-Montiel recently described a series of 2 cases of adenocarcinoma mixed with urothelial areas.[61] Cases of mucinous cystadenocarcinomas also exist.[104,110]

Clinical features: Adenocarcinoma of the renal pelvis and ureter typically occur in patients age 55 to 65. Stage may be advanced, with lymph nodes frequently involved. Busby *et al.* described 2 cases in the renal pelvis and ureter at stage pT3 and pT4.[104] Cases associated with urolithiasis and chronic infections have also been described.[111,112] Presentation with increased abdominal girth, flank pain, and hematuria has been reported.[113]

Gross appearance: Tumours often present as protruding solid masses, but diffuse infiltration of the ureter wall and kidney have been described. A predominantly cystic appearance has also been reported.[109] Tumours are often large and bulky. Hemorrhage, necrosis, and a gelatinous/mucinous appearance are not uncommon. Most cases are solitary tumours.

Histologic features: Most adenocarcinomas of the UUT have morphological features of colonic adenocarcinomas (**Figure 3-28**). Enteric-type tumours with villous, acinar, cribriform, and solid growth have been reported. Neuroendocrine differentiation also can be seen. Mucinous, tubulovillous, and colloid differentiation has been described recently in some reports.[112] Tubulovillous growth was the most common pattern, comprising up to 71.5% of cases in 3 series, followed by a predominantly mucinous pattern in another 21.5%.[104] In mucinous tumours, individual detached cells or clusters of cells are present within lakes of mucin, similar to mucinous carcinomas of other organs. A signet ring cell component may also be present.

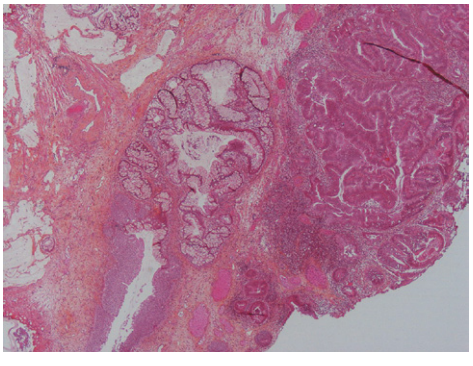


FIGURE 3-28
Adenocarcinoma of the renal pelvis.

Various amounts of mucin production have been noted in other types of upper tract cancers, such as those with urothelial and squamous differentiation. Five types of adenocarcinoma have been described in the bladder: enteric, mucinous or colloid, signet ring cell, adenocarcinoma not otherwise specified, and mixed forms, which show two morphologic patterns. No subclassification has been described for the UUT, however.

Various grading systems have been employed for these tumours, with signet ring considered as high grade. The most employed classification system is the WHO 2002.

Glandular metaplasia of the urothelium is frequently seen in association with adenocarcinoma. An adenocarcinoma *in situ* component can be helpful in making the diagnosis of a primary tumour of the UUT.

Differential diagnosis: The differential diagnosis includes all forms of metastatic adenocarcinomas from various origins, including the gastrointestinal tract and even prostate. Some primary signet cell carcinomas of the UUT resemble metastatic gastrointestinal tumours, and lobular carcinoma of the breast also may be included in the differential. Clinical history is important when excluding metastasis from another site.

Ancillary diagnostic tests: Periodic acid Schiff and Alcian blue staining can be positive, especially in cases of mucinous or signet cell ring carcinomas. Unfortunately, no specific immunoprofile for adenocarcinomas primary to the UUT exist. The carcinomas display staining for CK7 in 75%, CK20 in nearly 100%, MUC-2 in 100%, and CDX-2 in 50%.[114] Carcinoembryonic antigen can be positive. Beta-catenin stains positively in the cytoplasm. This latter finding is important when excluding metastasis from the gastrointestinal (GI) tract, as GI tumours display nuclear positivity for beta-catenin.

Prognosis: Although adenocarcinomas of the UUT have been described as being associated with collecting duct carcinomas, they are associated with more favorable prognosis in their pure forms.[115] Survival depends on the subtype of UUT adenocarcinoma. Tubulovillous adenocarcinomas are the most aggressive, with 30% overall survival at 5 years, while mucinous tumours are associated with a 5-year survival rate of 67%.[104]

3.7.13 Neuroendocrine carcinomas

Definition: This group comprises both small cell and large cell neuroendocrine carcinomas and those with mixed patterns.[116]

Incidence: In the bladder, small cell carcinomas account for less than 1% of tumours, and primary neuroendocrine carcinomas of the upper urinary tract are extremely rare. Only a few cases have been reported in the renal pelvis, and one case has recently been described in the ureter.[117–121] Large cell neuroendocrine carcinoma has only been described once in the UUT.

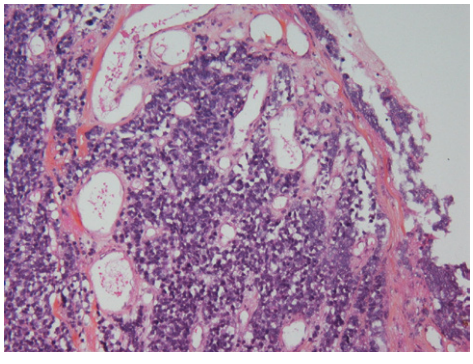
Clinical: Age at diagnosis is variable. The origin of neuroendocrine carcinomas in the UUT is unclear. Some authors have suggested that the UUT contains neuroendocrine cells. The second hypothesis is that these tumours derive from progenitor cells or pluripotent stem cells.[120] The most common symptoms are hematuria (gross and/or microscopic) and flank pain. Systemic endocrine symptoms have been reported.

Gross appearance: These are often solitary, ovoid, white masses that appear to arise from the mucosa, protrude into lumen, and also show invasion of the periureteral and peripelvic adipose tissue. Ulcerated masses have also been described.[122]

Microscopic features: Small cell neuroendocrine carcinomas have no particular architecture, often growing as diffuse sheets of cells. The tumour cells have little cytoplasm with nuclear crowding and molding. Nucleoli are inconspicuous and chromatin is evenly dispersed. The proliferation rate is high with mitotic figures readily identifiable. Crush artifact is frequent.[73,123]

Large cell neuroendocrine carcinomas are also poorly differentiated and high grade. At low magnification, the pattern is typically trabecular or as nests (**Figure 3-29**). Tumour cells are larger with irregular borders, have slightly more abundant cytoplasm, and prominent nuclei. Mitotic figures are again frequent.

FIGURE 3-29
Neuroendocrine carcinoma of the renal pelvis.



Differential diagnosis: Large cell neuroendocrine carcinomas might be mistaken for malignant lymphoma or poorly differentiated conventional UTUC. The pathologist must also be aware of the possibility of metastasis from another site. Alveolar rhabdomyosarcoma might be considered, as well as poorly differentiated adenocarcinomas of the prostate.

Ancillary diagnostic tests: Classic neuroendocrine markers such as synaptophysin, chromogranin A, cluster of differentiation 56 (CD56), and neuron-specific enolase (NSE) are often positive. Their expression is not necessary for the diagnosis of small cell carcinoma. Cytokeratin 7, CK20, and cytokeratin 19 (CK19) may also be positive, in addition to CAM 5.2 and CK AE1/3. Thyroid transcription factor 1 (TTF-1) can be positive in neuroendocrine tumours regardless of site of origin, but the only case described in the ureter was negative for TTF-1.[124] Mindbomb E3 ubiquitin protein ligase 1 and p53 show strong, diffuse staining.

Prognosis: Both large cell and small cell neuroendocrine carcinomas have a similar behavior, with most reported cases having had a dismal prognosis. The stage at time of detection is frequently advanced, and metastasis is not uncommon. Frequent sites of metastasis include lymph node, liver, bone, and lung. Numerous studies with different patient management have been reported in the literature, making it difficult to correlate outcome and disease specific survival. However, organ confined disease seems to have better outcome, and chemotherapy seems to improve survival. Performance status of the patient also influences prognosis.[120,123,125]

3.7.14 Carcinoid tumours

Definition: These are well-differentiated neuroendocrine tumours similar to carcinoids in other organs. They are part of the broad spectrum of neuroendocrine tumours.[116]

Incidence: Rare cases of carcinoid tumours of the UUT have been described.[121]

Clinical: Cases of patients from 29 to 75 years of age with carcinoid tumours arising anywhere in the urinary tract have been reported. There seems to be a male predominance. Hematuria is the most common symptom.

Gross appearance: These tumours normally present as small polypoid masses.[122]

Microscopic features: Like in other sites, theses tumours are often confined within the lamina propria. In the bladder they have been described in association with cystitis cystica. These well-differentiated tumours are composed of uniform, small, cuboidal cells with finely dispersed chromatin. The architectural growth pattern may be pseudoglandular, acinar, cribriform, or mixed.[126] Mitotic figures are infrequent.

Differential diagnosis: Carcinoid tumours may resemble the nested variant of UTUC. Metastasis from another site, including prostate, should be considered. Benign lesions such as inverted papillomas may also enter the differential.

Ancillary Diagnosis: Carcinoid tumours express neuroendocrine markers such as chromogranin A, synaptophysin, CD56, and NSE. They are also positive for CK AE1/3. Mindbomb E3 ubiquitin protein ligase 1 staining should not be markedly elevated.

Prognosis: Prognosis seems to be very good, based upon the few cases that have been described in the UUT. In other sites, such as the bladder or the urethra, these lesions also seem to have a good outcome.[127]

3.7.15 Other variants of urothelial carcinoma

Several other variants have been described in the urinary bladder but have not been reported yet in the UUT. These include the lipoid-rich variant, urothelial carcinoma with small tubules, and the large nested variant of urothelial carcinoma, among others. Nevertheless, any tumour that may arise in the urinary bladder may also, theoretically, be possible in the ureter and pelvis. These should be considered in the differential diagnosis when examining tumours of the UUT.

3.8 Cytology Specimens

Although urine cytology is known to have relatively low sensitivity for urothelial carcinoma, particularly in low-grade carcinomas[128–131] and in tumours of the UUT,[32,132–134] the specificity is excellent, especially for CIS and high-grade lesions.[135] In the UUT, positive urine cytology is highly suggestive of UTUC when evaluation of the lower tract reveals no disease. Furthermore, urine cytology has been shown to improve the detection and grading of tumours in biopsies,[23,24,32] and positive urine cytology in UTUC has been associated with higher stage (pT2+) tumours.[136] Directed sampling of the UUT via brushings and washings may help increase sensitivity, as can addition of fluorescence *in situ* hybridization (FISH) assays.[132–134]

Fluorescence *in situ* hybridization undoubtedly improves upon the sensitivity of urine cytology in the detection of UTUC, with sensitivities of FISH typically 2 to 4 times that of urine cytology alone, and approaching 100% in some studies.[132–134,137] However, the role of FISH in the surveillance of UTUC remains controversial due to its poor performance in detecting low-grade tumours, high false positive rate, and high cost.[137–140] Ideally, use of FISH should be limited to cases in which there is a clinical suspicion of UTUC but urine cytology and other diagnostic modalities are negative or equivocal.

Reporting of urine cytology specimens should follow the recommendations of the Papanicolaou Society of Cytopathology Practice Guidelines Task Force, which outlines a system similar to the Bethesda 2001 System for cervical cytology reporting.[141]

3.9 Immunohistochemical and Molecular Markers

3.9.1 Immunohistochemistry in the diagnosis of in situ and invasive upper tract urothelial carcinoma

Upper tract urothelial carcinoma shows IHC properties similar to *in situ* and invasive urothelial carcinomas of the lower tract. Under normal conditions, the urothelium shows diffuse expression of cytokeratin 7 and p63 in the urothelial cell compartment, and CD44 is selectively expressed in the basal compartment of the urothelium (**Figure 3-30**).[142,143] In contrast, umbrella cells, which are the most superficial cells of the urothelium, show strong cytokeratin 20 expression.

Alterations of this staining pattern in the surface urothelium suggest the possibility of dysplasia or CIS.[8,144] Specifically, the presence of full-thickness CK20 expression in the urothelium is characteristic of neoplastic change (**Figure 3-31**).[142,145–148] Additional markers used in the diagnosis of *in situ* urothelial neoplasia include p53, CD44, and MIB1/Ki-67. Tumour protein 53, a well-characterized tumour suppressor gene, undergoes mutation early in the course of urothelial cancer development.[149,150] Mutation of p53 is associated with aberrantly high levels of nuclear p53, as evidenced

by strong immunostaining. Use of CD44 can be helpful in identifying both reactive and dysplastic changes. Expression of CD44 is typically limited to the basal layer, as previously mentioned. Full thickness staining, though, may be present in reactive urothelium.[151] Dysplastic urothelium often loses expression of CD44. Finally, increased MIB1/Ki-67 labeling is present in CIS, but this finding is not specific and often not helpful in distinguishing carcinoma *in situ* from reactive atypia, as reactive lesions often also demonstrate increased proliferation rates.

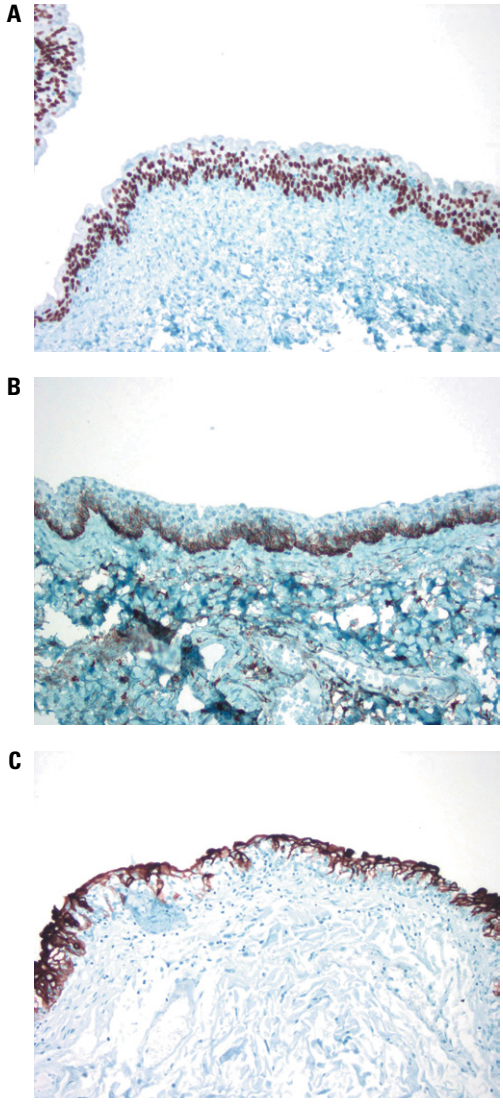


FIGURE 3-30
Immunohistochemical staining of normal urothelium.

A p63 is present in the nucleus of urothelial cells.

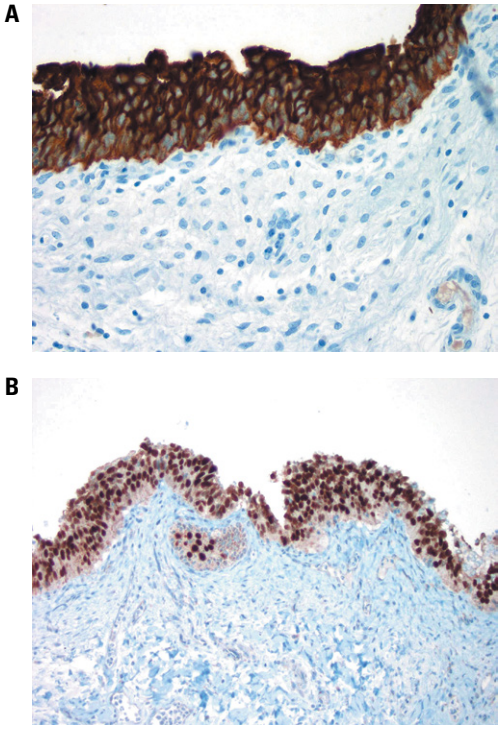
B CD44 is primarily expressed in the basal layer of normal, non-reactive urothelium.

C CK20 selectively stains umbrella cells.

FIGURE 3-31
Aberrant staining patterns in urothelial carcinoma in situ.

A Full thickness CK20 staining.

B Intense nuclear p53 staining in a large proportion of cells.



Invasive UTUC may require immunohistochemical stains in a few specific settings: 1) identification of urothelial carcinoma at a metastatic site; 2) diagnosis of unusual urothelial carcinoma variants in the kidney that lack a conventional urothelial carcinoma component; and 3) exclusion of renal cell carcinoma from the differential diagnosis. In the setting of metastatic disease, conventional urothelial carcinoma is frequently immunoreactive for high-molecular weight cytokeratin, cytokeratin 7, and p63. Focal immunoreactivity for cytokeratin 20 is also often seen. However, the presence of squamous differentiation may increase the complexity of the diagnosis, as most squamous carcinomas also express high-molecular weight cytokeratin and p63. This is most problematic in patients with a history of urothelial carcinoma who subsequently develop a lung cancer with squamous differentiation. As smoking contributes to the development of both cancers and since the demographics of both diseases are often similar, it is often difficult to determine whether the lung lesion reflects a metastatic focus of urothelial carcinoma or is a second primary carcinoma. One recent study has suggested that a panel that incorporates cytokeratin 7, cytokeratin 20, GATA-3, cytokeratin 14, desmoglein-3, and uroplakin III may be of value.[152]

Immunohistochemistry in the setting of UTUC variants is similar to that of the lower tract. Urothelial carcinoma variants are often associated with a conventional urothelial component that retains the staining pattern of conventional urothelial carcinoma. Only cases that have a high proportion of variant morphology are challenging. Similar to urothelial carcinoma of the lower tract, the most common variants identified in the upper tract are urothelial carcinoma with squamous and/or glandular differentiation.[102] As both squamous differentiation and glandular differentiation in any form (signet

ring cell, intestinal type, etc.) are relatively rare in renal cell carcinoma, the differential diagnosis in such cases favors a urothelial primary, especially if an *in situ* component is identified. However, less common variants may raise the possibility of metastatic disease. In such cases, the use of ancillary markers to assist in the diagnosis of urothelial carcinoma variants may be of value (**Table 3-3**).

Finally, distinguishing urothelial carcinoma from renal cell carcinoma may also necessitate immunohistochemistry. This diagnostic dilemma is generally only in cases of poorly differentiated urothelial carcinoma in which no *in situ* component can be identified. Occasionally, urothelial carcinoma with squamous differentiation may have clear cytoplasm,[153] which rarely could raise the differential diagnosis of clear cell renal cell carcinoma. The presence of papillary features in an inverted urothelial neoplasm may also raise the possibility of papillary renal cell carcinoma. In the latter setting, the presence of tubulopapillary hyperplasia or papillary adenomas favors a renal primary. Finally, poorly differentiated renal tumours, including collecting duct carcinoma and renal medullary carcinoma, can be the most challenging to distinguish from UTUC. In such settings, patient history and age, as well as immunohistochemical markers (**Table 3-4**) can be of value.[154–162] Positive immunoreactivity for high-molecular weight cytokeratin and p63, combined with an absence of PAX2 or PAX8 expression favors a urothelial carcinoma in this setting.

TABLE 3-3 Ancillary Markers in Bladder Cancer Variant Diagnosis

Variant	Ancillary markers
Nested UCa	Aberrant p53 expression and increased Ki-67 can help distinguish from von Brunn nests
Plasmacytoid UCa	Expression of CD138
UCa with rhabdoid differentiation	Use retention of nuclear INI (22q11.2) expression to exclude extrarenal rhabdoid tumour
Lymphoepithelial-like carcinoma (LEL)	Cytokeratin immunoreactivity; negative for Epstein- Barr virus
Osteoclast-rich undifferentiated carcinoma	CD51 and CD54 highlight osteoclast-like cells
Small cell	Positive for neuroendocrine markers: synaptophysin, chromogranin A, CD56

TABLE 3-4 Immunohistochemical stains to distinguish renal carcinomas from UTUC

Marker	Clear Cell RCC, %	Papillary RCC, %	Collecting duct, %	Medullary RCC, %	Urothelial ca, %
PAX8	95–97	78–100	71–100	100	9–17
p63	0	0	0–14	0	96–100
CK7	20–25	28–90	44–50	71–100	94
CA9	90–95	10–44	17	0	33
PAX2	70–95	56–76	43–50	100	6
HMWCK	0	0–13	26–33	29–50	94–100
AMACR	30–50	80–100	18–33	0	20–39

3.9.2 Molecular analysis of UTUC

Although morphology features and immunohistochemical analysis are similar in upper and lower tract carcinomas, it remains controversial as to whether the molecular properties of upper and lower tract carcinomas are identical. As the urothelium of the upper tract originates from a different embryologic site than the urothelium of the lower tract, it is likely that some genomic and proteomic differences exist.[163] Furthermore, whereas the bladder stores urine and thus has prolonged exposure to carcinogens, the urothelium of the upper tract likely experiences a more transient exposure to carcinogens. These differences may in part explain why a somewhat higher proportion of urothelial carcinoma variants may arise in the upper tract versus the lower tract.[61,102,164,165]

UTUC may also be unique in its expression of a select subset of genes and proteins, suggesting some differences between UTUC and lower tract UC. One study that used Affymetrix GeneChip® analysis to compare upper and lower tract urothelial carcinomas showed that a subset of genes associated with chloride ion transport were differentially expressed in upper and lower tract urothelial carcinomas.[166] One of these genes, chloride channel accessory 2, may be induced in a p53-dependent manner, suggesting a possible effector function following DNA damage in a subset of cases.[167] Further studies that evaluate the relationship of urothelial carcinomas from different locations of the urinary tract may be of benefit in the development of diagnostic and prognostic markers.

3.10 Examination, Handling, and Reporting

3.10.1 Clinical history

Given the limited tissue samples available from endoscopic biopsy of the UUT, correlation with clinical history and endoscopic appearance of the biopsied lesion is essential for the most accurate diagnosis. Tavora *et al.* reported a strong correlation between endoscopic appearance and the pathologic diagnosis of biopsy specimens from the UUT, with 75% concordance between clinical and radiographic impression and follow-up pathology.[25] The authors reaffirm the need to correlate the urologist's impression with the pathologist's specimen. Pathologists should be cautious when diagnosing a neoplasm of the UUT in the absence of a clinically evident mass.

In addition to the clinical impression, urologists should include on the specimen requisition form any prior history of upper or lower tract urothelial carcinoma. Prior therapeutic interventions and the presence of stents, calculi, or infection should also be reported to the pathologist, as these can cause marked reactive changes in the epithelium and potentially be misinterpreted as malignant change.

3.10.2 Urologist handling of specimens

In the study by Tavora *et al.*, nearly 1 in 4 UUT biopsies could not be definitively diagnosed, mostly due to insufficient tissue or the presence of crush artifact and architectural distortion of the specimen.[25] Thus, urologists should be careful when handling biopsy specimens in order to maximize the amount of tissue available for diagnosis and prevent artifactual changes that may interfere with the pathologist's ability to interpret the specimen. Biopsy specimens should immediately be placed into formalin jars for optimal fixation and prevention of specimen degradation or drying artifact.

Delicate handling of larger resection specimens is also warranted, as disruption of the specimen may lead to erroneously positive or uninterpretable surgical margins. In addition, given the friability of papillary tumours, excessive manipulation of the specimen may lead to detachment of papillary fronds. These fragments may be displaced into surrounding tissue. This may make it difficult to distinguish them from true stromal or vascular invasion, potentially leading to improper staging and/or prognostication. For partial ureterectomy specimens, designation of the proximal and distal ends of the specimen is recommended for orientation purposes.

3.10.3 Pathologist handling of specimens

3.10.3.1 Biopsies

Minimal and gentle use of forceps is necessary to prevent crush artifact that may interfere with diagnosis. All tissue fragments should be submitted for microscopic examination, and a minimum of three levels are recommended for routine evaluation. In case of diagnostic uncertainty or denuded biopsy specimens, examination of multiple additional levels would be prudent so that patients can receive the most accurate diagnosis. As mentioned previously, denuded biopsies are frequently seen in association with high-grade tumours, and additional microscopic sections to evaluate for residual, clinging tumour cells is recommended.[5]

3.10.3.2 Resections

The vast majority of resection specimens of the upper urinary tract will be radical nephroureterectomies with inclusion of an ipsilateral bladder cuff, as this remains the gold standard for treatment of UTUC. Partial ureterectomy, though, may be performed in select cases. In either case, the surface of the specimen should be inked for assessment of margin status. This includes the cauterized bladder cuff margin, which should be submitted as radial sections. The ureter should be opened along its length and inspected for tumours or erythematous areas suspicious for CIS. Sampling of the ureter should include all tumour foci, including areas demonstrating the deepest penetration of each tumour focus. Sampling also should include suspicious foci and additional representative sections along the length of the ureter, for mapping of CIS. In cases of partial ureterectomy, the proximal and distal margins should be designated by the surgeon and submitted separately as shaved, *en face* margins for microscopic examination. The kidney should be bivalved along its long axis and through the hilum, allowing complete visualization of the pelvicalyceal system.[168] All tumour foci within the renal pelvis should be documented and sampled thoroughly, and sections should demonstrate the deepest penetration of tumour into the peripelvic fat and/or renal parenchyma. Additional sections of the upper, mid, and lower poles should be submitted for mapping of *in situ* disease. At least one representative section of uninvolved renal parenchyma should be submitted for evaluation of medical

renal diseases, which is of particular importance since these patients now have solitary contralateral kidneys and may additionally require adjuvant chemotherapy. Close examination of the hilum for lymph nodes and complete submission of all identified lymph nodes is imperative for proper staging. Additional lymph nodes may be submitted separately, and these should also be entirely submitted.

3.10.3.3 Reporting grade and stage

Grading of tumours should use the WHO (2004)/ISUP classification system and staging should follow the tumour node metastisis system published by the American Joint Committee on Cancer.

3.10.3.4 Reporting lymph node involvement

Although lymph node dissection for UTUC has yet to gain traction in the urology community for a variety of possible reasons, lymph node involvement remains a strong, independent predictor of survival and is important for determining appropriate adjuvant treatment and follow up. All lymph nodes should be submitted for microscopic examination, both those that are part of the main resection specimen and any submitted separately by the surgeon. The number of lymph nodes identified, the number of positive lymph nodes, the size of the largest lymph node metastasis, and the presence of extranodal extension all have potential prognostic significance and are recommended to be reported.[169–172]

3.10.3.5 Reporting lymphovascular invasion

The presence of lymphovascular invasion is another important prognosticator in UTUC, and its presence should be included in pathologic reports. Several authors have demonstrated worse outcomes in patients with UTUC who have LVI.[173,174] Pathologists, though, should be aware of the pitfalls in diagnosing LVI, such as retraction artifact and carry over artifact, in order to prevent over-diagnosis of LVI.

3.10.3.6 Reporting variant histologies

Several studies have suggested that the presence of variant histology in UTUC is not associated with worse outcomes when adjusted for stage, or with lack of response to chemotherapy, as compared to conventional UTUC.[61,175,176] Reporting the presence (and quantification) of variant histology in the pathology report is still recommended for several reasons. First, UTUC with variant histology is associated with a more advanced stage, and although it has not been shown to be an independent prognostic factor, studies on this subject are limited and retrospective in nature. Future studies may find prognostic or even potentially therapeutic information related to particular histologic variants. Second, documentation of histologic variants in UTUC may be useful for identification of a metastasis as being primary UTUC. Knowing that a patient's urothelial tumour, for instance, had micropapillary features can be helpful in identifying a subsequent lung tumour in that patient as metastasis, as opposed to a second primary lung adenocarcinoma. Lastly, in order to continue research efforts to understand variant histologies, documentation in the pathology reports is important in order to capture these patients for clinical trials.

3.10.3.7 Use of frozen sections

The role of intraoperative frozen section (IFS) in evaluation of upper tract urothelial carcinoma is extremely limited. As with any surgery, IFS should only be requested if the results will alter the surgical procedure being performed. As a rule, IFS should neither be used for primary diagnosis of carcinoma nor for determination of the presence of invasion or tumour stage. As the most common surgery for UTUC is radical nephroureterectomy with removal of ipsilateral bladder cuff, evaluation of the distal margin is usually not necessary. In cases where partial ureterectomy is being attempted, IFS evaluation of the ureteral margins may be helpful in preventing positive margins. However, no study to date has examined the utility of IFS in this setting. In addition, the role of IFS in evaluation of distal ureteral margins during radical cystectomy, particularly for CIS, remains controversial.[177–179] Pathologists should be aware that normal upper tract urothelium nuclei are larger than those of the bladder and thus should use caution when evaluating for dysplasia and CIS, especially with the addition of frozen artifact during IFS.

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C4

Management of Low-Risk Disease: Endoscopy, Topical Therapy, Kidney-Preserving Surgery, and Surveillance

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Management of Low-Risk Disease: Endoscopy, Topical Therapy, Kidney-Preserving Surgery, and Surveillance

C4

Committee 4

4.1 Endoscopic Treatment of Low-Risk Upper Tract Urothelial Carcinoma

4.1.1 Introduction

The purpose of endoscopic management of upper tract urothelial carcinoma (ENDO-UTUC) is to locally treat or control tumour growth, prevent related disease progression, and avoid the need for nephroureterectomy. This approach is driven by indications for organ-sparing and renal-preservation strategies in patient care, developed in response to a growing concern over chronic kidney disease and the central role of renal function in relation to cardiovascular physiology. Also recognized, however, are the limitations associated with endoscopic techniques, the heightened oncologic potential for disease progression in urothelial cancers of the upper urinary tract, and the mounting evidence of an aggressive phenotype distinct from lower tract disease. Patients with upper tract urothelial carcinoma (UTUC) are also more difficult to stage clinically, as invasion is not easily assessed on biopsy or imaging. Thus, patients managed with endoscopic approaches are often highly selected, require specialized care, and need careful follow-up and long-term attention.[1–54] This guideline reviews the indications, techniques, and outcomes associated with endoscopic management of this challenging disease.

There are several imperative indications for ENDO-UTUC. These include cases of solitary kidney or functionally deficient contralateral kidney, patients with demonstrated bilateral disease, and those with increased lifelong risk for bilateral UTUC (Balkan nephritis, Chinese herbal disease, and Lynch syndrome). These last groups of patients are often difficult to identify prospectively, and they require a high index of clinical suspicion or appropriate genetic screening studies pre-surgically.[19] Relative indications include patients with severe chronic kidney disease who may be at risk for dialysis following unilateral nephrouterectomy. The relative success seen and reported among these highly compelling cases has prompted a developing interest in ENDO-UTUC for selected patients with elective indications. In a contemporary series from England, about 11% of all UTUCs were treated by ENDO-UTUC.[55]

The goal of accurately predicting true tumour grade of UTUC is a major driver of treatment decision making, because grade is used to infer stage. Low-grade disease on biopsy appears to be a reasonable predictor of low-stage disease (80%–90% positive predictive value), while high-grade on biopsy is somewhat more limited in predicting high-stage disease (65%–68% positive predictive value). Accurate clinical staging is difficult, due to limitations in instrumentation and the restriction of anatomic depth of resection. One major selection criterion in the diagnostic work-up when considering ENDO-UTUC is to exclude locally advanced (invasive) urothelial cancer, which is almost uniformly high-grade cancer. This is because oncologic outcomes are significantly worse with this form of disease, compared to low-grade and low-stage papillary tumours, if treated endoscopically (see **Tables 4-1** to **4-4**).

Clinical series reporting on results with ENDO-UTUC represent highly selected cases that were carefully evaluated and deemed amenable to this form of treatment based on weakly defined clinical and endoscopic findings, as well as surgeons' expertise. An understanding of the clinical and pathologic parameters associated with risk for disease progression, the limitations of treatment modalities, and the patterns of failure are essential to this form of management. Upper tract urothelial carcinoma is a rare disease, accounting for a minority of urothelial cancers, estimated at 5% to 10% of such cases. Roughly 25% to 30% are reported as multifocal, and co-existence with bladder cancer is seen in 17% of surgically resected specimens.[1,56,57] Around 5% of UTUCs develop contralateral UTUC, mandating careful follow-up.[57]

Similarly to patients with bladder cancer, UTUC patients tend to be older (in the sixth or seventh decade of life) and carry associated comorbidities; however, other features of the disease process are notably dissimilar. Unlike lower tract disease, a high proportion of UTUCs are high-grade (60%–70%), and more than 55% of patients harbour pT2 or higher disease at the time of surgery.[7,12,57] Cancer-related outcomes following nephroureterectomy are highly dependent on tumour grade and stage. The 5-year disease-specific survival rates for pathological stage pT0/pTa/pT1 are 93% and 91%, respectively; two-thirds of pT1 cases are high-grade.[58] Of radical nephroureterectomy (RNU) cases performed for UTUC, approximately 40% are very early cancers (pT0/pTa/pTis/pT1), which may represent cases amenable to ENDO-UTUC approaches.[12] Survival rates are quite poor, however, for higher-stage cancers, with 5-year survival rates of approximately 75% and 55% for pT2 and pT3 disease, respectively. A finding of high-grade disease, by itself, is also a poor prognostic sign, associated with a 5-year disease-specific survival rate of only 60% after nephroureterectomy.[58] The finding of high-grade cancer in the upper urinary tract is thus a sign of high-risk disease and the potential need for more aggressive surgical therapies, if appropriate. These data are a valuable reference to consider when evaluating a patient with UTUC and when counseling patients regarding alternative strategies, such as ENDO-UTUC.

Due to its rarity and the difficult clinical features of the disease, most available published data regarding the experience with ENDO-UTUC is limited to retrospective accounts of single-institution or individual surgeons' outcomes at selected centres. These case–control and retrospective cohort studies would fall into the category of Level 3 Evidence, typically evaluating the outcomes of ENDO-UTUC in highly selected patients with limited, non-standardized follow-up regimens for evaluation of outcomes such as local recurrence. In some cases, comparisons may be made to other patients conventionally managed by nephroureterectomy or ureterectomy procedures in a non-randomized fashion. The quality of these data is therefore influenced by patient selection features and surgeon biases, features that must be kept in mind when reviewing related outcomes data.

4.1.2 Diagnosis

4.1.2.1 Imaging

At present, imaging alone provides insufficient data to guide endoscopic treatment in most cases. Exceptions include clear radiographic evidence that excludes tumours suitable for endoscopic approaches, such as bulky, invasive cancers or obvious advanced disease (T3+ disease, N+ or M+ disease). Findings such as hydronephrosis on cross-sectional imaging or ultrasound are associated with invasive (pT2+) disease, which would be less likely to benefit from ENDO-UTUC.[59,60] Routine

imaging in high-risk patients (such as those post-cystectomy) as surveillance for upper tract recurrences is often of low yield and may be over-performed in some patients.[61] A recent systematic review including five high-quality articles showed a high sensitivity and specificity for computed tomography (CT) urography (96% and 99%, respectively; see **Figure 4-1**) and retrograde urography (96% and 96%, respectively) in detecting the presence of malignancy.[62] Magnetic resonance (MR) urography had a high specificity of 97% and a rather low sensitivity of 69%, and excretory urography had a low sensitivity of 80% and a low specificity of 81%. For all imaging modalities, sensitivities are lower with lower tumour burden.[62] Such features also bear noting in regard to the burden of patient follow-up after ENDO-UTUC and the limitations of modalities, such as ultrasound or cross-sectional imaging, in detecting non-invasive localized upper tract disease recurrence.

Recommendations: Imaging

- Imaging should be performed for exclusion of endoscopic treatment (Level 3, Grade B).
- CT urography should be performed for staging (Level 3, Grade B).
- Retrograde urography should be performed during endoscopic evaluation (Level 3, Grade C).

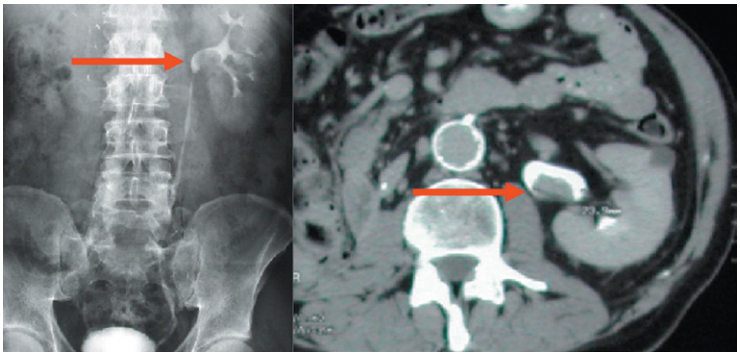


FIGURE 4-1
Large lesion of the left renal pelvis as shown on the CT urograpy compatible with UTUC. While this lesion may be invasive, definitive findings of invasive disease may not be easily identified on current imaging modalities.

4.1.2.2 Cytology and urinary markers for the decision to perform endoscopic treatment

Cytological examination is thought to play an important role in the diagnosis of high-grade urothelial carcinoma (UC) and carcinoma *in situ* (CIS) of the bladder. However, its role in the detection and management of UTUC is poorly investigated, and controversy exists in the utility of routine cytology testing in the absence of radiographic or direct visual endoscopic evidence of a tumour. Cytology samples, most commonly obtained from voided bladder samples, may help to indicate the presence of UTUC, particularly high-grade tumours or CIS. Yet these mixed samples do not help localize the site of the tumour, can be confounded by the presence of concomitant bladder tumours, and may be falsely positive or atypical in the setting of recent instrumentation. In cases where an upper tract source is suspected, selective ureteral samples (obtained by catheterization or during ureteroscopy, and particularly after initial biopsy or brushing when more cells may be dispersed) are performed to lateralize the source of the finding, but should be confirmed endoscopically when possible. False

findings from cytologic samples are not uncommon, and treatment decisions based on these results alone are unproven in regard to survival outcomes, as evidenced by ureteral findings at the time of cystectomy.[63,64] More recent interest in urinary biomarker studies for upper tract malignancies has developed, but robust data are still pending.[65]

Historically, in single-centre studies with RNU, the sensitivity of selective ureteral cytology for UTUC ranged from 43% to 78%,[66,67] with false-negative results as high as 50% for low-grade neoplasms.[68] In 1986, Highman[69] confirmed such observations in a cohort of 54 patients by noting positive cytology (voided or selective cytology) in 47% of low-grade tumours, with an increase to 75% for high-grade lesions. Recently, multicentre trials have shown poor performance of urine cytology. In 2011, Messer *et al.*[70] evaluated 326 patients who had undergone RNU or distal ureterectomy without previous history of bladder cancer and concluded that the positive urine cytology was not predictive of either muscle-invasive disease or high-grade urothelial lesions. The Organ-Sparing Surgery Collaboration for UTUC found that among 31 institutions, 27 (87.1%) used cytology, and 706 patients (46.1%) underwent at least one pre-operative conventional cytologic examination (median: 1; range: 1–9). Fluorescence *in situ* hybridization (FISH) and ImmunoCyt™ were used in 14 and 10 patients, respectively. Selective cytology of the upper tract was obtained in 83% of cases (n=587). A total of 404 patients (57%) had positive cytology. Positive cytology was associated with high-grade disease (p<0.0001), lymphovascular invasion (p=0.002), and more advanced pathological T stage (p<0.001), but not with the size of the index lesion (mean: 31.6±1.0 mm, p=0.64), location of the index lesion (ureter vs. pelvis, p=0.93), tumour multifocality (p=0.34), gender (p=0.95), or age (p=0.82). Selective upper tract cytology was more frequently positive than was voiding cytology (60.3% vs. 33.6%, p<0.001). Sensitivity was 45.0% for low-grade UTUC (n=302), 66.3% for high-grade UTUC (n=404), and 78.6% for isolated CIS (n=14). Overall, 136 patients with positive cytology (34%) had low-grade lesions, while 136 high-grade tumours (45%) were cytologically negative.[71]

Cytology might be of added value to biopsy results. The combination of positive urine cytology and a G2 tumour on biopsy may improve the detection of high-grade and invasive UTUC.[72] In a study by Williams *et al.*,[67] muscle-invasive UTUC was found in only one of six cases with G2 tumour on biopsy and negative cytology versus 8 of 14 cases with positive cytology and G2 tumour.

In summary, cytology has a low sensitivity and a high specificity. Variations may be seen according to the expertise of the cytopathologist, regardless of the technique used (voiding urine, selective urine, washing urine, or brushing urine).

4.1.2.3 Other urine markers

Only a few markers have been tested for the detection of upper tract tumours. The UroVysion FISH test (Abbott Molecular, Des Plaines, IL, USA) and the ImmunoCyt™/uCyt™ test (Scimedx Corp., Denville, NJ, USA)[65,73–77] have been evaluated (see **Table 4-5**). Both tests were described as having high sensitivity (76.6%–100%) in the detection of UTUC, but their specificity (80%–94.7%) was lower than that of conventional cytology. A high negative predictive value would help in differentiating benign and malignant lesions. However, a test allowing for the differentiation of low- from high-grade UTUC would be of much use when planning for endoscopic management.

Recommendations: cytology

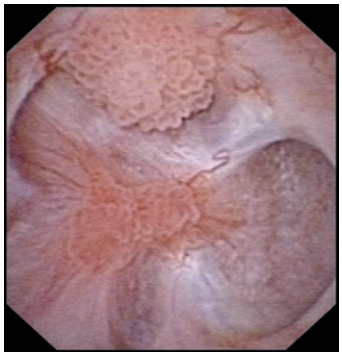
- Malignant tumour cells on urinary cytology suggest high-grade/CIS disease (Level 3, Grade B).
- Cytology should be performed, because it can add information for decision making; however, voided cytology may have little value in diagnosis of UTUC (Level 3, Grade C).
- Selective cytology from the upper tract should be considered to detect high-grade and CIS disease (Level 3, Grade B).
- Urine markers such as FISH can increase sensitivity in experienced hands (Level 3, Grade C).

4.1.3 The role of ureteroscopy in endoscopic treatment

Ureteroscopic evaluation of UTUC (see **Figure 4-2**) should assess for tumour localization, number, size, characteristics (papillary vs. sessile), and accessibility with either flexible ureteroscopy or a percutaneous approach. The treatment approach and outcomes are influenced by these parameters. Multifocal tumours (see **Figure 4-3**)[26,78,79] and high tumour burden have worse outcomes with endoscopic treatment (see **Tables 4-1** and **4-2**).

Tumour architecture is a surrogate marker for high-grade tumours.[80,81] El-Hakim *et al.*[82] showed that 29% of tumours considered to be low-grade on visual inspection were eventually classified as high-grade on final pathology, while 20% of high-grade tumours on visual inspection were actually low-grade. When comparing tumour grade on biopsies with RNU, the accuracy is estimated to be around 70% and is grade dependent (see **Table 4-6**). In low-grade tumours, accuracy is high (>90%), but drops to around 70% in G2 and G3 tumours.[72,82–84]

FIGURE 4-2
Ureteroscopy allows confirmation of the presence of two small adjacent papillary UTUC spreading on a papilla which may not be easily seen on imaging.



Grade is used as a surrogate marker for tumour stage, and the correlation between the two is around 80%.[72,83,84] Grade 1 tumours are non–muscle-invasive in 87% to 100% of cases and non-invasive in 68% to 100% of cases, whereas G3 tumours are muscle-invasive in 67% to 85% of cases. However, this concept cannot be applied to G2 tumours, as up to 28% of these tumours are already muscle-invasive.[81–87] The adoption of the World Health Organization (WHO) criteria for grading would eliminate the G2 classification (which is likely a heterogeneous group of tumours) and facilitate risk stratification simply based on low- or high-grade disease.

Since the size of biopsies is usually quite small, under-sampling is a common problem, occurring in 45% to 56.3% of cases (see **Figure 4-4**). Stage *c*Ta tumours on biopsy have a higher stage on final pathology in up to 50% of cases. Of these, 50% are muscle-invasive. With *c*T1 tumours, upstaging to muscle-invasive disease occurs in 69% of cases.[85–88] It should be noted that the *c*Tx classification is often applicable for this disease but is rarely (if ever) used. Tumours that cannot be assessed for invasion on biopsy, and for which imaging does not inform on invasion (except when invasion is seen), are correctly classified as *c*Tx.

During diagnostic ureteroscopy, placement of ureteral access sheaths before evaluation of the ureter may cause ureteric wall trauma, which could affect assessment of the distal ureter. However, the use of access sheaths has been shown to significantly increase the diagnostic efficacy of ureteroscopy.

FIGURE 4-3
Multiple, small papillary tumours of the renal pelvis.

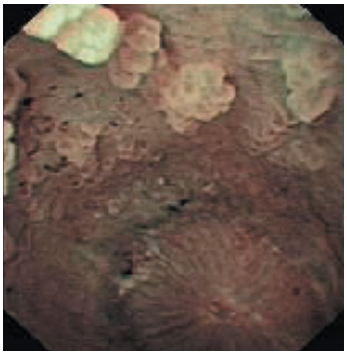
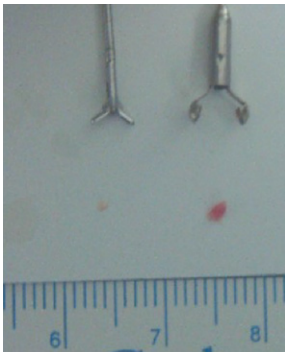


FIGURE 4-4
Size of biopsy fragments vary according to type of forcep used.



Recommendations: diagnostic ureteroscopy

- Ureteroscopic inspection of UTUC alone, without biopsy, has a very limited role; thus, biopsies are recommended (Level 3, Grade B).
- Tumour architecture, multifocality, number of lesions, size of lesions, and localization should be documented (Level 3, Grade C).
- Localizations should also be evaluated for accessibility (need for flexible ureteroscopy, percutaneous approach) (Level 3, Grade C).
- Cystoscopy should be performed to exclude bladder cancer, with consideration of biopsies to rule out carcinoma ***in situ*** if voided cytology was positive (Level 3, Grade B).

4.1.4 The role of ureteroscopy and biopsy

Biopsies can be taken with baskets, forceps, graspers, snares, and brushes. Baskets can be very helpful for papillary lesions (see **Figure 4-5**), whereas forceps and other devices can be useful in flat or solid lesions (see **Figure 4-6**).

Biopsies with a basket should be delivered under direct vision. Though small graspers can be pulled through the channels of the instruments, this risks the loss of tissue protruding from the graspers.

It is often helpful for the pathologist to have more than one biopsy, as non-diagnostic tissue materials are found in up to 25% of biopsies.[89]

The main objective of tumour biopsy is to determine the proper grade, rather than adequate staging. About 68% to 100% of G1 tumours on biopsy are non-invasive on final histology, while 62% to 100% of G3 tumours are invasive. Results for G2 tumours vary significantly, from 17% to 80%, again reflecting the likely inclusion of both low- and high-grade disease in this mostly historical subgroup. Grade is the most important predictive factor for oncologic outcome of endoscopic treatment. High-grade UTUC has worse oncological outcomes (see **Tables 4-1** to **4-4**).

FIGURE 4-5
Use of a nitinol basket for biopsy of a papillary lesion. Flat wire steel baskets also work well for papillary tumours.

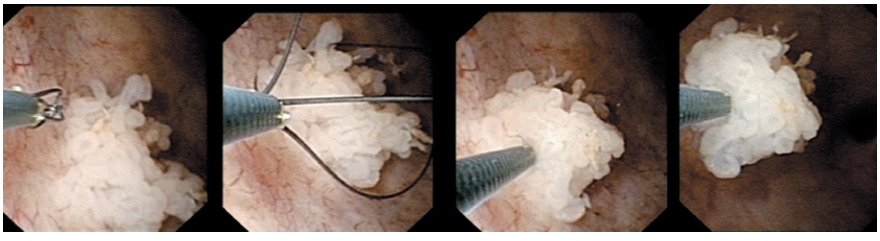
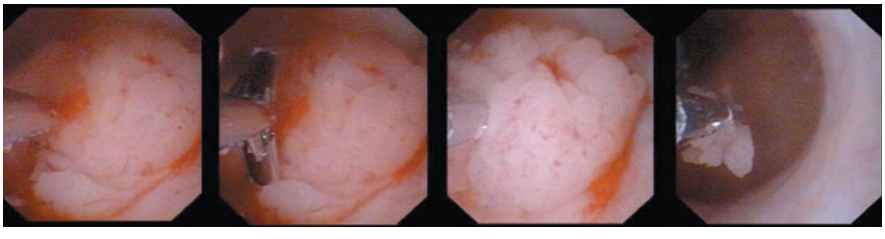


FIGURE 4-6
Biopsy of a tumour using forceps.



A study by Brown *et al.*[85] focused on the prediction of invasive disease. Patients with clinical grade 3 tumours had a 66.2% risk of having pT2 or higher disease and a 42.3% risk of having pT3 or higher disease. Conversely, patients with clinical grade 1 or 2 tumours had only a 28.3% risk of having pT2 or higher disease and only an 8.7% risk of having pT3 or higher disease.

4.1.5 Upper tract urothelial carcinoma after cystectomy

The overall prevalence of UTUC after cystectomy has been shown to range from 0.75% to 6.4%.[61,62] Recurrences appeared at a range of 2.4 to 164 months, in an advanced (64.6%) or metastatic (35.6%) state, and were associated with a poor survival rate. Upper tract urothelial carcinoma after cystectomy is more common in patients with high-grade lesions, CIS, invasive cancers, multifocal disease, a history of multiple urothelial recurrences, positive ureteral margins, positive urethral margins, urethral involvement, and a history of UTUC.[90]

In the case of upper tract involvement following cystectomy, access to the upper tract can prove challenging and often requires a percutaneous approach, though retrograde access can sometimes be performed.

Recommendations: biopsy

- Retrograde pyelography should be performed (Level 3, Grade C).
- Flexible ureteroscopy has technical advantages, especially for performing biopsies (Level 3, Grade C).
- The percutaneous approach is reserved for special indications (Level 3, Grade B).
- The biopsy can be performed using cup biopsies or using a basket (Level 3, Grade B).
- Ureteroscopic biopsy should be performed before endoscopic treatment (Level 3, Grade C).
- More than one biopsy should be performed (Level 3, Grade C).
- Biopsy should distinguish between low- and high-grade tumours (Level 3, Grade B).
- Grade is a surrogate marker. G1 correlates with low-grade and low-stage disease, whereas a high grade correlates with high-grade and high-stage disease (Level 3, Grade B).
- G2 alone is insufficient for the decision of endoscopic treatment, especially in elective cases (Level 3, Grade B).
- The use of access sheaths should be avoided during the diagnostic approach , particularly for the distal ureter (Level 4, Grade C).

4.1.6 Treatment

4.1.6.1 Oncologic outcomes with the ureteroscopic approach

4.1.6.1.1 Overall survival and cancer-specific survival rates

As previously noted, the maximal level of evidence in the current literature on ENDO-UTUC is limited (Level 3, Grade B). In most series, the number of patients ranges between 10 and 73 (see **Tables 4-1** to **4-4**). In all studies, patients were highly selected for favourable tumour characteristics (single tumour, low grade, and low tumour burden based on visual inspection and biopsy). Significant comorbidity is often described in such patients, reflected by high American Society of Anesthesiologists (ASA) scores (≥3) in more than 50% of patients.[7,12,27,28] This is also evidenced by the rather low overall survival rates relative to cancer-specific survival (CSS) in many studies (see **Tables 4-1** to **4-4**). In studies comparing RNU with ENDO-UTUC, particularly from single-institution experiences, major selection bias must be taken into account.

4.1.6.1.2 Endoscopic management of upper tract urothelial carcinoma—local recurrence rates

As a point of reference, data from the UTUC Collaboration revealed a 5-year recurrence-free survival (RFS) rate of 88% to 91.8% after RNU for pTa/pT1/pTis lesions.[58]

Endoscopic management of UTUC for the ureteroscopic approach had a high local recurrence (LR) rate (reported in 17 studies) and ranged between 15% and 90%. The average LR rate was 61% (349 of 572 patients). Local recurrence rates after a ureteroscopic or percutaneous approach are grade dependent. A recent review of the literature showed LR rates after ureteroscopy for G1 of 52% (77 of 149), 54% (45 of 84) for G2, 76% (28 of 37) for G3, 14% (13 of 27) for low-grade, and 60% (12 of 20) for high-grade. After a percutaneous approach, LR rates were 23% (11 of 47) for G1, 30% (17 of 56) for G2, 40% (20 of 50) for G3, 35% (26 of 75) for low-grade, and 42% (22 of 52) for high-grade.[7]

The described risk factors for LR are grade, multifocality, tumour size >2 cm, history of bladder cancer, more than three bladder tumours, and imperative indication.[6,9,12,15,20,26,46,79] Whether tumour location (ureter vs. pelvicocalyx) portends different outcomes remains a source of controversy.[20,46,47,79,91]

Increased intrarenal pressure during ureteroscopic saline irrigation and laser-induced tumour ablation has a theoretical potential for tumour cell migration. Studies have demonstrated that diagnostic ureteroscopy for UTUC showed no significant differences in recurrence rates, time to recurrence, or mortality rates. Similar results were reported between the groups of patients who had and did not have ureteroscopic treatment before salvage nephroureterectomy.[92–94]

4.1.6.1.3 Endoscopic management of upper tract urothelial carcinoma—bladder recurrence rates

The bladder recurrence (BR) rate (reported in 10 studies) ranged from 15% to 70%, and the average was 39% (137 of 347 patients; see **Table 4-2**). There appears to be a high incidence of bladder tumours regardless of treatment, indicating the need for mandatory long-term follow-up of the bladder.

4.1.6.1.4 Local and bladder recurrence rates with percutaneous treatment

Local and BR rates for the percutaneous approach were lower (36% and 28%, respectively; see **Tables 1** to **3**).

4.1.6.1.5 Endoscopic management of upper tract urothelial carcinoma—kidney preservation and progression rates

The risk for progression in low-risk tumours appears to be favourable, as seen with similar disease patterns involving the bladder.[78] The same cannot be said for high-grade tumours, of which as many as 88% may progress.[25] Delayed RNU is frequently necessary to treat disease progression. The kidney preservation rate ranged between 70% and 100% for ureteroscopic, and 50% and 94% for percutaneous ENDO-UTUC, and also reflects—taking into account the high LR rate—a major patient selection bias. Endoscopic management of UTUC is also frequently associated with multiple invasive endoscopic procedures for patients to become tumour free. In a study by Gadzinski *et al.*,[15] 46 procedures were necessary to treat 34 renal units.

Whether delayed RNU (i.e. rescue or salvage RNU) also worsens the outcome is unclear. Currently, it seems that a short delay has no impact,[92,93] but Waldert *et al.*[94] showed that a delay of more than 3 months worsens the outcome.

4.1.6.1.6 Endoscopic management of upper tract urothelial carcinoma—failure, complication, and seeding rates

The failure rate for ureteroscopic treatment is around 24% and around 32% for a percutaneous approach.[7] A biopsy of the tumour base after treatment of the lesions might be helpful to define success of treatment.

The overall pooled complication rates for ureteroscopy and the percutaneous approach were 14% and 27%, respectively. The most common complication after ureteroscopy is ureteral stricture, while transfusion (17%) is the most frequent after a percutaneous approach.[7]

Seeding is rarely reported[95]; Rastinehad *et al.*[96] reported seeding in only 1 of 133 cases (0.75%).

4.1.6.1.7 Metastatic-free survival rates

Only one study has reported 5-year metastatic-free survival rates: 94.4% for low-grade (n=23) and 85.7% for high-grade (n=7) tumours.[15] The median follow-up was 77 months.

4.1.6.2 Endoscopic treatment techniques

The evolution of small, semi-rigid and flexible ureteroscopes, as well as the development of digital techniques and advanced laser technology, allow for full, high-quality imaging and access to the whole upper urinary tract for effective treatment. The holmium:yttrium aluminum garnet (YAG) and the neodymium:YAG lasers are effective for neoplasms, and treatment can be delivered through small, flexible instruments. The additional use of ureteral access sheaths in selected cases allows for easy introduction and re-introduction of flexible ureterorenoscopes with low-pressure, continuous-flow irrigation for excellent intra-operative visualization.[29]

4.1.6.2.1 Lasers

The neodymium-doped (Nd):YAG laser, at a wavelength of 1,064 nm, destroys tissue with coagulation. Its depth of penetration is 5 to 6 mm in tissue or water; therefore, direct contact of the fibre with the tissue is not necessary. This depth of penetration may be a concern for the thin-walled ureter. It is therefore suggested to use following parametres: 20 to 30 W for 2 to 3 s, using fibre diameters that range from 200 to 600 mm.

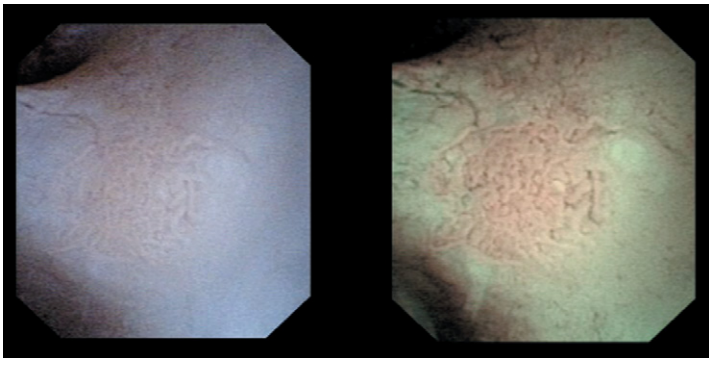
The holmium:YAG laser is a pulsed device with a wavelength of 2,100 nm and a depth of penetration of less than 0.5 mm (see **Figure 4**-7). It can cause coagulation at lower energies and higher pulse durations and can ablate the tissue.[95,97–99] Energy is highly absorbed by water and water-containing tissue, resulting in minimal thermal damage to the surrounding tissue; however, direct contact with the tissue during treatment is necessary.[95] Due to the need to operate the holmium:YAG laser in contact mode, tissue adherence to the fibre tip during ablation can occur, resulting in decreased visibility and decreased ablation capacity. Interruption of laser application and cleaning of the fibre, which results in extended operation times, may become necessary.

Other currently available technologies (such as diode laser systems and thulium laser systems) are available, but no clinical recommendations can yet be made, due to a lack of studies. Currently, no small fibres are available for the diode laser; thus, its use through flexible instruments is limited. While using lasers, the tip should always be under direct visualization.

With the holmium laser, a maximum coagulative effect can be obtained by defocusing the laser beam (i.e. leaving a small gap) on the tissue, whereas close approximation or contact with the tissue gives a more ablative effect and removes tissue. Generally, there is less bleeding with the coagulative technique.[97] Additionally, with longer pulse duration, the coagulation is more effective, while a shorter pulse leads to more ablation.

The type of laser used depends on the size and location of the lesion. For bulkier and larger tumours, Nd:YAG has advantages, whereas for smaller tumours and treatment at the ureter wall, holmium:YAG has major advantages. Using Nd:YAG with deeper penetration at the ureter wall can lead to more ureteric strictures.[97] Using the holmium:YAG laser can lead to staged ureteroscopic treatments in bulky and large tumours. Ureteric stricture rates range from 8.5% to 16.7%.[8,24,95,97] After laser treatment, most patients require ureteral stents for 1 to 6 weeks.

FIGURE 4-7
Tumour identification using white light compared with narrow-band imaging.



4.1.6.2.2 Resection—electro

Electro-diathermy or electro-resection can also be used, especially with a percutaneous approach.

Recommendations: best indications for endoscopic treatment

- The best indications for endoscopic treatment are as follows:
  - Unifocal (Level 3, Grade B)
  - Small lesions (<2 cm) (Level 3, Grade C)
  - Low-grade tumour on biopsy (Level 3, Grade B)
  - Negative cytology (Level 3, Grade C)
  - Complete visualization (Level 3, Grade B)
  - Papillary tumour (Level 3, Grade B)
  - Good compliance (Level 3, Grade B)

- All other tumour or patient features should be treated with endoscopic treatment only in very select patients (Level 3, Grade B).

4.1.6.2.3 The percutaneous approach

Percutaneous resection of low-grade and low-stage UTUC using electrocautery was first described 20 years ago. It has since been shown to be safe and effective for the treatment of small (<2 cm) tumours. Furthermore, percutaneous management provides access for the administration of intracavitary chemotherapy or immunotherapy to minimize recurrence. Second-look procedures are used to assess the effectiveness of the initial treatment and to remove any residual disease. Rouprêt *et al.*.[57] posit that with the evolution of techniques, the more morbid (12.5% transfusion rate) and potentially oncologically unsafe percutaneous approach (potentially causing tumour spillage and pyelolymphatic or pyelovenous backflow)[16,40,46] will be used less frequently than the ureteroscopic approach. This is confirmed by the nationwide practice of conservative treatment for UTUC in France.[100] However, in bulkier disease—especially in the lower calyx—the percutaneous approach can be helpful.

Some authors recommend the percutaneous approach to treating tumours in the renal pelvis because it provides a better working environment and the possibility of using more and larger tools through the nephroscope in patients with bulky (>1 cm) tumours or lower calyx tumours. Percutaneous treatment is associated with significantly higher rates of blood transfusion, and the overall complication rates of percutaneous treatment compare with those of ureteroscopic treatment. Nephrostomy tract tumour seeding associated with the antegrade percutaneous approach has been documented in few reports, whereas tumour seeding via ureteroscopic therapy is a theoretical risk.

4.1.6.2.4 New technologies

Recommendations for photodynamic diagnosis (PDD) or narrow-band imaging (NBI) (see **Figure 4-8**) cannot be made for either diagnosis or treatment, because the data are limited and not yet mature.[101–104] For bladder cancer, NBI shows promising results, detecting more patients with tumours and more tumours per patient.[105] These preliminary results will need to be translated to the upper tract.

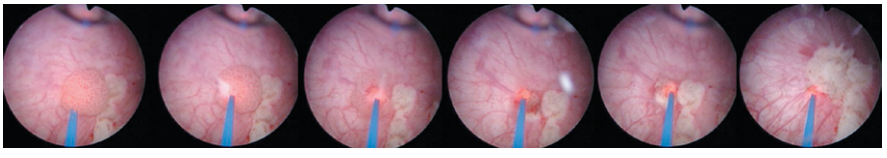


FIGURE 4-8
Tumour ablation using holmium:YAG laser photovaporization.

4.1.6.2.5 Stenting the ureter

If perforation occurs during tumour ablation, it is recommended to stop the procedure, place a stent, and re-treat after several weeks.

4.1.6.2.6 Follow-up ureteroscopy

It can be useful to perform a control ureteroscopy 4 to 6 weeks after the initial treatment, especially for more complex tumours or when in doubt that all tumours were resected.

4.1.6.2.7 Instillations

For instillation techniques, similar principles apply as in bladder cancer. The major differences in UTUC and bladder cancer are technical issues, which are discussed later in this chapter. However, instillation techniques should not be used to treat residual tumours, and complete endoscopic tumour resection/ablation is necessary before initiating topical instillation as an adjuvant. As primary therapy, bacillus Calmette-Guérin (BCG) is used for the treatment of CIS and as an adjuvant after resection/ablation of high-risk tumours.[106–117]

Recommendations: treatment

- For disease progression, salvage RNU should be considered (Level 3, Grade B).
- Multiple endoscopic treatments might be necessary for the patient to become tumour-free (Level 3, Grade C).
- Biopsies of the tumour ground to evaluate treatment success might be helpful (Level 4, Grade C).
- The use of access sheaths can reduce intrarenal pressure (Level 4, Grade C).
- The use of access sheaths can allow for easier access to the upper end of the upper tract, especially in flexible treatment (Level 4, Grade C).
- Lasers are advantageous in the treatment of ENDO-UTUC (Level 3, Grade B).
- The holmium:YAG laser is especially advantageous in the ureter, because of its short penetration distance, to avoid strictures (Level 3, Grade B).
- Circumferential treatment in the ureter should be avoided (Level 4, Grade C).
- Electro-diathermy and electro-resection can be used, especially with percutaneous access (Level 4, Grade C).
- Percutaneous access is reserved for special indications (Level 3, Grade B).
- Stenting of the ureter can be performed after ENDO-UTUC (Level 4, Grade C).
- Instillations with mitomycin or BCG can be performed after ENDO-UTUC (Level 3, Grade C).
- New technologies, such as NBI and other modern image filtering techniques, may be considered (Level 4, Grade D).

4.1.7 Conclusion

The endoscopic treatment of UTUC is a tool for organ-sparing and renal-preservation strategies in individualized patient care. It is especially useful for low-volume, low-grade papillary UTUC, because with other UTUC features, outcomes are worse. However, recurrence rates are high, and follow-up includes invasive and frequent endoscopic surveillance.

TABLE 4-1 Outcomes of series using ureteroscopic treatment for UTUC

Reference	Number of patients	Mean follow-up (months)	Recurrence (%) local/bladder	Overall survival (%)	Cancer-specific survival (%)	Kidney preservation rate (%)
Fajkovic *et al.*[12]	20	20	25/15	45	95	100
Cutress *et al.*[6]	73	54	68/53	60	90	81
Grasso *et al.*[17*]	66	51.5	77/61	5-year: 74	5-year: 87	83
Gadzinski *et al.*[15]	34	58	84/not reported	75 (25 for high-grade)	100 (86 for high-grade)	89
Cornu *et al.*[54]	35	24	60/40	100	100	89
Pak *et al.*[39]	57	53	90/not reported	93	95	81
Lucas *et al.*[34]	39	33 (median)	46/not reported	62	82	72
Painter *et al.*[38]	45	not reported	not reported	not reported	89	91
Krambeck *et al.*[27]	37[†]	32 (median)	62/37	35	70	70
Reisiger *et al.*[45]	10	73	50/70	100	100	90
Rouprêt *et al.*[46]	27	52	15/22	77	81[*]	74
Johnson *et al.*[24]	35	32	68/not reported	not reported	100	97
Iborra *et al.*[20]	23	not reported	35/not reported	not reported	96	91
Matsuoka *et al.*[36]	26[†]	33 (median)	26/15	not reported	89	not reported
Daneshmand *et al.*[8]	30	31 (median)	90/23	77	97	87[‡]
Chen & Bagley[3]	23	30	64/12	not reported	not reported	not reported
Engelmyer & Belis[118]	10	43	70/not reported	90	100	100
Gaboardi *et al.*[14]	18	15	50/not reported	100	100	94
Andersen & Kristensen[1]	10	25	not reported	not reported	not reported	80
Schmeller & Hofstetter[48]	16	14 (median)	19/not reported	100	100	100
OVERALL	634	14–73	61[§]/39[‖]	35–100	70–100	70–100

[*]Only low-grade patients. [†]Only imperative indications. [‡]Procedures include not only RNU, but also other treatments (e.g. partial nephrectomy). [§]Reported in 17 studies; 349 of 572 patients had local recurrence. [‖]Reported in 10 studies; 137 of 347 patients had bladder recurrence.

TABLE 4-2 Outcomes of series using a percutaneous approach for UTUC

Reference	Number of patients	Mean follow-up (months)	Recurrence (%) local/bladder	Overall survival (%)	Cancer-specific survival (%)	Kidney preservation rate (%)
Rastinehad *et al.*[43]	89	61	33/not reported	68	not reported	87
Rouprêt *et al.*[47]	24	62 (median)	13/17	79	83	79
Palou *et al.*[40]	34	51	44/not reported	74	94	74
Goel *et al.*[16]	20	64	65/15	not reported	75	50
Clark *et al.*[5]	17	24	33/not reported	75	82	88
Patel *et al.*[41]	26	45	35/42	75	91	94
Plancke *et al.*[42]	10	28	10/10	90	100	90
Fuglsig & Krarup[13]	26	21	31/not reported	96	100	65
Tasca *et al.*[2]	10	19	50/not reported	90	100	70
OVERALL	256	19–64	36*/28†	68–96	75–100	50–94

*Reported in all 9 studies; 92 of 256 patients had local recurrence. †Reported in 4 studies; 22 of 80 patients had bladder recurrence.

TABLE 4-3 Outcomes of studies using a percutaneous and ureteroscopic approach

Reference	Number of patients	Mean follow-up (months)	Recurrence (%) upper tract / bladder	Overall survival (%)	Cancer-specific survival (%)	Kidney preservation rate (%)
Raymundo *et al.*[44]	21	18	31/15	not reported	82	not reported
Thompson *et al.*[52]	83*	55 (median)	55/45	58	89	77
Suh *et al.*[79]	14	64	100/not reported	88	86	65†
Deligne *et al.*[9]	61	40	25/23	76	85	82†
Martínez-Piñeiro *et al.*[35]	54	31	23/not reported	75	91	90

*Only elective cases. †Procedures include not only RNU, but also other treatments (e.g. partial nephrectomy).

TABLE 4-4 Studies comparing endoscopic treatment with RNU

Reference	n (%) endoscopic	Follow-up (months)	5-year survival (%)		
			Survival type	Endoscopic	Radical
Gadzinski *et al.*[15]	34	77	Overall	25–27	48–72
			Cancer-specific	86–100	72–89
			Metastatic-free	86–95	64–88
Lucas *et al.*[34]	39	46	Overall	63	72
			Cancer-specific	82	83
Rouprêt *et al.*[46]	43*	55	Cancer-specific	81	84
			Recurrence-free	72	75
Fajkovic *et al.*[12]	20	20±30	Overall	45	76
			Cancer-specific	67	91†
			Recurrence-free	75	98
Grasso *et al.*[78]	66 (low-grade)	51.5	Overall	74	78†
			Cancer-specific	87	86
			Metastatic-free	84	78

*27 ureteroscopic; 16 percutaneous. †RNU only for pTa/pTis/pT1.

TABLE 4-5 Studies using FISH for diagnosis of UTUC

Reference	N (UTUC)	Sensitivity (%)	Specificity (%)	Predictive value	
				Positive (%)	Negative (%)
Mian *et al.*[77]	55 (21)	100	89.5	84.6	100
Akkad *et al.*[73]	16 (9)	87.5	80	87.5	80
Marín-Aguilera *et al.*[76]	49 (30)	76.6	94.7	95.8	72

TABLE 4-6 The accuracy of grading in ureteroscopic biopsies during diagnosis of UTUC

Reference	Number of UTUC cases (*n*)	Biopsies diagnostic n (%)	Grading correct n (%)	Number of low-grade tumours upgraded n (%)
Guarnizo *et al.*[83]	45	40 (89)	31 (78)	5 (19)*
Shiraishi *et al.*[86]	40	35 (87.5)	18 (58)	0 (0)
Smith *et al.*[81]	65		41 (63)	24 (43)
Williams *et al.*[67]	30	30 (100)	17 (56.7)	3 (50)†
Wang *et al.*[65]	184	48 (26)	83 (45)	23 (96)
Keeley *et al.*[84]	51	42 (82.4)‡	38 (90)	(10)
Skolarikos *et al.*[72]	62	51 (82)	35 (69)	No G1 was upgraded to G3, G2 unknown
OVERALL	477	246/412 (59.7)	236/477 (55.1)	(0–96)

*Upgrading was from G1 to G2, but 0% to G3. †Of 6 G1 on biopsy, two were G2 and three G3; of 17 G2 on biopsy, 13 were G2 and 4 G3; of 4 G3 on biopsy, 1 was G2. ‡Diagnostic was performed with cytology in eight cases, with cell block in 29 cases, and with routine histopathology in five cases.

4.2 Topical Therapy for Upper Tract Urothelial Carcinoma

4.2.1 Introduction

In patients diagnosed with UC of the bladder, adjuvant intravesical instillation therapy is recommended to reduce the risk for cancer recurrence and possibly the probability of disease progression. The European Organisation for Research and Treatment of Cancer (EORTC) Genito-Urinary Cancers Group, for instance, proposes basing the most appropriate treatment and follow-up plan on risk category (low-, intermediate-, and high-risk groups).[119] Irrespective of risk and the scheduled regimen, most urologists advocate a single, immediate (within 24 hours) chemotherapeutic instillation following tumour resection, which is indicated to prevent unwarranted implantation of floating cancer cells across denuded mucosa. As recurrence rates following endoscopic treatment of upper tract tumours have been relatively high, reported in 30% to 70% of patients,[24,26] there should be a role, at least in theory, for immediate adjunct instillation. The rationale is similar to that in bladder cancer: ureteroscopy may result in unwarranted damage to the ureteral wall due to instrumentation (e.g. by guide-wire passage or ureteral access sheath), and tumour cell seeding may occur at these locations.

While guidelines pertaining to adjuvant topical therapy in bladder cancer have now been widely endorsed by the urological community, there is no parallel policy for adjuvant treatment in patients with UTUC following endoscopic resection. Unlike in bladder cancer, the effective application of therapeutic agents to the upper urinary tract requires two major considerations: mode of delivery and adequate dwell time. The former inevitably translates into complex invasive manipulation (retrograde or antegrade), whereas the latter is particularly critical in cases where topical therapy with BCG is considered, as sustained close contact at the resected tumour site is essential for optimal effect.[120]

Because upper urinary tract tumours are rare, adequately powered randomized trials are very difficult to complete; thus, the optimal route and true benefit of adjuvant instillation therapy in the upper urinary tract remains unknown.

It should be clarified that topical treatment after complete resection of discrete papillary tumours is considered adjuvant therapy, whereas in cases of diffused CIS, topical therapy is considered actual primary definitive therapy. This delineation is important, given the paucity of data related to topical therapy, which is presented below. As in bladder cancer, it is critical that complete endoscopic tumour resection/ablation be performed prior to initiating treatment in order to derive the maximal benefit from topical therapy in the adjuvant setting.

4.2.2 Choice of agent

If adjuvant instillation therapy following endoscopic resection of upper tract tumours is used, the practice should be generally similar to that recommended in bladder cancer: chemotherapy in low-/intermediate-risk tumours and BCG for high-risk patients (including treatment of upper tract CIS). Unfortunately, the evidence supporting this policy has been largely inconsistent, with several series using different agents and various forms of application.[37,107,109,110,121,122] While benefit in favour of a particular intravesical chemotherapeutic agent in bladder cancer has never been proven, most experience with upper urinary tract instillations has been with mitomycin C, the only approved drug for instillation treatment in most countries worldwide.

4.2.3 Patient selection

4.2.3.1 Low- and intermediate-risk patients

The most appropriate candidates for conservative management of UTUC are patients with low-grade/low-stage/low-volume tumours and an intact contralateral kidney. In patients with a solitary kidney or compromised renal function, renal-sparing approaches should also be considered in high-grade tumours amenable to endoscopic resection. Depending on the size and location of the tumour, an antegrade percutaneous or retrograde ureteroscopic surgical approach may be preferred (see the previous section).

For patients in whom the resected tumour is endoscopically determined to be low-risk, an immediate chemotherapeutic instillation to the upper urinary tract may be considered. At present, there is no definitive proof to support any advantage of this approach in delaying tumour recurrence or disease progression, except for what is correlated from the treatment of bladder cancer. Technical obstacles limit the routine application of topical therapy in this setting; however, the variety of reports attests to the overall safety of drug instillation into the upper tract.[109,110,121,122]

4.2.3.2 High-risk patients

Patients with high-risk tumours (defined for the purposes of this chapter as CIS or high-grade non-invasive tumours) deemed candidates for conservative therapy should generally be offered adjuvant treatment with BCG instillations. Bacillus Calmette-Guérin can be delivered on an ablative/primary therapeutic basis (for CIS) or an adjuvant basis (following complete tumour removal). Supporting evidence has been very sparse and inconsistent, largely coming from non-randomized single-institution series.

Table 4-7 summarizes the available data pertaining to topical BCG therapy in patients with CIS of the upper urinary tract. These studies remain limited by the small number of patients, variable diagnostic tools (biopsy proven vs. cytology based), inconsistent mode of BCG application (antegrade vs. retrograde), dose of BCG or combination, and follow-up scheme. A new reverse thermosensitive polymer containing mitomycin has recently been evaluated in an animal study, but clinical studies and experience with this remain very limited.[245]

TABLE 4-7 Results of BCG instillation to the upper tract

Reference	Number of patients	Stage	Treatment	Follow-up	Outcome
Hayashida *et al.*[107]	10	CIS	BCG	50.9 months (median)	5/10 recurrence
Miyake *et al.*[111]	16	CIS	BCG	30 months (median)	3/16 recurrence
Giannarini *et al.*[106]	55	CIS: 42 RU Ta/T1: 22 RU	BCG	42 months (median)	Median 5-year RFS for CIS: 57% Median 10-year RFS for CIS: 49% 20/55 alive NED
Nonomura *et al.*[112]	11	CIS	BCG	4–41 months	2/11 recurrence
Okubo *et al.*[113]	11	CIS in 14 RU	BCG	60 months (median)	7/14 RU: NED 2 RU: recurrence 5 RU: NR
Irie *et al.*[108]	9	CIS in 13 RU	BCG	36 months	3/9 recurrence
Shapiro *et al.*[123]	11	CIS	BCG/IFN	13.5 months	8/11: CR 3/11: NR

BCG: bacillus Calmette-Guérin; **CIS:** carcinoma in situ; **CR:** complete response; **IFN:** interferon; **NED:** no evidence of disease; **NR:** no response; **RFS:** recurrence-free survival; **RU:** renal unit.

Recommendations: choice of agent

- The choice of topical therapy in patients with upper urinary tract tumours should be risk-tailored (Level 3, Grade B).
- Low- and intermediate-risk patients should be managed with topical chemotherapy (Level 4, Grade C).
- In patients diagnosed with CIS or high-risk non-invasive tumours, adjuvant topical therapy with BCG following endoscopic resection might be advantageous (Level 3, Grade C).
- Delivery of BCG and chemotherapy to the upper tract is well tolerated, with infectious complications being most reported (Level 3, Grade B).

4.2.4 Mode of delivery

Several techniques for instilling drugs into the upper urinary tract have been described: an antegrade route through a percutaneous nephrostomy tube,[106,116] a retrograde route via a single-J or open-end ureteral catheter,[110,113] and an intravesical route after induction of vesico-ureteral reflux (VUR) using a double-J stent or wide resection of the ureteral orifice in the corresponding affected side.[108,124] While each of these techniques has its own merits and limitations, for a long time, none had been proven superior to the others in an appropriate comparative setting, and still have not been shown clinically.[125] However, a recent well-conducted animal study showed the superiority of delivery using a ureteral catheter over nephrostomy tube or use of double-pigtail stent.[126]

The antegrade approach requires the insertion of a nephrostomy tube and demonstration of an unobstructed flow before initiation of therapy. The instillation bag should not be placed higher than 20 cm above the renal pelvis level, and treatment should be administered under antibiotic prophylaxis. A unique adverse consequence of this approach is the risk for tumour tract seeding, especially in high-risk patients.[43,127]

A double-J stent has been used to induce reflux into the upper urinary tract system with the patient placed in the Trendelenburg position.[108,114] Instillation therapy is administered intravesically on a weekly basis. However, VUR is not a guaranteed consequence of double-J stent placement, particularly at the low volume of instillation typically used. Therefore, if upper urinary tract instillation with the double-J technique is considered, a cystogram should be done first in order to confirm the occurrence of reflux, determine the intravesical volume required to induce reflux, and ascertain that the pertinent section of the ureter or pelvicaliceal system from which the tumour was initially removed is opacified during the study.[124] A yet-to-be-defined time interval should be allowed between insertion of the stent and reflux assessment. Even if reflux is confirmed on a cystogram, there is no guarantee that reflux will occur during subsequent instillations. This technique is not recommended.

Insertion of an open-end ureteral catheter into the involved renal unit can be done on an outpatient basis using flexible cystoscopy and a guide wire.[109] The theoretical risk of this approach is mucosal damage or perforation, leading to increased systemic absorption of the instilled drug, and possibly ureteral strictures from weekly manipulations. In the previously mentioned animal study, this approach was superior to the other two methods.[126]

Recommendations: delivery methods

- The optimal technique to deliver instillation treatment into the upper urinary tract has not yet been clinically determined (Level 3, Grade C).
- The use of a ureteral catheter for delivery of agent to the upper tract has been shown to be most effective in an animal model (Level 3, Grade A).
- The use of double-J stents with resulting reflux is unreliable and therefore discouraged (Level 3, Grade B).

4.2.5 Oncologic outcomes: results of adjuvant instillation therapy

Several single-institution series have reported the outcomes of adjuvant instillation therapy for UTUC, all limited by their retrospective nature, resulting in a high level of bias.[5,22,35,37,43,49,106, 114,117,122,128] The recurrence rate following topical therapy is in the range of 30%, and adjuvant instillations seem to be beneficial, especially in patients presenting with CIS.[20,28] At present, there is no conclusive evidence to support any long-term oncological benefit of this approach. Based on the limited data, it does appear that the use of BCG has the best benefit for primary treatment of CIS, and its use as an adjuvant is less promising oncologically.

4.2.6 Treatment algorithm and follow-up

Given the lack of conclusive evidence, the optimal drug, schedule, mode of delivery, and follow-up scheme cannot be determined at this time. Instillation of BCG into the upper urinary tract following endoscopic resection of high-risk tumours or for primary treatment of CIS appears to be the only setting in which clinical benefit of adjuvant topical therapy has been shown. Currently, there is no evidence regarding the role of immediate instillation of mitomycin C or of maintenance therapy.

Irrespective of the technique used to deliver the drug, sterile urine should be confirmed invariably, and prophylactic antibiotic treatment is recommended. The follow-up schedule is discussed in the last section of this chapter.

The long-term oncological benefit of upper urinary tract instillation therapy has not yet been determined (Level 4, Grade C).

The optimal treatment schedule and follow-up regimen for upper urinary tract instillation therapy remain unknown (Level 4, Grade C).

4.2.7 Conclusion

Adjuvant topical therapy with chemo- or immunotherapeutic agents following endoscopic resection of tumours in the upper urinary tract is still considered investigational. The choice of drug and method of delivery have not yet been standardized, but recent animal evidence suggests that delivery via ureteral catheter may be optimal.

There are no defined patients in whom adjuvant instillation therapy to the upper urinary tract is considered mandatory.

In patients diagnosed with high-risk upper tract tumours considered candidates for conservative management, adjuvant BCG instillations have been shown to provide clinical benefit in single-series retrospective studies.

Standardized criteria to guide surveillance protocols following endoscopic resection and upper tract instillations are lacking. Combining imaging with serial ureteroscopies is advised, at intervals that have yet to be defined.

4.3 Conservative Surgery: Segmental and Distal Ureterectomy, Partial Nephrectomy, Patient Selection, and Techniques

4.3.1 Introduction

Radical nephroureterectomy with bladder cuff removal is the reference standard for patients with UTUC. Less radical approaches are historically reserved for imperative indications, such as the presence of a solitary kidney or other conditions predisposing for significant decline in global renal function post-RNU, and the need for lifelong renal replacement therapy.[129] Growing worldwide experience in the management of renal cell carcinoma (RCC) suggests that RNU is associated with a significantly higher probability of chronic kidney disease (CKD) and attendant risks for cardiovascular morbidity

compared to nephron-sparing strategies.[130,131] There is evidence that nephron-sparing approaches in RCC patients provide similar oncological outcomes as RNU.[132] Unlike in RCC, patients with UTUC are older, with higher rates of CKD and cardiovascular comorbidities at diagnosis. According to several large, multicentre, population-based studies, up to 80% of patients develop stage III CKD after RNU.[133] An increasing body of literature indicates that nephron-sparing modalities, particularly partial ureterectomy, may provide acceptable oncologic and functional outcomes in select patients with UTUC.[134,135] Organ-preserving approaches include endoscopic resection, segmental ureteral excision, and partial nephrectomy.

4.3.2 Patient selection for an organ-sparing surgical modality

The most appropriate option for each patient depends on tumour- and patient-related factors. These factors should be taken into account to individualize the treatment options offered to each patient. Although there are many features associated with outcomes in UTUC, most of these may not actually impact treatment decisions.

4.3.2.1 Tumour-related factors

Upper tract urothelial carcinomas are best divided into low- and high-risk tumours using grade and possibly stage (which clinically may be limited and thus a selection of other factors may be used for risk stratification). This chapter focuses on low-risk tumours. These are low-grade lesions that are non-invasive (pTa). Low-risk UCs have a low risk for progression to invasion (<3%), metastasis, and death, but often recur as non-invasive lesions elsewhere in the urinary tract.[129,136] Following treatment of their primary upper tract cancer, around 50% to 70% of patients with UTUC develop bladder cancer, and 5% develop contralateral UTUC.[137] This recurrence may be due to residual tumour cells (leading to monoclonal spread) within the urinary tract or to the development of a new unrelated (oligoclonal) tumour clone following global urothelial exposure to carcinogens.[138,139] Given the low risk for progression of these low-risk cancers, it is best to consider organ preservation when possible. However, various tumour-related factors affect the decision to perform nephron-sparing surgery.

4.3.2.2 Risk of progression and recurrence: pathological factors

Nephron-sparing approaches should be considered for tumours in which the likely natural history is indolent disease that is unlikely to progress to invasion. There are numerous pathological features that predict future recurrence and progression risk. For example, these risks have been shown to vary with respect to tumour multiplicity and multifocality,[140] tumour size and growth pattern, tumour grade, location,[141,142] dysplasia and CIS within flat urothelium,[143] whether the tumour is primary or recurrent following previous disease, and the natural history of the patient's previous tumours.[144,145] Many of these features are shared between UCs of all locations.[146] A thorough ureteroscopic evaluation is mandatory in patients considered for a nephron-sparing approach, as the presence of multifocality essentially rules out this option.

To identify the tumour grade, cells from the tumour should be obtained by direct washings, exfoliated cytology, a biopsy (obtained by ureteroscopy), or a combination of these approaches. Biopsies are often too small to reliably identify stage, but should allow for the classification of tumour grade (low- versus high-grade). High-grade tumours are of high risk for progression and metastases, so caution should be exercised before using nephron-sparing surgery. Ureteroscopy is also extremely

useful for determining growth pattern (papillary/exophytic lesions vs. sessile lesions), size of the tumour, state of the flat urothelium (erythematous with telangiectasia suggestive of CIS), and location of the tumour.

Cross-sectional imaging (either CT or MR tomography, with and without contrast) should be used to determine tumour size, multifocality, location, and distant metastases. Cross-sectional imaging is also best for approximating the stage of the primary lesion (by looking at tissue planes around the urinary tract). Those that appear advanced (with lymphadenopathy or tissue invasion) usually make poor candidates for nephron-sparing surgery.

4.3.2.3 Tumour location

In addition to predicting behaviour, anatomical tumour location is important for planning the surgical approach.[137,141,142] For example, distal and mid-ureteric lesions are often suitable for segmental ureteric resection, in contrast to renal pelvic and calyceal tumours. With the latter, partial nephrectomy is technically difficult and could increase the complication rate (e.g. urinary leaks and obstruction) compared to RNU, which may be an issue for frail patients. Obtaining negative urothelial margins in these cases is also quite challenging with tumours that are not strictly confined to the upper or lower pole of the kidney. Furthermore, most recurrences occur distal to the original tumour. For example, recurrence following a distal ureteric tumour is usually within the bladder, which is easily assessable for follow-up. For renal pelvic tumours, however, recurrence may occur further down the same ureter, which may be harder to assess due to post-operative changes. Therefore, solitary mid- and distal ureteric lesions are the best candidates for nephron-sparing resection, while those within the renal pelvis may be better tackled by endoscopic surgery (if nephron-sparing is necessary).

4.3.2.4 Status of the flat urothelium

The status of the flat urothelium is important for predicting future risk for recurrence or progression.[143,146] By definition, low-risk tumours exclude those with CIS in the flat urothelium, but low-risk tumours occasionally have dysplasia within the adjacent urothelium. If possible, these tumours should be identified pre-operatively (from abnormal cytology or abnormal-looking urothelium) and a wider excision performed. More commonly, dysplasia in low-risk tumours is found post-operatively, in the final pathological sample. Patients with these tumours should be monitored more closely, as the risk for progression is slightly increased compared to similar cancers without dysplasia.[136]

4.3.3 Patient-related factors

There are many patient-related factors that affect the choice of UTUC treatment. These include factors generic to the whole patient (such as comorbidities, gender, and risk factor exposure) and factors specific to the urinary tract (e.g. status of the contralateral upper urinary tract, renal impairment, and status of the lower urinary tract).

4.3.3.1 Gender and race

Although UTUC is more common in men than in women, the difference between the genders is smaller than with bladder cancer. This is likely a reflection of differences in the etiology of UTUC compared to UC of the bladder. For example, chronic analgesic consumption is more common in

female than in male patients and accounts for UTUC arising from phenacetin ingestion, whereas UCs within Lynch syndrome occur mostly in the upper tract and are balanced in incidence between men and women.[147] Large population-based analyses have suggested differences in stage and grade for UTUC at presentation with respect to gender (women present with more advanced cancers than men), but also suggest that this may reflect delays in diagnosis rather than differences in tumour biology.[144] As the outcomes of UTUC do not appear to vary with gender, this factor should not be used to adjust treatment strategy. Similar findings are observed with patient race. Although more advanced cancers are found in black non-Hispanic patients, this probably reflects variations in health care pathways rather than tumour biology.[148]

4.3.3.2 Age and comorbidity

Older patients have worse outcomes of UC, regardless of location in the bladder or upper urinary tract.[149,150] This reflects either the fact that definitive treatments are used less commonly in elderly patients (due to comorbidity and lack of fitness for treatment) or that the disease is more aggressive in older patients. It is unclear which of these factors explains these age-related differences, and it is likely that both may contribute. Regardless of biology, patient age should not be used to exclude treatment choices for UTUC. Most patients remain free of significant disease following curative treatment; in those with relapse, extirpative treatment may offer the best palliation of symptoms in select patients.

However, comorbidity and fitness for surgery are important factors that should be considered when deciding on treatment. For example, patients with significant cardiovascular disease require the smoothest operation (in terms of changing blood pressure and blood loss), while those with chronic pulmonary disease may struggle to exhale large volumes of carbon dioxide (such as those used for the pneumoperitoneum with laparoscopy). The most robust manner of scoring comorbidity and comparing between patients is the use of a performance status scoring system, such as the Charlson or Eastern Cooperative Oncology Group (ECOG) performance status scores. The latter is popular for its simplicity and has been shown to predict survival outcomes in more aggressive UTUC, but probably has little role in low-risk tumours.[150] With regard to low-risk UTUC, the management of these tumours in patients with significant co-existing morbidity may be more focused on preservation of renal function or symptom relief rather than cancer cure. Therefore, less radical procedures may be acceptable for patients with a poor performance status, although this must be individualized in each case.

4.3.3.3 Risk factors

In general, continued exposure to the causative risk factor increases patients' risk of a further UC. Therefore, nephron-sparing surgery should be attempted, when safe and possible, in patients with current carcinogen exposure. In most patients, the causative factor is unknown or no longer present, but in some, such as smokers or patients with known exposure to aristolochic acid or proven Lynch syndrome, it can be identified.

Cigarette smoking is the most common carcinogenic exposure for UC. Tobacco smoke is important in both the etiology and pathology of urothelial tumours.[151] With regard to UTUC, Rink *et al.*[152] found that current smoking (versus ex-smoking or never smoking) and extent of exposure (duration and cigarette dose) were prognostic factors for the extent of the tumour at diagnosis and for future recurrence patterns. Current smokers were more likely to develop recurrence within the urinary tract, regardless of the stage of the primary disease. Patients who smoke should be strongly advised to stop

at diagnosis, but this factor should not alter treatment options. The second most common risk factor for UC is occupational carcinogen exposure.[151,153] Around 10% of UCs are thought to arise from this route. Since the delay between exposure and cancer is typically around 30 years, the exposure has usually ceased by the time of diagnosis, but should be sought in patients still working with chemicals.

With regard to UTUC, there are three important risk factors that increase the risk of recurrence (especially to the contralateral upper urinary tract) and that should be evaluated specifically[151]: (1) chronic ingestion of the analgesic phenacetin, (2) exposure to aristolochic acid (the causative factor for both Chinese herbal and Balkan nephropathies), and (3) Lynch syndrome.[147,154] Nephron-sparing surgery should always be considered in individuals affected by one of these factors, as they are at high risk of further UTUC. The presence of the former two risk factors may be established by questioning, but patients with Lynch syndrome may be unaware of their syndrome at diagnosis. Clues indicating the possible presence of Lynch syndrome include a strong familial or previous medical history of tumours within the spectrum (such as right-sided colonic, endometrial, small bowel, ovarian, or sebaceous cancers and UTUC) occurring in multiple generations and/or at a young age. It should be noted that few data exist regarding the rate of recurrence of UTUC in Lynch syndrome patients, but given the genetic nature of the disease, a considerate approach is sensible.

4.3.3.4 Renal function

Radical excision of either upper urinary tract deliberately reduces overall renal function. In patients with anatomical (e.g. due to previous nephrectomy) or functional (e.g. with a poorly functioning contralateral kidney) solitary renal units or poor global renal function (e.g. from glomerulonephritis or renal vascular disease), removal of the better or only kidney could result in dialysis dependency. When staging a tumour prior to RNU, attention should be paid to the contralateral kidney on cross-sectional imaging. It is important to assess whether it looks to be of good size and to evaluate its uptake and excretion of contrast. In case of doubt, quantitative renography (such as a MAG3 renogram) should be performed to assess the contribution of the diseased kidney to overall renal function (glomerular filtration rate—GFR). A retrospective review showed that RNU reduced patients' GFR by 24% and reduced the proportion of patients eligible for cisplatin-based chemotherapy from 88% preoperatively to 55% after surgery[155]).

Therefore, nephron-sparing surgery should be strongly considered for patients who would be put at risk for renal failure or dialysis dependency by RNU. This is especially true for patients with low-risk UC in whom the risk for cancer-specific death is relatively low. Excision can be important in patients with obstruction of either kidney from their tumour. This is more likely with ureteric lesions and lesions that are faster growing.

4.3.3.5 Other factors

A variety of other factors have been reported to affect outcomes in UTUC.[144] These include pre-operative C-reactive protein, obesity, systemic symptoms, and hydronephrosis, and may be used to identify patients at higher risk for recurrence.[156] In general, nephron-sparing surgery should be encouraged (when technically feasible) for all low-risk UC and in those at higher risk for recurrence when compared to other cancers.

In conclusion, nephron-sparing surgery should be considered for all low-risk tumours, as the likelihood for cancer-specific death is low. However, the ability to correctly identify risk in tumours pre-operatively can be poor in low-risk disease. The main risk is that a high-risk or invasive tumour is misclassified pre-operatively as low-risk disease and treated in a manner less safe for higher-risk tumours. Retrospective surveys suggest that this can occur in up to 25% of cases.[157] Therefore, care should be taken with tumours in which either investigation suggests worse disease than is apparent (such as by positive cytology, large tumour on imaging, presence of hydronephrosis, or sessile tumours). If needed, a frozen section can be sent intra-operatively to determine the likely degree of invasion.

Recommendations: selection of patients for conservative surgery

- Tumour grade should be assessed by biopsy during ureterorenoscopy (Level 3, Grade B).
- Information about confounding factors such as growth pattern, tumour size, location, and multiplicity should be obtained during ureterorenoscopy (Level 3, Grade B).
- Cross-sectional imaging (CT urography preferred) should be performed to complete staging (Level 3, Grade B).
- Kidney-preserving approaches should be considered for small-volume, low-grade tumours and in imperative situations (Level 3, Grade B).
- Systematic surveillance should be carried out after kidney-preserving surgery using a combination of imaging, urine testing, and endoscopy (Level 3, Grade B).

4.3.4 Surgical techniques

4.3.4.1 Partial nephrectomy

Partial nephrectomy for UTUC has largely been supplanted by percutaneous or ureteroscopic resection. However, this technique can be used in highly selected cases to both excise the tumour and preserve the kidney. In terms of surgical approach, the open surgical technique is well described, while newer techniques such as robotic and laparoscopic partial nephrectomy have not yet been applied as treatment for UTUC.

The open partial nephrectomy technique for UTUC is similar to that used for RCC, with a few important provisions. Prior to incision, a clear understanding of the tumour's location within the collecting system of the kidney and its relationship to outer surface landmarks is of paramount importance. As in partial nephrectomy of completely intrarenal tumours, one cannot discern the proper dissection plane based on surface landmarks. Therefore, intra-operative ultrasound is considered mandatory by the few experts who have performed this rare procedure. Cross-sectional imaging provides useful information, but there is little substitute for intra-operative ultrasound, not just for the determination of parenchymal margins, but also of the urothelial margins deep within the parenchyma. The flank approach may be preferred, given its ability to isolate any spilled urine within the retroperitoneum.

Once the kidney is exposed and the renal vasculature isolated, the requisite portion of kidney may be removed and the renal parenchyma reconstructed. Care should be taken to minimize spillage of urine. Isolation of the kidney from the wound with dry laparotomy sponges may contain any spillage. A meticulous closure of the collecting system with absorbable sutures minimizes post-operative urine leak, and the placement of a drainage tube in the retroperitoneum can eliminate any urinoma. Frozen section analysis of the urothelial margin is also considered.

Results following partial nephrectomy for UTUC are limited in number and quality, with most of the information drawn from small retrospective case series from the 1980s and one more recent series.[158] Within these series, the tumour recurrence rate following partial nephrectomy varied with grade, but was largely between 30% and 40%.[159–161]

4.3.4.2 Segmental ureterectomy

Of the nephron-sparing options available for low-risk UTUC, segmental ureterectomy is perhaps one of the more attractive to perform, but is rarely indicated or possible. The procedure was first publicized in 1963 for a benign lesion and has remained popular since.[150,162–164]

The aim of segmental ureterectomy is to remove a diseased portion of ureter and re-anastomose the remaining ureter, with or without the need for additional tissue (such as bowel interposition). Therefore, it is best suited to mid- and upper ureteric tumours, where the remaining ureter may be sufficiently mobilized to allow anastomoses that are very focal and not amenable to ureteroscopic management. Lower ureteric tumours are better managed by segmental resection and re-implantation into the bladder.[163]

This chapter focuses on low-risk UTUC, in which there are few contraindications to segmental ureterectomy. Caution should be used in patients with normal contralateral renal units and extensive UTUC who may require bowel interposition to bridge the gap, as this procedure has poorer drainage and more complications than RNU.

4.3.4.3 Oncological outcomes

Several authors have compared oncological outcomes for segmental ureterectomy with RNU (see **Table 1**).[32,135,163–170] For example, Jeldres *et al.*[164] found identical outcomes in 2,044 selected patients with UTUC who were treated by either segmental ureterectomy or RNU. These data were confirmed by Colin *et al.*,[163] who cautioned that although short-term oncological outcomes with segmental ureterectomy are comparable to RNU for UTUC in selected patients in these retrospective studies, RNU is still the gold standard for the treatment of UTUC in most patients. One group investigated 15 patients with low-grade UTUC and reported ipsilateral recurrences in two patients (6.7%) and CSS of over 93% after 5 years.[170]

4.3.4.4 Non-oncological outcomes

Few authors have specifically looked at non-oncological outcomes of segmental ureterectomy in patients with low-risk UTUC. Segmental ureterectomy preserves nephrons and avoids the reduction in GFR (of around 24% on average) associated with RNU.[155] Therefore, the rates of renal failure/dialysis dependency are lower in patients treated by segmental ureterectomy. Specific complications

of segmental ureterectomy include strictures at the anastomotic site and impairment of renal drainage from slow transit (seen with bowel interposition). There are few other complications specific to this operation, making it an appealing choice when it can be sensibly applied.

4.3.4.5 Management of the distal ureter and distal ureterectomy

The choice of approach for distal tumours depends on technical limitations and the anatomic location of the tumour. Although most tumours located below the level of the iliac vessels are candidates for distal ureterectomy, the location and extent of the tumour in the distal ureter are important for the surgical approach.[171]

Distal ureterectomy is traditionally performed through a Gibson or mid-line incision, and the distal ureter is dissected beyond the bifurcation of the iliac vessels. Direct contact with the tumour is avoided through proximal ligation of the ureter and a wide cuff of bladder. Generally, ureteral re-implantation using the psoas hitch technique is performed.[171] Division of the contralateral lateral pedicle is more easily done using a mid-line incision rather than a Gibson. Frozen sections of the proximal segment of the ureter should be performed if needed. In case of intra-operative positive margins, the proximal end of the ureter should be re-resected until frozen sections are negative. Some perform intra-operative ureterorenoscopy, although there is a risk for tumour spillage if more tumours are found.

During the past decade, significant innovations have changed the armamentarium for the treatment of distal ureter tumours. Newer approaches include the use of endoscopic techniques, laparoscopy, and robotics, which are also applied for the distal ureterectomy and bladder cuff, and are discussed further below.[172–174]

4.3.4.6 Open distal ureterectomy versus robotic/laparoscopic ureterectomy

The patient is placed in the lateral decubitus position, the colon is mobilized to expose the retroperitoneum, and after the ureter is identified crossing the iliac artery, the ureter and a wide margin of peri-ureteral tissue is dissected down to the bladder.[171] Manipulation of the ureteral catheter stent can expedite the identification of the ureter. A bulge within the ureter may reveal the location of the tumour, and there may be peri-ureteral inflammation caused by the tumour itself. The ureter is mobilized proximally and may be encircled with a vessel loop for traction. In addition, a tourniquet may be applied to the proximal ureter to minimize urine spillage during the dissection. The dissection is carried down as distally into the pelvis as possible. The bladder can be filled with sterile water at this time to facilitate dissection of the intramural ureter. The bladder is entered, and the previously placed ureteral stent ensures complete removal of the distal ureter and safety of the contralateral orifice. A wide cuff of bladder is resected with the distal ureter, and the proximal ureter is transected 1 cm above the mass while the stent is *in situ*.

When laparoscopy is performed, the patient is placed in the Trendelenburg position, up to four trocars are placed in configuration in the lower quadrant, and the procedure is performed using the same approach.[171] In the case of a robotic procedure, the da Vinci robot is docked from the foot of the bed. The hook electrode and bipolar forceps are used, and the ureter is dissected fully to the bladder. Once the ureter is dissected from the bladder, the specimen is placed in an entrapment bag

and removed. The bladder is sutured closed, and the ureter is anastomosed to the dome of the bladder over a double-J stent using interrupted sutures. The abdomen is then irrigated copiously with sterile water, and a drain is placed in the pelvis.

Recent studies investigating the equivalence of laparoscopic or robotic versus open procedures have not found differences in oncological outcomes between the various approaches, so they are considered equivalent at this point (175–178).

4.3.4.7 Ureterocystoneostomy

The bladder should be mobilized to facilitate ureteral re-implantation. The peritoneum overlying the lateral to the bladder is incised and the space of Retzius entered. Adequate bladder mobilization is imperative, as it may allow for direct ureteral re-implantation. The bladder is incised over the site of the new ureteral orifice until detrusor fibres are seen, and the bladder is entered. The new orifice should be positioned to allow for straight entry of the ureter into the bladder. The anastomosis is then created between the bladder and the spatulated ureter, starting at the six o'clock position of the ureter and bladder. Before completion of the anastomosis, the distal end of the stent is inserted into the bladder. Once the anastomosis is complete, the final stich is tied down.

Ureterocystoneostomy is an excellent option for low-grade tumours of the ureter when endoscopic resection is not able to provide complete resection (e.g. due to size or multiplicity).[135,150,163,164]

4.3.4.8 Re-implantation of the ureter with the psoas hitch technique or a Boari flap

Re-implantation with the psoas hitch technique is required when a tension-free anastomosis cannot be achieved.[171] First, the psoas tendon is located and cleared of any surrounding tissue. A 2-0 suture is placed through the psoas tendon and then through the most superior and ipsilateral portion of the bladder. The stitch is tied down in figure-8 fashion, which is repeated a second time to secure the bladder in place. If adequate contralateral mobilization is conducted, it is usually not necessary to divide the contralateral bladder pedicle as in the classic psoas approach.

The bladder is incised over the site of the new ureteral orifice as for ureterocystoneostomy.[171] The new orifice should be medial to the psoas tendon to allow for straight entry of the ureter into the bladder. The anastomosis is then created between the bladder and the spatulated ureter, starting at the six o'clock position of the ureter and bladder. Before completion of the anastomosis, the distal end of the stent is inserted into the bladder. Once the anastomosis is complete, the final stich is tied down.

4.3.4.9 Bladder cuff versus endoscopic treatment

Open distal ureterectomy can be done trans-vesically through an anterior cystotomy, extra-vesically by securing the bladder cuff with a right-angle clamp, or by combined modalities.[171] A variety of endoscopic approaches have also been described, including trans-urethral resection of the ureteral orifice (the pluck technique).[179–181] Apart from ureteral stripping, all other techniques for managing the distal ureter are currently considered not inferior to taking an open bladder cuff; however, patients must be adequately counseled about the higher risk for intravesical recurrence with endoscopic strategies.[134]

For the pluck technique, the patient is placed in the dorsal lithotomy position, and standard resectoscopes with a Collins knife are used to score the mucosa surrounding the ureteral orifice.[179] If no double-J stent is in place, an optional open-ended ureteral catheter can be placed in the ureter to aid in identification. The cystoscopic incision around the orifice is taken down through the detrusor fibres surrounding the orifice, with care not to incise through the bladder wall. A Foley catheter is then placed and secured to the patient.

4.3.4.10 Lymphadenectomy

Much of the debate regarding lymphadenectomy has revolved around a standardized definition of an appropriate template for nodal removal and whether lymphadenectomy is beneficial regarding outcomes. Lymphadenectomy provides the most adequate staging for nodal disease in UTUC, as cross-sectional imaging does not always provide accurate information. Lymphadenectomy is usually performed at the surgeon's preference and is commonly used for patients in whom nodal-positive disease is suspected. However, as low-grade tumours are unlikely to metastasize, lymphadenectomy seems not as important in these patients as in their counterparts with high-grade disease, and will not be further discussed in this chapter.

Recommendations: surgical options for organ-sparing surgical management of upper tract urothelial carcinoma

- There are no data showing superiority of any of the kidney-preserving techniques (Level 3, Grade C).
- Segmental ureterectomy should be performed for proximal/mid-ureteral tumours when kidney preservation is feasible based on tumour characteristics (Level 3, Grade C).
- Distal ureterectomy can be performed for isolated distal ureteral tumours if kidney sparing is feasible based on tumour characteristics (Level 3, Grade B).
- Distal ureterectomy can be performed open, laparoscopically, or robotically (Level 3, Grade C).
- Reconstruction (ureteroureterostomy, ureteroneocystostomy, a psoas hitch, a Boari flap): Anastomosis should be tension free, watertight, and stented (Level 3, Grade B).
- Removal of a bladder cuff is the reference standard, but endoscopic approaches (besides pluck and stripping) are also acceptable (Level 3, Grade B).
- Lymphadenectomy for known low-risk tumours is optional and likely not needed (Level 3, Grade C).

4.4 Surveillance After Treatment of Upper Tract Urothelial Carcinoma and Bladder Monitoring

4.4.1 Introduction

Upper tract urothelial carcinoma is a rare and heterogeneous disease that accounts for only 5% to 10% of all UC,[182] with an estimated incidence of 2.08 cases per 100,000 person-years.[183,184]

Urothelial carcinomas are the fourth most common tumours after prostate (or breast) cancer, lung cancer, and colorectal cancer.[182,185] The location can vary from either the lower urinary tract (bladder and urethra) or the upper urinary tract (pyelocaliceal and ureter). Bladder tumours account for 90% to 95% of UCs and are the most common malignancy of the urinary tract.[184,185] However, UTUCs are less common and account for only 5% to 10% of UCs.[182,186] Recurrence of disease in the bladder occurs in 22% to 47% of UTUC patients post-surgical resection,[143,187,188] whereas recurrences in the contralateral upper tract are observed in 2% to 6% of patients.[189,190]

Upper tract urothelial carcinomas are more common in men than in women and in Caucasians than in African-Americans. Two recent multi-institutional analyses did not show any differences in pathologic characteristics or cancer-control outcomes between men and women.[191,192]

Due to the relative preponderance of UC of the bladder, much of the clinical decision making regarding UTUC is extrapolated from bladder cancer experience.[193,194]

The pathophysiology underlying BR before or after treatment for UTUC is not completely understood. The explanations that have been put forward include the field change theory and metastatic seeding of the upper tract tumour into the bladder. The field change theory postulates that discrete areas of urothelium independently undergo malignant transformation in response to carcinogenic insults. The metastatic seeding theory, on the other hand, is supported by recent molecular genetic studies showing that multifocal urothelial tumours have a common clonal origin. Clinically, it has been observed that patients with UTUC have a much higher risk of developing BR than recurrence in the contralateral upper urinary tract, while patients with primary bladder cancer have a much higher risk of developing subsequent UTUC if VUR is present.[195]

Due to the rarity of the disease, there are insufficient data in the current literature to provide high-grade, strong recommendations.[184]

4.4.2 Post-operative surveillance and follow-up

Careful lifelong follow-up is mandatory after endoscopic treatment of all UTUCs. Johnson and Grasso (25) underscored the necessity of endoscopic surveillance, finding that 75% of tumours identified by ureteroscopy are missed radiographically. Due to the high rates of BR, it is also necessary to follow

the bladder for urothelial recurrences. A surveillance schedule was presented by Ho and Chow,[18] consisting of cystoscopy and cytology every 3 months, alternating with cystoscopy, retrograde pyelogram, cytology, and flexible ureteroscopy every 6 months for the first 2 years, then cystoscopy every 6 months, and ureteroscopy annually. It is mandatory to continue endoscopic surveillance, because isolated recurrences have been noted more than 5 years after primary ureteroscopic resection.[9,32,50]

Recommendations: surveillance after endoscopic treatment

- The bladder should be monitored with cystoscopies and possibly cytology (Level 1, Grade A).
- For follow-up of the upper tract, occasional ureteroscopy is recommended, because recurrence may not be seen on imaging (Level 3, Grade B).
- A follow-up ureteroscopy can be performed 4 to 6 weeks after treatment (Level 4, Grade C).
- Careful lifelong follow-up is necessary (Level 3, Grade B).

4.4.3 Post-operative surveillance of the upper urinary tract and urinary bladder

Post-surgical surveillance following a nephron-sparing treatment of UTUC is of utmost importance. Recurrence rates are significant, ranging from 24% to 90%, and may include the kidney and ureter where the UTUC was originally diagnosed, the contralateral kidney, or the bladder.[8,35] The multiple modalities used for post-surgical follow-up include imaging tests, urine tests, and endoscopy, but these vary in sensitivity and specificity, and there are limited data on the optimal modality and surveillance schedule following nephron-sparing treatment. In order to better address the question of surveillance, the topic will be divided into imaging, urine tests, endoscopy, and surveillance schedule.

4.4.3.1 Imaging surveillance of the upper tract

Multiple imaging modalities have been used for initial diagnosis and follow-up after nephron-sparing resection for UTUC, including intravenous pyelogram (IVP), retrograde pyelogram, CT, and magnetic resonance imaging (MRI). Many of the data on the sensitivity and specificity of imaging tests come from work done on the initial diagnosis of an upper tract lesion, as opposed to surveillance following resection. There is only limited work pertaining specifically to follow-up after nephron-sparing surgery.

Retrograde pyelography and IVP are two readily available tests traditionally performed for UTUC. These tests are easily performed, but their sensitivity varies widely. In a population of previously untreated patients going on to RNU, retrograde pyelography identified filling defects in 27 of 30 patients (90%). Intravenous pyelogram was done in 25 of the 30 patients, but located only two filling defects (8%).[157] In a surveillance population of patients with negative cytology and previous

endoscopic resection, retrograde pyelography identified only 4 of 16 recurrences (25%).[26] The authors of these studies hypothesized that the tumours in the surveillance population were smaller and more difficult to identify on retrograde pyelography, resulting in a lower sensitivity and suggesting a limited role for retrograde pyelography in surveillance.

Computed tomography urography has traditionally been a secondary option to IVP, but the increased resolution offered by multidetector CT scanners has largely changed this hierarchy. In comparing the two modalities, little information exists for CT urography following nephron-sparing surgery. However, two recent retrospective studies compared IVP and CT urography for sensitivity and specificity of UTUC detection in the setting of newly diagnosed hematuria.[196,197] Combined, these two series retrospectively analyzed 188 patients with hematuria who had undergone both IVP and CT urography. Given the inclusion criteria, there is a clear possibility of selection bias toward patients needing the more extensive evaluation offered by CT scan. However, in these two series, CT urography compared to IVP showed sensitivities of 93.5% versus 80.4%, and 98.8% versus 75%.[196,197] Specificity for the same tests was 94.8% versus 81%, and 100% versus 86%.[196,197] The differences between CT and IVP were statistically significant in all cases. These studies were conducted with newly diagnosed patients with UTUC as opposed to those on surveillance, but CT scan also appears to be superior to IVP for diagnosis of UTUC.

The final modality of clinical interest is MRI. Magnetic resonance urography is done using T2-weighted hydrographic sequences and T1 contrast-enhanced excretory sequences. As with the other imaging modalities, there is little information specific to a surveillance population and few overall studies. Of the available studies, an analysis of 110 patients undergoing MR urography is most pertinent.[198] In an attempt to mimic a surveillance population, the authors determined the sensitivity (74%) of MR urography for lesions <2 cm. They also determined that the excretory T1 contrast-enhanced images are key to diagnosing UTUC with MRI.

4.4.3.2 Urine tests for surveillance of the upper tract

Multiple urine tests have been investigated as potential surveillance tests for UTUC, including urinalysis, cytology, and fluorescence *in situ* hybridization (FISH). The data on these tests are limited and largely retrospective in nature.

Urinalysis for hematuria is a relatively cheap and simple urine surveillance test, but has only limited evidence of benefit. In 23 patients with previous ureteroscopic treatment of UTUC, urinalysis had a sensitivity of only 37.5%, but a specificity of 85% (199).

Cytology offers an improvement on this low sensitivity, but only a limited one. The available data on the use of cytology in a surveillance population are limited to 23 patients eventually found to have low-grade UTUC who had undergone a bladder drainage cytology specimen following surveillance cystoscopy. In this population, the sensitivity and specificity of cytology were 50% and 100%, respectively.[199] Although studies have shown greater sensitivity of ureteral wash cytology for initial diagnosis of UTUC, few data exist in the surveillance population to improve on this low sensitivity number.

Fluorescence *in situ* hybridization analysis of urine to identify abnormalities in chromosomes 3, 7, 17, and 9p21 has previously been used to diagnose UTUC. For patients without a previous history of UTUC, FISH has a sensitivity of 75% to 88% and a specificity of 80% to 95%.[73,75,76] Two retrospective series examining FISH in a surveillance population with previously treated UTUC exist. These series were small, encompassing 35 and 43 patients, respectively.[200,201] At best, these studies showed sensitivities of 60% to 67% for low-grade tumours, 50% to 100% for high-grade tumours, and a specificity of 78% to 80%.

4.4.3.3 Endoscopic surveillance of the upper tract

Ureteroscopic visualization remains the gold standard for surveillance of the upper tract following nephron-sparing treatment of UTUC. Imaging and urine tests have traditionally been used as components of follow-up, in order to limit the frequency of more invasive and expensive ureteroscopic examination. However, multiple authors have concluded that the poor sensitivity of these tests limits their utility and necessitates regular ureteroscopy.[140,199]

4.4.3.4 Bladder surveillance

The risk of developing a metachronous UC of the bladder following nephron-sparing resection is 17% to 47%.[16,17,40,47,53,202] This is very similar to the recurrence rate of 25% to 50% following RNU.[187,203–206] A number of studies have investigated specific risk factors for BR following RNU. Multifocality of the tumour in the upper tract was consistently identified as a risk factor for BR in these studies.[26,154,203,207,208] Other factors, such as tumour size, pathologic stage, tumour location, and surgical modality, yield conflicting results on analysis, with some studies identifying these characteristics as significant risk factors and other studies disputing those conclusions. In terms of means of surveillance, cystoscopy remains the gold standard for diagnosis of BR following UTUC.

4.4.3.5 Surveillance schedule following nephron-sparing treatment of upper urinary tract urothelial carcinoma

Multiple authors have described varying surveillance schedules, but information supporting a specific surveillance schedule is limited. Overall, these schedules are similar and involve the use of upper tract imaging, urine tests, and endoscopic evaluation of the bladder and upper tract. The guideline on UTUC from the European Association of Urology (EAU) offers a representative sample.[129] Following nephron-sparing surgery, they recommend urine cytology and CT urography at 3 months, 6 months, and then annually. Cystoscopy, ureteroscopy, and ureteral wash cytology are to be performed at 3 months and 6 months, then every 6 months over 2 years, then annually. This surveillance is to go on for at least 5 years.

Work has been done to identify risk factors for recurrence (a history of more than three previous bladder tumours) and progression (a history of more than three previous bladder tumours or tumour in the renal pelvis). However, the patient sample for this study was small (54 patients), and these risk factors have not been incorporated into surveillance protocols to date.[20]

In conclusion, multiple modalities, including imaging, urine tests, and ureteroscopy, have been used for the surveillance of the upper tract following nephron-sparing treatment of UTUC. Although the data on the effectiveness of these tests are limited, it is important to recognize the relatively low sensitivity of both imaging studies and urine tests. Despite its more invasive nature and higher cost, ureteroscopic visualization remains the gold standard against which other tests are measured.

4.4.4 Bladder cancer and the development of subsequent upper tract urothelial carcinoma

A history of UC of the bladder is a known risk factor for development of UTUC, with the incidence of UTUC following UC of the bladder ranging from 0.7% to 4%.[209,210]

Several studies have shown that multicentricity, recurrent tumours, CIS, VUR, and BCG treatment are factors associated with greater risk for UTUC after a diagnosis of bladder cancer.[209,211] The development of upper tract tumours in patients with a solitary bladder tumour is rare, and the majority of these UTUCs (66%) develop during the first 6 years after bladder tumour resection.[209]

The incidence of UTUC in primary bladder cancer patients is strongly related to the primary tumour risk stratification. Risk stratification of the primary bladder cancer facilitates the identification of patients with a higher risk of developing UTUC. For example, if one selects only the high-risk non–muscle-invasive bladder cancer patients who received intravesical BCG, the incidence rate of subsequent UTUC may increase to 20% to 25%. Hurle *et al.*[212] stratified 591 bladder UC patients into low-, intermediate-, and high-risk groups for UTUC: 0.9% of low-, 2.2% of intermediate-, and 9.8% of high-risk patients developed UTUC. Millán-Rodríguez *et al.*[213] studied the UTUC evolution in a cohort of 1,529 patients and found that a higher risk for UTUC must be expected in cases of multicentric non–muscle-invasive bladder cancer (relative risk: 2.7), with a relative risk of 1 for low-risk, 1.8 for intermediate-risk, and 4.1 for high-risk non–muscle-invasive bladder cancer.

Patients with bladder UC and VUR have a several-fold greater risk of developing UTUC.[214] In a prospective study, Ricos Torrent *et al.*[215] demonstrated the development of reflux in 40.6% of patients after trans-urethral resection of a bladder tumour located on the trigone. De Torres Mateos *et al.*[214] demonstrated a global incidence of reflux of 26% and even higher (77%) in tumours located on the peri-ureteral orifice, with a statistically significant incidence of ipsilateral UTUC ($p<0.001$). Mukamel *et al.*[216] also identified reflux as a factor for UTUC, as well as CIS and multifocal disease. Mazeman *et al.*[217] found that 26.4% of UTUC patients had reflux, and development of UTUC was 19.2% and 1.2% in patients with and without reflux, respectively. Similarly, Amar and Das[218] found the incidence to be 6.4% and 0.44%, respectively.

In 1993, Miller *et al.*[219] published their finding that patients with bladder tumours that were high grade, multifocal, and/or CIS were at higher risk for UTUC development after surgical resection, and 13.4% developed UTUC at a median of 38 months. Herr *et al.*[220] with a longer follow-up, showed a 21% incidence of UTUC in patients treated with BCG due to high-grade non–muscle-invasive bladder cancer and/or CIS. Their post-operative surveillance protocol included IVP every 2 to 3 years. Wright *et al.*[221] also showed that high-grade and non–muscle-invasive bladder cancer were predictive of upper tract recurrence, as were tumours located at the trigone/ureteral orifice.

4.4.5 Concurrent primary upper tract urothelial carcinoma and bladder cancer

There is a paucity of literature on the simultaneous diagnosis of primary UTUCs and bladder carcinoma, although their incidence appears to be low. The incidence of concurrent UTUC and bladder tumour ranges between 8% and 17%.[56,222] There appears to be only one study that has evaluated clinical factors that predict the simultaneous presence of UTUC and bladder tumour related to the incidence of bladder cancer according to the characteristics of the upper urinary tract tumours. Cosentino *et al.*[223] demonstrated that the location of the tumour in the upper tract was related to the simultaneous incidence of bladder cancer, with a higher incidence when the tumours were located in the lower ureter.

4.4.6 Concurrent primary bladder cancer and upper tract urothelial carcinoma

Goessl *et al.*[224] studied 314 patients with bladder tumours (33% had muscle-invasive bladder tumours). Only one UTUC was detected with IVP at initial diagnosis of bladder tumour, and it was classified as stage pT3b grade 3. The authors note that the IVP was suspicious for UTUC in five patients, but that there was no confirmation of UTUC in these patients. The authors recommend that IVP is not necessary as a routine diagnostic procedure in newly diagnosed bladder cancers. Herranz-Amo *et al.*[225] studied 793 patients with primary bladder tumours, with 28% being T2 or a higher stage in the bladder. They reported nine cases (1.1%) of synchronous UTUC, whereas IVP only diagnosed six cases; in two of the nine patients, the bladder tumour was invasive. The authors do not recommend that IVP be routinely performed in the diagnostic workup of patients with urothelial cell tumour of the bladder. Miyake *et al.*[226] studied 106 primary UTUCs, and the 44 patients who had associated bladder cancer were divided into three groups: UTUC preceding bladder cancer, UTUC with concurrent bladder cancer, and UTUC with subsequent bladder cancer. The authors found that patients with concurrent bladder cancer had worse prognosis, due to the increased incidence of high-stage and high-grade tumours in both UTUC and the bladder.

Palou *et al.*[227] examined a cohort of 1,529 patients treated with trans-urethral resection and random bladder biopsy for primary superficial UC of the bladder. Twenty-eight patients of those 1,529 (1.8%) had UTUC at initial diagnosis of bladder cancer. The tumours were most often located in the lower ureter (42.9%), and 46.3% were invasive (see **Table 2**); 46.3% were invasive UTUC, and nearly 87% were grade 2 or 3 tumours. In this study, the only variable with significance for predicting the occurrence of UTUC was the trigonal location of the bladder tumour ($p<0.0005$), with a risk ratio of 5.8 (95% CI: 2.18–15.9). These UTUCs constituted 7% (11 of 159) of all bladder tumours in this location and corresponded to 41% of the UTUCs first diagnosed.

Although the incidence of synchronous UTUC and superficial bladder tumour is low, UTUC lesions are invasive in a high proportion of cases. Due to the low incidence of synchronous UTUC and superficial bladder tumour, recommendations for routine examination of the upper urinary tract in the diagnosis of superficial bladder tumour remain controversial. However, patients with a tumour on the trigone have a six-fold higher risk of having a tumour synchronously in the upper urinary tract.

4.4.7 Upper tract urothelial carcinoma and the development of subsequent bladder cancer

Many risk factors for the development of BR after UTUC have been proposed and studied, but there is a notable lack of agreement on the subject. There is agreement that routine bladder monitoring is needed, since there is a 24% to 47% incidence of bladder cancer, and 5% of these patients may develop muscle-invasive tumours.[228]

Multifocality of upper tract disease is one risk factor that has been found in several studies to be an independent predictor of BR (203,207). One study of 92 patients described a relative risk of 3.52 in patients with multifocal upper tract tumours.[229]

Upper tract tumour location has also been found to independently predict risk for BR. Zigeuner *et al.* (187) studied 191 patients, of whom 20% had upper tract tumours in the renal pelvis and 40% had ureteric tumours. Of the patients with pelvic tumours, 24% developed bladder cancer versus 47% of the patients with ureteric tumours (relative risk: 2.1, p=0.02). However, a separate large study of 324 patients with UTUC at a single institution did not find any significant difference in the risk for 5-year disease recurrence (including BR) between pelvic and ureteric tumours.[230]

In a European study of 231 patients, a previous history of bladder cancer was found to confer an increased risk of BR after treatment for UTUC (hazard ratio [HR]: 2.83, p<0.001).[189]

A multivariate analysis by Pieras *et al.*[231] showed that patients with concomitant upper tract CIS have a major risk of developing subsequent bladder cancer. A study by the UTUC Collaboration examined the risk for BR in patients treated for pure upper tract CIS. They found a 40% risk for BR in this group of patients, with an even higher risk in patients with multifocal upper tract CIS (p=0.032). However, it is also worth noting that 60% of this group had a history of previous bladder cancer.[143]

Current or previous smoking history also seems to have an impact on the risk for BR. In one study, 245 patients with UTUC were analyzed based on their smoking history. The bladder cancer RFS rates at 3 years for current, former, and non-smokers were 32.6%, 37.6%, and 61.7%, respectively. A smoking history of more than 50 pack-years resulted in a significantly greater risk (HR: 2).[232] Interestingly, a separate study suggested that the impact of smoking on outcomes of UTUC after nephroureterectomy was gender specific, with female smokers having worse outcomes than males.[233]

Recently, Sternberg *et al.*[61] evaluated the usefulness of upper tract imaging in patient follow-up for non–muscle-invasive bladder cancer, and 29% of the UTUCs in the 935 patients followed were diagnosed on routine imaging. Routine imaging is not efficient, and a combination of history taking, physical examination, urine cytology, and sonography sonography may be sufficient in this select low-risk population.

4.4.8 The impact of nephroureterectomy technique on recurrence

Some earlier studies suggested that the laparoscopic technique for nephroureterectomy was associated with a higher risk for BR, possibly because the longer operating time required for the laparoscopic procedure resulted in a longer period of tumour exposure[234]; however, several large-scale comparative studies have since demonstrated the superiority of the laparoscopic technique to the open technique.[175] In a systematic review of the subject, laparoscopic nephroureterectomy resulted in a significantly lower BR rate (HR: 0.83).[178] However, in these studies, patients undergoing laparoscopic nephroureterectomy tended to have more favourable pathology, making direct comparison difficult. One recent retrospective study of 773 patients included 703 patients undergoing open nephroureterectomy and 70 patients undergoing laparoscopic nephroureterectomy. Patients in the two groups were well matched. In this study, 5-year recurrence-free and cancer-free survival were equivalent between the groups.[235]

Radical nephroureterectomy, the gold standard of treatment in UTUC, involves the *en-bloc* removal of the kidney and the entire ureter and ureteric orifice, as well as the excision of a bladder cuff. A recent retrospective study analyzed the impact of various techniques for resecting the distal ureter on oncological outcomes, after either open or laparoscopic RNU. They found no difference in BR rates between the trans-vesical and extra-vesical approach (21.4% and 20.3%, respectively, p=0.40), but the cystoscopic approach was associated with a higher risk for BR (34.1%, p=0.02).[236] Previously, in a multicentre study, Xylinas *et al.*[237] evaluated 482 patients who underwent nephroureterectomy. In a multivariate analysis, they found that prior history of bladder cancer, tumour multifocality, and a laparoscopic approach were predictors of intravesical recurrence.

4.4.9 Methods of reducing the risk for bladder tumour recurrence post-resection of upper tract urothelial carcinoma

In a 2010 retrospective study, Wu *et al.*[238] evaluated the incidence of bladder cancer after UTUC treated with intravesical therapy. Patients were divided into those who received Mitomycin C, epirubicin, or no adjuvant treatment. The investigators found that those who received intravesical treatment had a lower incidence of BR and a higher mean time to BR.

The One Dose Mitomycin C (ODMIT-C) trial, published in 2011, was the largest randomized trial performed in the management of UTUC. It investigated the use of a single dose of intravesical mitomycin C after RNU to reduce the risk for BR. A total of 284 patients were randomized to receive either Mitomycin C or standard care. The use of mitomycin C was associated with an absolute risk reduction of 11% and a relative risk reduction of 40%. Treatment was well tolerated, with only 4% of patients unable to complete the full duration of treatment.[239]

Another prospective randomized trial with pirarubicin also demonstrated a decrease of intravesical recurrence rate at 2 years, from 42% to 16.9% in the control group versus the treatment group.[240]

The presence of a previous or synchronous bladder cancer seems to be an independent predictor of lower RFS and CSS rates. Mullerad *et al.*[205] demonstrated that a history of bladder cancer had an adverse effect on the prognosis of patients with UTUC.

In a multicentre European study, Novara *et al.*[241] observed that prior bladder cancer history and the presence of muscle-invasive bladder cancer at RNU were independent predictors of worse CSS.

The presence of a bladder cancer history should always be evaluated in patients with UTUC, because these patients may be considered for more aggressive treatment and a more rigorous follow-up schedule.[242,243]

4.4.10 Post-operative surveillance guidelines after management of upper tract urothelial carcinoma

The EAU guidelines recommend close oncological follow-up for at least 5 years,[184] and the National Comprehensive Cancer Network (NCCN) recommends follow-up for 2 years, including an upper tract evaluation. Although there is no consensus on a surveillance protocol, many individual reports recommend regular imaging of the upper urinary tract and urine cytology for high-risk groups. Many urologists use upper tract surveillance in patients with bladder cancer, but there is wide variation in the duration, frequency, and length of follow-up, as well as the type of patient selected for surveillance. Some have argued that monitoring of the upper tract can be omitted in cases of low-grade bladder cancer and reserved for groups at higher risk.[244] Some groups have suggested that these patient populations either do not require follow-up or can be followed with ultrasonography and cytology only (see section 4.4.3.5 and associated recommendations).[61]

4.4.11 Recommendations: bladder and systemic surveillance

- A single dose of intravesical chemotherapy should be given after nephroureterectomy (Level 2, Grade A).

- A single dose of intravesical chemotherapy should be given after endoscopic and kidney-preserving surgery (Level 4, Grade D).

- Upper tract surveillance after diagnosis of bladder cancer (Level 4, Grade C):
  - Low-risk tumours: no follow-up is required, because UTUC incidence is negligible.
  - Intermediate-risk tumours: the incidence of UTUC is very low; follow-up is optional.
  - High-risk tumours: follow-up is advised; CT scan and cytology are recommended. There are no established intervals, but every 6 to 12 months for the first 5 to 10 years would be reasonable, as there is lifelong risk in multifocal high-grade disease.
  - In those with demonstrated VUR, closer follow-up is advised, at least for the first 6 years.

- Synchronous UTUC and bladder cancer (Level 4, Grade C):
  - The global incidence of simultaneous UTUC after diagnosis of a primary bladder cancer is very low; CT scan is recommended in patients with tumours located in the trigone or peri-ureteral orifice, and in patients with upper tract dilatation or any suspicious lesions on primary sonography evaluation.
  - The incidence of simultaneous bladder cancer after diagnosis of a primary UTUC is relatively high (15%), and some of these may be invasive. The incidence is higher for tumours located in the distal ureter.
  - Routine cystoscopy and cytology are recommended in primary UTUC.

- Bladder surveillance after diagnosis of UTUC (Level 1, Grade A):
  - The incidence of bladder cancer after UTUC is high, especially during the first 2 years.
  - Instillation of chemotherapy into the bladder after nephroureterectomy is well tolerated in patients with confirmed absence of leakage and significantly reduces bladder tumours.
  - All patients treated for UTUC should be followed with periodic cystoscopy and cytology. In patients with multifocality, high-grade, or associated CIS of the upper tract, more aggressive follow-up is recommended.

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C5

Treatment of Localized, Muscle-Invasive UTUC

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CO-CHAIR

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William Huang, United States
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Badrinath Konety, United States
Pilar Laguna, Netherlands

Committee 5

CONTENTS

Treatment of Localized, Muscle-Invasive UTUC

5.1 Extent, Technique, and Outcomes of Radical Nephroureterectomy (Part I)

Radical nephroureterectomy (RNU) is considered the treatment standard for clinically infiltrating upper tract urothelial carcinoma (UTUC). It consists of the removal of the entire kidney and ureter, along with excision of the ipsilateral bladder cuff.[1] During surgery, care has to be taken to avoid tumour spillage or positive surgical margins, as these increase the risk for intravesical or local recurrence.[2] Clipping the distal ureter at the beginning of the procedure has been shown to reduce the risk for tumour spillage and subsequent recurrence.[3] Different techniques for removal of the distal ureter/bladder cuff are highlighted in Chapter 4.

In patients with clinically infiltrating UTUC, regional lymph node dissection (LND) is considered a part of the procedure.[1] As patients with histologically confirmed lymph node (LN)–negative UTUC exhibit improved survival compared with those with node-positive disease,[4–6] the diagnostic significance of LND is beyond question. However, the therapeutic role of LND at RNU and the appropriate extent of LND according to primary tumour location are not well defined.[7–10] The role of LND at RNU is outlined in detail in Chapter 3.

Radical nephroureterectomy can be performed either by an open RNU (ONU) or a laparoscopic nephroureterectomy (LNU) approach. A recent systematic review identified one randomized trial and 23 observational studies that compared peri-operative and oncologic outcomes in patients undergoing open or laparoscopic RNU.[11]

In a prospective single-institution study, a total of 80 patients were randomized 1:1 to either open or laparoscopic RNU, performed by a single experienced surgeon.[12] Patients were considered eligible for study inclusion if they had nonmetastatic UTUC without prior bladder cancer. Significant differences in peri-operative outcomes favouring the laparoscopic approach were found for mean blood loss (104 vs. 430 mL; $p<0.001$) and mean hospital stay (2.3 vs. 3.7 days; $p<0.001$). No differences were observed for mean operative time (78 vs. 82 min; $p=0.72$) or primary pathologic tumour characteristics, suggesting that the treating surgeon was experienced with both techniques. At a median follow-up of 44 months, only a trend toward improved metastasis-free survival (MFS) and cancer-specific survival (CSS) was noted for the open versus the laparoscopic procedure (MFS: 77% vs. 73%, $p=0.12$, respectively; CSS: 90% vs. 80%, $p=0.2$, respectively). Notably, a subanalysis of patients with locally advanced (≥pT3) or high-grade disease showed that MFS and CSS rates were considerably higher in patients with open versus laparoscopic RNU (for ≥pT3, MFS: $p=0.004$ and CSS $p=0.039$; for high-grade tumours, MFS: $p=0.014$ and CSS: $p=0.078$). However, there are considerable limitations with this study. First, the number of patients was relatively small, which hampered the final survival analysis. The low number of patients also precluded a multivariable analysis to investigate the effects of the treatment method and primary tumour characteristics on survival. Second, in this prospective study, no LND was performed in either group, which may have led to considerable selection bias in the survival subanalysis for patients with locally advanced disease.[12]

Of the 23 observational studies,[13–35] 19 reported improved peri-operative outcomes for LNU versus ONU. Mean blood loss in the LNU group was 144–580 mL and 300–750 mL in the ONU group.[14–17,20,21,23,24, 26,28–37] Mean hospital stay was shorter in the LNU group (2–13 days) compared with the open group (4–21 days), while mean operative durations were generally reported to be higher in the LNU group, except in five studies.[29,31,33,35,38] A lower rate of urinary tract recurrence in favour of LNU was reported in 17 studies (pooled odds ratio [OR]: 0.64; 95% CI: 0.50–0.82; $p<0.001$).[14,16,17,19–21,25–34,37] Likewise, distant MFS rates were reported to be lower in the LNU versus ONU group (pooled OR: 0.72; 95% CI: 0.54–0.97; $p=0.03$).[15,16,19–21,25–34,37] No differences were observed for local recurrence rates (pooled OR: 0.64; 95% CI: 0.50–0.82).[16,19–21,25–34]

The patient´s eligibility for adjuvant systemic treatment in high-risk UTUC depends mainly on post-operative renal function, age, and performance status. Chronological age has been shown to be an independent predictor for peri-operative outcomes or disease-specific survival (DSS), a poor Eastern Cooperative Oncology Group (ECOG) performance status (0 vs. ≥1) and poor American Society of Anesthesiologists (ASA) score (3 vs. 1).[39–42] However, as has been shown in some series, chronological age has a clear impact on pre- and post-operative renal function.[43–45] In a multicentre analysis of 666 patients with UTUC who were scheduled for RNU, the pre-operative estimated glomerular filtration rate (eGFR) was ≥60 mL/min in only 37% of the patients. The rate significantly decreased to 16% after the procedure ($p<0.001$). Patients above the age of 70 years were more likely to experience a decrease in post-operative renal function compared with younger patients ($p<0.001$). In the total cohort, eGFR was not associated with disease recurrence or cancer-specific mortality (CSM) after RNU. However, in a subgroup of patients who did not experience recurrence or were subjected to adjuvant chemotherapy, those with pre-operative eGFR ≥60 mL/min and postoperative eGFR ≥45 mL/min exhibited improved overall survival (OS).[45] In a similar single-centre retrospective series of 336 patients with UTUC undergoing RNU, 48% of the patients had a preoperative eGFR of ≥60 mL/min. This rate decreased postoperatively to 22% ($p<0.001$). In 144 of the 336 patients (43%) with locally advanced disease staged pT2 to T4 and/or pN1 to N3, only 40% and 24% of patients, respectively, were considered candidates for adjuvant cisplatinum-based combination chemotherapy based on post-operative eGFR.[44]

Conclusions

	LOE
In experienced hands, laparoscopic radical nephroureterectomy is an alternative to the open procedure.	3
Laparoscopic radical nephroureterectomy is associated with decreased intra-operative blood loss and hospital stay compared with the open procedure.	3

Recommendations	GOR
Radical nephroureterectomy includes the removal of the entire kidney, ureter, and ipsilateral bladder cuff.	A
Open radical nephroureterectomy is the standard of treatment for high-grade or clinically infiltrating UTUC.	B
In experienced hands, laparoscopic radical nephroureterectomy are alternatives to the open procedure.	C

5.2 Outcomes of Radical Nephroureterectomy (Part II)

The results of RNU can be defined by a variety of outcomes, including recurrence in the soft tissues surrounding the primary tumour (local recurrence), recurrence within the regional lymph nodes, recurrence within distant organs, urothelial recurrence within the contralateral upper tract, and urothelial recurrence within the bladder. As with all other tumour types, length of follow-up, intensity and type of follow-up, as well as reporting variations all affect the published outcomes in various series. Many clinical and pathologic variables have been proposed as possible prognostic variables affecting RNU outcomes. Surgical techniques may affect all defined outcomes, including recurrence in the bladder/ureteral stump, depending on the handling of the distal ureter. As surgical techniques such laparoscopy and robot-assisted laparoscopy have evolved, shortened follow-up periods, as well as patient selection may play larger roles in the reported outcomes. Issues regarding surgical technique, handling of the ureteral stump, and the role of the LND are addressed in more detail in other sections of this chapter. The focus of this section is on potentially serious recurrences following RNU, including local soft tissue recurrence, regional LN involvement, and distant organ recurrence.

5.2.1 Clinical variables affecting outcomes

5.2.1.1 Age

Advanced age and associated comorbidity remain closely linked to the risk for death from any cause. As such, OS has an expected association with these variables. Studies have also suggested that age at the time of RNU is associated with disease-specific outcomes, including recurrence-free survival (RFS) and CSS.[46] While the effect of increasing age does not have a defined cutoff above which RNU may not be effective, age appears to be a linear variable associated with poorer disease-specific outcomes.[4]

5.2.1.2 Gender

Unlike urothelial carcinoma (UC) of the bladder, in which the prevalence in men compared with women is 3-4:1, the ratio for UTUC is 2:1. Some series have suggested that, similar to bladder cancer,[47-49] stage-adjusted outcomes may be worse in women with UTUC.[50-53] However, more recent reports have challenged this assumption. These studies have noted a higher risk for women to present with more aggressive disease, and a higher percentage of women present with high-grade tumours and pT3 disease compared with men.[54] Despite these findings, women do not appear to have worse disease-specific outcomes, including recurrence risk or death from disease, when stratified for pathologic stage.[54,55]

5.2.1.3 Location

Defining the location of the primary tumour as renal pelvis or ureteral has been evaluated in order to determine whether this affects RNU outcome. Approximately half of all lesions are located in the renal pelvis or calyces. Lesions located in the ureter make up at least 25% of cases of UTUC, and the remaining 25% of UTUC cases involve both sites. Histopathologic characterization of renal pelvic versus ureteral primary tumour has revealed inconsistent findings. Some investigators have reported a higher risk for more advanced stage at presentation for cancers of the renal pelvis.[6,56,57] Others, however, have noted a higher risk for ureteral lesions that are more advanced at presentation.[58] Outcome analyses based on tumour location (renal pelvis vs. ureter) have also revealed conflicting results. Several multivariate analyses have shown worse DSS for patients with ureteral primary tumours,[57–59] while others have noted no difference in disease-specific outcomes.[5,6,56] To date, the evidence does not definitively support a higher risk for poorer outcomes based on primary tumour location.

5.2.1.4 Pathologic variables

Pathologic variables, particularly grade, stage, and LN status, are the most important prognostic characteristics associated with RNU outcome. Other relevant pathologic variables include concomitant carcinoma *in situ* (CIS), tumour architecture, tumour size, lymphovascular invasion (LVI), and margin status.

5.2.1.5 Grade

Grade is an important pathologic feature predicting outcome after RNU for upper tract transitional cell carcinoma (UTUC),[52,60–66] regardless of which classification system is used. A very strong association between tumour grade and stage has been established for UTUC. On final pathologic review at RNU, 10–20% of UTUC cases are low-grade lesions compared with the 80–90% that have high-grade features. Low-grade tumours treated with RNU demonstrate DSS rates approaching 95–100%. A contemporary series notes a decreasing percentage of patients undergoing RNU having purely low-grade disease, highlighting changes in selection criteria for radical versus conservative therapy[14] (see Chapter 8 on nephron-sparing surgery).

5.2.1.6 Pathologic tumour stage

Pathologic stage is the most important prognostic variable associated with cancer-specific RNU outcomes.[59,60–63,65,66,67–72] Approximately 25% of patients undergoing RNU have non-invasive disease (pT0, pTa, or CIS only), 25% have pT1, 20% have pT2, and 30% have pT3/4 on final pathologic review. Recurrence risk to the soft tissues surrounding the removed kidney/ureter, the retroperitoneum, or

distant organs is closely associated with the stage of the primary tumour. Similarly, disease-specific mortality (DSM) is associated with pathologic stage. Cancer-specific outcomes have improved over the last several decades and may represent changes and improvements in treatment or a stage migration at presentation.[14,53,73,74] Overall, 5-year CSM is approximately 20–25% for all patients undergoing RNU, regardless of stage. Increasing pathologic stage, however, is strongly associated with an increasing risk for death due to disease. A multicentre analysis of 2,244 patients with RNU, at 23 institutions, reported the hazard ratio (HR) for DSM and median estimated 5-year RFS and CSS for various stages of disease (see **Table 5-1**).[4]

TABLE 5-1 Survival after RNU

Study	DSM HR	RFS (%)	CSS (%)
pTa	1.00	95	95
pCIS	–	80	85
pT1	1.08	90	90
pT2	2.17	82	85
pT3	5.40	60	60
pT4	8.37	20	30

CIS: carcinoma *in situ*; CSS: cancer-specific survival; DSM HR: disease-specific mortality hazard ratio; RFS: recurrence-free survival; UTUC: upper tract urothelial carcinoma.

1. Reference: Cha EK, Shariat SF, Kormaksson M, *et al.* Predicting clinical outcomes after radical nephroureterectomy for upper tract urothelial carcinoma. Eur Urol. 2012;61:818–825.

5.2.1.7 Lymph node status

Variations in clinical staging, surgical technique, and pathologic review have affected the ability to clarify the risk for LN involvement in patients with UTUC. Whether a LN dissection is performed at RNU is dependent on both the surgeon and the technique. An open series has demonstrated an equally inconsistent use of regional LND compared with minimally invasive surgery techniques, with the series reporting that only 50% of patients undergo an LND at RNU.[14] The extent of the LND also demonstrates wide variations. These factors dramatically limit both the overall accuracy of LN-positive rates and the pattern of LN involvement in RNU series based on pathologic stage of the primary tumour. Approximately 5–15% of patients reported in RNU series have LN involvement. However, the NX (no LN dissection completed) rate in these series varies from 20–72%. In a large combined series of 44 institutions, 62% of patients did not undergo an LND and were classified as pNX.[18] Patients selected for LND at RNU include those with high-risk primary lesions (bulky or invading the kidney or surrounding organs), obvious LN involvement on pre-operative imaging, and lymphadenopathy identified at the time of surgery. Several studies have investigated whether open or minimally invasive techniques affect LN yield. Laparoscopic nephroureterectomy is associated with similar LN yields compared with open RNU. However, some comparative series suggest that patients undergoing LNU are less likely to receive an LN dissection.[14,18,21,25,26,75] Finding regional LN involvement at RNU dramatically impacts disease-specific outcomes. Node-negative disease is independently associated with an improved DSS compared with node-positive disease. The HR for

death due to recurrent disease is 2.3–2.9 for node-positive patients compared with those without LN involvement.[4–6] A proportion of patients who do not receive a regional LND will harbour LN involvement and, as such, have an expected intermediate risk for recurrence.

Conclusions	LOE
Radical nephroureterectomy is an effective form of treatment for patients with UTUC.	3
Radical removal of the kidney, entire ureter, and regional lymph nodes maximizes staging and local/regional disease control.	3
Approximately 75% of all patients undergoing RNU for UTTCC are free of disease at 5 years; however, important clinical and pathologic features, particularly pathologic stage, tumour grade, and lymph node status, will affect anticipated disease-specific outcomes.	3

5.3 Regional Lymph Node Dissection at Radical Nephroureterectomy

5.3.1 General considerations

Currently, despite the lack of randomized studies, LND at the time of radical cystectomy for muscle-invasive bladder cancer is widely accepted,[76] while LND at the time of RNU is often performed at the discretion of the treating surgeon. As in urothelial carcinoma of the bladder, it can be hypothesized that LND in UTUC not only allows for improved lymph node staging, but also has some prognostic benefit.[76] This prognostic benefit may or may not be related to the extent of lymphadenectomy; however, it mainly depends on established risk factors, such as tumour stage and soft-tissue surgical margins.

5.3.2 Lymphatic tumour spread in the retroperitoneum

As the lymphatic drainage patterns of the renal pelvis and ureter vary considerably, defining specific LND templates according to primary tumour location may enable an adequate LND in patients at high risk for lymph node disease. In a study of 181 patients treated with RNU, the metastatic node sites were recorded according to primary tumour location. In tumours of the right renal pelvis, the primary metastatic sites were preferentially the right renal hilar, paracaval, and retrocaval nodes. Tumours of the upper two-thirds of the right ureter primarily metastasized to the retrocaval and inter-aortocaval nodes. In tumours of the left renal pelvis, the primary sites were the left renal hilar

and para-aortic nodes. Tumours of the upper two-thirds of the left ureter primarily metastasized to the para-aortic nodes. Importantly, tumours of the lower ureter metastasized primarily to nodes inferior to the aortic bifurcation.[77]

5.3.3 Defining the extent of lymph node dissection in UTUC

As lymphatic spread of UTUC in the retroperitoneum and pelvis has not been established to date, it may be more sensible to first define a minimum number of lymph nodes to ensure adequate lymph node staging and to guide the necessity for further adjuvant treatment, allowing the number of removed nodes to be a proxy measure for the extent and accuracy of node dissection.

It is important to note that, despite removing an adequate number of nodes in which the lymphatics of the primary tumour location drain, pathological lymph node staging may be still be inaccurate. In this respect, one of largest multicentre series to date reported on the accuracy of lymph node staging based on the number of retrieved lymph nodes. Among 551 patients treated with RNU and regional LND between 1992 and 2006, positive lymph nodes were present in 25% of patients. The removal of 8 nodes resulted in a 75% probability to detect at least one positive node, while a more extensive LND with 13 removed nodes yielded a probability of 90%.[78] These data suggest that an extensive LND in UTUC improves the accuracy of nodal staging. However, the question remains whether more meticulous LND might also translate into improved survival. Another study based on the same cohort of patients found that the number of lymph nodes removed independently predicted CSM, with a cutoff value of 8 nodes being the most informative value.[9]

As the definition of adequate LND in muscle-invasive bladder cancer has shifted from a minimum number of lymph nodes needed to be removed to the definition of LND templates,[76] it seems reasonable to address this issue in invasive UTUC as well. Indeed, increasing evidence suggests that the anatomical extent of regional LND also plays a critical role for survival in lymph node–positive UTUC. A single-centre, retrospective series evaluated lymph node metastatic patterns as well the underlying anatomical templates in 81 patients treated with RNU for nonmetastatic UTUC of the renal pelvis or ureter.[8] Survival was significantly dependent on the extent of LND. Patients with stage ≥pT3 derived the highest prognostic benefit from LND. Likewise, patient survival improved when the number of removed lymph nodes increased. However, this study had several methodological limitations that need to be highlighted. Lymph node dissection (defined as either complete or incomplete) was not significant on univariate analysis, but it was significant on multivariate Cox proportional hazard analysis. This suggests collinearity or interaction with another variable (perhaps tumour stage). In addition, half of the patients did not receive LND, and their lymph node recurrence rate was not different compared with those who underwent complete LND.

There is growing evidence suggesting that tumour stage may be helpful in guiding clinicians to perform a more extended LND at RNU. According to a smaller series, performance of LND is associated with a lower risk for local recurrence, but it does not appear to influence DSS.[79–81] In patients with lymph node–positive disease, lymph node density (defined as the ratio of tumour-bearing nodes to removed nodes) was critical for outcome, as patients with a threshold LND value of >20% showed decreased RFS.[81] Importantly, in patients with clinically node-negative pT1–T4 UTUC, a "complete" LND, as outlined above,[77] improved CSS after adjusting for adjuvant chemotherapy, while the

number of removed nodes did not.[7] Another multicentre series compared outcomes in 1,130 patients with stage pT1–T4 UTUC. While in stage pT1, a significant difference between patients staged pN0 and pNX was not noted, LND in the group of patients with pN0 T2–T4 disease resulted in improved CSS compared with those in whom LND was omitted.[82] These results were also confirmed in a retrospective, multicentre series of 785 patients treated with RNU, in which patients with pN0 disease displayed significantly improved CSS in the presence of pathologically advanced tumour stages (pT2–T4).[83] In summary, the current body of evidence suggests that, in addition to improved nodal staging, LND at time of RNU may have an impact on survival in muscle-invasive UTUC.

Conclusion	LOE
Lymph node dissection in patients with muscle-invasive UTUC improves local staging and influences survival.	3

Recommendation	GOR
Lymph node dissection in patients with muscle-invasive UTUC or greater is a part of RNU, but its extent has not been established.	C

5.4 Management of the Distal Ureter During Nephroureterectomy and Prevention and Management of Bladder Cancer Following Nephroureterectomy

5.4.1. Management of the distal ureter during nephroureterectomy

Radical nephroureterectomy for UTUC has been defined to include the excision of the ipsilateral bladder cuff.[84,85] Indeed, if not excised, the distal ureter/bladder cuff remains at risk for tumour recurrence in up to 64% of patients,[86–88] and represents a particularly difficult area to survey if not removed. Moreover, it is imperative to prevent tumour seeding by avoiding entry into the urinary tract during UTUC resection.[84,89] Though multiple techniques exist for bladder cuff excision, no prospective randomized trials have compared the different approaches to provide Level 1 Evidence (LOE 1) to support the recommendation of any single technique.

The traditional/gold standard management of the distal ureter is open, en bloc excision during nephroureterectomy. This approach may be undertaken during either open or laparoscopic nephroureterectomy, and may be performed either transvesically or extravesically.[85] The transvesical approach entails an anterior cystotomy, visualization of the contralateral ureteral office, and then circumferential dissection around the orifice of the involved ureter to remove a cuff of bladder with the specimen, followed by bladder closure. A pure laparoscopic approach to the distal ureter using traction sutures on the bladder cuff to guide the area of excision has been described,[90] although this method is technically difficult to perform. Similarly, a combined transvesical laparoscopic approach with cystoscopic Collins knife incision for detachment of the distal ureter during the laparoscopic approach to nephroureterectomy has been described,[91] although this approach may likewise be time-consuming and technically challenging. As experience with the robotic approach to nephroureterectomy increases, it remains to be seen whether the increased range of motion with this technology facilitates a minimally invasive transvesical approach to the distal ureter.

Extravesical excision of the distal ureter avoids the need for an anterior cystotomy and may thereby decrease the length of post-operative catheterization. However, as this technique involves an essentially blind clamping of the ureteral hiatus with a right-angle clamp or stapler while placing traction on the ureter, contralateral ureteral integrity may be compromised,[92] and complete bladder cuff removal is difficult to ensure.[85] A similar approach that actually opens up the bladder cuff at the point of ureteral insertion is practiced by many, but is porly described. The results of this approach in comparison have not been described to the best of our knowledge. A stapled extravesical approach to the distal ureter has also been described laparoscopically, whereby gentle traction is applied to the ureter to "tent up" the wall of the bladder for placement of a laparoscopic GIA™ tissue stapler.[32,85,92] This is preceded by cystoscopic unroofing of the intramural ureter.[32] However, this technique has been associated with a higher rate of positive surgical margins and a trend toward inferior RFS.[92,93]

Another option for the management of the distal ureter is the endoscopic or "pluck" technique.[94] Here, patients initially undergo cystoscopy with transurethral resection of the ureteral orifice and intramural ureter, which is carried until perivesical fat is encountered, using either loop electrocautery[95,96] or a Collins knife.[97] Patients are then repositioned for the remainder of the nephroureterectomy, which may be performed with either an open or minimally invasive approach.[97] Once the kidney is circumferentially dissected and the renal hilum divided, the distal ureter is secured by applying gentle traction to separate the specimen from the bladder.[96] Concerns regarding the oncologic soundness of this procedure include tumour spillage from extravasated urine (although techniques for endoscopic ligation of the distal ureter stump have been described[97]) and the potential for incomplete resection of the intramural ureter due to avulsion of the specimen.[97,98] As such, it has been recommended that this technique be avoided for distal ureteral tumours.[98,99]

Ureteral stripping, or the intussusception technique, represents an additional alternative for managing the distal ureter during nephroureterectomy.[85] With this approach, a ureteral catheter is initially placed cystoscopically, and a full-thickness endoscopic incision is made around the ureteral orifice.[100] Division of the ureter is then performed during renal mobilization, and the distal ureter is secured to the ureteral catheter.[85,96,100] The distal ureter is then inverted and removed trans-urethrally via traction on the catheter, which intussuscepts the ureter into the bladder as the ureter is stripped down through the bladder wall under direct visualization.[85,100] However, complete removal of the

intramural ureter and bladder cuff is difficult to ensure with intussusception.[85] In addition, as this technique involves ureteral transection, it is contraindicated for ureteric tumours.[85] In fact, a 10% complication rate has been reported with this approach.[96] Furthermore, in a prospective, non-randomized study of 60 patients, the ureteric stripping technique was associated with a significantly higher rate of subsequent intravesical tumour recurrence versus patients treated with a conventional nephroureterectomy with bladder cuff (3-year intravesical RFS rate of 57.7% for ureteric stripping vs. 75% for conventional NU; p=0.03).[100] As such, this technique has not been recommended during nephroureterectomy.[84]

No prospective randomized trials have compared the efficacy of these various techniques. However, several recent large retrospective studies have provided an assessment of the relative cancer recurrence and survival rates among different approaches to the management of the distal ureter, though with the potential for significant selection bias. For example, Li and colleagues (2010) reported their single-institution experience in 301 patients undergoing nephroureterectomy with a median follow-up of 33 months.[101] Of these patients, 26.9% underwent intravesical excision of the distal ureter, 42.9% underwent an extravesical approach, and 30.2% were treated with endoscopic trans-urethral incision.[101] The investigators found no difference in bladder recurrence rates (23.5% vs. 24.0% vs. 17.6%, respectively; p=0.485) or in CSS (p=0.502) based on the approach to the distal ureter. This finding supports comparable oncologic efficacy among the three techniques. Similar results were reported from a large, multicentre study in which bladder cuff excision was not found to be significantly associated with CSM.[18] All of these studies suffer from a retrospective methodology subject to unquantifiable selection bias.

On the other hand, using the population-based Surveillance, Epidemiology, and End Results (SEER) dataset, Lughezzani *et al.* (2010) reviewed data on 4,210 patients treated with nephroureterectomy between 1988 and 2006, with a median follow-up of 40 months.[102] They found that omission of a bladder cuff excision with nephroureterectomy was associated with a significantly increased risk for CSM among patients with pT3N0/x (HR: 1.25; p=0.04), pT4N0/x (HR: 1.45; p=0.02), and pT(any) N1–3 (HR: 1.38; p=0.04) tumours.[102] These results suggest an importance of bladder cuff excision for optimizing cancer control in patients with locally advanced disease, although data on recurrence was not available in this series. More recently, Xylinas *et al.* (2014) compared the outcomes associated with transvesical (n=1,811), extravesical (n=785), and endoscopic (n=85) approaches to the distal ureter in a multicentre study of 2,681 patients who underwent nephroureterectomy over a 20-year period.[103] These investigators found that patients who underwent an endoscopic approach had a significantly lower 5-year intravesical RFS rate (42%) than patients who underwent either a transvesical (58%) or extravesical (51%) approach to the distal ureter (p=0.02 for both), although no significant difference in intravesical recurrence was found between the transvesical and extravesical approaches (p=0.40). Indeed, the endoscopic approach to the distal ureter remained associated with a significantly increased risk for subsequent intravesical tumour recurrence on multivariate analysis (HR: 1.74; p=0.01).[103] Notably, however, there was no difference reported in cancer-specific or overall survival among the three approaches to the management of the distal ureter.[103]

Overall, while the optimal approach to the management of the distal ureter remains to be determined, evidence from retrospective series Level 3 Evidence [LOE 3] support a Grade B Recommendation (GOR B) that several approaches may be valid alternatives to the distal ureter during nephroureterectomy as long as complete excision of the bladder cuff is achieved.

5.4.2 Prevention and management of bladder cancer following nephroureterectomy

Although synchronous bladder cancers among patients with UTUC have been reported in a minority of patients (8–13%),[98,104,105] these patients remain at considerable risk for the development of metachronous bladder tumours following nephroureterectomy. Indeed, bladder cancer has been reported following nephroureterectomy in 15–50% of patients,[2,98,106–110] such that the bladder is the most common site for tumour recurrence following UTUC management.[98] Hypotheses for the mechanism of bladder cancer following UTUC have included tumour seeding from the upper tract and a field-change defect within the urothelium.[98] Though bladder tumour prevention has been tested in the clinical trial setting, no Level 1 Evidence (LOE 1) from prospective randomized trials exists to guide the identification of risk factors for bladder tumour recurrence. Regardless, understanding the potential clinicopathologic features associated with the development of bladder tumours after nephroureterectomy, as well as the potential interventions to prevent these cancers, remains important to optimize patient counseling and management, and to establish surveillance regimens.

Numerous retrospective series have evaluated features associated with the development of bladder cancer following nephroureterectomy. Interestingly, these studies have demonstrated conflicting evidence regarding the prognostic value of variables such as UTUC tumour stage, size, grade, and location,[2,98,106,108–111] as well as techniques for the management of the distal ureter.[106,51] Two factors which have consistently been associated with an increased risk for bladder cancer following UTUC treatment are a history of bladder cancer prior to UTUC diagnosis and UTUC tumour multifocality.[98,108,109,110] Given the natural history of bladder cancer, with its high propensity for intravesical recurrences, the link between a prior history of bladder tumours and an increased risk (between 2–3 fold[106]) for bladder cancer following UTUC management is not surprising. Moreover, the presence of multifocal UTUC has been associated with a 2–3 fold increased risk for subsequent bladder cancer,[109] and one-third of UTUC cases are multifocal.[57,58,98,105] Validation of these features as risk factors for bladder cancer recurrence may allow for individualized surveillance regimens to be developed for patients following nephroureterectomy.

The majority of bladder cancer recurrences has been reported to occur within the first two years after UTUC management, although patients do remain at lifelong risk.[98,106,109] As such, continued bladder surveillance following treatment for UTUC, typically with cystoscopy and urine cytology, has been included in practice guidelines.[84] Nevertheless, future studies are warranted to develop an evidence-based surveillance regimen.[98] The majority of reported intravesical recurrences after nephroureterectomy has been non–muscle-invasive tumours, with a correlation of up to 90% in grade between the UTUC and the bladder tumour.[98,107,109] However, the impact of bladder tumour recurrence on survival remains to be determined.

With regard to the prevention of bladder tumour recurrence following nephroureterectomy, consideration has been given both to intra-operative and post-operative measures that may impact patients' risk for subsequent bladder cancer. For example, Wong and Leveillee (2002) advocated early ligation of the ureter with a clip during surgery to avoid distal migration of tumour cells during kidney dissection.[112] Although there is concern that the pneumoperitoneum pressure during laparoscopic nephroureterectomy may increase the risk for tumour cell dissemination to the bladder,[27,98] no consistent association between a minimally invasive approach to nephroureterectomy and increased bladder tumour recurrence risk has been demonstrated.[98] Indeed, a large systematic review of 21 published reports noted that laparoscopic nephroureterectomy was associated with a 17% decreased risk for intravesical tumour recurrence compared with open nephroureterectomy (p=0.02).[113] Importantly, these authors acknowledged that the studies included in their analysis were largely retrospective, thus disease features and surgical approach could not be comparatively balanced between the cohorts, limiting the conclusions that can be drawn from their data.[113] Ultimately, determining the impact of surgical approach and early ureteral ligation on the risk for subsequent bladder tumour development necessitates testing in a prospective clinical trial setting.

The utility of intravesical chemotherapy to prevent bladder tumour recurrence after nephroureterectomy has been investigated post-operatively as well. The rationale extends from data among patients with primary tumours of the bladder, in whom post–trans-urethral resection of the bladder followed immediately with intravesical chemotherapy was found to prevent recurrence.[114,115] Specifically, Wu and colleagues (2010) retrospectively evaluated 196 patients undergoing nephroureterectomy, of whom 31 received post-operative intravesical epirubicin, 27 received post-operative intravesical mitomycin C, and 138 were not treated with prophylactic instillation after surgery.[116] A multivariate analysis controlling for clinicopathologic disease features found that receipt of mitomycin C was associated with a 51% reduction in bladder tumour recurrence (HR: 0.49; p=0.04), while receipt of epirubicin trended toward a decreased risk for intravesical recurrence (HR: 0.56; p=0.065).[116] More recently, O'Brien *et al.* (2011) reported data from the One Dose Mitomycin C (ODMIT-c) trial, a prospective, randomized, multicentre study that evaluated the efficacy of a single dose of 40-mg mitomycin C at the time of catheter removal following nephrouretectomy.[117] These investigators found that the absolute risk reduction with mitomycin C treatment (by per-protocol analysis) was 11% (p=0.03), with a relative risk reduction of 40%.[117] As such, the number needed to treat to prevent one bladder tumour recurrence was 9, and no serious adverse events were reported as a result of mitomycin C instillation.[117,118] Even more recently, another randomized prospective trial by Ito *et al* (JCO 2013) showed significant benefit of epirubicin when given 2 days after nephroureterectomy. At 1 year, recurrences were very similar to outcomes of the study from O'Brien *et al,* and at 2 years the benefit persisted. Also similar to the prior study, the administration of chemotherapy was found to be safe and well tolerated. Data from this trial provide Level 1 Evidence (LOE 1), which, together with the retrospective series reviewed here,[116] supports a Grade A Recommendation (GOR A) for prophylactic intravesical chemotherapy to prevent bladder tumour recurrence following nephroureterectomy.

Conclusions	LOE
Excision of the bladder cuff during nephroureterectomy is associated with decreased risk for subsequent intravesical tumour recurrence, although no significant association has been noted between the technique for distal ureteral excision and post-operative cancer-specific survival.	3
Post-operative intravesical chemotherapy following nephroureterectomy is associated with a significantly decreased risk for bladder tumour recurrence, although the optimal agent/timing of administration remains to be determined.	1

Recommendations	GOR
Several approaches may be valid alternatives to the distal ureter during nephroureterectomy as long as complete excision of the bladder cuff is achieved.	A
Prophylactic intravesical chemotherapy is indicated following nephroureterectomy to prevent subsequent bladder tumour recurrence.	B

5.5 Upper Tract Urothelial Carcinoma: Neoadjuvant and Adjuvant Chemotherapy

There is no current standard regarding the use of peri-operative chemotherapy in the treatment of upper tract urothelial carcinoma. Upper tract urothelial tumours remain quite rare and account for less than 5% of all urothelial cancers.[119] As a result, there have been no randomized trials and very few prospective studies. In addition, the high incidence of renal insufficiency in patients with obstructed ureters or large masses involving the renal pelvis, or following definitive resection of the kidney, has limited our ability to prospectively study cisplatin-based chemotherapy regimens in the peri-operative setting. Therefore, the literature mostly cites retrospective patient reviews and smaller prospective series of patients treated in the context of neoadjuvant bladder trials at academic centres.

Our inability to accurately stage upper-tract disease has also limited our ability to select patients who are most likely to benefit from neoadjuvant chemotherapy. The presence of muscle-invasive urothelial cancer as a standard in selecting neoadjuvant treatment for urothelial tumours of the bladder is not possible in upper-tract disease. Indeed, resection of muscle in the upper tract is to be assiduously avoided, as this would coincide with perforation of the upper tract. Therefore, it is important to determine alternate prognostic factors regarding the risk for relapse in upper tract urothelial cancer.

5.5.1 Prognostic factors

The inability to accurately stage upper tract tumours pre-operatively means that clinical staging is largely unusable in predicting a need for neoadjuvant chemotherapy. Identification of prognostic factors associated with adverse outcomes may help in the appropriate selection of patients for peri-operative chemotherapy. Retrospective studies have identified several prognostic factors correlating with a higher risk for relapse and death in upper tract urothelial cancer. These include the grade and stage of tumours,[62,63,104,120] the size of the mass in the upper tract,[105,120–122] hydronephrosis,[122–125] tumour necrosis,[126–128] multifocal cancer,[129] lymphovascular invasion,[63,70,130–132] pathologic nodal status,[9,63,82,120,133] and the presence of variant histologies such as micropapillary differentiation.[134–136] However, it is not feasible to determine many of these factors prior to definitive surgery, and they remain largely inadequate for identifying patients for neoadjuvant chemotherapy. Though they may be useful in predicting those at high risk for relapse who would benefit from adjuvant chemotherapy, most patients are no longer candidates for adjuvant cisplatin-based chemotherapy once their kidney has been removed.

The Upper Tract Urothelial Carcinoma Collaboration recently reported a large retrospective review of prognostic factors in 1,300 patients treated with radical nephroureterectomy.[63] Independent predictors for CSS on multivariate analysis included advanced patient age (p=0.001), high-grade disease (p=0.001), increasing pathologic T stage (p<0.001), the presence of lymph node metastases (p<0.001), sessile architecture (p=0.002), and lymphovascular invasion (p=0.02). The majority of these factors may be useful in the adjuvant setting by selecting patients at risk for relapse. Use of these factors in the neoadjuvant setting, however, is largely limited by endoscopic techniques and the ability to obtain tissue or assess for a sessile mass on ureteroscopy, or visualize a sessile mass on radiographic imaging.

Tumour size may also be assessable via radiographic imaging and may be useful in identifying patients for neoadjuvant strategy. Three separate studies have suggested that a tumour diametre of >3 cm (1.5 cm in Cho's work[122]) was associated with adverse outcome.[123–126] However, only one of these studies suggested that tumour size was an independent predictor for CSS.[125]

5.5.2 Adjuvant chemotherapy

The use of adjuvant chemotherapy in the treatment of upper tract urothelial cancer remains largely limited due to the decline in renal function following nephroureterectomy. It is estimated that only 20% of patients have a glomerular filtration rate of greater than 60 mL/min following nephroureterectomy.[43,137] As a result, the published experience with adjuvant cisplatin-based chemotherapy has been limited to retrospective studies. Overall, these studies suggest that the use of adjuvant chemotherapy has minimal impact on overall or disease-specific survival compared with patients who are observed following definitive surgery. However, it is certainly possible that selection bias, where patients with the worst prognostic factors are selected for adjuvant chemotherapy compared with their counterparts, may limit the ability to detect any difference in outcome.

The Upper Tract Urothelial Carcinoma Collaboration published a large retrospective series of patients treated with adjuvant chemotherapy.[138] Of the approximately 1,300 patients undergoing a nephroureterectomy, 39% were classified as having a high-risk relapse based on their pathologic stage

being ≥pT3N0 and/or having node-positive disease. However, only 22% of these high-risk patients ultimately received adjuvant chemotherapy. The median survival in this cohort of high-risk patients was approximately 24 months, with no significant difference in overall or cancer-specific survival compared with patients who did not receive adjuvant chemotherapy (p=0.687 and p=0.129, respectively). Approximately 90% of patients received cisplatin-based chemotherapy, with 59% receiving methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC). As adjuvant chemotherapy was used more commonly in tumours of higher grade and stage (p<0.001 for each), it is possible that selection bias could have limited their ability to detect a meaningful impact on patient survival.

The French Collaborative National Database on Upper Tract Urothelial Carcinoma also did not find any significant benefit in patient outcomes despite the use of adjuvant chemotherapy.[139] Again, only about 22% of high-risk patients with a pathologic stage ≥pT3N0 and/or N+ and/or M+ disease received adjuvant chemotherapy, with only 50% treated with a cisplatin-based regimen. The 5-year overall and cancer-specific survival rates were 43% and 60%, respectively, with no difference in outcomes compared with the group who did not receive adjuvant chemotherapy (p>0.5, each). It is again notable that patients offered adjuvant chemotherapy had a higher pathologic stage and a higher-grade disease (p=0.001 for each) compared with the observation group. Therefore, it is possible that selection bias could be limiting the ability to detect a meaningful difference in survival.

There is currently only one published prospective clinical trial of adjuvant chemotherapy in upper tract urothelial carcinoma. This trial, by the Hellenic Cooperative Oncology Group, treated 36 patients with ≥pT3b and/or N+ disease with 4 cycles of adjuvant paclitaxel with carboplatin.[140] The 5-year overall survival rate was only 52%, with a 5-year disease-free survival (DFS) rate of only 40%. The authors concluded that this treatment may reduce the risk for distant metastases in high-risk upper tract tumours. It should be noted that 20% of patients had grade 2 disease, which has been associated with more favourable outcomes. In fact, none of the grade 2 tumours relapsed. However, the relapse rate was 60% for patients with grade 3 disease. Therefore, it is hard to conclude that adjuvant chemotherapy with paclitaxel and carboplatin is curative in a large number of patients with upper tract tumours.

5.5.3 Neoadjuvant chemotherapy

Because of the inherent difficulties in giving cisplatin-based chemotherapy following nephroureterectomy, some centres have adopted the use of neoadjuvant chemotherapy in patients with upper tract urothelial carcinoma. The potential benefits of this approach include the treatment of early microscopic metastases and the ability to administer full-dose cisplatin with curative intent when patients still have both kidneys. In addition, the pathologic downstaging in response to chemotherapy may also be useful in predicting patients that may have a higher risk for relapse following neoadjuvant chemotherapy and definitive surgery for their upper tract tumour.

One single-institution series from the M. D. Anderson Cancer Center reported on 43 patients with upper tract urothelial carcinoma treated with neoadjuvant chemotherapy.[141] In this retrospective review, 77% of patients received neoadjuvant chemotherapy with either a cisplatin-based or ifosfamide-based combination. When compared with a historical cohort of patients who underwent initial surgery, pathologic downstaging was significantly higher in patients receiving neoadjuvant chemotherapy (p=0.004). This is despite a higher rate for sessile tumour architecture in the patients

treated with neoadjuvant chemotherapy (p=0.018). The pathologic T0 rate (pT0N0) was 14%, similar to the rate in a small cohort of 15 patients previously published by Igawa *et al.*.[142] Due to the short follow-up in the M. D. Anderson Cancer Center cohort, long-term survival was not reported. However, a recent update of the M. D. Anderson Cancer Center experience reported 5-year disease-specific survival rates of 90%.[143]

An additional retrospective study from the Upper Tract Urothelial Carcinoma Collaboration reported that only 3% of patients with upper tract tumours (41 patients) received neoadjuvant chemotherapy.[63] The pathologic T0 rate in those patients was 12%, with more than 83% of patients receiving cisplatin-based chemotherapy. Long-term outcomes of these patients were not reported. As investigators from the M. D. Anderson Cancer Center study also participated in this collaboration, it is possible that there is significant overlap among these patients.[63,141]

There is limited prospective data in the neoadjuvant treatment for UTUC. One prospective clinical trial of neoadjuvant ifosfamide-based chemotherapy in urothelial tumours of the bladder and upper tract reported pathologic downstaging to ≤pT1N0 disease in 3 of 5 patients with high-grade upper tract disease.[144] Long-term outcomes were not reported separately for patients with upper tract tumours, although the long-term survival was similar to what was reported with MVAC.[145]

Investigators from the M. D. Anderson Cancer Center recently presented data from a neoadjuvant clinical trial of dose-dense MVAC with bevacizumab in patients with urothelial carcinoma of the bladder and upper tract.[146] Of the 60 patients enrolled, 16 had tumours of the renal pelvis and/or ureter. Patients with upper tract tumours were included on the basis of either high-grade disease on biopsy or a sessile mass on imaging or ureteroscopy. Pathologic downstaging to pT0N0 was similar between upper tract tumours and urothelial carcinomas of the bladder (pT0N0=38% for each). Early follow-up results suggested 3-year overall and disease-specific survival rates of 93% for patients with upper tract tumours. While this is promising as compared with historical cohorts, additional follow-up and larger trials are needed to confirm these findings.

5.5.4 Conclusions

Patients tend to have adverse outcomes in the setting of high-stage, high-grade histology, sessile architecture, or lymphovascular invasion. However, many of these prognostic criteria are useful only in the adjuvant setting. As we are unable to clinically assess patients with upper tract tumours for the presence of muscle invasion, current potential selection criteria for neoadjuvant chemotherapy include the presence of high-grade tumours and/or sessile mass with additional limited data on the presence of a 3-cm mass. Additional studies are necessary to determine the validity of these findings. While adjuvant chemotherapy has not been shown to improve survival, the studies reported to date are limited by both the small numbers of patients receiving adjuvant chemotherapy and their retrospective reporting. These studies may also be biased toward giving adjuvant chemotherapy to patients with the worst clinical outcome. Currently, neoadjuvant chemotherapy is showing significant promise in the treatment of upper tract urothelial tumours, with one small study suggesting a 3-year disease-specific survival rate of 93% and pathologic downstaging rates similar to what has been observed in urothelial tumours of the bladder. Neoadjuvant cisplatin-based chemotherapy may also be tolerable in more patients prior to the removal of one kidney. Based upon the current limited

literature, it seems reasonable to consider 3 to 4 cycles of neoadjuvant chemotherapy with a cisplatin-based regimen in the treatment of UTUC, though additional studies are needed to confirm the benefits of therapy.

Recommendations	LOE, GOR
The current criteria for neoadjuvant chemotherapy for muscle-invasive bladder cancer cannot be applied in the treatment of upper tract tumours, as muscle resection would result in perforation.	4, C
There is no current standard for prognostic factors in the neoadjuvant treatment of upper tract urothelial cancer. Currently, the most promising prognostic factors include high-grade disease, a sessile mass, and possibly the presence of a 3-cm or greater mass.	3, B
Adjuvant chemotherapy may be considered in patients at high risk for relapse for ≥pT3 or N+ disease; however, its utility is limited due to the decline in renal function following nephroureterectomy. There have been no prospective trials of adjuvant cisplatin-based chemotherapy, and retrospective studies have selection bias impacting the ability to determine benefit from adjuvant therapy. Whether giving chemotherapy as adjuvant or awaiting development of clinically evident disease is better, is unknown.	4, C
Neoadjuvant cisplatin-based chemotherapy is possible in more patients prior to nephroureterectomy. Recent prospective trials suggest a survival advantage compared with historical standards. Larger clinical trials are needed to confirm this benefit.	3, B

5.6 Upper Tract Urothelial Carcinoma: The Impact of Chemoradiation

Currently, there is limited value regarding the role of radiation or chemoradiation in the treatment of upper tract urothelial cancer. One small case series of 31 patients reported that the addition of concurrent cisplatin to radiation therapy improved the outcome of patients with locally advanced transitional cell carcinoma of the renal pelvis and ureter. Patients receiving concurrent cisplatin with adjuvant radiation therapy had a 5-year disease-specific survival rate of 76% compared with 41% in patients receiving radiation therapy alone (p=0.06).[147] However, all 9 patients treated with concurrent cisplatin during radiation also received adjuvant chemotherapy with 2 to 4 cycles of methotrexate, cisplatin, and vinblastine prior to chemoradiation. Given the potential impact of adjuvant chemotherapy in controlling urothelial cancer,[148–151] it seems more likely that these results reflect the impact of adjuvant chemotherapy. Another series followed 67 patients who received external beam radiation following surgery for T3 or T4 upper tract urothelial cancer.[152] However, the OS rates between radiated and non-radiated groups was not significantly different (p=0.198). A subset analysis in patients with stage T3/T4 cancer suggested a potential benefit with adjuvant external beam radiation (median OS: 29.9 vs. 11.4 months, p=0.006, for the radiation and non-radiation groups, respectively). It is not clear whether the imbalance

between the treatment groups could have contributed to this finding, as more patients treated on the radiation therapy arm received a complete nephroureterectomy (p=0.004) compared with a local resection, and twice the number of patients in the non-radiation therapy arm had T4 disease.

Statement

Given the overall paucity of data, we cannot recommend routine chemoradiation or radiation in the treatment of UTUC.

5.7 Risk Factors for Intravesical Recurrence and Survival After Radical Nephroureterectomy

Radical nephroureterectomy is the gold standard in UTUC.[153] Many factors have been reported to influence tumour recurrence or patient survival after RNU, based on varying levels of evidence. This guideline summary covers the prognostic factors influencing intravesical recurrence and patient survival.

5.7.1 Intravesical recurrence

Incidence of intravesical recurrence (IVR) after radical nephroureterectomy is high, at about 30–50%.[2,106] Several factors have been recognized to predict the risk for IVR.

5.7.1.1 Clinical factors

5.7.1.1.1 Gender

Male gender is reported to be a prognostic factor for IVR.[154,155] This may be associated with the role of androgen receptors in bladder carcinogenesis, but the detailed mechanism remains unclear.

5.7.1.1.2 Smoking

Smoking is reported to be a predictive factor for early onset of IVR after RNU.[156] While this is the conclusion from univariate analysis, there is no actual influence on patient survival. Thus, the influence of smoking on the oncological outcome after RNU remains equivocal.

5.7.1.1.3 Chronic kidney disease

Chronic kidney disease (CKD) is reported to be a risk factor for IVR. Chung and colleagues (2007) reported that risks for bladder recurrence were 2.43 and 3.95 times greater in patients with CKD stages 1–4 and stage 5, respectively, compared with patients without CKD.[157] Possible explanations include immunosuppressive condition, chronic bladder irritation, and/or exposure to greater concentrations of some urinary carcinogenic substances, and tumour cells shed from the upper tract before RNU.[157]

5.7.1.1.4 History of bladder cancer

A history of bladder cancer is a strong predictive factor for subsequent bladder cancer recurrence after RNU.[65,158,159] Patients with a previous history of bladder cancer are likely to have urothelial carcinoma of the upper urinary tract (UCUUT) tumours with more aggressive biological potential.[103] In addition, this factor is related to multi-centricity of urothelial carcinoma.[160]

5.7.1.1.5 Tumour location

Ureteric location is reported to be associated with IVR.[2,155,157] This finding may be related to a higher urine flow rate and intraluminal pressure in the ureter, facilitating detachment of tumour cells from the ureter, and subsequently dissemination to the bladder.[2]

5.7.1.1.6 Positive urine cytology

Positive urine cytology is shown as an independent predictive factor for worsening IVR.[161] Positive urine cytology means that tumour cells are disseminating from the upper urinary tract to the bladder.

5.7.1.2 Pathological factors

5.7.1.2.1 Multiplicity

Some studies use the term "multifocality" for tumours located at both the renal pelvis and ureter. Similarly, "multiplicity" is used when tumours are found at two or more loci. Multifocality has been reported to be a strong independent predictor for IVR.[109,110,159,162] This is related to the fact that urothelial carcinoma is likely to occur in multiple sites through two possible mechanisms: the clonogenic theory and the field change theory.[160]

5.7.1.2.2 Stage and grade

Advanced stage and grade are reported to be strong independent predictive factors for poor patient survival.[39,163] Intravesical recurrence is likely to depend on high stage or high grade.[103,154,156] In contrast, some investigators report that low-stage tumours are more likely to develop subsequent bladder cancer IVR.[108,110] Thus, the influence of stage on IVR remains unclear.

5.7.1.2.3 Concomitant CIS

Concomitant carcinoma *in situ* is reported to be an independent predictive factor for high IVR,[103,164] as it may reflect a pre-malignant state of the entire urinary bladder surface, confirming the multifocality of UTUC and its higher bladder recurrence rate.[164]

5.7.1.2.4 Other factors

The multi-institutional study covering a total of 2,681 patients shows pathological node metastasis to be an independent predictive factor for the high incidence of IVR.[103] Tumour size[164] and papillary architecture[154] are also reported as independent predictive factors. In addition, a positive surgical margin and tumour necrosis are independently associated with IVR.[111]

5.7.1.3 Intervention

5.7.1.3.1 Laparoscopic RNU

Some multi-institutional studies with large patient numbers suggest that laparoscopic RNU shows a higher incidence of IVR compared with open RNU.[103,159] However, Ariane and colleagues (2012) reported a similar RFS in both these modalities.[15] Those authors emphasize the importance of

avoiding direct contact of instruments with tumours and avoiding tumour spilling and seeding when entering the urinary tract during laparoscopic RNU. Another possible reason for high IVR occurrence may be related to the entire endoscopic management of the distal ureter.[103]

5.7.1.3.2 Prophylactic intravesical chemotherapy

Wu and colleagues (2010) retrospectively examined the intravesical instillation of mitomycin C or epirubicin[116] and reported that prophylactic intravesical chemotherapy is effective for preventing bladder recurrence and prolonging the time to first bladder recurrence. O'Brien and colleagues (2011) conducted a prospective randomized study and showed that a post-operative single instillation of mitomycin C reduces the risk for a subsequent bladder tumour after RNU by 40%.[117]

5.7.1.3.3 Adjuvant chemotherapy

Cisplatin-based systemic chemotherapy is reported to reduce the risk for IVR.[111,165] However, this may not apply in the same fashion for intravesical chemotherapy given for preventing bladder recurrence as discussed in Section 5.4.2.

5.7.1.4 Biomarkers

A range of biomarkers have been used to look for independent predictive factors for IVR, including negative expression of N-cadherin,[166] higher percentage of CD8+ cells in peripheral blood lymphocytes,[167] high Ki-67 labeling index,[168] and chromosome 20q13.2 gain.[169] However, these studies were conducted in single institutes, and a prospective, multi-institutional study is required to validate their significance.

5.7.2 Patient survival

5.7.2.1 Clinical factors

5.7.2.1.1 Age

Multi-institutional studies show higher age to be independently associated not only with shorter OS, but also worse RFS and CSS.[39,46] Population-based studies also show age to be an independent factor for poor CSS.[62,170] This may be due to more aggressive malignant potential of the tumours occurring in elderly patients.[171] Chromecki and colleagues (2011) also reported that advanced age is an independent factor for CSS, but not when ECOG performance status was added in the multivariate analysis.[39] Thus, those authors emphasize that chronological age is not an independent predictor for clinical outcomes after RNU.

5.7.2.1.2 Gender

Some reports show no influence of gender on patient survival.[102,172] On the other hand, Raman and colleagues (2011) reported male gender to be an independent prognostic factor.[170] In contrast, Lughezzani and colleagues (2010) reported that female patients are likely to have higher stage and higher grade, although female gender is not an independent factor.[54] The importance of gender on patient survival remains controversial.

5.7.2.1.3 Race

Race has shown to be a prognostic factor, where the black race is reported to independently predict worse CSS[170] and OS[173] after RNU. Japanese patients do not show any difference from Caucasian patients in CSS.[174] However, patient comorbidity, socioeconomic status, marital status, and other measures of social support were not controlled in these studies. Thus, it is difficult to draw a definite conclusion.

5.7.2.1.4 Pre-operative comorbidity

American Society of Anesthesiologists score and ECOG performance status are both reported to be independent predictive factors for poor CSS.[175,176] On the other hand, some studies report that ECOG performance status is independently associated with OS, but not with CSS.[39, 41] The Charlson Comorbidity Index is also used to evaluate the pre-operative patient status, but it impacts only OS, not CSS.[177]

5.7.2.1.5 Chronic kidney disease

Chronic kidney disease is reported to be an independent predictive factor for poor CSS[67] and IVR.[157] The possible explanations for this are delayed diagnosis due to less urine production and delayed hematuria or suppressed immunosurveillance due to uremia.[67]

5.7.2.1.6 Smoking

One population-based case-control study shows that cigarette smoking increases the risk for disease occurrence 3.1 fold.[178] However, the impact of smoking on oncological outcome varies in studies.[156, 67]

5.7.2.1.7 Obesity

Ehdaie and colleagues (2011) report high body mass index (BMI) to be associated with worse CSS.[179] This may be due to the increased insulin-like growth factor 1 in obese patients, which either stimulates cell proliferation and suppresses apoptosis or is activated by systemic inflammation. In contrast, Gadzinski and colleagues (2010) have shown that lower BMI is an independent predictive factor for poor CSS.[177] Further studies are needed to clarify the role of obesity.

5.7.2.1.8 Timing of RNU

In bladder cancer, a longer interval between diagnosis and radical cystectomy is associated with poor patient outcome.[180] Waldert and colleagues (2010) reported that a long interval (>3 months) between diagnosis and RNU is associated with a more advanced stage of UTUC,[181] with no adverse influence on patient CSS. Sundi and colleagues (2012) also showed that delayed RNU does not have a negative impact on CSS.[176] The reason for delayed surgery in this study is due to the administration of neoadjuvant chemotherapy.

5.7.2.1.9 History of bladder cancer

A history of bladder cancer is a strong independent factor for high incidence of IVR.[65,158,159] However, the influence of history of bladder cancer on patient survival is controversial.[65,182] One multi-institutional study showed that the history of bladder carcinoma *in situ* independently influences both IVR and patient survival with lower RFS and CSS.[183]

5.7.2.1.10 Tumour location

Recent multi-institutional studies have shown ureteric location of the tumour to be an independent prognostic factor for poor CSS.[69,184] If tumours are located in both the renal pelvis and ureter, CSS is even worse. Several possible reasons have been proposed: 1) the layer of ureteric adventitia containing an extensive plexus of blood vessels and lymphatics facilitates tumour lymphatic and hematogenous spread, 2) the thin smooth muscle layer of the ureter allows higher stage with minimal tumour invasion, and 3) the thicker adventitial layer of the renal pelvis and abundant renal parenchyma provide a protective role for tumour invasion.[184]

In contrast, some studies with large patient numbers fail to show any significant impact of tumour location on patient survival after adjusting for other prognostic parameters.[6,56,182] This may be because ureteral carcinomas tend to be symptomatic due to the early occurrence of ureteral obstruction in its narrow lumen, and they are detected earlier than renal pelvic cancer.[56] Thus, whether the ureteric location of the tumour is predictive for patient survival remains controversial.

5.7.2.1.11 Incidental/Symptomatic

Pre-operative symptoms are present in more than 70% of patients with UTUC.[153] However, Raman and colleagues (2011) reported that local symptoms do not influence patient prognosis compared with incidentally detected UTUC.[185] On the other hand, systemic symptoms, including anorexia, weight loss, and malaise, are likely to be predictive for CSS.

5.7.2.1.12 Hydronephrosis

Hydronephrosis is likely to be associated with poor pathological parameters and to influence CSS.[122,125] A high grade of hydronephrosis is associated with aggressiveness of the disease and predicts poorer DFS and MFS.[124] However, Bozzini and colleagues (2013) reported that hydronephrosis is not predictive for CSS.[186]

5.7.2.1.13 C-reactive protein

The pre-operative serum C-reactive protein (CRP) level is considered to reflect the increased systemic inflammatory response by tumours and to be associated with poor oncological outcomes.[187] In patients with UTUC, elevated pre-operative CRP level is reported to be an independent predictive factor for poor RFS and CSS.[188,189] Therefore, the serum-level CRP may be a biomarker for UTUC prognosis.

5.7.2.1.14 Pre-operative serum sodium

The pre-operative serum sodium level is reported to be an independent factor for poorer CSS.[190] Hyponatremia may result from the increased interleukin-6 production from tumour cells upregulating vasopressin expression, which can stimulate cancer cell proliferation.

5.7.2.1.15 Balkan endemic nephropathy

Balkan endemic nephropathy (BEN) is an interstitial non-inflammatory disease of the kidney, which is related to a part of Serbia. Frequency of UTUC is higher in patients from the BEN area.[191] Milojevic and colleagues (2012) report that belonging to a BEN area is an independent predictor for RFS but not for CSS.[182]

5.7.2.2 Pathological factors

5.7.2.2.1 Tumour stage

Most multi-institutional studies report pathological tumour stage to be an independent predictive factor for poor oncological outcomes.[4,39,163,192] Population-based studies using SEER registries also show tumour stage to be an independent factor.[62,193] In these studies, the risk for cancer-specific mortality escalates as the tumour stage increases when pTa/pTis/pT1 is used as a reference in the multivariate analysis.

5.7.2.2.2 Tumour grade

The 1973 World Health Organization (WHO) classification divided urothelial carcinoma into three subgroups. The revised 2004 WHO classification includes only two categories: low and high grade.[194] Multi-institutional and population-based studies show tumour grade to have an independent impact on CSS by the 1973 grading system.[62,163,192,193] With the new 2004 grading system, however, a high-grade tumour is a significant factor for poor CSS when assessed by univariate analysis, but not by multivariate analysis.[4,39] This may be attributed to the loss of the grade 3 category in the 2004 grading system, which is more likely to indicate a highly aggressive tumour. Thus, it is postulated that the 1973 grading system is more suitable for predicting prognosis in urothelial carcinoma.[195]

5.7.2.2.3 Tumour size

The role of tumour size has been rarely examined for predicting oncological outcomes. Simone and colleagues (2009) reported a tumour of 3 cm or larger to be an independent predictive factor for worse RFS and MFS.[121]

5.7.2.2.4 Pathological node metastasis

Pathological node metastasis (pN+) is one of the strong independent predictive factors. Most multi-institutional studies[4,163,192] and population-based studies[62,193] confirm pN+ to be independently predictive for lower RFS or CSS. In patients with pN+, extranodal extension (tumour invasion beyond the lymph node capsule) is reported to be an independent predictive factor for poorer CSS.[196]

5.7.2.2.5 Lymphovascular invasion

Lymphovascular invasion is observed in 20–25% of patients with UTUC (4,39,132). Most studies support an independent role of LVI for predicting poor RFS or CSS. These findings appear reasonable, as invasion of cancer cells into blood or lymphatic vessels may be the first step in developing systemic dissemination of cancer cells, which is subsequently followed by tumour recurrence and cancer death.

5.7.2.2.6 Positive surgical margin

Positive surgical margin (PSM) is reportedly found in ~10% of patients with UTUC after RNU.[192,197] This incidence is higher (16.5%) in advanced UTUC (≥pT3 and/or pN+ and/or M+).[139] A multi-institutional study shows that PSM is an independent predictive factor for lower MFS, but not for CSS or RFS.[192] In advanced disease, however, an independent predictive role of PSM has been shown.[139]

5.7.2.2.7 Concomitant carcinoma *in situ* in the upper tract

The incidence of concomitant CIS in the upper tract is about 10–22%.[4,198] Concomitant CIS is seen as an independent predictive factor for high incidence of IVR,[103,164] poor RFS, and poor CSS.[4,198] Even in patients with organ-confined disease (≤pT2N0M0), concomitant CIS is independently associated with worse RFS and CSS.[199]

5.7.2.2.8 Multiplicity (Multifocality)

Multiplicity is an independent predictive factor for IVR, and its predictive role is reported for oncological outcomes. Multifocal tumours, that is tumours located in both the renal pelvis and ureter, have an incidence of 7–17% and are an independent predictive factor for poorer RFS and CSS.[69,184] Multiplicity, that is tumours with two or more loci has an incidence of 23–43%, and is also an independent factor for poorer CSS.[65] The multi-institutional study shows this predictive significance is limited to organ-confined tumours.[129]

5.7.2.2.9 Extensive tumour necrosis

Tumour necrosis is often observed in urothelial carcinoma. Necrosis is considered extensive when the area of necrosis occupies more than 10% of all the tumour lesion. Extensive tumour necrosis is found in 18–27% of UTUC patients and is an independent predictive factor for CSS[128] and MFS.[121,126] This relationship may be attributed to rapid growth of a tumour that has outgrown its blood supply, creating a hypoxic microenvironment and subsequently causing tumour cell death.

5.7.2.2.10 Tumour architecture

As opposed to papillary tumours, sessile architecture is likely to be an independent predictive factor for poor CSS according to multi-institutional studies.[4,63,200] Sessile tumours are found at 23–28% of patients with UTUC. As tumour architecture can be determined by ureteroscopy before surgery, it may help to determine the therapeutic strategy.[201]

5.7.2.2.11 Histological subtype

Urothelial carcinoma frequently involves different histological variants in 20–60% of patients,[82] including squamous cell, adenocarcinoma, small cell, micropapillary, sarcomatoid, lymphoepithelioma-like, and more. When compared with pure UC, the tumours with variant histology appear to be biologically aggressive in UTUC.[203]

Pure squamous cell carcinoma (SCC) can infrequently occur in the upper tract, in about 2%.[204] Survival is much shorter in patients with SCC than in those with UC, but there is no significant difference in CSS between SCC and UC in the same disease stage.[204]

5.7.2.3 Intervention

5.7.2.3.1 Laparoscopic radical nephroureterectomy

Laparoscopic RNU has been widely performed as a minimally invasive surgery. Laparoscopic RNU may be associated with a higher incidence of IVR compared with open RNU.[159] Many studies have compared the oncological outcome of laparoscopic RNU with that of open RNU. Multi-institutional studies with large numbers of patients show equivalent CSS and RFS between laparoscopic and open RNU.[15,18] A meta-analysis also found no surgical inferiority of laparoscopic RNU compared with open RNU.[113] However, a prospective randomized study showed in subset analysis a trend for worse

CSS in laparoscopic RNU in patients with pT3 or high-grade cancers, which was not statistically significant.[12] Thus, one should be aware of the possibility that laparoscopic RNU might result in poorer oncological control in advanced disease.

5.7.2.3.2 Bladder cuff management

One multi-institutional study reports that omitting bladder cuff excision does not influence the oncological outcome of patients with UTUC.[18] However, a population-based study shows that bladder cuff excision was spared in 40% of patients who underwent RNU and was an independent prognostic factor for poorer CSS.[102] This is more prominent in patients with pT3 or higher. Thus, excision of the bladder cuff remains a standard of care for patients who undergo RNU.

The technique of bladder cuff excision includes endoscopic, transvesical, and extravesical approaches. Although there is no difference in CSS among these three approaches,[101] the endoscopic approach is associated with a higher incidence of IVR.[103]

5.7.2.3.3 Diagnostic ureteroscopy

Ureteroscopy is useful in determining the presence of a tumour and in allowing surgeons to perform biopsies to confirm the histology. There has been some concern about the risk for tumour implantation and dissemination of tumour cells during manipulation of the ureteroscope. Ishikawa and colleagues (2010) reported that diagnostic ureteroscopy does not influence IVR and CSS.[205]

5.7.2.3.4 Lymphadenectomy

While most retrospective studies show lymphadenectomy to be an independent factor for improving CSS,[8,9,206] others fail to show any benefit.[79,83] Further studies are required to confirm the therapeutic role of lymphadenectomy.

5.7.2.3.5 Adrenalectomy

There are very few studies addressing the necessity for adrenalectomy during RNU. Huang and colleagues (2009) report that, for patients with localized UTUC, sparing adrenalectomy does not adversely influence RFS and CSS after RNU.[207]

5.7.2.3.6 Peri-operative chemotherapy

Few studies have examined the influence of peri-operative chemotherapy, and its role remains undetermined.[208] In a multi-institutional study of adjuvant chemotherapy, peri-operative chemotherapy did not significantly improve CSS or OS in patients with high-risk UTUC.[138] Another study also failed to show statistical significance of adjuvant chemotherapy in reducing the risk for cancer-specific mortality.[139]

5.7.3 Nomogram

Most nomograms have been proposed to more accurately predict survival after surgery, or probability of cancer death, in each patient. Cha and colleagues (2012) show the nomogram predicting 2- and 5-year RFS and CSS by using age, pT stage, grade, pN stage, LVI, architecture, and concomitant CIS.[4] Yates and colleagues (2012) propose a nomogram predicting 3- and 5-year OS by using age, pT stage, pN stage, and tumour location and grade.[163] Both these models are derived from the results

multi-institutional studies. Jeldres and colleagues (2010) show a nomogram predicting 5-year CSS based on results from the SEER database,[193] including age, pT stage, pN stage and grade. These models have an accuracy of 75–80%. In one of the only studies evaluating preoperative factors, Margulis and colleagues (2010) propose a nomogram =predicting the risk for non-organ confined disease by using tumour location, grade, and architecture.[201] The accuracy of this nomogram is 76% and may help to determine the therapeutic strategy.

5.7.3.1 Biomarkers

Many biomarkers could be used as possible prognostic factors. This section describes the biomarkers that have independent significance by multivariate analyses. However, most of these studies were conducted in single institutes, each looking at particular types of biomarkers. Therefore, a prospective, multi-institutional study is required to validate their significance.

Biomarkers that were associated with poorer oncological outcome include aldehyde dehydrogenase 1 as a putative cancer stem cell–like/tumour-initiating cell marker[209]; higher density of vasohibin-1 as a novel angiogenic molecule[210]; gain of N-cadherin[166]; high expression of cytokeratin 19 fragments Cyfra21-1[211]; elevated Snail as representing epithelial-mesenchymal transition (EMT)[212]; down-expression of parvin-beta as a tumour suppressor gene[213]; increased nuclear phosphorylated AKT[214]; increased Rac1 activity and Pak1 overexpression as metastases related genes (215); increased nuclear expression of nuclear factor-kappaB (NF-kappaB) as a transcription factor involved in carcinogenesis[216]; increased nuclear expression of aryl hydrocarbon receptor as a carcinogenesis marker[217]; increased cytoplasmic prothymosin-alpha expression as a nuclear growth-promoting protein or oncoprotein[218]; increased survivin as an apoptosis-related marker and a high apoptotic index,[219] increased caveolin-1 as an oncogenesis marker,[219] DNA repair gene polymorphisms,[220] loss of uroplakin III as an urothelium-specific marker,[221] loss of E-cadherin as an adhesion molecule,[222] high microsatellite instability indicating mutations or epigenetic alterations in mismatch repair genes,[223] increased hypoxia-inducible factor-1 (HIF-1),[224] weak overexpression of HER2 as a proto-oncogene,[225] co-expression of cyclooxygenase (COX)-2, and the prostaglandin E2 receptors, EP4R as a carcinogenesis factor, positive expression of tissue inhibitor of metalloproteinase (TIMP)-1,[226] and increased sialyl-Lewis A (sLe(a)) related to E-selectin–mediated adhesion of cancer cells.[227]

Conclusion	LOE
Among all reported risk factors, previous history of bladder cancer has consistently been reported to be a risk factor for subsequent intravesical tumour recurrence.	3

5.8 Renal-Sparing Surgery in Localized Upper Tract Urothelial Carcinoma

While the standard therapy for treatment of patients with localized, high-grade, non-invasive UTUC is RNU, conservative management with renal-sparing approaches is considered acceptable in certain cases.[84] Conservative management was initially considered in patients with imperative indications in the hopes of preserving renal function and avoiding hemodialysis following RNU. These indications include patients who would be rendered functionally anephric following RNU (those with solitary kidney, bilateral disease, or severe renal insufficiency). Following demonstration of feasibility and acceptable outcomes of renal-sparing approaches, further studies expanded the indications to selected elective cases in patients with normal contralateral kidneys, with the aim of preserving maximal kidney function.[228–230]

Techniques for renal-sparing management of UTUC depend primarily on tumour size, location, and grade, and include endoscopic treatment or ureterectomy. Endoscopic techniques can be performed via either a trans-urethral retrograde or percutaneous antegrade approach and are generally reserved for stage Ta/T1 and low-grade tumours. Ureterectomy is acceptable for low- and high-grade stage Ta/T1/T2 tumours, as well as CIS. Depending on tumour location, ureterectomy can include just the distal ureter for distal tumours, segmental ureterectomy with primary reanastamosis for mid-ureteral tumours, or total ureterectomy with ileal interposition for upper ureteral tumours.

Patient selection for conservative management of UTUC remains difficult given the inherent issues with accurate pathologic staging and grading via endoscopic techniques. Ureteroscopy should be performed prior to consideration of conservative approaches so that the tumour can be evaluated, and biopsies and cytology must both be obtained to determine the presence of high-grade disease or CIS.[231,232] Accurate clinical staging of UTUC with endoscopic techniques is problematic, as it is generally not possible to obtain deep biopsies to evaluate for muscle invasion. However, higher tumour grade from endoscopic biopsy has been shown to highly correlate with tumour grade (84–91%)[233–235] and stage at time of RNU.[236,237] Therefore, tumour grade can be used as a surrogate for stage and clinical decision making. It is important to note that ureteroscopic appearance does not reliably predict tumour grade in approximately 30% of cases (either low or high grade). Thompson *et al.* (2008) demonstrated that 21% of tumours thought to be low grade on visual inspection were subsequently found to be high grade on pathologic review of the RNU specimen.[230] Initial concerns that diagnostic ureteroscopy may delay RNU and impact subsequent survival have been dispelled, and diagnostic ureteroscopy with biopsy and cytology are imperative prior to consideration of renal-sparing treatment for UTUC[238–240] (LOE 3).

Given the benefits of adjuvant treatment of non-invasive bladder urothelial carcinoma with intravesical chemotherapy and immunotherapy (bacillus Calmette-Guérin [BCG]),[241,242] the concept of intracavitary therapy with these agents as an adjunct to endoscopic management of UTUC has been explored. Challenges include difficulty of access to the upper tract and greater safety concerns

compared to the bladder. Studies have described both antegrade and retrograde techniques, each with its own advantages and disadvantages. Study numbers are small and also need to be considered in the context of inherent limitations of proper staging of UTUC and diagnosis of upper tract–only CIS.[243] Overall, results in patients with Ta/T1 disease have not demonstrated any benefit to adjuvant therapy with respect to recurrence or DSM; however, BCG may have a therapeutic role in patients with CIS[244] (LOE 3).

There is a paucity of high-level data regarding the role of conservative management of UTUC, with the majority of studies providing only LOE 3 and 4.[244] In this review, we will describe the various renal-sparing techniques used for UTUC, including data on adjuvant therapy, with emphasis on RFS and complications.

5.8.1 Renal-sparing techniques

5.8.1.1 Ureterectomy

Upper tract urothelial carcinoma is often multifocal and not amenable to segmental resection. Thus, the traditional treatment for mid-to-proximal ureteral tumours has been RNU. In order to maintain renal function, however, ureterectomy is a feasible option for carefully selected patients with imperative indications. The approach is highly dependent on the location of the tumour and available reconstructive options, with the possibility of distal, segmental, or total ureterectomy. Although conservative management with renal-sparing techniques appears to have similar results compared with RNU, close radiographic and endoscopic surveillance is mandatory. The risk for recurrence in the retained upper tract segment following conservative treatment is 2.7–63%.[245,246] Because tumour recurrences in the upper tract have been observed more than 15 years after treatment of urothelial carcinoma, patients require lifelong follow-up.[247] In patients with a normal contralateral kidney, the risk for recurrence and progression of disease must be tempered with the loss of renal function, particularly in high-grade disease. In general, it appears that ureteral resection is a safe alternative to radical RNU for low-grade, low-stage tumours and in select cases with higher-grade, invasive tumours (LOE 3).

5.8.1.1.1 Distal ureterectomy

Tumours located in the distal ureter that are not amenable to endoscopic management can be treated with segmental resection of the distal ureter with an appropriate bladder cuff and ureteroneocystostomy. While this approach is generally advocated only for low- and intermediate-grade tumours, several authors have described acceptable results in higher grade and higher stage tumours.[248] Simonato *et al.* (2012) reported on long-term outcomes of 73 patients with distal UTUC treated by distal ureterectomy with different methods of reconstruction, including psoas hitch (52%), end-to-end anastomosis (28.8%), direct ureteroneocystomomies (15.1%), and Boari flap reconstruction (4.1%).[246] Different stages were represented in this study, including 42.5% pTa, 31.5% pT1, 17.8% pT2, and 8.2% pT3, as well as both low- and high-grade (41.1%) tumours. With a median follow-up of 87 months, the investigators noted an overall 5-year bladder RFS rate of 82.2% and CSS rate of 94.1%. When stratified by stage, CSS was worse with increasing stage, with no patients with pTa disease dying from disease and CSS rates of 77.8% in pT2 tumours (at 77 months) and 75% in pT3 tumours (at 70 months). Additionally, higher-grade disease was only noted to have a significant impact on worsening survival in pT1 but not pTa patients.[246]

Distal ureterectomy can be performed with an open or laparoscopic approach, or a combination. A lower midline or Gibson incision provides excellent exposure to the distal ureter and bladder for distal ureterectomy and bladder cuff excision. Laparoscopic and robotic-assisted distal ureterectomy with psoas hitch reimplantation have been described but generally lack adequate number of patients or follow-up.[249–252] Operative times were long, averaging 252–268 minutes, and complications, including anastomotic strictures and port-site recurrences, have been described and remain a concern.[251,253] As local recurrence due to residual tumour is a devastating and often not salvageable complication, meticulous attention is mandatory to ensure that there is absolutely no tumour spillage, regardless of the approach used.

The ureter is generally reimplanted at the dome of the bladder. However, if a significant portion of the distal ureter is removed and additional length is required, the bladder can be mobilized and a psoas hitch can be performed. The choice of a refluxing versus non-refluxing anastomosis is generally left to the discretion of the surgeon, given the lack of evidence to guide the urologist either way. While a non-refluxing anastomosis may theoretically limit infection and seeding of the tumour to the upper tract, stricture rates may be higher, and endoscopic surveillance may be more difficult (LOE 4).

5.8.1.1.2 Segmental ureterectomy

In rare instances, a tumour involves the mid portion of the ureter without distal or proximal involvement. Low-grade tumours and focal high-grade tumours may be treated with segmental resection and primary anastomosis, although this approach has to take into account the high probability for recurrence. The appendix has also been used as a ureteral substitution to bridge significant gaps.[254] Patients undergoing segmental resection require careful endoscopic surveillance as well as cross-sectional imaging in cases of high-grade tumours. Given the paucity of cases, there are few studies on the long-term oncological outcomes of segmental resection.

Using a large multi-institutional database, Colin *et al.* (2012) retrospectively compared CSS in 52 patients who underwent segmental ureterectomy with 416 patients who had RNU.[245] With a median follow-up of 26 months, the 5-year CSS and RFS rates were similar at 87.9% and 37%, respectively, following segmental ureterectomy compared with 86.3% and 47.9%, respectively, for RNU.[245] Jeldres *et al.* (2010) compared DSM in patients who underwent segmental ureterectomy with RNU for UTUC using the SEER database.[255] From a total of 2,044 patients with T1–T4 ureteral carcinoma, 569 (27.8%) underwent segmental ureterectomy compared with 1,222 (59.8%) who had RNU with bladder cuff removal and 253 (12.4%) who underwent RNU without bladder cuff removal. The 5-year DSM rate was similar among the three groups (86.6%, 82.2%, and 80.5%, respectively). Multivariate analysis showed no significant effect of the type of surgery on cancer outcomes. Based on these results, the authors suggested that essentially all patients (including those with advanced T stage) should be considered for segmental resection. However, this study suffers from major selection bias and possible inconsistencies with such claims-based data.[255] In a similar study, the same authors tested the effects of T stage and nodal status on CSM while adjusting for tumour grade, age, gender, primary tumour location, and type and year of surgery. In multivariable analyses, the pathologic T and N stages were independently associated with outcome, and the authors found that neither tumour location nor type of surgery was an independent prognostic factor.[62] Although there

is significant selection bias in these studies, it appears that oncological outcomes following conservative management of ureteral tumours with segmental resection are comparable to RNU, at least in the short term (LOE 3).

5.8.1.1.3 Total ureterectomy

Urothelial carcinoma infrequently involves the proximal segment of the ureter without renal calyceal involvement. Although RNU still remains the gold standard for management of such tumours, imperative indications or a large-volume, low-grade tumour may necessitate renal-sparing approaches. It is important that a thorough endoscopic evaluation of the kidney is performed to rule out the presence of any tumour within the collecting system. In cases of subtotal ureterectomy, a Boari flap may be used from the anterior bladder wall to reach the proximal ureter. However, in most cases, a bladder flap will not reach the ureteropelvic junction, and in this instance, an ileal ureteral substitution is necessary. In the presence of preexisting renal dysfunction, the segment of ileum can be tapered and a psoas hitch performed to minimize sequelae from urinary reabsorption through bowel mucosa. Renal autotransplantation to the iliac vessels following total ureterectomy has also been described, although this should only be considered as a last resort given the potential for loss of the kidney.[256]

5.8.1.2 Endoscopic management

The principles of endoscopic management include access to the tumour via either an antegrade or retrograde approach and ablation of the tumour with electrocautery, holmium:YAG, or neodymium:YAG lasers. The benefits of the retrograde approach include maintaining a closed urinary system and less morbidity than the antegrade approach. With the advent of better-deflecting, high-definition, flexible ureteroscopes that improve visualization, the retrograde approach is favoured, except in specific cases. Generally, a flexible ureteroscope is used in order to perform both complete pyeloscopy and ureteroscopy to rule out tumours in the renal calyces. However, rigid ureteroscopy can be used to perform ablation in distal tumours. In cases of larger tumours, lesions in the lower renal calyces not accessible by retrograde ureteroscopy and in patients with urinary diversions creating difficult retrograde access, an antegrade approach may be more feasible, as larger instruments can be used, and direct access to the affected calyx can be achieved.

The majority of studies regarding endoscopic management for UTUC are small case studies (LOE 4) or comparative studies unmatched for tumour stage (LOE 3).[244] These studies are summarized in **Table 5-2** and include important outcomes, such as upper tract recurrence, and rates of RNU and DSM. Assessment of these outcomes is complicated, as most of the studies do not stratify by stage or grade, both of which are known to affect outcomes.

TABLE 5-2 Endoscopic management of UTUC

Reference	N (RUs)	Biopsy confirm, n (%), [HG]	Follow-up, months	UT recurrence, n (%)	RNU, n (%)	DSM, n (%)	Complications, n (%)
Ureteroscopic							
Gaboardi *et al.*[257]	18	18 (100) [0]	Mean: 15	8 (50)	1 (6)	0	Sepsis 2 (11)
*Chen & Bagley[228]	23	23 (100) [1]	Mean: 35	15 (65)	4 (17)	0	Strictures 2 (8.7)
*Elliot *et al.*[258]	21	12 (57) [2]	Mean: 73	8 (38)	5 (24)	0	Strictures 0
Daneshmand *et al.*[236]	30	27 (90) [14]	Median: 31	27 (90)	4 (13)	1 (3)	Strictures 5 (17)
Matsuoka *et al.*[259]	27 (30)	21 (70) [0]	Median: 33	7 (26)	–	3 (11)	Stricture 1 (4)
+‡Roupret *et al.*[260]	27	27 (100) [8]	Median: 51.5	4 (15)	7 (26)	19	Ureteral perforation 2 (7)
Sowter *et al.*[261]	40 (41) [37#, 2@, 2$)	35 (85) [4]	Mean: 42	30 (74)	12 (30)	–	
*Thompson *et al.*[230]	83 [76#, 7@]	40 (48) [8]	Median: 55	46 (55)	27 (33)	9 (11)	–
+‡Lucas *et al.*[262]	39 (41)	39 (100) [12]	Median: 33	17 (46)	11 (28)	LG (14), HG (33)	–
Cornu *et al.*[263]	35	22 (63) [6]	Median: 30	21 (60)	4 (11)	0	Sepsis 3 (9)
Tada *et al.*[264]	15	15 (100) [3]	Median: 25	5 (33)	3 (20)	0	Pseudoaneurysm 1 (7)
+Fajkovic *et al.*[265]	20	17 (85) [3]	Mean: 20.4	5 (25)	0	1 (5)	–
+‡Grasso *et al.*[266]	80	80 (100) [14]	Mean: 38.2	LG 51 (77), HG 14 (100)	LG 11 (17), HG 4 (29)	LG 8 (12.1), HG 12	–
+‡Cutress *et al.*[267]	73 [10$]	59 (81) [6]	Median: 54	50 (69)	14 (19)	7 (10)	Stricture 12 (16%)#, 1 ureteral perforation#, 1 RNU for hemorrhage@
Percutaneous							
Clark *et al.*[268]	17 (18)	18 (100) [4]	Mean: 24	6 (33)	2 (12)	3 (18)	Transfusion 2 (12)
+Lee *et al.*[269]	50	49 (98) [13]	Mean: 46.6	6 (12)	–	4 (8)	–
Goel *et al.*[270]	20	20 (100) [5]	Mean: 64	13 (66)	10 (50)	5 (25)	2 RNUs

DSM: disease-specific mortality; HG: high grade; LG: low grade; RNU: radical nephroureterectomy; RUs: renal units; UT: upper tract; UTUC: upper tract urothelial carcinoma.
*Pure elective indications; +Compared with RNU; ‡Stratified by grade.
#: URS, @: PCN, $: Combined.

continued **on page 234**

TABLE 5-2 Endoscopic management of UTUC, *Cont'd*

Reference	N (RUs)	Biopsy confirm, n (%), [HG]	Follow-up, months	UT recurrence, n (%)	RNU, n (%)	DSM, n (%)	Complications, n (%)
Palou *et al.*[271]	34	33 (97) [5]	Mean: 51	14 (44)	9 (26)	2 (6)	1 (3) RNU for hemorrhage, 1 (3) stricture
Roupret *et al.*[272]	24	24 (100) [7]	Median: 62	4 (17)	5 (21)	4 (17)	3 (12.5) transfusion, 1 (4) colon perforation
Rastinehad *et al.*[273]	82 (89)	89 (100) [39]	Mean: 61	30 (33)	12 (13.5)	–	–
Combination Ureteroscopy and Percutaneous							
Martinez–Pineiro *et al.*[274]	54 (59) [39#, 20@]	55 (93)	Mean: 31	10 (17)	6 (11)	2 (4%)	–
Deligne *et al.*[275]	61	61 (100) [8]	Mean: 40	15 (25)	11 (18)	8/55 (15)	–
Suh *et al.*[237]	27 [13#, 14@]	27 (100) [8]	Median: 21	23 (85)	7 (26)	–	1 transfusion@, 1 pneumothorax@, 2 strictures#
Krambeck *et al.*[276]	37 (26#, 8@, 3$]	22 (59) [7]	Median: 32	23 (62)	11 (30)	11 (30)	5 (14) strictures, 1 transfusion, 1 RNU for hemorrhage
+Gadzinski *et al.*[177]	33 (34)	34 (100) [8]	Mean: 58	27 (84)	12 (35)	LG (6), HG (25)	–
+Raymundo *et al.*[277]	21	20 (95) [6]	Mean: 18	13 (62)	–	1 (5)	–

DSM: disease-specific mortality; HG: high grade; LG: low grade; RNU: radical nephroureterectomy; RUs: renal units; UT: upper tract; UTUC: upper tract urothelial carcinoma.
*Pure elective indications; +Compared with RNU; ‡Stratified by grade.
#: URS, @: PCN, $: Combined.

5.8.1.2.1 Ureteroscopy

Ureteroscopic treatment for UTUC is usually performed at the time of initial biopsy if the tumour is thought to be small enough to be completely ablated. Laser ablation is preferred to electrocautery, and the use of baskets and graspers can also facilitate resection.

Evaluation of DSM reveals rates ranging from 3–33% for studies including high- and low-grade disease. A study by Lucas *et al.* (2008) reviewed outcomes of ureteroscopic treatment versus immediate RNU stratified by low- and high-grade disease.[262] Of the 48 patients with low-grade disease, 27 (56%) were managed with ureteroscopy and 21 (44%) with immediate RNU. No difference was found in the 5-year DSS rate (86.2% vs. 87.4%, respectively).[262] These findings were supported by other studies that stratified patients by grade, with no significant difference in DSS between low-grade patients and patients treated with immediate RNU.[177,260,266,267] Conclusions relating to high-grade tumours are limited given the low number of patients treated with ureteroscopic ablation, but generally, patients with high-grade UTUC did poorly. On multivariate analysis, only grade and BMI were predictors for DSM[177,260,267] (LOE 3).

Rates of upper tract recurrence range from 15–90% in studies not stratified by grade, although they appear to be higher in studies containing more high-grade patients. This was supported by both the Grasso *et al.* (2012) study, which demonstrated recurrence rates of 77% in low-grade tumours and 100% in high-grade tumours,[266] and by Cutress *et al.* (2012), with grade-related 5-year RFS rates of 63%, 34%, and 17% in G1, G2, and G3, respectively (p=0.011).[267] This raises the important point that recurrence rates, even in low-grade tumours, are extremely high, and that lifelong, close, active surveillance of these patients is mandatory if such renal-sparing approaches are pursued. Predictors for upper tract recurrence include higher grade, larger tumour size, location in the renal pelvis, multifocal tumours, and history of prior bladder tumours[232,237,275,278] (LOE 3).

The need for eventual RNU in patients managed conservatively for either progression of stage, grade, or other reasons ranges from 0–28% in studies not stratified by grade. When stratified by grade, Grasso *et al.* (2012) found that there is a higher rate for RNU for high- rather than low-grade tumours (25% vs. 17%).[266] Cutress *et al.* (2012) demonstrated 5-year renal unit survival rates of 96%, 71%, and 20% in G1, G2, and G3, respectively (p<0.001).[267] Generally, a renal preservation rate of 70–90% can be achieved with ureteroscopic management of UTUC, particularly in low-grade tumours. Patients requiring RNU following attempted ureteroscopic management do not appear to do worse than patients who underwent upfront RNU with regard to subsequent stage at RNU or DSS[240,279] (LOE 3).

Complications related to ureteroscopy primarily include distal ureteral strictures, with rates up to 17% of cases, sepsis in up to 11%, and ureteral perforation in up to 9%. Care must be taken during ablation with electrocautery or lasers to prevent perforation of the ureter, as the thickness is less than that of the bladder, thus requiring good visualization during active ablation. This leads to an inherent difficulty in achieving complete ablation of UTUC endoscopically, with the potential of leaving residual tumour behind, and thereby possibly resulting in the observed high rates for recurrence.[243]

5.8.1.2.2 Percutaneous nephroscopy

Percutaneous management of UTUC is helpful for larger tumours in the renal calyces, as larger instruments can be used, and direct access into a particular renal calyx is possible. Also, in patients with urinary diversions or when access in a retrograde fashion is not possible, antegrade access is beneficial.

As seen in **Table 5-2**, although the majority of patients treated with an exclusive antegrade approach are low grade, there are differential rates of high-grade tumours in these studies. As results are generally not stratified by grade, any inferences should be made cautiously. Rates of DSM range from 6–25% in studies not stratified by grade. Recurrence rates in the upper urinary tract range from 12–66% with Lee *et al.* (1999) demonstrating higher rates in high- versus low-grade disease (31% vs. 5%).[269] The most recent and largest study by Rastinehad *et al.* (2009) consisted of 89 renal units treated by percutaneous nephroscopy (PCN), of which 39 were high grade.[273] They routinely performed a second-look nephroscopy within 1 week, with re-resection if necessary, and a third-look nephroscopy at 3 months to re-evaluate for recurrence. They found a recurrence rate of 33% with a higher rate in high- (38%) than low-grade (30%) disease.[273] Subsequent need for RNU for progression is higher than in ureteroscopy and has been reported in 12–50% of cases. This may be due to the tumours being bulkier and located in the renal pelvis, thereby recurring more frequently, as well as from complications of PCN such as bleeding needing RNU.

Complications following percutaneous management for UTUC include up to a 5% chance of RNU, 13% rate of blood transfusions for hemorrhage, and a <5% chance of stricture formation. Additionally, there have been some rare case reports of tumour seeding of the percutaneous nephrostomy tract, but this is considered very rare and is not a primary concern.[273,280,281]

5.8.1.3 Adjuvant therapy

Intracavitary instillation of different chemotherapeutic agents (mitomycin C and thiotepa) or BCG (with and without interferon-alpha2B) following endoscopic resection of UTUC have been studied as adjuvant therapy in an attempt to decrease recurrence and progression.[244,282] Complications that may arise from BCG instillation include BCGosis, sepsis, fevers, and irritative voiding symptoms. Instillation should be performed 2 weeks following resection or biopsy to ensure the urothelium has healed. Topical mitomycin C is fairly well tolerated, but care should be taken by the provider to follow proper safety precautions for instillation and discarding the waste.

5.8.1.4 Techniques

The route of administration can either be antegrade or retrograde, and depends partly on the type of endoscopic resection that was performed and convenience, as no method has been demonstrated as superior. Considerations should be given to the dwell time and contact of the adjuvant therapy with the tumour. Bacillus Calmette-Guérin is given once weekly for a 6-week course, while mitomycin C is given once at the time of resection.

5.8.1.4.1 Antegrade

The antegrade approach is performed by placement of a percutaneous pigtail catheter into the renal pelvis. This can either be placed *de novo* or following percutaneous resection and left capped. If the resection was via a percutaneous approach, then this seems most appropriate, as the tract already exists. However, some proponents prefer this approach even if ureteroscopic resection was performed, as they feel there is better contact of the tumour with the adjuvant agent.[283] Criticism of this approach includes the notion of tumour seeding of the tract following percutaneous resection, which was noted in 1 case of 133 in a study by Rastinehad *et al.* (2009).[273,280,281] As the incidence is still very low and is more likely to occur in high-grade tumours that should not be treated with this approach, it remains an acceptable option (LOE 4).

Prior to each instillation, an antegrade nephrostogram should be performed under fluoroscopy, with the patient in the supine position to ensure that there is unobstructed flow from the pelvis into the bladder without pyelovenous or pyelolymphatic backflow. In a protocol by Thalman *et al.* (2002), 360 mg of BCG Pasteur or 243 mg of Immucyst is dissolved in 150 mL of normal saline, placed 20 cm above the kidney, and connected to the nephrostomy tube. Instillation is performed at a continuous rate of approximately 1 mL/minute for 2 hours.[284] Following each instillation, repeated weekly for 6 weeks in the case of BCG, the nephrostomy tube is capped and the patient is observed overnight and discharged with the nephrostomy tube in place until treatment is completed.

5.8.1.4.2 Retrograde

The retrograde approach can be performed in several ways, including creating artificial vesicoureteral reflux with instillation of agent into the bladder or placing an open-ended ureteral catheter into the renal pelvis with instillation through the ureteral catheter.

Vesicoureteral reflex can be created by placement of a double-j ureteral stent or performing bilateral ureteral meatotomies. This approach has the advantage of allowing treatment via simple placement of a urethral catheter and instillation of agent into the bladder with subsequent reflux into the renal calyces.[273,285] Prior to each instillation, with the patient in the Trendelenburg position, a cystogram should be performed and the volume necessary to generate reflux should be recorded; this may range from 80–250 mL or no reflux may occur at all in up to 41% of cases with stents.[285] For the instillation, BCG is then diluted with enough normal saline to the volume at which reflux occurs to constitute a final concentration of 1–2 mg/mL. With the patient in the Trendelenburg position, the solution is instilled into the bladder through a catheter and left for a dwell time of 15–30 minutes, then voided out 30 minutes to 2 hours afterwards.[285]

An open-ended ureteral catheter can be placed by flexible cystoscopy prior to each instillation.[286] As in the antegrade approach, BCG is diluted and instillation is performed under 20 cm H_20 gravity. It is helpful to measure and record ureteral length at the time of ureteroscopic resection, if performed, to ensure that the ureteral stent reaches into the renal calyces.[282] Concerns with this approach include inadequate exposure of the tumour to the agent, possible obstruction and subsequent pyelovenous backflow, and urothelial trauma during placement.

5.8.1.5 Outcomes

Given the different biology of Ta/T1 disease and CIS, these patients should be viewed differently. Results of studies with more than 10 renal units are summarized in **Table 5-3**.

TABLE 5-3 Incavitary treatment of UTUC with BCG or Mitomycin C

Reference	N (RUs)	HG	Follow-up, months	Type of treatment	Route of instillation/ Endoscopic treatment	UT recurrence, n (%)	RNU, n (%)	DSM, n (%)
Ta/T1								
Martinez–Pineiro *et al.*[274]	(25)	–	Mean: 31	Mitomycin C (14) BCG (11)	Anterograde or Retrograde/ URS or PCN	Mitomycin C (14) BCG (12.5)	–	–
Patel & Fuchs[287]	13 (16)	0	Mean: 15	BCG	Retrograde/ URS	2 (13)	2 (13)	0
Clark *et al.*[268]	17 (18)	4	Mean: 11	BCG	Anterograde/ PCN	6 (33)	2 (12)	3 (18)
*Katz *et al.*[286]	10 (11)	7	Mean: 51	BCG	Retrograde/ URS	–	–	–
+Rastinehad *et al.*[273]	(50)	39	Mean: 61	BCG	Anterograde/ PCN	18 (36)	9 (50)	–
Giannarini *et al.*[288]	(22)	–	Median: 42	BCG	Anterograde/ –	13 (59)	5 (23)	5 (23)
+Cutress *et al.*[267]	18	–	Median: 54	Mitomycin	Anterograde or Retrograde/ URS or PCN	(46)	–	–
CIS						**PR, n (%)**	**Recurrence, n (%)**	**DSM, n**
Sharpe *et al.*[289]	11 (17)		Median: 36	BCG	Retrograde	13 (76)	2 (18)	1
Nonomura *et al.*[290]	9 (11)		NR	BCG	Retrograde	6 (82)	2 (22)	1
Okubo *et al.*[291]	11 (14)		18–82	BCG	Retrograde	9 (64)	5 (45)	1
Irie *et al.*[285]	9 (13)		36	BCG	Retrograde	13 (100)	1 (11)	0
Miyake *et al.*[292]	16 (16)		30	BCG	Anterograde or Retrograde	13 (81)	3 (19)	0
Hayashida *et al.*[293]	10 (11)		51	BCG	Anterograde or Retrograde	11 (100)	5 (50)	4
+Kojima *et al.*[294]	11		Median: 58.3	BCG	Retrograde	9 (82)	3 (27)	1
Giannarini *et al.*[288]	(42)		42	BCG	Anterograde	–	17 (40)	–
*Shapiro *et al.*[295]	11 (11)		Median: 13.5	BCG	Retrograde	10 (91)	1 (9)	0

BCG: *Bacillus Calmette-Guérin;* DSM: disease-specific mortality; HG: high grade; NR: no response; PCN: percutaneous nephroscopy; PR: positive response; RNU: radical nephroureterectomy; *R*Us: renal units; UT: upper tract; UTUC: upper tract urothelial carcinoma.
*With IFN-alpha2B.
+Compared with control.

5.8.1.5.1 Ta/T1

In patients with endoscopically resected Ta/T1, there have been several small case reports demonstrating the feasibility and outcomes of instillation of adjuvant intracavitary therapy. Only two studies contained control arms, and they failed to show any difference between adjuvant and no adjuvant

therapy.[267,295] Cutress *et al.* (2012) compared 18 patients treated with mitomycin C at the time of resection (administered either antegradely or retrogradely, depending on resection technique) with 55 patients who received no adjuvant therapy. They observed no difference in estimated 5-year RFS rates (53.8% vs. 54.2%, respectively).[267] In a study by Rastinehad *et al.* (2009) with patients with low- and high-grade UTUC treated with PCN, 50 patients receiving a 6-week course of BCG were compared with 39 patients with no adjuvant therapy, and no difference was noted in recurrence when stratified by stage and grade.[296] Although study numbers are small, there does not appear to be a significant role for adjuvant therapy with mitomycin C or BCG in patients with Ta/T1 disease, and no evidence for CIS, in preventing recurrence or progression (LOE 4). This may be due to inherent differences in the biology of UTUC to bladder cancer or possibly due to incomplete resection of UTUC endoscopically, thereby leaving residual tumour behind and negating possible benefits of adjuvant therapy.

5.8.1.5.2 Carcinoma in situ

Diagnosis of CIS in the upper tract without involvement of the bladder is difficult, as one is usually relying on selective ureteral cytologies that can be contaminated by the bladder, or, more rarely, on biopsies that are positive in the upper tract with negative random biopsies of the bladder. Therefore, ruling out concomitant bladder CIS is not truly possible in many cases. Additionally, subsequent follow-up for determination of recurrence is plagued by these same issues, and true response rates may not be accurate. Regardless, studies evaluating the role of BCG in patients with exclusive CIS of the upper tract have been carried out, although the numbers are too small to make definitive conclusions and there was only one study comparing outcomes with controls.

As seen in **Table 5-3**, positive response rates (negative follow-up cytology) to a 6-week course of BCG were noted to be 64–100%, with subsequent rates of recurrence noted in 9–50% of patients. A study by Kojima *et al.* (2006) with patients with pure CIS of the upper tract compared 11 patients treated with BCG with 5 patients treated with immediate RNU and found no difference in the 5-year RFS rate (78% vs. 67%) or the 5-year DSS rate (91 vs. 80%).[295] Again, while BCG may have a role in patients with CIS of the upper tract, it is difficult to truly distinguish between pure upper tract and possible concomitant bladder CIS. Therefore, these results may just demonstrate the known effect of BCG on bladder CIS; however, the good response rates still support its use in either case (LOE 3).

5.8.2 Follow-up/surveillance

Given the extremely high rates for recurrence and progression requiring further therapy for UTUC, renal-sparing surgery should only be offered if the physician and patient are committed to a regimented follow-up and lifelong surveillance protocol. Generally, surveillance consists of cystoscopy for bladder recurrence, ureteroscopy and upper tract imaging (retrograde or excretory pyelography, computed tomography [CT], or magnetic resonance imaging [MRI]) for upper tract recurrence, and cytology for CIS and lesions possibly missed visually. After nephroscopic resection, Rastinehad *et al.* (2009) routinely performed second-look nephroscopy within 1 week, while other studies either never did or did it only if there was concern that initial resection may not have been sufficient.[270,271,273] We recommend that second-look nephroscopy or ureteroscopy be performed within 2 weeks in cases where inadequate resection is suspected.

Our recommendations for surveillance of endoscopically treated UTUC are cystoscopy and cytology every 3 months for the first year, then every 6 months for the next 2 years and annually thereafter; upper tract imaging (retrograde pyelography, CT, or MRI) every 6 months for the first 2 years then annually thereafter; and ureteroscopy at 3 and 6 months, then every 6 months for the next 1.5 years and annually thereafter (LOE 4).

5.8.3 Conclusion

Renal-sparing approaches for the management of UTUC are an acceptable alternative to RNU in select patients. Low-grade, stage Ta/T1 tumours of the renal pelvis or calyces can be managed endoscopically with ureteroscopy or with PCN in the case of bulky tumours or those that cannot be accessed retrogradely. Low-grade, stage Ta/T1 tumours in the ureter can be managed with ureteroscopy or with segmental ureterectomy, particularly if tumours are more distal and bulky. Distal ureteral tumours that are high grade or invasive can also be successfully managed with segmental ureterectomy. Patients with imperative reasons (solitary kidney, bilateral UTUC, or renal insufficiency), who have high-grade tumours within the renal pelvis or calyces and would be delegated to hemodialysis following RNU, can potentially be managed endoscopically. However, there is little evidence that this is successful and very close surveillance should be performed. While patients with pure or concomitant CIS of the upper tract can be treated with adjuvant intracavitary instillation of BCG, as of now there does not appear to be a role for adjuvant therapy in Ta/T1 disease.

Vigilant follow-up and surveillance for recurrence and possible progression of UTUC is crucial if planning to utilize renal-sparing approaches. The rate for recurrence is very high in these patients, both in the upper tract and in the bladder. Subsequent recurrences can be managed with endoscopic resection if there is no evidence for progression. However, should progression from low- to high-grade disease or muscle invasion occur or be suspected, then conservative management should be aborted and the patient should undergo RNU. A delay to RNU has not been shown to result in worse survival if appropriate surveillance is performed.

Renal-sparing surgery may afford patients reduced morbidity over RNU and is a reasonable treatment approach, particularly in patients with low-grade, low-stage disease who are motivated to adhere to lifelong surveillance.

Recommendations	LOE	GOR
1. Diagnostic ureteropyloscopy with biopsy/cytology and cross-sectional imaging with contrast prior to consideration of renal-sparing treatment of UTUC.	3	B
2. Renal-sparing surgery for manageable, low-grade tumours of any segment of the ureter as an alternative to RNU for patients with imperative or elective indications.	3	B
3. Endoscopic management for manageable, low-grade tumours of the renal pelvis or calyces as an alternative to RNU in patients with imperative or elective indications.	3	B
4. Renal-sparing surgery with distal or segmental ureterectomy of high-grade and/or clinically invasive tumours of mid-to-distal ureter as an alternative to RNU for patients with imperative or elective indications.	4	C
5. Endoscopic management of high-grade tumours in the renal pelvis or calyces may be considered for patients in the presence of symptoms and/or if complete eradication of tumour is deemed technically feasible as an alternative to RNU.	4	C
6. Bacillus Calmette-Guérin therapy may be considered for patients with CIS only or concomitant CIS of the upper tract.	3	B
7. Vigilant follow-up and surveillance for recurrence and progression of disease after renal-sparing treatment for UTUC.	3	B

5.9 Role of Salvage Surgery After Kidney-Sparing Approach in Upper Tract Urothelial Carcinoma

Conceptually, salvage treatment is known as *"any other treatment given after no response to the primary treatment or when relapse."* It can be considered as a final attempt to cure the disease. A more extensive definition includes any therapy indicated when the individual cannot tolerate other available therapies for a particular condition.[297] Salvage treatment may consist in surgery, systemic chemotherapy, or local radiation. In general, salvage therapy has more adverse effects than primary therapy, whether it is applied by means of surgery or by systemic drug administration.

The diverse primary modalities of kidney-sparing surgery (KSS) in UTUC include endoscopic procedures: ureterorenoscopy (URS) or percutaneous approach and open surgery, the latter consisting mainly in segmental ureterectomy (SU). Open partial pyelectomy or partial nephrectomy with urinary tract resection and ureterectomy and autotrasplantation represent a small amount of open KSS for UTUC.

The main guidelines on UTUC indicate the opportunity for elective KSS treatment in the presence of normal contralateral kidney and low-risk tumours (low grade/low stage, smaller than 1 cm, and without concurrent CIS).[84,298] Selective KSS is indicated in the presence of low-risk tumour in a solitary kidney or in case of high-risk tumour when comorbid conditions preclude other types of surgery or when dialysis is to be avoided.[84,298] Segmental resection is indicated for low- and high-risk tumours of the distal ureter in the European Guidelines[84,255] and for low-grade mid-ureter and distal-ureter lesions in the National Comprehensive Cancer Network (NCCN) Guidelines.[298]

Epidemiological studies show that in UTUC, the rates for KSS vary widely among countries and regions, and are subjected to local practices. Overall, KSS accounts for 11.3–21% of all surgical procedures for UTUC.[62,299,300] The rate of endoscopic management varies from 1.3% to 69%,[299,301–303] although the proportion performed with diagnostic purposes or in a curative setting remains unclear. An increasing trend[299,303] in endoscopic procedures has been observed in the last decade: a recent population-based study shows that up to 28% of the ureter tumours are treated by SU.[255]

The three key considerations for salvage therapy after UTUC KSS are: indications, type of treatment, and timing of salvage surgery.

5.9.1 Indications for salvage therapy after kidney-sparing surgery

When assessing the role of salvage therapy after KSS in UTUC, the clinical factors that modulate the primary indication for KSS are of outmost importance. Salvage therapy can only be properly framed after elective KSS mode. Any factor that prevented primary radical surgery in high-grade/risk tumour will subsequently interfere in the indication or pursuit of salvage surgery. Selective KSS treatment is indicated in anatomical or functional solitary kidneys, when there is a risk for renal failure or a high comorbidity load, and in general when the disadvantages of renal replacement supersede the oncological advantages of nephroureterectomy. In this setting, high-risk tumours may be subsequently salvaged by surgery, but the same conditions that precluded a radical surgery in first instance will generally prevail in case of recurrence.

Salvage surgery after elective KSS is indicated in the case of tumour progression, from low to high risk, or in the case of high-volume, low-risk recurrence not suitable to control by ulterior KSS.[84] In high-risk tumours, any local recurrence should mandate salvage surgery. A patient's condition and mode of treatment type (selective vs. elective) will ultimately determine the opportunity for salvage surgery. Before proceeding with salvage surgery, nodal status and the presence of metastasis should be assessed. In the case of advanced local disease, the same sequence and protocol for treatment as for primary radical treatment will be applied.

For the purposes of this review, only ipsilateral progression necessitating subsequent surgery or other treatment after an initial attempt of KSS will be considered. Development of a contralateral tumour with its surgical/medical implications will not be considered as salvage therapy.

An important concept to be retained is that the rates of secondary nephroureterectomy (NU) after KSS include not only salvage surgery due to tumour recurrence or progression, but also the small percentage of renal units that require secondary surgery, either because of the impossibility to completely treat the tumour endoscopically or for reasons other than oncological ones (e.g. development of hydronephrosis, terminal kidney, or the patient's or physician's desire).[240,304] Conversely, although salvage treatment may be indicated, it might not be pursued in those cases where renal replacement is not an option. Consequently, when critically analyzing the literature in UTUC, the respective rates for recurrence, progression, and salvage surgery are not necessarily coincidental.

5.9.2 Difficulty in extracting data on the literature/level of evidence

Overall, the observational series on KSS for UTUC appropriately describe the rates for local recurrence and progression, although the rates for secondary and salvage surgery are not systematically reported.

However, multiple limitations hinder a meaningful analysis in terms of indications and results of salvage surgery after nephron-sparing surgery. The relatively abundant information on UTUC KSS is mainly based on retrospective observational or non-matched case-control series, with small and heterogeneous sample sizes and limited follow-up.[11,244] Furthermore, distinctions between elective and imperative indication for primary surgery are not always clear. Pathological stage is subject to biopsy limitations, it is not otherwise systematically performed in endoscopy series, and there are no uniform criteria to proceed with salvage surgery. There is no randomized control trial on the subject, and the Level of Evidence is 3b–4 for all studies, with the exception of two systematic reviews on cohort studies without information on heterogeneity (2B /3A).[11,244] The type of salvage treatment consists almost exclusively of surgery, and specific outcomes are not described. In fact, these limitations respond to the low prevalence of the condition and the restrictive character of the KSS for UTUC. The known difficulties on establishing accurate staging based on endoscopic biopsy grade and cytology introduce additional bias in the form of endoscopic understaging.[305–308]

5.9.3 Ipsilateral recurrence and progression after conservative management

5.9.3.1 After endoscopic management

A systematic review compiled data on recurrence and progression after endoscopic treatment for UTUC.[244] The 33 studies included 22 on URS (including a few cases with the percutaneous approach) and 11 on pure percutaneous management, with a cohort size of at least 10 patients. The authors emphasized that a systematic biopsy verification on grade and pathology was lacking, and that follow-up was limited to a mean of 3 years in most of the series. There was a selection bias favouring endoscopic treatment in low-grade tumours. Furthermore, distinction between elective and compelling or mandatory treatment was not clear in some series.

The pooled analysis of the URS series showed a recurrence rate in the upper urinary tract of 53% (range: 15–90%). The pooled rate for local progression for those series that described it was 15% (range: 0–21%), and the rate for metastatic progression 9% (range: 7–30%).[230,236,257,260,262,263,267,276,278,302,309–313] Secondary NU, including a few partial pyelectomies or PNs, was described in 20 of the series, for a pooled rate of 19% (range: 0–33%).[244] Similar pooled results were described for the 11 series on percutaneous treatment. In this case, overall recurrence in the upper urinary tract was 37% (range: 10–65%); progression rate 17% (0–33%), including metastatic sites[237,268,270,272,273,314–316]; and NU rate 22% (range: 10–50%).[244] More recent literature not included in the systematic review shows similar variability in the outcomes.[264,266,279,317,318] Progression in grade was noted in 15.2% of the 66 low-grade lesions, with negative cytology treated by elective URS in the study of Grasso *et al.*,[266] and in 43% of the 7 low-grade lesions treated by Gadzinski *et al.*[279] Mean/median time to progression in low-grade tumours varies from 13 to 38.5 months (range: 4.6–115 months).[266,319] Salvage NU was performed in 16.7% of the patients in the low-grade group, including some NU because of reasons other than progression. All the patients with high-grade lesions treated in a palliative manner recurred, with 4 of them (28.5%) ultimately receiving NU.[266]

Whether the ultimate rate for salvage NU or SU after endoscopic treatment differs depending on tumour grade is unclear, but it has been described as independent in the study of Lucas *et al.*.[262] Although a detailed description of the reasons that prompted the NU or other types of excisional surgery is lacking in a considerable number of reports, recurrence or progression is the most important one, followed by the patient's or physician's election, poor renal unit function, tumour irresectability, and complications.[230,236,262,263,267,275,276,278,279,312,320,321] Time interval from endoscopic conservative management varies from 1 to 72 months, with most series describing a mean/median time of 21–24 months.[262,263,279,312,321]

5.9.3.2 After open KSS excision

Segmental ureter resection has been advocated mainly for UTUC located in the distal ureter. However, some series also include mid-ureter tumours. In contrast with series on endoscopic treatment for UTUC, pathological stage is known after open KSS, a fact that should provide an ideal substrate for "per stage" comparison.

Most of the series on open KSS are dated from the 1970–1990s and represent the basis for the conservative management of ureteral tumours.[322,323] The most recent retrospective series focuses mainly on comparison of oncological outcomes between NU and SU. Together with population-based studies, they show different distribution in stage and grade between the two comparison cohorts. The SU group has a higher rate (~75%) of pT1-2 and low-grade tumours than the group of patients treated by nephroureterectomy.[62,246] Recent population-based studies comparing NU and SU in ureter tumours without nodal or distant metastases confirm the non-inferiority of SU in terms of CSM freedom.[245,255] However, these studies do not provide information on the local recurrence or salvage NU rates.

Most of the ipsilateral recurrences after conservative surgical treatment occur distal to the primary treated tumour, and only occasionally do they present proximal to the primary location. Grade 1 tumours rarely develop recurrence, which is similar for grade 2 stage pTa-pT1 tumours.[322] Information on stage T2 or higher is very scarce, although recurrence may account for up to 30% of patients.[324] In a detailed series, Iborra *et al.*[273] describe a much higher recurrence rate for renal pelvis tumours (66%)

when compared with ureteral tumours (12.5%).[278] In their series, 60% of recurrences of renal pelvis tumours were accompanied by progression.[278] In high-risk cases, the fate will most likely be defined by the metastatic or nodal progression than by the local recurrence.

The results of recent series with information on secondary/salvage surgery are in **Table 5-4**.[246,278,325] These three series illustrate the recurrence and progression of different types of open KSS depending on the location of the tumour and the different possibilities for salvage surgery, from endoscopic or second excisional conservative management to radical NU. It is worthwhile to note that in the salvage setting, NU is more frequent than a second conservative treatment, and available data on the subject are too scanty to pronounce a sound statement.

TABLE 4 Data on excisional KSS on UTUC

Reference	n (type of surgery)	Time to Recurrence, n (months)	Time to Progression, n (months)	Salvage surgery, n	Type salvage surgery, n
Iborra *et al.*[278]	15 (elective PN or PP) 16 (elective SU)	4 pelvis (6–67) 2 ureter (13–55)	6 pelvis (9–175) 0	8 2	6 NU, 1 SU, 1 endo-urology, 1 NU, 1 endo-urology
Simonato *et al.*[246]	73 (elective SU)	1 (56) *pTaG2	1 (98) *pT1G3	2	1 NU 1 endo-urology
Giannarini *et al.*[325]	19 (elective SU)	2 (42 and 105) *pTaG2 & pT2G3	0	2	1 endo-urology 1 SU

KSS: kidney-sparing surgery; NU: nephroureterectomy; PN: partial nephrectomy; PP: partial pyelectomy; SU: segmental ureterectomy.
*Pathology of primary conservatively treated tumour.

The need for salvage surgery after open KSS is described to be between 2.5% and 23% of patients.[246,278,325] Recurrence or progression may present at any time during follow-up.

5.9.4 Timing of salvage therapy after kidney-sparing surgery in upper tract urothelial carcinoma

There are no studies comparing outcomes of upfront NU with salvage radical surgery. The studies investigating the impact of a delayed NU are retrospective non-matched cohorts. Furthermore, most of them exhibit a bias in grade and stage distribution between the cohort receiving primary NU and delayed NU. Overall, the rate for low-risk tumours is higher in the group receiving delayed NU. The main reason for delayed NU is endoscopic diagnostic or treatment procedures, although other reasons (e.g. neoadjuvant chemotherapy) are also considered.

Although a longer interval from diagnosis and radical treatment is associated with aggressive pathological features,[56] there is no evidence that diagnostic URS or endoscopic treatment has a deleterious effect on oncological outcomes.[205,240,326] Ureteroscopy ablation or endoscopic treatment with curative intention does not significantly affect 5-year DFS, CSS, MFS, or bladder recurrence,[238,319,327] either in groups with comparable pathological stage at the moment of the radical treatment[279] or in the respective subcohorts with muscle-invasive tumours.[181,238] The delay between endoscopic treatment and radical NU in all these series is relatively, varying between 10 and 13 months.

When a similar cutoff (3 months) as bladder cancer is used as a risk factor, no differences in long-term oncological outcomes have been found.[176,181]

The evidence, although weak (3b), is that conservative management does not have a negative impact when follow-up is strict and indications for NU are properly timed.

Conclusions	LOE
Salvage NU is required in approximately 20% of low-grade UTUC treated by endoscopic techniques, due to either non-controllable recurrence or progression. Median time from endoscopic treatment to salvage NU varies between 21 and 24 months, although with a wide range.	2b-3a
All high-grade UTUC treated by endoscopy eventually recur or progress. Salvage NU is reported in up to 30% of these cases. The selective criteria mandating endoscopic treatment in this setting preclude any other type of radical surgery in most cases.	2b-3a
Information on salvage nephrectomy after open KSS is scarce. The rates for salvage nephrectomy vary between 3% and 30%, most likely as a result of selection criteria and inclusion of low-stage tumours in these series.	4
Currently there is no evidence that diagnostic URS or primary endoscopic treatment influence negatively oncological outcomes.	4

Recommendation	GOR
Salvage nephroureterectomy after kidney-sparing surgery is recommended in cases of progression or recurrence not amenable to a second kidney-sparing approach.	B

5.10 References

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C6

Treatment of Metastatic Cancer

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Treatment of Metastatic Cancer

6.1 Background and Introduction

Upper tract urothelial cancer (UTUC) accounts for approximately 8% to 10% of urothelial carcinomas. The management of metastatic disease is largely extrapolated from the treatment paradigms used for metastatic bladder cancer. A multimodality approach to the management of advanced disease is often required. It includes chemotherapy, radiation therapy, salvage surgery, metastatectomy, and palliative care. In spite of such an approach, metastatic UTUC is rarely curable and thus a great need for novel approaches and therapeutics exists.

6.2 Chemotherapy for Metastatic UTUC

6.2.1 First-line chemotherapy for metastatic UTUC

- Historically, patients with metastatic urothelial cancer (UC) originating from the upper urinary tracts have been included in the same clinical trials as patients with metastatic UC originating from the bladder. This has been done both for practical reasons, given the difficulty in accruing to metastatic UC trials even for the more common bladder primaries, and due to the uncertainty regarding the relevance of the primary site in the setting of established metastatic disease. Although UTUC differs from UC of the bladder with regard to epidemiology, biology, and prognosis for lower-stage disease, there has been a paucity of data regarding the prognostic and therapeutic implications of the primary tumour site in patients with metastatic disease. Hence, the bulk of the data guiding the treatment of patients with metastatic UTUC is derived from studies that predominantly involve patients with UC of the bladder. Aside from potential differences in biology and prognosis, there are some unique aspects to the treatment of patients with upper tract tumours that may have relevance with regard to systemic therapy. For instance, a large proportion of patients with metastatic tumours arising from the upper tracts have a solitary kidney, exacerbating concerns regarding potential chemotherapy-related nephrotoxicity (**Table 6-1**).

TABLE 6-1 First-line Chemotherapy for Metastatic UTUC (Cisplatin-eligible)

Regimen	Level of Evidence	Grade of Recommendation
M-VAC	1	B
DD-MVAC	1	B
GC	1	B

DD: dose dense; GC: gemcitabine and cisplatin; M-VAC: methotrexate, vinblastine, adriamycin, and cisplatin.

The M-VAC (methotexate, vinblastine, doxorubicin, plus cisplatin) regimen was developed in the 1980s, combining the most active single agents for the treatment of metastatic UC available at the time.[1] Given the high response rates achieved with this regimen, M-VAC was subsequently evaluated in a series of randomized trials demonstrating superior survival outcomes when compared with single-agent cisplatin[2] and cisplatin, cyclophosphamide, plus doxorubicin (CISCA),[3] and superior response proportions compared with 5-fluorouracil, doxorubicin, plus interferon-alfa-2b (FAP).[4] The M-VAC regimen subsequently became a treatment standard, but was limited by toxicity, particularly myelosuppression and mucositis. The introduction of granulocyte colony-stimulating factor both mitigated these toxicities[5] and even facilitated administration of M-VAC in dose-dense regimens.[6] Dose-dense M-VAC did not achieve a significant improvement in survival compared with standard administration of M-VAC in the initial publication of a European Organization for Research and Treatment of Cancer (EORTC) phase III trial.[6] However, a 7-year follow-up report demonstrated a 5-year survival rate of 21.8% with dose-dense administration, versus 13.5% with standard administration.[7] There was no increase in toxicity with dose-dense administration of M-VAC. Given the promising long-term outcome, this regimen has become integrated into the standard armamentarium.

During the 1990s and early 2000s, a newer generation of cytotoxic therapies was explored in metastatic UC, particularly regimens integrating gemcitabine or the taxanes. Randomized trials comparing taxane-based doublets with M-VAC failed to demonstrate improvements in outcome, although these trials suffered from suboptimal stratification or early closure.[8,9] On the other hand, a randomized trial of gemcitabine plus cisplatin (GC) versus M-VAC demonstrated similar survival outcomes between both arms (hazard ratio [HR], 1.04; 95% confidence interval [CI], 0.82–1.32; p=0.75), but better tolerability with GC.[10] The median survival was 13.8 months (95% CI, 12.3–15.8 months) with GC and 14.8 months (95% CI, 13.2–16.8 months) with M-VAC. The proportion of patients with upper tract primary tumours in this study was not reported. Although this trial was designed as a superiority trial and not as a non-inferiority study, these results have led to the widespread adoption of GC as a standard therapy for "cisplatin-eligible" patients with metastatic UC.

Recent attempts to improve upon GC have included the addition of paclitaxel and dose-dense administration. An EORTC phase III trial randomized 626 patients with metastatic UC to treatment with GC versus GC plus paclitaxel.[11] The triplet regimen was associated with a median overall survival (OS) of 15.8 months versus 12.7 months with the doublet (HR, 0.85; p=0.075). Notably, 12% to 13% of patients on both arms had upper tract primary tumours. Interestingly, in an unplanned analysis, when the patient population was restricted to patients with bladder primary tumours, the survival improvement with the triplet did reach statistical significance (15.9 vs. 11.9 months, respectively; HR, 0.80; 95% CI, 0.66–0.97; p=0.025). The implication of this hypothesis-generating analysis with regard to the treatment of patients with upper tract primary tumours is not clear. Given the lack of survival benefit and the associated toxicity, the triplet regimen has not been widely adopted.

Bamias and colleagues[12] compared dose-dense administration of GC with dose-dense M-VAC in a phase III trial. Unfortunately, the trial suffered from slow accrual and funding difficulties, leading to early closure with only 130 patients enrolled. Notably, 8% and 19% of patients had upper tract primary tumours on the M-VAC and GC arms, respectively. The site of the primary tumour was not

significantly associated with survival on univariate analysis. This trial demonstrated similar survival outcomes between the two arms, but less toxicity with dose-dense GC, although the findings must be interpreted in the setting of the early closure and small sample size.

Some good quality randomized controlled trials with a Level 1 of Evidence (LOE 1) are available to guide the first-line treatment of patients with metastatic UC. A caveat with regard to the treatment of patients with upper tract primary tumours is the small proportion of such patients included in the available randomized trials. Another is the remaining uncertainty regarding whether the primary tumour site is of prognostic and/or therapeutic relevance in the setting of established metastatic disease. As a result, while Level 1 Evidence is available for UC, the recommendations are given a grade of B.

For "cisplatin-eligible" patients with metastatic UC of the upper tract (see recommendations for cisplatin-ineligible patients below), enrollment in a clinical trial is encouraged. Other treatment options include:

- M-VAC: LOE 1, Grade of Recommendation [GOR] B
- Dose-dense M-VAC: LOE 1, GOR B
- Gemcitabine plus cisplatin: LOE 1, GOR B

6.2.2 Chemotherapy for metastatic UTUC patients with comorbidities

In UTUC, comorbidities are generally related to:

- Smoking history, which is the most important risk factor for developing UC
- Solitary kidney after nephroureterectomy
- Age as the major risk factor for increased comorbid conditions (**Table 6-2**)

TABLE 6-2 First-line Chemotherapy for Metastatic UTUC (Cisplatin-ineligible)

Chemotherapy	Level of Evidence	Grade of Recommendation
Carbo/Gem	1	B

Carbo/Gem: carboplatin and gemcitabine.

Therefore, the presence of comorbidities is common in UC patients and may preclude the use of standard cisplatin-based combination chemotherapy.[13] Not being "fit" for cisplatin was recently defined by a consensus panel. Patients were considered unfit for cisplatin if they met at least one of the following criteria: Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 2, creatinine clearance (CrCl) <60 mL/min, grade ≥2 hearing loss, ≥2 neuropathy, and/or New York Heart Association class III heart failure.[14]

Among the most common and significant comorbidities in UTUC is impaired renal function. Calculated CrCl with current formulas tends to underestimate CrCl in patients aged >65 years compared with measured CrCl.[15] Recently, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation for estimating renal function for cisplatin-based chemotherapy eligibility in

patients with UC was compared with calculated CrCl using the Cockroft-Gault formula.[16] More patients were eligible for cisplatin when using the CKD-EPI equation; however, these findings require further validation. Approximately 50% of bladder cancer patients are considered ineligible for cisplatin.[15] In a cohort of 388 patients with UTUC undergoing nephroureterectomy, the mean glomerular filtration rate (GFR) decreased by 24% after surgery.[17] Using a cutoff of 60 mL/min per 1.73 m^2, 49% of patients would have been deemed eligible for cisplatin-based chemotherapy before surgery. Only 19% of patients remained "eligible" post-operatively.

The EORTC conducted the only randomized phase II/III study for strictly defined cisplatin-unfit patients.[18] In this trial, 21.9% had upper tract tumours, although the study was not stratified by location of the primary tumour. In this study, methotrexate/carboplatin/vinblastine (M-CAVI) and carboplatin/gemcitabine (carbo/gem) were compared. The EORTC definition of "cisplatin unfit" was a PS of 2 and/or impaired renal function (GFR <60 mL/min). Both regimens were active, but with lower response rates and median survival compared with contemporary controls receiving cisplatin-based regimens. The intent-to-treat analysis of the primary end point revealed a median overall survival of 9.3 months in the carbo/gem arm and 8.1 months in the M-CAVI arm (HR, 0.94; 95% CI, 0.72–1.22). Severe acute toxicity was 13.6% in patients given carbo/gem versus 23% on M-CAVI. The overall response rate was 42% on carbo/gem and 30% on M-CAVI. Based also on a better toxicity profile, the carbo/gem regimen was preferred. Further analysis showed that in patients with PS 2 and impaired renal function, combination chemotherapy was generally of very limited benefit.

A small body of literature suggests that modified dosing of cisplatin may be safe in patients with mild renal impairment. Two small phase II studies have evaluated GC (with cisplatin administered at a dose of 35 mg/m^2 on days 1 and 8 every 21 days) in patients with metastatic UC and permitted enrollment of patients with a GFR of >35 and 40 mL/min, respectively.[19,20] Both trials demonstrated activity without evidence of nephrotoxicity, although the relative safety and efficacy of this regimen compared with gemcitabine plus carboplatin has not been established. A single prospective trial has explored the renal safety of cisplatin-based chemotherapy in patients with metastatic UC post-nephroureterectomy.[21] Sixty patients were enrolled, and a median of six cycles of chemotherapy were administered. The estimated GFR was significantly lower after cycle 3 compared with baseline; however, severe toxicities were uncommon (two patients required temporary hemodialysis). Low-estimated GFR at baseline was associated with the development of severe renal toxicity with borderline significance.

For patients with comorbidities that preclude cisplatin, in particular those with either PS 2 or impaired renal function, outside of a clinical trial, first-line treatment with carboplatin-containing combination chemotherapy, preferably with carbo/gem, is recommended. Carbo/gem is also less toxic than M-CAVI. Level of Evidence 1 (LOE 1), GOR B (due to only approximately 20% of UTUC patients included).

6.2.3 Second-line chemotherapy for metastatic UTUC

Second-line therapy following platinum-based front-line therapy for advanced UC, including UTUC, represents a significant unmet medical need. No trials exploring second-line therapy in patients solely with metastatic upper tract tumours, or analyzing results separately in patients with upper tract primary tumours, were identified. Vinflunine, a vinca alkaloid, was approved by the European

Medicines Agency based on the results of a phase III trial comparing best supportive care (BSC) versus BSC plus vinflunine in the second-line metastatic setting.[22] In this trial, although survival was not prolonged on intent-to-treat analysis, when adjusting for prognostic factors, vinflunine significantly extended OS (p=0.036) and reduced the risk for death by 23%. Moreover, in the eligible population (n=357), the median OS was significantly longer for vinflunine + BSC than BSC (6.9 vs. 4.3 months; p=0.040). As these analyses were not based on intent to treat, vinflunine was not submitted for approval by the Food and Drug Administration (FDA) and is not available in the United States, though it is available in many European countries, Australia, New Zealand, Singapore, North Africa, Russia, and selected South American countries (**Table 6-3**).

TABLE 6-3 Second-line Chemotherapy for Metastatic UTUC

Chemotherapy	Level of Evidence	Grade of Recommendation
Vinflunine*	1	B
Paclitaxel, docetaxel, or pemetrexed	2	C

*In countries with regulatory approval.

The median survival when employing other agents, including the taxanes and pemetrexed, as second-line therapy for metastatic UC is approximately 6 to 9 months.[23–25] The combination of vandetanib, a vascular endothelial growth factor and epidermal growth factor receptor inhibitor, with docetaxel did not enhance outcomes in a randomized phase II trial.[26] Hence, more active agents are urgently needed, and enrollment in clinical trials should be strongly considered given the poor activity of all currently available agents.

A caveat when comparing outcomes in phase II trials is that they may be substantially influenced by prognostic factors independent of the activity of an agent. Eastern Cooperative Oncology Group PS >0, the presence of liver metastasis, and hemoglobin <10 gm/dL were identified and externally validated to be important clinical prognostic factors.[27] Four subgroups based on the presence of 0, 1, 2, or 3 prognostic factors demonstrated a median OS of 14.2, 7.3, 3.8, and 1.7 months, respectively. Additionally, the critical molecular drivers of disease progressing after prior chemotherapy need delineation. A better understanding of the biology of the disease will assist in the rational development of second-line therapy in conjunction with the discovery of biomarkers predictive of benefit from specific agents.

Similar to the first-line metastatic setting, recommendations in the second-line setting are extrapolated from trials that have enrolled patients with metastatic disease, regardless of the site of the primary tumour within the urothelial tract. However, the recommendations in the second-line setting are further limited by the paucity of Level 1 Evidence. Patients eligible for second-line therapy should be enrolled in clinical trials investigating new agents or regimens. Other options include:

- Vinflunine (in countries with regulatory approval): LOE 1, GOR B
- Paclitaxel, docetaxel, or pemetrexed: LOE 2, GOR C

6.2.4 Chemotherapy for metastatic UTUC with variant histology

Due to the rare nature of UTUC, and the even rarer entity of upper tract tumours with variant histology, most literature reviewed was from patients with primary bladder cancer. Currently the World Health Organization recognizes 13 different histologic variants of UC.[28] All of the variant histologies have been described in the upper urinary tract. In the largest series of UTUC reported in the literature, 24.2% of patients were found to have variant histology (complete or mixed with pure urothelial carcinoma).[29] The most common histologic subtype was squamous cell carcinoma (9.9%), followed by glandular/adenocarcinoma (4%), sarcomatoid (2.4%), micropapillary (1.9%), small cell (1.9%), and plasmacytoid (0.2%) (**Table 6-4**).

TABLE 6-4 Chemotherapy for Metastatic UTUC with Variant Histology

Variant	Chemotherapy	Level of Evidence	Grade of Recommendation
SCCa	ITP	3	D
Adenocarcinoma	ITP	3	D
Small Cell	EP/ ifosfamide/doxorubicin	3	D
Micropapillary	NA	NA	D

EP: etoposide and cisplatin; ITP: ifosfamide, paclitaxel, and cisplatin; NA: not available; SCCa: squamous cell carcinoma.

Controversy surrounds the true implication of variant histology on disease outcome, especially in the setting of mixed histologic features that include conventional urothelial carcinoma. Much of the literature composed of case reports and series suggest that variant histology is more resistant to systemic chemotherapy and early cystectomy should be considered in the setting of localized bladder cancer. In a small, retrospective analysis, no survival advantage was seen in patients with upper tract tumours with variant histology receiving multimodal therapy versus those that did not.[30] However, a secondary analysis of a Southwest Oncology Group phase III study of neoadjuvant chemotherapy (S8710) utilizing M-VAC followed by cystectomy versus cystectomy alone demonstrated a slight survival advantage in patients with variant histology receiving chemotherapy compared with the cohort with pure urothelial carcinoma (LOE 2).[31] A careful review of the literature suggests that patients with variant histology present with more advanced–stage disease compared with conventional urothelial carcinoma. This suggests that stage is the reason for poorer outcomes. However, variant histology may have implications on the choice of systemic chemotherapy.

6.2.4.1 Small cell carcinoma

The bulk of the literature regarding management of variant histologies of bladder cancer is limited to small retrospective series. Reports in patients with small cell carcinoma of the bladder have generally recommended the use of systemic chemotherapy extrapolating from neuroendocrine primaries of

other sites, such as small cell lung cancer.[32–35] In one of the only prospective trials of chemotherapy for small cell carcinoma of the bladder, 12 patients with clinically localized or advanced disease were treated with an alternating doublet regimen of ifosfamide/doxorubicin and etoposide/cisplatin.[36] Overall, 8 of 12 patients had a complete response, with 3 patients experiencing a partial response and 1 patient unevaluable. Relapse occurred in almost all patients, with a median OS of 13.3 months (95% CI, 8.5–not achieved).

6.2.4.2 Squamous cell carcinoma

Squamous cell carcinoma (SCCa) of the upper urinary tract is believed to arise in the setting of chronic inflammation, with recurrent nephrolithiasis being the most common inciting irritant. In one of the largest series of SCCa of the upper urinary tract, Holmang and colleagues[37] identified 65 cases among a cohort of 743 patients with upper-tract disease treated over 30 years. Patients with SCCa presented at a more advanced stage compared with patients with conventional urothelial carcinoma. Only 6 patients received chemotherapy, and there was no data provided regarding the chemotherapy regimens utilized. In a review of 67 patients treated with chemotherapy for advanced SCCa of the bladder or upper urinary tract, Kastritis and colleagues[38] identified 15 patients with pure SCCa and 42 patients with mixed histology. All patients received cisplatin- or carboplatin-based regimens. There was no difference between any of the groups (pure squamous, mixed, pure urothelial) in survival.

In one of the only prospective trials exploring chemotherapy for patients with non-bilharzial metastatic SCCa of the bladder, Galsky *et al.*[39] treated 20 patients with non-transitional histologies (including 8 patients with squamous cell carcinoma) with a regimen of paclitaxel, ifosfamide, plus cisplatin. Complete responses were observed in 2 of 8 patients, and the median survival for this group was 8.9 months (95% CI, 5.4–not reached).

6.2.4.3 Adenocarcinoma

Little data is available on therapy for adenocarcinoma of the upper urinary tract, although most reports suggest that this is the second most common variant histology seen. More data exists for adenocarcinoma of the bladder, with most of it focused on urachal carcinoma, another rare entity. In a series from M. D. Anderson Cancer Center, 26 of 42 patients with urachal carcinoma had metastatic disease, and the median survival from recognition of metastatic disease was 24 months.[40] Chemotherapy for metastatic disease, using a variety of regimens, produced only 4 significant responses, including 3 of 9 patients treated with 5-fluorouracil and cisplatin–containing regimens.

In a prospective trial exploring paclitaxel, ifosfamide, plus cisplatin in patients with metastatic non-transitional cell carcinomas of the urothelial tract, 11 patients with adenocarcinoma were enrolled.[39] Objective responses were achieved in 4 of 11 patients, and the median survival was 24.8 months (95% CI, 10.2–32.3).

6.2.4.4 Micropapillary

Micropapillary bladder cancer is considered a highly aggressive variant. Very few reports exist on micropapillary cancer of the upper urinary tract. Using the same cohort as described for SCCa above, Holmang and colleagues[37] identified 26 patients with upper tract urothelial cancer with at least 10% micropapillary histology, and only 1 patient was treated with chemotherapy. In a case series

of 38 patients from the Cleveland Clinic with some component of micropapillary bladder cancer, all 15 patients receiving peri-operative cisplatin-based chemotherapy ultimately died of metastatic disease.[41] This suggests that micropapillary tumours may be more chemo-resistant than conventional urothelial carcinoma, but this finding requires further validation.

Variant histology likely represents a similar percentage of histology in the upper tract as in bladder cancer, with squamous cell, adenocarcinoma, and small cell carcinoma representing the most common variants. The Level of Evidence for the available literature is predominantly 3. Because of the level of evidence, and focus on bladder cancer rather than upper tract malignancies, the Grade of Recommendation for chemotherapeutic management of metastatic variant histology of the upper tract urinary cancer is D.

6.3 Surgery/Metastatectomy for Metastatic UTUC

An early, retrospective study demonstrated that in patients who presented initially with local-regional metastases treated with cisplatin-based chemotherapy, including cisplatin with cyclophosphamide and doxorubicin (CISCA) or M-VAC, 74% had a relapse within a similar site, whereas only 26% relapsed with visceral disease.[42] For those initially presenting with visceral metastases, only 38% who responded to chemotherapy relapsed in the site of their initial disease, without clear progression involving other sites.[42] Based on the pattern of failure in patients with local-regional metastases, a subset may benefit from post-chemotherapy surgery. Studies evaluating the resection of local-regional nodal metastases have been rarely reported in tumours of the upper urinary tract,[43,44] with only a slightly higher frequency in reporting of urothelial cancers originating in the bladder.[45–49] Surgical consolidation has most often been considered for patients with lymph node metastases who respond well to upfront cisplatin-based chemotherapy,[46–49] and only rarely in the setting of visceral metastases (**Table 6-5**).[45,46,49]

TABLE 6-5 Surgery/Metastatectomy for Metastatic UTUC

	Level of Evidence	Grade of Recommendation
Metastatectomy s/p cisplatin-based therapy with local-regional metastases	3	C
Metastatectomy of visceral metastases	3	D

s/p: status post.

There are no clear prospective data to guide the selection of patients with metastatic UC for surgical consolidation following chemotherapy. In a retrospective analysis of 203 patients with metastatic UC treated with M-VAC, 50 patients underwent post-chemotherapy surgery. Thirty patients had residual UC completely resected (complete response to chemotherapy and surgery) and 10 (33%) remained alive at 5 years.[46] Patients most likely to survive for 5 years included those with unresectable primary

tumours or lymph node metastases only. A retrospective series from Germany reported a 28% 5-year survival in 44 patients who underwent surgery for metastatic UC with curative intent.[49] Multiple sites of metastatic disease were included, and no significant prognostic factors could be determined due to the small sample size. The authors concluded that metastatectomy remains investigational and may be considered with limited disease as a combined modality approach with chemotherapy.

Only limited information specific to surgery for metastatic UTUC exists. A review in 18 patients with UTUC and clinical lymph node involvement reported a 44% 5-year disease-specific survival with pre-operative chemotherapy, followed by surgical consolidation. Due to the multicentre and retrospective nature of this report, standardization of lymph node dissections was not possible. However, it should be noted that this series excluded 223 patients who were classified as having an inadequate lymphadenectomy from their analysis.[43]

The response to chemotherapy appears to have a major impact on outcome after surgical consolidation. In one report, patients who had surgical consolidation after having a major response to chemotherapy, described as a greater than 90% reduction in the tumour, experienced a 40% 5-year survival, compared with only 10% 5-year survival for a less than maximal response (p=0.04).[50] Similar outcomes were reported in another series, where a complete response to upfront chemotherapy in histologically proven lymph node–positive disease was associated with a 42% 5-year survival, compared with 19% in those who had only a partial response.[48] In 11 patients with node-only metastases involving retroperitoneal lymph nodes responding to systemic chemotherapy, the 4-year disease-specific survival was 36% with surgical consolidation, including an extensive retroperitoneal lymph node dissection, in addition to cystectomy and pelvic lymph node dissection. The presence of viable tumour in 2 or fewer lymph nodes had a statistically significant impact on disease-specific survival (p=0.006).[47]

In a retrospective study evaluating the impact of multimodal treatment on metastatic UC survival, more than 5 cycles of chemotherapy (p=0.0022), absence of liver, bone, and local recurrence (p=0.0146), and metastatectomy (p=0.0006) were independent predictors of survival.[51] It is notable that the literature for post-chemotherapy surgical consolidation has generally used M-VAC,[4,43,45,46] with only limited cases treated with carboplatin or non-cisplatin–based chemotherapy.[49]

Surgical resection of visceral metastases remains less well studied. At the M. D. Anderson Cancer Center, metastatectomy of visceral metastatic disease has been performed in patients with a solitary visceral site, most commonly in the lung, who experience a major response to systemic chemotherapy and have no evidence of rapid progression elsewhere. Even in this highly selected patient group, the 5-year survival from metastatectomy was 33%.[45]

The data are limited by their retrospective nature. In the majority of cases involving UC of the bladder, there appears to be a potential role for surgical consolidation of unresectable or local-regional nodal metastases in patients with UTUC who achieve a major response to upfront cisplatin-based chemotherapy (LOE 3, GOR C). Very limited data exists for metastatectomy of visceral metastases and for surgical consolidation after non-cisplatin–based chemotherapy, such that in spite of the predominant Level of Evidence of 3, the Grade of Recommendation is D.

6.4 Radiation Therapy for Metastatic UTUC

6.4.1 Palliative radiation therapy for local or distant recurrence

In cases of isolated local or regional recurrence, salvage or palliative radiation may be considered to relieve symptoms and possibly improve overall outcome. A study of radiotherapy for UTUC investigated its role in treating recurrence after surgery.[52] Twenty patients received radiotherapy as adjuvant treatment for advanced disease, and 20 patients received radiotherapy as salvage treatment (10 soft tissue, 10 lymph node). The median dose of radiation was 50 Gy delivered to the site of recurrence with a 1-cm extension. Eight patients had distant failure at the time of radiotherapy, and cisplatin-based chemotherapy was given to 18 of 20 patients. For the patients who received salvage radiation for recurrence, the 3-year overall survival and progression-free survival rates were 16% and 12%, respectively. The OS improved with a radiotherapy dose > 50 Gy versus < 50 Gy (23 vs. 8 months). It is difficult to understand whether there is any benefit of radiotherapy alone, given the concurrent use of chemotherapy as well as the high rate for simultaneous distant failure in these patients (**Table 6-6**).

TABLE 6-6 Radiation Therapy for Metastatic UTUC

	Level of Evidence	Grade of Recommendation
Local Recurrence	3	D
Distant Recurrence*	3	B
Adjuvant (+LN involvement)	3	D

*Recommendation based on established convention in other malignancies with distant metastases.
LN: lymph node.

Patients with locally advanced UC of the bladder at presentation may have symptoms including dysuria and hematuria. In cases where primary surgery is not an option, radiotherapy may be considered for symptomatic relief and to improve quality of life. A randomized study compared the efficacy and toxicity of two radiotherapy schedules (35 Gy in 10 fractions and 21 Gy in 3 fractions) for palliation of bladder tumour symptoms in patients considered unsuitable for curative surgical treatment.[53] The primary outcome measures were overall symptomatic improvement of bladder-related symptoms at 3 months, and changes in bladder- and bowel-related symptoms from pre-treatment to end of treatment, and at 3 months of follow-up. Of the 500 patients recruited, data on symptomatic improvement at 3 months was available on 272 patients. Of these, 68% achieved symptomatic improvement (71% for 35 Gy and 64% for 21 Gy), with no evidence of a difference in either efficacy or toxicity between the two arms. There was no evidence of a difference in survival between the two schedules (HR, 0.99; 95% CI, 0.82–1.21; p=0.933). The use of 21 Gy in 3 fractions appeared to be as effective as 35 Gy in 10 fractions. Hypofractionated radiation therapy has previously been reported to achieve good palliation in this patient population.[54–57] Advanced UTUC at presentation may cause symptoms including

flank pain, hematuria, recurrent infections, and hydronephrosis with loss of renal function. These patients are generally treated with chemotherapy. There is no clear data in patients with symptomatic locally advanced UTUC to guide the use of either radiation alone or chemoradiation.

Palliative radiotherapy to symptomatic metastatic sites of disease in other organs (i.e. bone, central nervous system) should follow the conventions established for other malignancies.[58] The common palliative radiation fractionation schedule delivers doses of 20 to 40 Gy in 5 to 20 fractions.[59] Shorter radiation schedules have also been studied to optimize the balance between symptomatic relief, convenience, and toxicities. Large, hypofractionated, single-fraction doses of 10 Gy, repeated once or twice at monthly intervals to the pelvis appeared excessively toxic.[60] Twice-daily fractionation (3.70 Gy/fraction, twice daily) in 2 days, repeated twice at monthly intervals, appeared less toxic and retained efficacy.[61] Conformal short-course radiotherapy in twice-daily fractions for 2 consecutive days was well tolerated up to a total dose of 18 Gy.[62] Palliative radiotherapy is an important component in the multimodality approach to cancer pain management of symptomatic metastases.

6.4.2 Adjuvant radiation therapy in lymph node–positive patients with UTUC

The incidence of lymph node metastases at the time of nephroureterectomy for UTUC has been reported to be approximately 20%.[63,64] Similarly to UC of the bladder, lymph node involvement is by definition stage IV disease and an independent risk factor for cancer-specific death.[64] Recurrent UTUC following surgery generally behaves in an aggressive manner, with a median time to death of 10 months.[65] Based on the poor outcome associated with lymph node metastases, the use of adjuvant radiation has been investigated following nephroureterectomy in patients with positive lymph node involvement. In one report of a 27-year experience with adjuvant radiation therapy following attempted curative surgery for UTUC, the majority of the patients (28 of 31) had stage III or IV disease, including 10 with lymph node involvement.[66] The tumour bed and regional lymph nodes were treated with a median total dose of 46.9 Gy, and 9 patients were treated with concurrent cisplatin-based chemotherapy. At a median follow-up of 2.6 years, 16 (52%) patients had developed recurrent disease, with only one patient experiencing an isolated local recurrence (6 patients with concurrent local and distant recurrence). The 5-year OS and disease-free survival (DFS) rates were 39% and 52%, respectively. The use of concurrent chemotherapy resulted in a significant improvement in 5-year OS versus radiation therapy alone (67% vs. 27%, respectively). Any clear conclusion regarding the use of adjuvant radiation therapy in node-positive patients in this report is difficult to make given the lack of a non-radiation therapy group, the long study period, and the concurrent use of chemotherapy.

Another retrospective study of 133 patients evaluated the role of adjuvant radiation therapy following surgical management of UTUC.[67] Patient data was prospectively collected from 1998 to 2008. It included 67 patients who received adjuvant radiation therapy without systemic chemotherapy. The study population included 52 patients with pT3/4 disease, but only 9 patients with lymph node involvement, thus limiting conclusions on the impact of adjuvant radiation therapy on pathologically confirmed regional lymph node metastases. The median radiation dose delivered was 50 Gy to the renal fossa, ureter, bladder, paracaval, and paraaortic lymph nodes. In addition, 14 patients received radiation to the "tumour bed" mainly secondary to positive surgical margins. The 5-year OS rates for the radiotherapy and non-radiotherapy groups were 49.6% and 44.7%, respectively, with a median

survival of 55.0 and 52.4 months, respectively (not significant). When the groups were subdivided by stage, there was a significant improvement in survival seen in T3/4 patients who received adjuvant radiation therapy (median survival, 29.9 vs. 11.4 months for non-radiotherapy). In multivariate analysis, receiving radiation therapy remained a significant factor leading to an improvement in survival. There was also a significant decrease in local recurrence (surgical bed/regional lymphatics) in patients receiving radiation therapy (9.5% vs. 31.5% for non-radiotherapy).

In a previously discussed retrospective study including 40 patients, the role of adjuvant and salvage radiation therapy following nephroureterectomy was evaluated.[52] The study is limited by the lack of initial pathologic staging data and margin status in patients receiving salvage radiation therapy. Twenty patients received adjuvant radiation therapy. The median dose was 50 Gy to tumour bed and paraaortic nodal area for high-risk pathologic features, which included all patients with T3/4 and 5 with positive lymph node involvement (in remaining 15 patients, 4 N0, 11 Nx). Sixteen (80%) patients received concurrent cisplatin-based chemotherapy. The 3-year OS rate for the adjuvant radiation therapy group was 45%. There was a decrease in local-regional recurrence in the adjuvant versus salvage radiation therapy groups (15% vs. 30%, respectively). These patients were further stratified by radiation dose (< or > 50 Gy). Similarly to the salvage group, there was an improvement in the 3-year OS rate from 25% to 56% when a dose of > 50 Gy was used in the adjuvant group.

A small series reported on the use of adjuvant intraoperative electron radiotherapy (IOERT) and external beam radiotherapy (EBRT) in 17 consecutive patients with resectable T3, T4, or lymph node–positive UTUC arising from the ureter (renal pelvis excluded).[68] This was a high-risk cohort, with 16 of 17 patients having T3/4 tumours, 6 with lymph node metastases, and 5 with positive surgical margins. All patients received both IOERT (tumour bed only) and EBRT (tumour bed and lymph nodes), with a biological equivalent dose ranging from 69.7 to 93.2 Gy based on the residual disease (unresectable residual disease vs. close margin vs. clear margin). Similarly to other studies, 10 of 17 patients received adjuvant cisplatin-based chemotherapy. Despite the high-risk pathologic features, the OS and local-regional disease control rates at 1, 3, and 5 years were 82%, 65%, and 46%; and 82%, 64%, and 51%, respectively, with a median follow-up of 4 years. Only 3 patients developed a local or lymph node recurrence as the initial site of recurrence.

Another small series compared 17 patients with stage III/IV UTUC who received adjuvant radiation therapy (median dose, 50.4 Gy delivered to the tumour bed and regional nodes) with a historical control group of 46 patients with stage III/IV or positive surgical margin UTUC who did not receive radiation therapy.[69] The positive surgical margin rate and use of adjuvant cisplatin-based chemotherapy was higher in the study versus control group, 41% versus 15%, and 52% versus 28%, respectively. There was an improved 2-year local-regional recurrence-free rate in the adjuvant radiation therapy group, 84% versus 65% (NS). There was no difference seen in the 2-year OS rate between the groups, 68% versus 67%. This study is limited by its retrospective nature and lack of thorough clinical data, mainly related to rates of lymphadenectomy and lymph node positivity.

Overall, the available data on the use of adjuvant radiotherapy in patients with lymph node–positive UTUC is very limited. Furthermore, it is difficult to collectively interpret this data for several reasons. These studies are retrospective, with relatively small numbers of patients who were treated over long time periods. The data is complicated by the lack of a comparison arm in most studies, heterogeneous

patient populations, variable radiotherapy techniques, and the inconsistent use of chemotherapy. Despite several small studies suggesting an improvement in local disease control,[52,67,69] a definitive conclusion on the use of radiotherapy in this setting cannot be made given the quality of the available literature (LOE 3, GOR D).

6.5 Palliative Strategies for Metastatic UTUC

The goal in supportive and palliative treatment is to reduce suffering and prevent treatment-related toxicity, while supporting the best possible quality of life for the patient afflicted with advanced UTUC.[70] In the setting of advanced UTUC, this often means controlling symptoms related to the primary tumour, including pain, bleeding, and urinary obstruction. It also means controlling or preventing adverse events related to treatment. In a landmark study in patients with advanced non-small cell lung cancer, early palliative care led to substantial improvements in quality of life as well as mood; also, despite less aggressive care toward the end of life, there was an improvement in OS compared with those who received standard treatment.[71] Based upon this study and others, recommendations now exist for the integration of palliative care into standard oncology practice.[72] General measures of supportive care for advanced UTUC include analgesics, radiotherapy (see section 6.4, Radiation Therapy for Metastatic UTUC), chemotherapy (see section 6.2, Chemotherapy for Metastatic UTUC), and bone targeted therapy. However, other potential possibilities for supportive and palliative care include anticoagulation, ureteroscopic intervention, and ureteral stenting.

6.5.1 Bone targeted therapy

Urothelial cancer can metastasize to bone, with approximately one third of patients with advanced disease harbouring bone metastases. Bisphosphonates have proven useful in a range of malignancies in decreasing skeletal-related events (SREs) related to osseous metastases; patients with UC were included in one of the pivotal studies leading to the approval of zoledronic acid for the treatment of bone metastases.[73] A small study restricted to patients with bone metastases from bladder cancer, who were receiving palliative radiotherapy, randomized 40 patients to zoledronic acid or placebo. This study demonstrated that zoledronic acid reduced the risk for SREs by 59% in multiple event analysis and led to an improvement in the 1-year survival rate (36.3 ± 11.2 vs. 0%, respectively).[74] Denosumab, a monoclonal antibody targeting RANK ligand, is also approved to decrease SREs in patients with solid tumour malignancies and osseous metastatic disease.[75] Unlike zoledronic acid, denosumab may be used in patients with renal dysfunction, which represents a potential benefit in patients with UTUC and a solitary kidney.

6.5.2 Management of urinary obstruction

Urinary obstruction in the setting of UC may occur from primary or secondary tumours within the urinary tract or as related to external compression from metastatic lymphadenopathy. Chemotherapy and/or radiation may be of benefit to such patients. Ureteral stents are often employed and appear

to be most helpful in the setting of a focal area of extrinsic obstruction.[76–78] Percutaneous nephrostomy placement can be an effective method to relieve urinary obstruction, often when stenting is not feasible or has been unsuccessful. This often leads to improvement in renal function, but may also impact quality of life.[79]

6.5.3 Management of treatment-related toxicity

As previously reviewed (see section 6.2, Chemotherapy for Metastatic UTUC), platinum-based chemotherapy remains the cornerstone for systemic therapy, both for curative and palliative intent, in patients with metastatic UC. Although there are no clear differences in chemotherapy toxicity for UC based on the site of the primary tumour, renal function in the setting of a solitary kidney is a more common issue in UTUC.[80] Whether a tumour arises in the upper or lower urinary tracts, any obstructive etiology contributing to renal dysfunction should be addressed in order to deliver optimal chemotherapy and minimize toxicity. Standard guidelines for supportive care, including aggressive management of chemotherapy-induced nausea and vomiting, and the use of hematopoietic growth factors apply in the setting of UTUC.[81–84] As with chemotherapy, no specific studies on the treatment or prophylaxis of complications due to radiation for UTUC exist, and standard guidelines apply.[82,85]

6.5.4 Management and prophylaxis of venous thromboembolism

Venous thromboembolism (VTE) is a significant problem in the setting of active cancer, with an approximate 7 times higher risk in patients with malignancy compared with matched controls.[86] Urologic malignancies, including UC, are associated with an increased risk for VTE, both in the clinically localized peri-operative setting and in the advanced-disease setting.[86,87] Increased age and comorbidities, including renal dysfunction, are additional risk factors in the advanced UC patient population, with as high as a 41% VTE risk in some studies.[86,88,89] Recommendations for prophylaxis of VTE in the peri-operative setting and in hospitalized patients exist, whereas prophylaxis of ambulatory patients receiving outpatient chemotherapy is controversial.[90] Treatment and secondary prophylaxis of patients with UC who are diagnosed with proximal deep vein thrombosis and/or pulmonary embolism should occur with long-term, low-molecular weight heparin as in other patients with active malignancy, with caution in those with renal insufficiency.[90]

6.6 Conclusion

Recommendations for the management of metastatic UTUC, including the use of systemic chemotherapy, surgery/metastatectomy, radiotherapy, and other palliative strategies, are largely extrapolated from bladder cancer studies. Under the circumstances, no grade A recommendations are possible. In spite of the limitations of the available data, the committee has provided guidelines based on best available evidence for the management of metastatic UTUC. There is a clear need to embark on prospective studies to better define a standard of care for patients with metastatic UTUC.

6.7 References

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SIU Central Office | 1155 University Street, Suite 1012, Montreal, Quebec, Canada H3B 3A7
Telephone: +1 514 875 5665 Fax: +1 514 875 0205 Email: central.office@siu-urology.org

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For information and orders:
SIU Central Office
1155 University Street
Suite 1012
Montréal (QC)
Canada H3B 3A7

T: +1 514 875-5665
F: +1 514 875-0205
E-mail: communications@siu-urology.org
Website: www.siu-urology.org

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