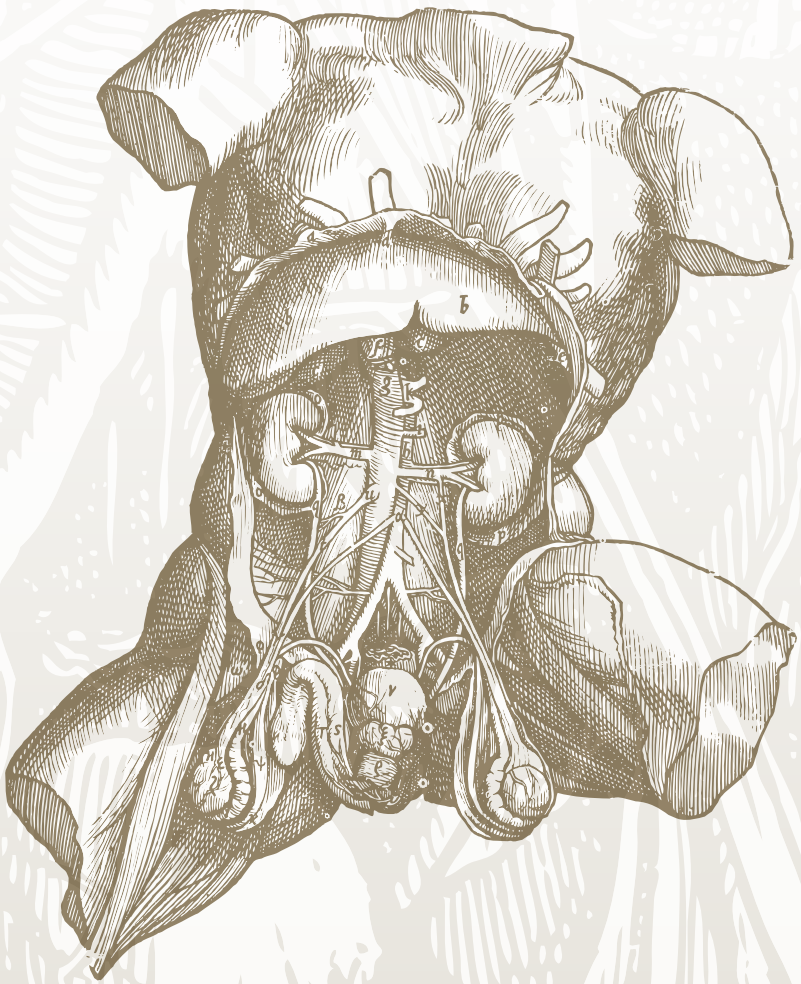
TESTICULAR CANCER

EDITED BY:
Susanne Osanto, MD, PhD and Jerome P. Richie, MD



International Consultation on Testicular Cancer

Shanghai, China, November 1–5, 2009

Co-sponsored by
SIU (Société Internationale d'Urologie)
EUOG (European Uro-Oncology Group)
ICUD (International Consultation on Urological Diseases)

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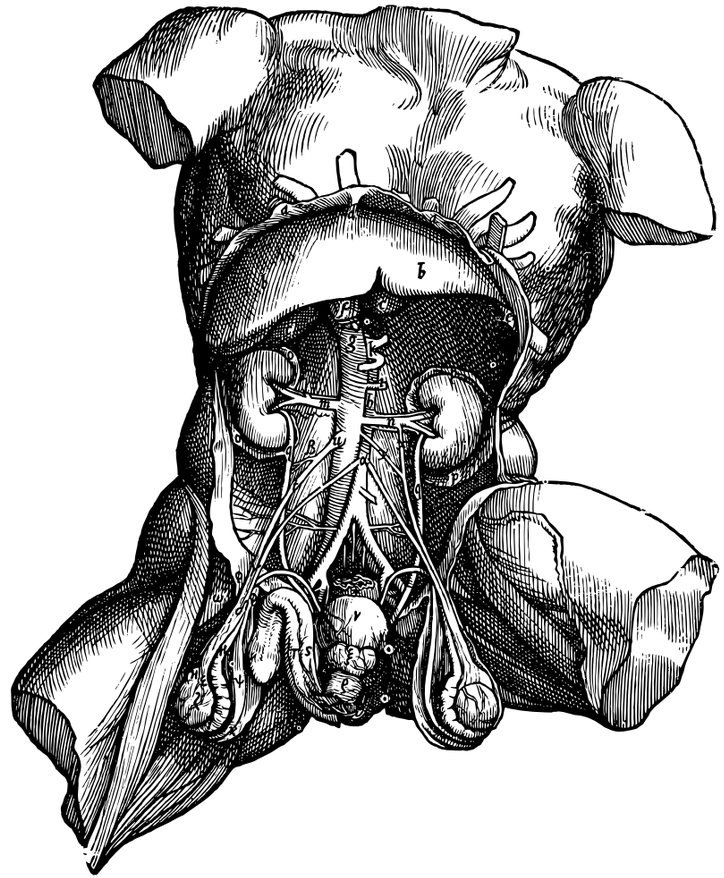

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Editors
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About the Cover Illustration

Andreas Vesalius (1514–1564)

Andreas Vesalius was a Flemish physician and anatomist whose work revolutionized anatomy and helped correct many beliefs held since ancient times about how the human body functioned. His important innovations were to perform postmortem dissections and to make use of illustrations in the teaching of anatomy.

Vesalius was born in Brussels (then in the Habsburg Netherlands) in 1514. He first attended the University of Leuven and then went to the University of Paris (1533–1536), where he studied medicine and anatomy, and then on to complete his studies at the University of Padua where he was awarded his medical degree. He obtained the post of lecturer at the University of Padua and remained there as professor from 1537 to 1542.

Dissatisfied with the quality of the teaching he felt he had received, Vesalius set out to undertake his own research and observations in order to disprove certain widely held beliefs. At that time, dissection of the human body was illegal and penalties could often be severe. Vesalius, however, was able to carry out a number of postmortem dissections, and through these was able to demonstrate that the anatomical teachings of Galen, still highly revered in medical schools, were based on fundamental anatomical errors.

In 1543 Vesalius published his revolutionary book *De humani corporis fabrica* (On the Structure of the Human Body), seven volumes in total on the structure of the human body. All were illustrated in detail by artists using Vesalius' own drawings. Never before had illustrations of this quality been seen in a medical book. It was the most accurate and detailed anatomical text ever to have been produced.

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Abbreviations Used in the Text

AFP	alpha-fetoprotein
AHCPR	Agency for Health Care Policy and Research
ASCT	autologous stem-cell transplantation
AUC	area under the curve
BEC	also known as CEB (carboplatin, etoposide, bleomycin)
BEP	bleomycin, etoposide and cisplatin
BEPxn	number (n) of cycle(s) of bleomycin, etoposide and cisplatin treatment
BOP	bleomycin, vincristine and cisplatin
BPH	benign prostatic hyperplasia
CEB	carboplatin, etoposide, bleomycin
Cg A	chromogranine A
CISCA/VB	cyclophosphamide, doxorubicin, cisplatin, vinblastine and bleomycin
CNS	central nervous system
CR	complete response (also called complete remission)
CS	clinical stage
CT	computed tomography
DATECA	Danish Testicular Cancer Study Group
DFS	disease-free survival
EAU	European Association of Urology
EBM	evidence-based medicine
EC	embryonal carcinoma
EORTC	European Organization for Research and Treatment of Cancer
EP	etoposide and cisplatin
EPx	number (n) cycle(s) of etoposide and cisplatin treatment
ESMO	European Society for Medical Oncology
EUOG	European Uro-Oncology Group
FDG-PET	fluorodeoxyglucose-positron emission tomography

FSH	follicle-stimulating hormone
GCT	germ cell tumours
G-CSF	granulocyte colony-stimulating factor
GETUG	Genito-Urinary Group of the French Federation of Cancer Centre
GFR	glomerular filtration rate
GI	gastrointestinal toxicity
hCG	human chorionic gonadotrophin
HDCT	high-dose chemotherapy
HR	hazard ratio
HRQOL	health-related quality of life
ICUD	International Consultation on Urological Diseases
IGCCCG	International Germ Cell Cancer Collaborative Group
IGCNU	intratubular germ cell neoplasia, unclassified type
LH	luteinizing hormone
LDH	lactate dehydrogenase
LVI	lymphovascular invasion
MRC	Medical Research Council
MRI	magnetic resonance imaging
MSKCC	Memorial Sloan-Kettering Cancer Centre
NCI	National Cancer Institute
NSGCT	non-seminomatous germ cell tumour
NED	no evidence of disease after surgery
NR	not reported
OR	odds ratio
OS	overall survival
Oxford	Oxford Centre for Evidence-Based Medicine
p	p-value
PC-RPLND	post-chemotherapy retroperitoneal lymph node dissection
PEI/IPE	cisplatin, etoposide, ifosfamide
PEB	cisplatin, etoposide and bleomycin
PET	positron emission tomography
PFS	progression-free survival

PLAP	placental alkaline phosphatase
PMH	Princess Margaret Hospital
PRm-	partial remission, negative tumour markers
PRm+	partial remission, positive tumour markers
PS	pathologic stage
pT	depth of invasion
PV	cisplatin and vinblastine
PVB	cisplatin, vinblastine, bleomycin
PVeBV	cisplatin, vinblastine, bleomycin, etoposide
RCT	randomized controlled trial
RPLND	retroperitoneal lymph node dissection
RT	radiotherapy
SEER	Surveillance Epidemiology and End Results
SECSG	Southeastern Cancer Study Group
SIU	Société Internationale d'Urologie
SMN	second malignant neoplasm
STM	serum tumour markers
TIN	testicular intraepithelial neoplasia
TIP	paclitaxel, ifosfamide, cisplatin
TNM	tumour node metastasis
UICC	International Union Against Cancer
VAB-6	cyclophosphamide, vinblastine, bleomycin, dactinomycin, and cisplatin
VIP/VeIP	cisplatin, ifosfamide and etoposide (or vinblastine)
VIP-B	etoposide, ifosfamide, cisplatin and bleomycin
VP-16	etoposide
vs.	versus
WHO	World Health Organization

Foreword

Paul Abrams, MD
Professor of Urology,
University of Bristol, UK

On behalf of the SIU and the ICUD steering committee, we wish to thank the Consultation Chairs, Drs. Jerome P. Richie and Joel Sheinfeld, as well as the various subcommittee chairs and members, for the time and effort that they devoted to all aspects of the process of compiling the material for this publication.

Testicular cancer affects a younger group of men than any other adult urological cancer. Despite the huge advances in management over the last 30 years, it is still a devastating diagnosis for the young man discovered to have a malignant testicular mass. The book deals with the changing prevalence of this form of cancer, brings us up to date on its pathogenesis, and tackles the continued controversies on its management, including the extent of surgery.

The International Consultation on Testicular Cancer was designed to present state-of-the-art information on, and understanding of, the many aspects of this neoplasia that factor into decisions related to its assessment and therapy. This book represents the consensus recommendations of five committees of international experts, whose task it was to review the literature based on the best evidence, summarize a text overview of each chapter, and finally to make recommendations. The task of the committee chairs was to unify the material and reach a consensus wherever possible.

It is now time to share this textbook with our readers, in the hope that the concepts discussed herein will prove useful in caring for their patients, as well as inspire further studies and research into this disease. We would be remiss in not underscoring the invaluable contribution of the editors, our colleagues Susanne Osanto and Jerome P. Richie, whose tireless efforts have brought this volume to fruition.

Paul Abrams, MD
Chairman of the International Consultation on Urological Diseases

Preface

Susanne Osanto, MD, PhD
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International Consultation on Testicular Cancer 2009

The current edition of *Testicular Cancer* marks the international consultation and collaboration between specialists from various continents in their multidisciplinary care of cancer patients. This volume bears the logos of the Société Internationale d'Urologie (SIU), the International Consultation on Urological Diseases (ICUD) and European Uro-Oncology Group (EUOG), and also contains a CD-ROM version. It is also available electronically on the SIU website (free of charge for SIU members) to permit ready access to information. The SIU and ICUD, with the support of the EUOG, organized the 2009 International Consultation on Testicular Cancer, gathering experts from around the world in Shanghai on November 1–5, 2009. The chairmen of each of the five committees all did a tremendous job, created a forum for discussing the relevant evidence, and finalized the elements of consensus in their respective committees. The committees went through a consensus process that followed the Oxford grading system levels of evidence, and used the four grades from this system for their recommendations. This was done by searching electronic databases such as Medline, PubMed, Embase and the Cochrane Library. They searched in relevant journals and evaluated all the papers.

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Clinical chapters have been written primarily by surgical, radiation, and medical oncologists to ensure a multidisciplinary approach to this disease, while pathology is included in the first chapter, "Biology, Diagnosis and Staging". We are fortunate in having been able to attract preeminent clinicians to this consultation. We thank our colleagues for their contributions and in particular, we would like to thank and formally acknowledge Dr. Ferran Algaba and Dr. Hein van Poppel for providing us with numerous illustrations for this edition of *Testicular Cancer*, and their generous permission to use their material for this book.

We are grateful to Dr. Saad Khoury, who first formulated the idea of an international consultation on urologic diseases. This farsighted concept was adopted by the European Association of Urology (EAU) who, together with the SIU, organize an international consultation on a specific urological topic on alternate years.

This edition once again offers the clinician up-to-date information that underlies contemporary practice, with an emphasis on the level of evidence achieved and recommendations to clinicians who care for testicular cancer patients and may be faced with clinical dilemmas. Together, we have successfully created an effective resource available for doctors and students of oncology at all levels.

It is our hope that this book will not only contribute to the continuing education of urologists, other clinicians and a variety of health professionals, but also aid in the care of patients with testicular cancer and contribute to ultimately improving their quality of life and health outcomes.

Since we realize that many interested clinicians are not able to read a comprehensive book, we deliberately kept this book as concise as possible in order to offer it as a resource that allows the user to select his or her topics of interest. As Editors, we wish to exercise the prerogative of highlighting part of the chapters of this book, including the recommended guidelines from the various committees.

Epidemiology and Diagnosis

Testicular cancer remains an exciting topic. Cancer of the testis is a relatively uncommon disease, accounting for approximately 1% of all cancers in males, but it is most common among males aged 15 to 35 years. It has one of the highest cure rates of all cancers. However, it is an important disease in the field of oncology, since it represents a paradigm of a highly curable cancer whose incidence is focused on young patients at their peak of productivity. Tumours of the testis are heterogeneous. Various classification systems exist, but more recently, the various histologies, seen often with tumours harbouring more than one element of a specific histology, are classified into seminomas (comprising approximately 40% of all malignant tumours) and non-seminomas (including tumours with both seminoma and non-seminoma elements).

Testicular Intraepithelial Neoplasia

Testicular intraepithelial neoplasia (TIN) still poses a challenge to clinicians, especially when treating patients who have already undergone an orchiectomy for testicular cancer. Preserving fertility without jeopardizing the ultimate favourable outcome for their patients can sometimes pose difficult decisions for clinicans.

Bilateral Testicular Cancer

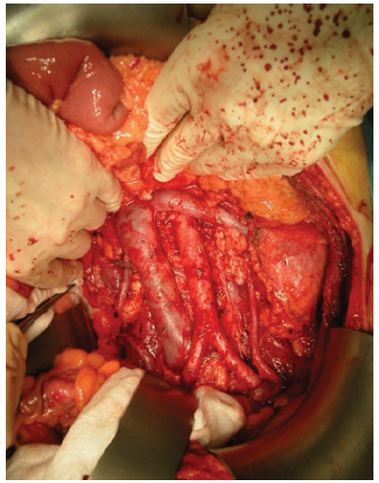
Organ-preserving surgery may be considered in cases with synchronous bilateral testicular tumours, metachronous contralateral tumours, or in a tumour in a solitary testis with normal pre-operative testosterone levels, provided that the tumour volume is less than 30% of the testicular volume and adequate oncological safe surgery is ensured.

Markers

Since the 1970s, tremendous progress has been made in the diagnosis and treatment of patients with testicular cancer. Serum markers and diagnostic imaging have become increasingly important in the management of patients with testicular cancer.

Retroperitoneal Lymph Node Dissection

Testicular carcinoma is the most common urologic indication for retroperitoneal lymph node dissection, commonly referred to as RPLND. RPLND may be the primary treatment modality for low-stage non-seminoma germ cell tumors (NSGCT). One potential risk of an RPLND is damage to the sympathetic chain, resulting in retrograde ejaculation.



RPLND is frequently performed as salvage treatment for residual masses following first-line chemotherapy for advanced disease. Importantly, post-chemotherapy surgical resection of seminoma is often technically more demanding than resection of a post-chemotherapy non-seminoma residual mass and carries a higher morbidity due to treatment-induced reactive changes typical for seminoma in the sites of residual masses.

RPLND (both upfront as well as post-chemotherapy) should be performed by experienced surgeons (see photo courtesy Prof. H. van Poppel). A major difference between Europe and the United States is that RPLND is considered a standard approach for low stage NSGCT in the US.

Stage I and II Seminoma

The management of patients with stage I or II seminoma has changed considerably in the last decade. Previously, adjuvant radiotherapy was used in many centres. Subsequently, a shift in treatment options occurred, with the adoption of a risk-adapted approach in which patients are advised based on risk factors of the initial primary tumour. In addition, treatment options vary, ranging from single agent, carboplatin, to watchful waiting, or even combination chemotherapy in high-risk patients.

Systemic Chemotherapy

Since the introduction of cisplatin in the 1970s, chemotherapy has developed at an incredible pace, resulting in a cure for most patients with disseminated disease. Large randomized trials were rapidly performed stepwise to elucidate the value of less chemotherapy – either with fewer treatment courses or reduced doses without jeopardizing efficacy – while minimizing toxicity which can occasionally be fatal. As a result, testicular cancer has truly become a model for the treatment of other cancers.

Testicular Cancer: A Paradigm

Despite the rarity of the diagnosis, testicular cancer serves as a paradigm of a form of cancer which became highly treatable by surgeons, radiotherapists and medical oncologists. Effective therapy that can now cure the majority of patients – even with disseminated disease – became available in the early 1970s. The high cure rate with low morbidity is a product of careful application of the principles of surgical oncology and radiation therapy, as well as of several decades of stepwise execution of well-planned clinical trials. The challenge for the new century is to accelerate the pace of clinical investigation to translate new insights in

chemoresistance of testicular cancer and knowledge of cellular pathways, into novel targeted therapy upfront for poor-prognosis patients or, after failure of standard chemotherapy, to explore and incorporate new therapeutic avenues to effectively salvage patients after failure of first-line chemotherapy. New insights will lead to better cancer prevention in an era of steadily increasing incidence rates of testicular cancer, introduction of new imaging techniques leading to improved early detection, and more effective therapy for poor-prognosis patients with chemoresistant tumour cells. At the same time, we aim to reduce morbidity of radiotherapy and chemotherapy in long-term survivors of testicular cancer who – after effective treatment decades ago – are now at risk for metabolic abnormalities, cardiovascular disease associated with prior treatment, as well as potential development of secondary cancers.

The Editors
Susanne Osanto, MD, PhD and Jerome P. Richie, MD

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

Abbreviation: RCT= randomized controlled trial

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CONTENTS

Testicular Cancer: Biology, Diagnosis and Staging

1.1 Introduction

Testicular cancer is a rare tumour before the age of 15, but the most common type of cancer among males in their second and third decade of life. Testicular cancer represents between 1% and 1.5% of male neoplasms and 5% of urological tumours in general, with three to six new cases occurring per 100,000 males per year in Western society (1–3). A striking increase in the incidence of testicular cancer was detected during the 1970s and 1980s, particularly in Northern European countries, and a clear trend towards an increased testicular cancer incidence in the last 30 years in the majority of the industrialized countries in North America, Europe and Oceania, although surprising differences in incidence rates are seen between neighbouring countries (4,5). Data from the Surveillance Epidemiology and End Results (SEER) program during the years 1973 to 1998 show a continuing increased risk among Caucasian men in the USA only for seminoma (4).

There is a great variation in histological tumour types, but the large majority (90%–95%) of all tumours arising in the testis are classified as so-called germ cell tumours (1). Interestingly, patients with germ cell tumours of the testis have an increased risk to develop a tumour in the contralateral testis and 1%–2% of cases present with bilateral tumours at diagnosis.

Germ cell tumours are often divided into seminomas, and the remaining tumours as non-seminomas. Peak incidence is in the third decade of life for non-seminoma and in the fourth decade for pure seminoma. Familial clustering has been observed, particularly among siblings.

Epidemiological risk factors for the development of testicular tumours are: a history of cryptorchidism or undescended testis, Klinefelter's syndrome, familial history of testicular intraepithelial neoplasia (TIN) tumours among first-grade relatives (father/brothers), the presence of a contralateral tumour or TIN, and infertility (6–11). A specific genetic marker has been described in all histological types of germ cell tumours (13); testicular intraepithelial neoplasia (TIN) has been found to show the same chromosomal abnormalities, while p53 locus alterations have been found in TIN (14).

Testicular tumours show excellent cure rates. The main factors contributing to this are careful staging at the time of diagnosis; adequate early treatment based on chemotherapeutic combinations, with or without radiotherapy and surgery; and very strict follow-up and salvage therapies. From 1995 to 1992, a decrease in the mean time delay to diagnosis and to treatment has been observed (15). In the treatment of testicular cancer, the choice of centre where this treatment is administered is of capital importance. Although early stages can be successfully treated in a non-reference centre, the relapse rate is higher (16). In poor-prognosis non-seminomatous germ cell tumours, it has been shown that overall survival within a clinical trial depended on the number of patients treated at the participating centre (worse, with < five patients enrolled) (17).

1.2 Data Acquisition

These guidelines are based on a structured review of the literature, and represent data from meta-analyses studies, Cochrane evidence, and the recommendations of earlier published consensus statements (e.g., the European Germ Cell Collaborative Consensus Group) (18–24) and have been presented at the ICUD Meeting on Testicular Cancer at the SIU Congress in Shanghai (November 2009).

1.3 Histopathological Classification System of Testicular Tumours

Although tumours can be derived from any type of cell in the testis, germ cell tumours (GCT) comprise approximately 95% of all tumours arising in the testis. The remaining tumours are mostly sex cord-gonadal stromal tumours arising from Leydig cells or Sertoli cells.

The recommended pathological classification, modified from the 2004 version of the World Health Organization (WHO), is shown below (25).

Germ cell tumours

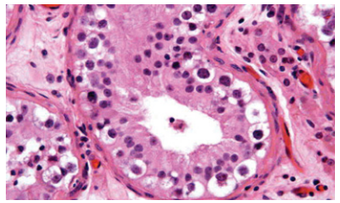
- Intratubular germ cell neoplasia
- Seminoma (including cases with syncytiotrophoblastic cells)
- Spermatocytic seminoma (mention if there is sarcomatous component)
- Embryonal carcinoma
- Yolk sac tumour
- Choriocarcinoma
- Teratoma (mature, immature, with malignant component)
- Tumours with more than one histological type (specify % of individual components)

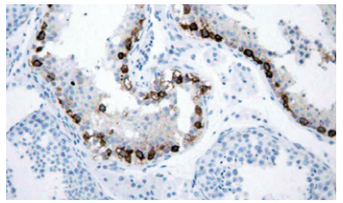
Sex cord/gonadal stromal tumours

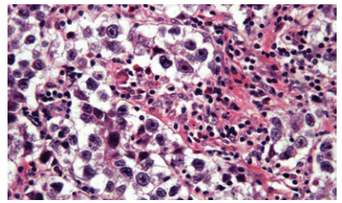
- Leydig cell tumour
- Malignant Leydig cell tumour
- Sertoli cell tumour
  - Lipid-rich variant
  - Sclerosing
  - Large cell calcifying
- Malignant Sertoli cell tumour
- Granulosa cell tumour
  - Adult type
  - Juvenile type
- Thecoma/fibroma group of tumours
- Other sex cord/gonadal stromal tumours
- Incompletely differentiated
- Mixed
- Tumours containing germ cell and sex cord/gonadal stromal (gonadoblastoma)

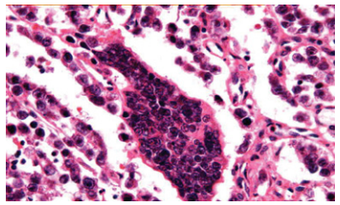
Miscellaneous non-specific stromal tumours

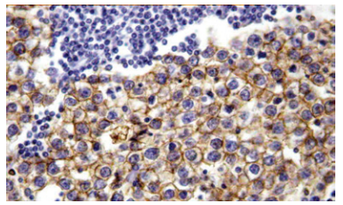
- Ovarian epithelial tumours
- Tumours of the collecting ducts and rete testis
- Tumours (benign and malignant) of non-specific stroma

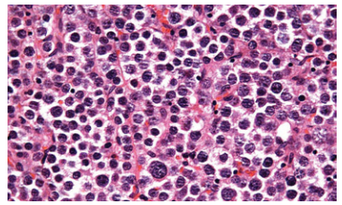

Intratubular germ cell neoplasia c-kit expression

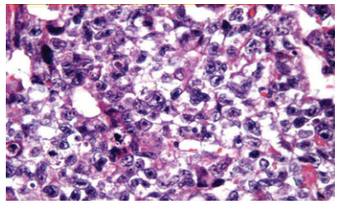

Intratubular germ cell neoplasia

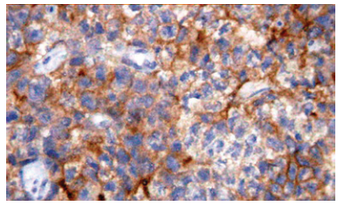

Classic seminoma

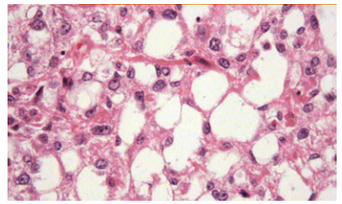

Seminoma with trophoblast cells

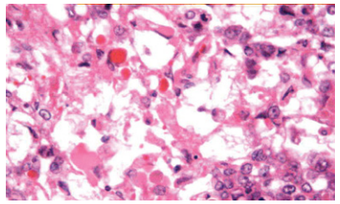

Seminoma c-kit expression

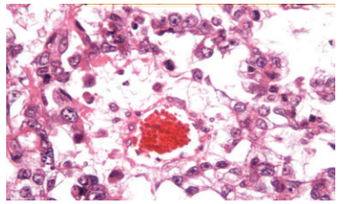

Spermatocytic seminoma

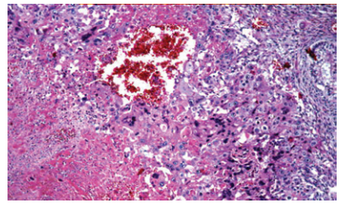

Embryonal cell carcinoma

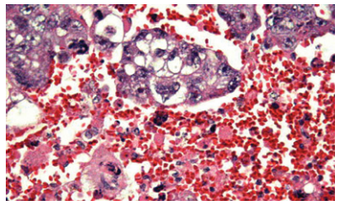

Embryonal cell carcinoma CD30 expression

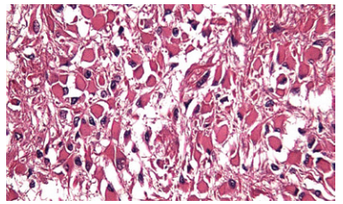

Yolk sac tumor microcystic type

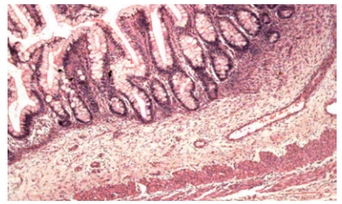

Yolk sac tumor with hyaline material


Yolk sac tumour with Schiller-Duval body


Choriocarcinoma


Choriocarcinoma with haemorrhage area


Malignant somatic sarcoma in teratoma


Pre-puberal teratoma

(Courtesy of Prof. Ferran Algaba)

1.4 Diagnosis and Workup

1.4.1 Clinical examination

Most patients present with a painless mass within the testis (26). In approximately 20% of cases, the first symptom is scrotal pain, and up to 27% of patients with testicular cancer may have local pain (1).

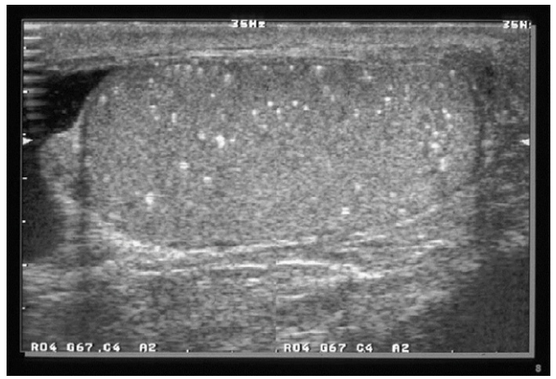
Gynaecomastia appears in 7% of cases and is more common in non-seminomatous tumours. Back and flank pain are present in about 11% of cases (1).

In about 10% of cases, patients present with testicular discomfort or swelling suggestive of an orchio-epididymitis, with consequent delay of the correct diagnosis (1,2). Unilateral enlargement of the testis, with or without pain, should raise concern for testis cancer and in all patients with a scrotal mass, or when in doubt, ultrasound should promptly be performed. Physical examination reveals the features of the mass and must always be carried out in conjunction with a general examination in order to find possible (supraclavicular) distant metastases, a palpable abdominal mass or gynaecomastia. A correct diagnosis must be established in all patients with an intrascrotal mass (27).

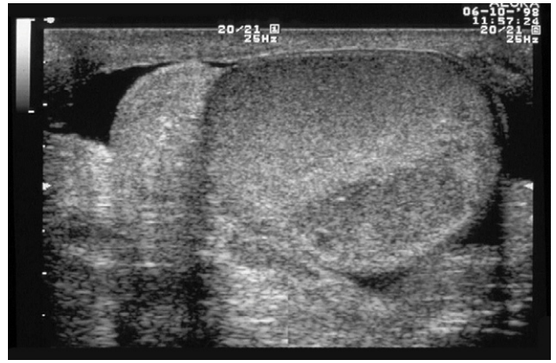
1.4.2 Imaging of the testis

Currently, diagnostic ultrasound serves to confirm the presence of a testicular mass and to explore the contralateral testis. Its sensitivity in detecting a testicular tumour is almost 100%, and it has an important role in determining whether a mass is intra- or extratesticular (28). Ultrasound is an inexpensive test and should be performed even when the presence of a testicular tumour is clinically evident (29). Ultrasound of the testis must be performed in young men without a palpable testicular mass who have retroperitoneal or visceral masses or elevated serum human chorionic gonadotrophin (hCG) or alfa-fetoprotein (AFP) or in men consulting for fertility problems (30-32). Ultrasound can be utilized in the follow-up of the contralateral testis in patients at risk (33), when other risk factors such as microlithiasis are present. The sole presence of microlithiasis is not an indication for a regular scrotal ultrasound (34).

SCROTAL ULTRASONOGRAPHY SHOWING MULTIPLE MICRO-CALCIFICATIONS
snowstorm image. Scrotal ultrasonography showing multifocal lesions in the left testicle suspicious for non-seminomatous testis tumor
(Courtesy of Prof. H. van Poppel)



SCROTAL ULTRASONOGRAPHY SHOWING MULTIFOCAL LESIONS
in the left testicle suspicious for non-seminomatous testis tumor
(Courtesy of Prof. H. van Poppel)



Magnetic resonance imaging (MRI) offers higher sensitivity and specificity than ultrasound for diagnosing tumours (28,35) and may be able to differentiate seminomatous from non-seminomatous tumour. MRI of the scrotum offers a sensitivity of 100% and a specificity of 95%–100% (36), but its high cost does not justify its use for diagnosis.

1.4.3 Serum tumour markers at diagnosis

Serum tumour markers are prognostic factors and contribute to diagnosis and staging (37). The following markers should be determined:

- AFP (produced by yolk sac cells)
- hCG (expression of trophoblasts)
- LDH (lactate dehydrogenase)

Elevation of LDH is usually a reflection of tissue damage and destruction. Overall, there is an increase in these markers in 51% of testicular cancer cases (15,26). Alpha-fetoprotein is elevated in approximately 50%–70% of patients with non-seminomatous germ cell tumour (NSGCT), and elevated hCG is seen in 40%–60% of patients with NSGCT. About 90% of non-seminomatous tumours present with a rise in one or two of the markers. Up to 30% of seminomas can present or develop an elevated hCG level during the course of the disease (38,39). LDH is a less specific marker, which may be elevated in 80% of patients with advanced testicular cancer. Clearly, a negative marker does not exclude the diagnosis of a cell tumour. Other markers studied include placental alkaline phosphatase (PLAP), which may be of value in monitoring patients with pure seminoma. Assessment of cytogenetic and molecular markers is not routinely available in all centres, and these are currently not used in the clinical diagnosis and clinical decision making. However, measurement of serum AFP, hCG and LDH (in advanced tumours) is mandatory, while PLAP is optional.

1.5 Treatment of the Primary Tumour

1.5.1 Surgical management

Orchiectomy

Every patient with a suspected testicular mass must undergo inguinal exploration with exteriorization of the testis within its tunics, and immediate orchiectomy with division of the spermatic cord at the internal inguinal ring must be performed if a tumour is found. If the diagnosis is not clear, a testicular biopsy is taken for frozen-section histological examination.

Prior scrotal surgery may alter normal lymphatic drainage of the testis, and after such scrotal violation the scrotal scar should be excised and hemiscrotectomy with removal of the testis tumour should be performed instead of an orchiectomy via inguinal incision.

SCROTAL VIOLATION

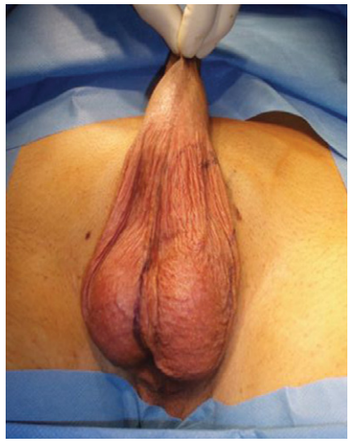
A A longitudinal scrotal incision was performed elsewhere for a hydrocele not suspecting a testis tumour. Note the longitudinal scar and intended surgical margins marked with blue dye prior to definitive surgery

B, C A hemiscrotectomy was performed because of the scrotal violation

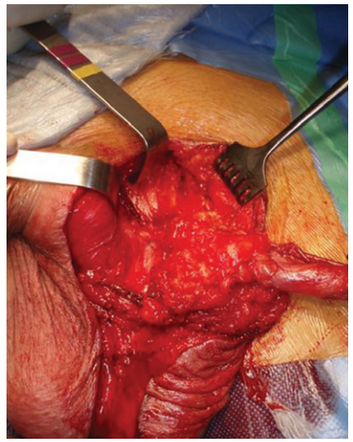
D Surgical specimen consisting of the left hemiscrotum and testis tumour

(Courtesy of Prof. H. van Poppel)

A



B



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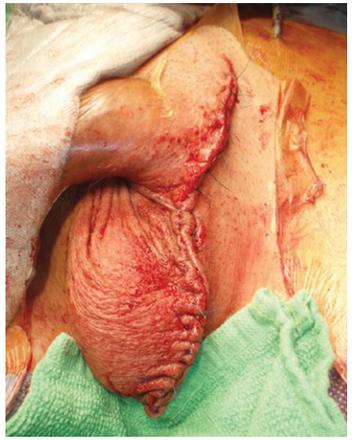
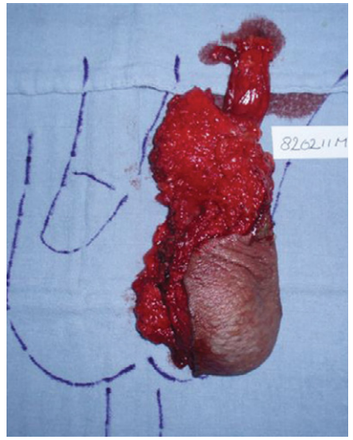


D



In cases of disseminated disease and life-threatening metastases in the lungs with respiratory insufficiency, orchiectomy should be delayed and it is mandatory to first start with chemotherapy. In those specific cases, orchiectomy may be delayed until sufficient tumour cells have been destroyed. This ensures that clinical improvement of lung function has been achieved. Once such clinical stabilization has occurred, orchiectomy can be performed.

Organ-sparing surgery

Radical orchiectomy remains the standard treatment for testis tumours and organ-sparing surgery is not indicated in the presence of non-tumoural contralateral testis. However, under specific circumstances organ-sparing surgery can be considered as an alternative to orchiectomy with all the necessary precautions.

EXPOSURE OF TESTIS AND SPERMATIC CORD THROUGH INGUINAL INCISION AND ULTRASOUND

A Exposure of the testis and spermatic cord through an inguinal incision

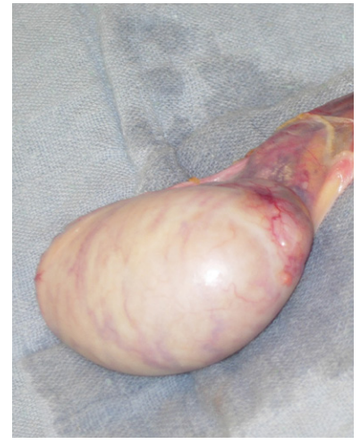
B Intra-operative ultrasound to localize the small testicular tumor

C Partial orchiectomy with the tumor excised within healthy parenchyma

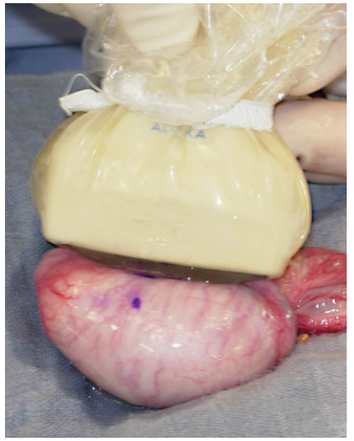
D Status after closure of the tunica albuginea after partial orchiectomy

(Courtesy of Prof. H. van Poppel)

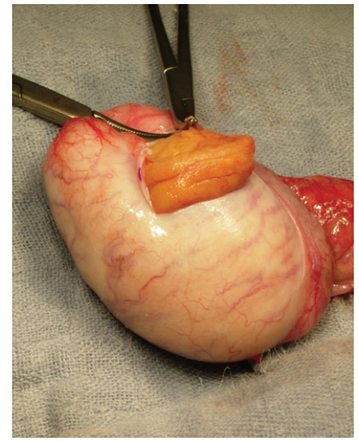
A



B



C



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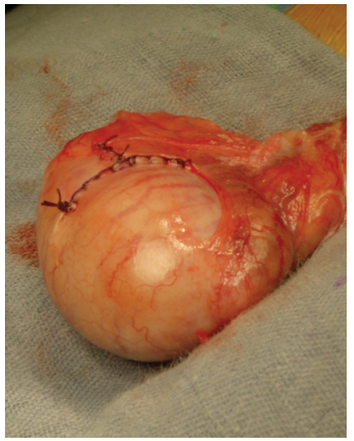

In patients with synchronous bilateral testicular tumours, metachronous contralateral tumours, or in case of a tumour in a solitary testis with normal pre-operative testosterone levels, organ-preserving surgery can be performed when the tumour volume is less than 30% of the testicular volume and surgical rules are respected. In those cases, the rate of associated TIN is high (at least up to 82%), and all patients must be treated with adjuvant radiotherapy (20 Gy) at some point (40). Infertility will result after radiotherapy and the risk of long-term Leydig cell insufficiency after radiotherapy of a solitary testis is increased (41). Radiation treatment may be delayed in fertile patients who wish to father children. The option must be carefully discussed with the patient and surgery performed in a centre with experience (42,43).

1.6 Histopathology Report of the Testis and Pathological T-staging

There are several requirements to the pathology report. These include:

- Documentation of macroscopic information including the side of the tumour, the size of the testis and the maximum size of the tumour, as well as macroscopic features of epididymis, spermatic cord and tunica vaginalis.
- Appropriate sampling (a 1 cm^2 section for every centimetre of maximum tumour diameter, including normal macroscopic parenchyma (if present), albuginea and epididymis, with selection of suspected areas).
- At least one proximal and one distal section of spermatic cord plus any suspected area) is required.
- Information from microscopy of hematoxylin and eosin (H&E) staining sections (i.e. the microscopic features and the histological type of the tumour, with specification of individual components and estimated amount as percentage according to WHO 2004 (25).
- The presence or absence of peri-tumoural venous and/or lymphatic invasion.
- Presence or absence of albuginea, tunica vaginalis, rete testis, epididymis or spermatic cord invasion.
- Presence or absence of intratubular germ cell neoplasia (TIN) in non-tumour parenchyma intratubular germ cell neoplasia.

For appropriate tumour-node-metastasis (TNM) staging, the pT category according to TNM 2009 is required (44). Furthermore, additional immunohistochemical (IHC) stainings should preferably be performed in seminoma and in mixed germ cell tumour, AFP and hCG staining.

Useful (immunohistochemical stainings for) markers which can be helpful to ascertain the diagnosis, if there is doubt, are:

- In seminoma: the cytokeratins (CAM 5.2), PLAP, c-kit
- In intratubular germ cell neoplasia: PLAP and c-kit
- To distinguish seminoma from embryonal carcinoma: CD30, AE1:AE3
- Other useful markers: chromogranine A (Cg A), Ki-67 (MIB-1).

1.7 Management of Carcinoma In Situ

1.7.1 Diagnosis and management of carcinoma in situ (testicular intraepithelial neoplasia)

Testicular intraepithelial neoplasia (TIN) of the testis is the non-invasive precursor of testicular germ cell tumours and a contralateral biopsy has been advocated to rule out the presence of TIN (45). Although this is routine policy in some countries, the low incidence of TIN and contralateral metachronous testicular tumours (up to 9% and approximately 2.5%, respectively) (46,47), the morbidity of TIN treatment, and the fact that most of these metachronous tumours are at a low stage at presentation make it controversial to recommend a systematic contralateral biopsy in all patients (48-50). It is still difficult to reach a consensus on whether the existence of contralateral TIN must be identified in all cases. However, biopsy of the contralateral testis should be considered in high-risk patients for contralateral TIN with a testicular volume of less than 12 mL, a history of cryptorchidism, or poor spermatogenesis. A contralateral biopsy is not needed for patients above age 40 years (51-56). A double biopsy is preferred to increase sensitivity (53). Once TIN is diagnosed, local radiotherapy (20 Gy in fractions of 2 Gy) is the treatment of choice. Because this may produce infertility, the patient must be carefully counselled before treatment commences (48,57). In addition to infertility, Leydig cell function and testosterone production may be impaired in the long term following radiotherapy for TIN. Radiation treatment may be delayed in fertile patients who wish to father children.

1.8 Staging Procedures at Diagnosis

1.8.1 Staging at initial diagnosis of the primary tumour

Physical examination, laboratory tests and imaging of the testis will be performed to assess the stage (extent) of the tumour. The most widely used staging system is the TNM staging system. The extent of the primary tumour is classified after radical orchiectomy, and for this reason, a pathological stage is assigned. The TNM system collects information about the size of the primary tumour (T), whether lymph nodes are affected based on clinical (imaging) information (N), and whether the tumour has metastasized (M) to other distant sites of the body. Testicular cancer staging also includes a category that describes the patient's blood serum (S) marker levels.

Consequently, it is mandatory to assess:

- Pre-orchiectomy levels of serum markers and the post-orchiectomy half-life kinetics of serum tumour markers
- The status of retroperitoneal and supraclavicular lymph nodes, and the liver
- The presence or absence of mediastinal nodal involvement and lung metastases
- The status of brain and bone, if any suspicious symptoms are present

1.8.2 Diagnostic tools

The currently available tests include:

- Physical examination
- Serial blood sampling
- Chest X-ray
- Abdominopelvic and thoracic computed tomography (CT) scan
- Abdominal and retroperitoneal ultrasound, MRI
- Positron emission tomography (PET) scan
- Other specific examinations, depending on clinical suspicion

Serum tumour markers: assessment pre- and post-orchiectomy

The mean serum half-life of AFP and hCG is 5–7 days and 2–3 days, respectively (38). Tumour markers must be re-evaluated after orchiectomy to determine half-life kinetics. Marker decline in patients with clinical stage I disease should be assessed until normalization has occurred. Post-orchiectomy markers are important in order to classify the patient according to the International Germ Cell Cancer Collaborative Group (IGCCCG) risk classification. The persistence of elevated serum tumour markers after orchiectomy might indicate the presence of metastatic disease (macro- or microscopically), while the normalization of marker levels after orchiectomy does not rule out the presence of tumour metastases. During chemotherapy, the markers should decline; persistence has an adverse prognostic value.

Imaging of lymph nodes and organs: abdomen and chest CT scan

Radiological evaluation of retroperitoneal, mediastinal and supraclavicular lymph nodes and viscera

Retroperitoneal and mediastinal lymph nodes are best assessed by means of a CT scan. The supraclavicular nodes are best assessed by physical examination.

Abdominopelvic CT scanning offers a sensitivity of 70%–80% in determining the state of the retroperitoneal nodes. Its accuracy depends on the size of the nodes, sensitivity, and the negative predictive value increase using a 3 mm threshold to define metastatic nodes in the landing zones (56). Those figures decrease slightly in stages I and II (57,58) with a rate of understaging of 25%–30% (59). New generations of CT scans do not seem to improve sensitivity.

Magnetic resonance imaging is currently optional. It produces similar results to CT scanning in the detection of retroperitoneal nodal enlargement (60,61) but MRI is not available in all hospitals and the costs may be prohibitive. MRI may be of additional value when abdominopelvic CT or ultrasound are inconclusive (60), in rare cases of CT contrast allergy, or if the cumulative radiation dose is a concern.

A chest CT scan is the most sensitive way to evaluate the thorax and mediastinal nodes. This exploration must be recommended in all testicular cancer patients since up to 10% of cases can present with small subpleural nodules that are not visible radiologically (62). The CT scan has high sensitivity but low specificity (60).

There is not enough evidence to support the use of the fluorodeoxyglucose-positron emission tomography (FDG-PET) scan in the staging of testis cancer (63,64). It is recommended in the follow-up of patients with seminoma at least 6 weeks after chemotherapy with any residual mass in order to decide upon watchful waiting or active treatment (65-68).

Other examinations, such as brain or spinal CT, bone scan or liver ultrasound, should be performed if there is suspicion of metastases to these organs. A CT or MRI scan of the skull is advisable in patients with NSGCT and widespread lung metastases. Table 1 shows the recommended test for staging.

TABLE 1 Recommended Tests for Staging at Diagnosis

Test	Recommendation Grade B
Serum tumour markers	AFP hCG LDH (for advanced tumours)
Abdominopelvic CT scan	All patients
Chest CT scan	All patients
Testis ultrasound	Clinical suspicion and normal scrotum at palpation
MRI	When abdominal scan is inconclusive
PET scan†	Follow-up residual masses in seminoma
Fertility investigations (should be offered):	Total testosterone LH FSH Semen analysis Sperm banking

hCG = human chorionic gonadotrophin; LDH = lactate dehydrogenase; CT = computed tomography; NSGCT = non-seminomatous germ cell tumour; MRI = magnetic resonance imaging; PET = positon emission tomography.

†There is currently no indication for PET scan at diagnosis.

1.9 Staging and Prognostic Classifications

1.9.1 Classification system

The classification system recommended in these guidelines is the TNM system of the International Union Against Cancer (UICC) (Table 2) (44). This includes:

- Determination of the anatomical extent of disease
- Assessment of serum tumour markers, including nadir values of hCG, AFP and LDH after orchiectomy (S category)
- Clear definition of regional nodes
- Some N-category modifications related to node size.

TABLE 2 TNM Classification of Testicular Cancer According to TNM 2009 (44)

pT	Primary Tumour[1]
pTX	Primary tumour cannot be assessed[1]
pT0	No evidence of primary tumour (e.g. histological scar in testis)
pTis	Intratubular germ cell neoplasia (carcinoma in situ)
pT1	Tumour limited to testis and epididymis without vascular/lymphatic invasion: tumour may invade tunica albuginea but not tunica vaginalis
pT2	Tumour limited to testis and epididymis with vascular/lymphatic invasion, or tumour extending through tunica albuginea with involvement of tunica vaginalis
pT3	Tumour invades spermatic cord with or without vascular/lymphatic invasion
pT4	Tumour invades scrotum with or without vascular/lymphatic invasion
N	**Regional Lymph Nodes Clinical**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis with a lymph node mass ≤ 2 cm at largest or multiple lymph nodes, none more than 2 cm at largest
N2	Metastasis with a lymph node mass > 2 cm but not > 5 cm at largest, or multiple lymph nodes, any one mass > 2 cm but not > 5 cm at largest
N3	Metastasis with a lymph node mass > 5 cm at its largest
pN	**Pathological**
pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis with a lymph node mass ≤ 2 cm at largest and ≤ 5 positive nodes, none > 2 cm at largest
pN2	Metastasis with a lymph node mass > 2 cm but not > 5 cm at largest; or > 5 nodes positive, none > 5 cm; or evidence of extranodal extension of tumour
pN3	Metastasis with a lymph node mass > 5 cm at largest

N indicates the upper limit of normal for the LDH assay.

LDH = lactate dehydrogenase; hCG = human chorionic gonadotrophin; AFP = alpha-fetoprotein.

[1] Except for pTis and pT4, where radical orchiectomy is not always necessary for classification purposes, the extent of the primary tumour is classified after radical orchiectomy; see pT. In other circumstances, TX is used if no radical orchiectomy has been performed.

continued on **page 17**

TABLE 2 TNM Classification of Testicular Cancer According to TNM 2009 (44), *Cont'd*

M	Distant Metastasis		
MX	Distant metastasis cannot be assessed		
M0	No distant metastasis		
M1	Distant metastasis		
M1a	Non-regional lymph node(s) or lung metastasis		
M1b	Other sites		
S	**Serum Tumour Markers**		
Sx	Serum marker studies not available or not performed		
S0	Serum Marker Study Levels Within Normal Limits		
	LDH (U/l)	hCG (mIU/ml)	AFP (ng/ml)
S1	< 1.5 x N and	< 5,000	and < 1,000
S2	1.5–10 x N or	5,000–50,000 or	1,000–10,000
S3	> 10 x N or	> 50,000 or	> 10,000

N indicates the upper limit of normal for the LDH assay.

LDH = lactate dehydrogenase; hCG = human chorionic gonadotrophin; AFP = alpha-fetoprotein.

[1] Except for pTis and pT4, where radical orchiectomy is not always necessary for classification purposes, the extent of the primary tumour is classified after radical orchiectomy; see pT. In other circumstances, TX is used if no radical orchiectomy has been performed.

1.9.2 Clinical staging based on TNM classification

Classification of stage I testicular cancer

Stage I testicular cancer refers to tumours that are confined to the testis and epididymis (Table 3). Stage IA reflects the absence of tumour cells in the blood vessel of the testis and epididymis, without microscopic vascular of lymphatic invasion by tumour cells, without spread to locoregional lymph nodes or other organs, and no signs of metastases on clinical examination or imaging. Post-orchiectomy serum tumour marker levels are within normal limits (marker level decline in patients with clinical stage I disease should be assessed until normalization); Stage IB have a more locally invasive primary tumour, without signs of distant metastases. Stage IS indicates persistently elevated serum markers or an increase in serum marker levels after radical orchiectomy, indicating the presence of subclinical (microscopic) tumour or possibly a contralateral germ cell tumour in the remaining testis. If serum tumour marker levels are declining according to the expected half-life decay after orchiectomy, the patient needs to be followed up until normalization.

In Table 3, the pTNM classification used to assess the clinical stage of the disease is shown. In a population-based patient series, 75%–80% of seminoma patients, and about 55% of patients with NSGCT cancer have stage I disease at diagnosis (69,70). True stage IS (persistently elevated or increasing serum marker levels after orchiectomy) is found in about 5% of non-seminoma patients. If staging by retroperitoneal lymph node dissection (RPLND) was to be performed in stage IS patients, nearly all patients would be found to have pathological stage II disease (pN+) (1,13,69,71).

TABLE 3 Staging of Testicular Cancer

Stage 0	pTis	N0	M0	S0
Stage I	pT1–4	N0	M0	SX
Stage IA	pT1	N0	M0	S0
Stage IB	pT2	N0	M0	S0
	pT3	N0	M0	S0
	pT4	N0	M0	S0
Stage IS	Any T	N0	M0	S1–3
Stage II	AnyT	N1–3	M0	SX
Stage IIA	AnyT	N1	M0	S0
	AnyT	N1	M0	S1
Stage IIB	AnyT	N2	M0	S0
	AnyT	N2	M0	S1
Stage IIC	AnyT	N3	M0	S0
	AnyT	N3	M0	S1
Stage III	AnyT	Any N	M1a	SX
Stage IIIA	AnyT	Any N	M1a	S0
	AnyT	Any N	M1a	S1
Stage IIIB	AnyT	N1–3	M0	S2
	AnyT	Any N	M1a	S2
Stage IIIC	Any T	N1–3	M0	S3
	Any T	Any N	M1a	S3
	Any T	Any N	M1b	Any S

1.9.3 Prognostic classification system of advanced disease

In 1997, the IGCCCG defined a prognostic factor-based staging system for metastatic testicular tumours based on identification of some clinically independent adverse factors. This staging system has been incorporated into the TNM classification and uses histology, location of the primary tumour, location of metastases and pre-chemotherapy marker levels in serum as prognostic factors to categorize patients into good-, intermediate- or poor-prognosis groups. (See Chapter 4, table 1, page 74.)

1.9.4 Prognostic risk factors

For seminoma stage I, tumour size of more than 4 cm and invasion of the rete testis have been identified as predictors for relapse in a multivariate analysis (18). However, these risk factors have not been validated in a prospective setting except that the absence of both factors indicated a low recurrence rate (6%) (72).

For non-seminoma stage I, vascular invasion of the primary tumour in blood or lymphatic vessels is the most important predictor of occult metastatic disease. The proliferation rate, as well as the percentage of embryonal carcinoma, are additional predictors that improve upon the positive and negative predictive value of vascular invasion (73,74).

The significant prognostic pathological risk factors for stage I and clinical risk factors for metastatic disease are listed in Table 4.

TABLE 4 Prognostic Factors for Occult Metastatic Disease in Testicular Cancer

Pathological (for Stage I)	Seminoma	Non-Seminoma
	▪ Tumour size (> 4 cm) ▪ Invasion of the rete testis	▪ Vascular/lymphatic invasion or peri-tumoural invasion ▪ Proliferation rate > 70% ▪ Percentage of embryonal carcinoma > 50%
Clinical (for Metastatic Disease)		
	▪ Primary location ▪ Elevation of tumour marker levels ▪ Presence of non-pulmonary visceral metastasis	

1.10 Fertility-Related Issues

Impact on fertility and fertility-associated issues

Sperm abnormalities are frequently found in patients with testicular tumours. Furthermore, chemotherapy and radiation treatment can also impair fertility. In patients of reproductive age, pre-treatment fertility assessment (testosterone, LH and FSH levels) should be performed, and semen analysis and cryopreservation should be offered. If cryopreservation is desired, it should preferably be performed before orchiectomy, but in any case, prior to chemotherapy treatment (41,75–81).

In cases of bilateral orchiectomy or low testosterone levels after treatment of TIN, lifelong testosterone supplementation is necessary (82). For more detailed information, the reader is referred to the EAU Male Infertility Guidelines (www.uroweb.org/guidelines/archive).

1.11 Levels of Evidence and Grades of Recommendation

TABLE 5 Guidelines for the Diagnosis and Staging of Testicular Cancer

	Grade of Recommendation
1. Testicular ultrasound is a mandatory assessment.	B
2. Orchiectomy and pathological examination of the testis are necessary to confirm the diagnosis and to define the local extension (pT category). In a life-threatening situation due to extensive metastases, chemotherapy must be started before orchiectomy.	B
3. Serum determination of tumour markers (AFP, hCG, and LDH in metastatic disease) must be performed before and after orchiectomy for staging and prognostic reasons.	B
4. The state of the retroperitoneal, mediastinal and supraclavicular nodes and viscera must be assessed in all testicular cancer patients by CT scan.	B

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C2

Management of Localized Seminoma, Stage I and II

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Management of Localized Seminoma, Stage I and II

2.1 Introduction

The estimated incidence of testicular tumours worldwide is more than 52,000 new cases per year (1). In 2008, there were 9,000 deaths from the disease (1). The incidence of germ cell tumours (GCTs) continues to rise in most populations across the world, although the increases were most consistent among populations of European ancestry (2). For most populations, the incidence of seminoma was slightly greater than that of non-seminoma. This increase in testicular cancer rates remains unexplained, although changes in the prevalence of important risk factors for this disease may be responsible.

There is evidence that poor-risk group patients with germ cell cancer benefit from treatment in centres with special experience in the field (3). However, it is also of considerable importance that clear, comprehensive and up-to-date consensus guidelines be available which represent the current "state of the art" in diagnosis and management of germ cell cancer. The European Germ Cell Cancer Consensus Group (EGCCCG) and the European Society of Medical Oncology (ESMO) both published recommendations on the management of GCTs in 2008 and these reflect the "European" approach to management (4–6). The Canadian Germ Cell Cancer Consensus Group has recently published the Canadian consensus on the management of germ cell cancer (7). In November 2009, an international consensus meeting was held under the sponsorship of the SIU and ICUD to review recent updates in the literature and develop international consensus guidelines on the management of testicular cancers.

The management of patients with stage I/II seminoma has changed considerably in the last five years with the increasing use of surveillance in stage I disease and chemotherapy in patients presenting with stage II disease. This chapter will present the SIU/ICUD consensus on the management of this group of patients. Levels of evidence and grades of therapeutic interventions are based on the ICUD system (8).

2.2 Management of Stage I Testicular Seminoma

Although radiotherapy (RT) has been the standard treatment for clinical stage I seminoma patients in the past, there has been growing recognition since the early 1990s that adjuvant RT is associated with an increased risk of late side-effects including second non-germ cell malignancies and cardiovascular disease (13–18). Concerns regarding late toxicity of RT, success of surveillance in stage I NSGCTs, as well as improvements in diagnostic imaging, have led to an assessment of close surveillance after orchiectomy for stage I seminoma, with treatment reserved for those who relapse. In addition, adjuvant carboplatin chemotherapy has been shown to give similar results to RT. With any of these approaches (surveillance, radiation or carboplatin chemotherapy), a five-year disease-specific survival of 99% or higher is expected (11).

2.2.1 Surveillance

Numerous prospective non-randomized studies of surveillance have been performed and their results are summarized in Table 1 (16–21). The data in these series are now mature and relapse rates have consistently been reported to be approximately 15% in unselected populations of patients with stage I disease. The predominant site of relapse in all studies was in the para-aortic lymph nodes; 41 of 49 (82%) of relapses in the Danish Testicular Cancer Study Group (DATECA) study and 57 of 64 (85%) in the Princess Margaret Hospital (PMH) series (19,20). The median time to relapse ranged from 12 to 18 months, but late relapses (> 5 years) have been reported in some series. Disease-specific survival is 99% overall and thus comparable to other options.

TABLE 1 Summary of Surveillance Studies in Stage I Seminoma

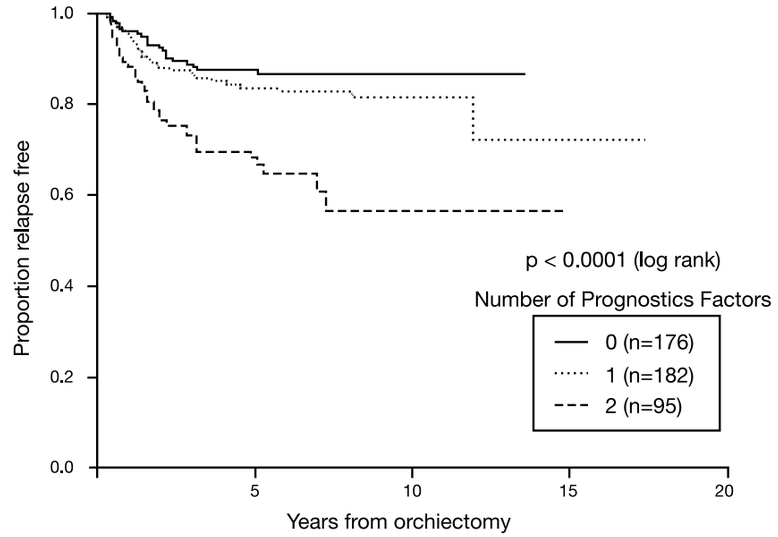
Author	Year	Median FU (mo)	# of Patients	Relapse (# patients)	% Relapse	Cause-Specific Survival
Daugaard *et al.* (18)	2003	60	394	69	17.5	100%
Germa Lluch *et al.* (17)	2002	33	233	38	16	100%
Cummins *et al.* (21)	2009	162	164	22	13	98.7%
Oliver *et al.* (16)	2001	98	110	21	19	100%
von der Maase *et al.* (19)	1993	48	261	49	18.8	98.9%
Warde *et al.* (20)	2005	98	421	64	15.2	99.7%

Tumour size and rete testis invasion have been shown in a pooled analysis of 638 cases from four centres to predict for relapse (Fig. 1) (22). Using this prognostic model, a risk-adapted approach to management has been reported by the Spanish Germ Cell Cancer Cooperative Study Group with surveillance reserved for low-risk patients and adjuvant therapy for patients with 1 or 2 adverse prognostic factors (23). This study confirmed that low-risk patients (no adverse factors) had a small risk of relapse. However, a risk-adapted approach to management cannot be recommended at the present time because the prognostic model suffers from two major problems. Firstly, in an independent data set, the model was not validated (i.e., tumour size was found to be the only factor predicting relapse) and secondly, the model does not have sufficient discrimination to be clinically useful (i.e., even patients in the high-risk group have a greater than 65% chance of being relapse-free on surveillance) (24).

At relapse, most patients can be successfully treated with retroperitoneal RT alone. One concern regarding the routine use of surveillance was the potential for the increased use of chemotherapy. However, data from PMH indicates that the 10–year actuarial risk of requiring chemotherapy at any time in the management of patients was 4.6% in patients managed by surveillance, and 3.9% in those managed by adjuvant RT. These data suggest that there is no significant increase in the use of chemotherapy in patients followed on surveillance (20).

An optimal follow-up strategy for patients on surveillance has not yet been determined. Most relapses occur within two years of diagnosis but late relapse has been reported (20,25). A number of protocols have been suggested in the literature. It would seem reasonable to follow patients for five to ten years, with cross-sectional imaging performed every four months in the first two years and less frequently thereafter (26,27). Routine chest x-ray and serum marker estimation are likely of no value in follow-up protocols (28).

FIGURE 1
Relapse-free rate based on number of adverse prognostic factors



2.2.2 Adjuvant radiotherapy

Adjuvant retroperitoneal RT was the standard treatment of stage I seminoma for more than 60 years. The overall survival rate in most series in the modern era ranges from 92% to 99% at ten years, with few deaths, if any, from seminoma. In large single or multi-institutional series, the relapse rate has varied from 0.5% to 5% (20,29–32). The most common sites of relapse following adjuvant RT are the mediastinum, lungs, and the left supraclavicular fossa. In patients who received therapy directed to the para-aortic nodes alone, relapses are also seen in the pelvic nodes. A small proportion of patients, usually with predisposing factors, relapse in the inguinal nodes. Chemotherapy is the treatment of choice for supra-diaphragmatic relapse and provides close to a 100% cure rate.

FIGURE 2a
RT fields for stage I disease

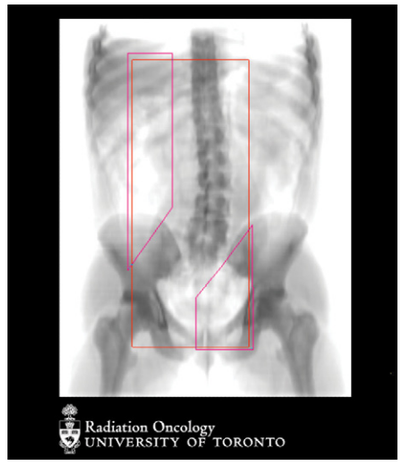
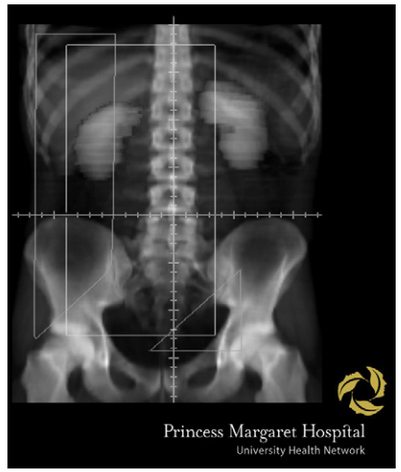


FIGURE 2b
RT fields for stage I disease



The traditional management of stage I seminoma patients after orchiectomy has consisted of RT to the para-aortic and pelvic (retroperitoneal) lymph nodes (Fig. 2a). In most studies, the superior border of the radiation fields is at T10–11 vertebral body (31,33). Care should be taken to ensure that no cardiac tissue is included in the treatment volume. The low incidence of pelvic lymph-node involvement in stage I seminoma led to the investigation of adjuvant RT directed to the para-aortic lymph nodes alone. The Medical Research Council (MRC) Testicular Study Group randomized 478 patients to traditional para-aortic and pelvic radiation therapy or para-aortic irradiation therapy alone (31). Patients treated with para-aortic RT alone had a 4% relapse rate, as compared to a 3.4% relapse rate in those who received therapy directed to the para-aortic and pelvic lymph nodes. All patients who received para-aortic and pelvic RT relapsed in supra-diaphragmatic sites, but 1.6% of the patients in the treated para-aortic lymph nodes-alone group failed, with disease in the pelvis. The time to first normal post-RT sperm count was significantly longer in the extended-field group. However, the difference declined with continued follow-up, and at three years from the start of RT, an estimated 92% of para-aortic and pelvic RT patients had attained a sperm count of at least 10×10^6 /ml (31).

This trial showed that treating the para-aortic nodes alone gives excellent results, but when used, a small risk of pelvic disease remains. Therefore, if this treatment approach is adopted, interval imaging with CT of the pelvic lymph nodes must be performed to ensure that if pelvic relapse occurs, that it is detected at an early stage. Data from the Christie Hospital in Manchester, where no routine evaluation of the pelvis is carried out after para-aortic radiation alone, has shown that the median size of the pelvic lymph nodes at time of detection of relapse is 5 cm (range 2.5–9 cm) (34,35).

A possible compromise between traditional RT fields and para-aortic RT alone is to irradiate the para-aortic and ipsilateral common iliac lymph nodes by positioning the inferior border of the radiation fields at midpelvis as is currently done at some Canadian centres (Fig. 2b). This encompasses the lymph nodes that are typically removed at lymphadenectomy in patients with non-seminomatous tumours and also covers the vast majority of pelvic nodal recurrences in patients treated with para-aortic RT alone (33,36). This approach would likely reduce the risk of a second malignancy by reducing the integral dose of RT and an added potential to reduce the scatter dose to the remaining testis and preserve fertility without the requirement for ongoing pelvic surveillance (37).

In most centres across the world, a dose of 25–35 Gy has traditionally been used in stage I seminoma. The MRC conducted a randomized controlled trial (RCT), TE18, using a non-inferiority design, to assess the possibility of reducing RT doses without compromising efficacy in stage I seminoma (30). A total of 625 patients were randomized to a conventional dose of 30Gy in 15 fractions over 3 weeks, or a reduced dose of 20Gy in 10 fractions over 2 weeks. The vast majority of patients in both groups received para-aortic strip irradiation only (88.1% in the 30Gy group and 88.7% in the 20Gy group). Following the closure of the TE18 study, a total of 469 patients from another trial (TE19/30982 – comparing adjuvant chemotherapy to adjuvant RT), who were randomized to receive RT, were further randomized with respect to dose (30Gy versus 20Gy). Both TE18 and TE19 studies were updated and presented at the American Society for Clinical Oncology (ASCO) 2008 annual meeting (38). With a median follow-up of seven years, there were 27 relapses from 550 patients in the 30Gy arm versus 16 relapses from 544 patients in the 20Gy arm. The updated combined five-year relapse rates were 4.9% versus 3%, for the 30Gy and 20Gy groups respectively. This difference was reflected in a hazard ratio (HR) of 0.59 (90% CI 0.35–0.99). If adjuvant RT is used in stage I seminoma, 20Gy in 10 fractions over 2 weeks (or a biologically similar regimen) should be the treatment regimen of choice.

In a study, 38,907 one-year survivors of testicular cancer from 14 population-based registries across the world had a slightly higher risk of dying from noncancerous causes, including circulatory diseases, than the normal population (39). Those patients less than 35 years of age treated with RT in 1975 or later had a higher mortality from all circulatory diseases (SMR 1.7, 95% CI 1.21–2.31) (39). Data from the M.D. Anderson and Royal Marsden Hospitals also suggest that long-term survivors of testicular seminoma treated post-orchiectomy with RT are at significant excess risk of cardiac disease (9,14). In the M.D. Anderson series of 453 patients treated between 1951 and 1999, the standardized cardiac mortality ratio for patients with more than 15 years following RT (infra-diaphragmatic RT, no mediastinal RT) was 1.80 (95% C.I. 1.01–2.98) (9). Huddart reported a similar increase in cardiac events in a cohort of 992 patients treated at the Royal Marsden Hospital, with a risk-ratio of 2.4 (95% C.I. 1.04–5.45) in those treated with infra-diaphragmatic RT as compared to those managed by surveillance (14).

An increased risk of second cancers after radiation therapy for stage I seminoma has been documented in a number of studies, and since this increased risk is expressed more than 10 to 15 years following RT, it is often not apparent in a series with a shorter follow-up (10,40). The largest study of second cancers in long-term survivors of testicular cancer was conducted by Travis *et al.* at the National Cancer Institute Cancer Epidemiology Division (13). This report combined 14 population-based registries including 10,534 patients with seminoma (all stages) treated with RT. Compared with matched cohorts from corresponding registries, the overall relative risk of a second non-testicular malignancy was 2.0 (95% C.I. 1.8–2.2). For a 35-year-old patient with seminoma, the cumulative 40–year risk of a second malignancy was 36%, compared with 23% in the normal population. These results were confirmed in a Dutch population-based study of more than 2,700 long-term GCT survivors in which the second malignancy risk with subdiaphragmatic RT was increased by 2.6–fold as compared to surgery alone (11). The increased risk associated with RT was similar to the increased cancer risk seen with smoking. There is some data from a modeling study to suggest that the increased risk of second cancer from adjuvant RT may be reduced by half if the para-aortic nodes alone are treated (41).

The testicular germinal epithelium is exquisitely sensitive to ionizing radiation. Although the contralateral testis is not located directly in the radiation field, scatter dose can be significant and may cause profound depression of spermatogenesis and compromise future fertility. Limiting RT target volume to the para-aortic and common iliac area reduces, but does not eliminate, concerns regarding RT-induced fertility (42). In the MRC randomized trial of para-aortic radiation alone versus para-aortics and pelvis radiation, the median time to a normal post-treatment sperm count was 13 months in those patients who received treatment directed to the para-aortics alone. This was significantly better than the patients with treated para-aortic and pelvic lymph nodes (20 months). However, at three years of follow-up, there was no significant difference in sperm counts between the two groups. Testicular shielding has been shown to reduce testicular dose, even in patients with treated para-aortics alone, and should be used in all patients who wish to retain fertility after treatment (43).

Most relapses occur within two years of RT. Follow-up efforts should therefore concentrate on the first two years after RT and include clinical examination, chest x-ray (CXR) and pelvic computed tomography (CT) (only if a para-aortic strip RT is used).

2.2.3 Adjuvant chemotherapy

Another strategy that has been investigated to reduce the long-term toxicity of adjuvant radiation therapy in stage I seminoma is the use of adjuvant chemotherapy. The MRC/EORTC has conducted a randomized phase III study of 1,447 patients comparing adjuvant RT and a single course of carboplatin. A recent update of the study with 6.5–years median follow-up reported that the 5–year relapse rates were 4% and 5.3%, respectively for RT and chemotherapy with a HR of 1.25 (90% C.I. 0.83–1.89) (48). Sixty-seven percent of those who relapsed in the carboplatin arm did so in the retroperitoneum alone. An unexpected finding in this study was a reduction in the observed number of second primary germ cell tumours in patients treated with adjuvant chemotherapy with a five-year event rate of 1.96% with RT versus 0.54% with chemotherapy.

Data from other single institution series indicate that if adjuvant chemotherapy is given in this setting, two courses of carboplatin results in a lower relapse rate compared to that seen with a single dose. A prospective cohort study reported eight relapses in 93 patients treated with a single cycle carboplatin compared to no relapses in 32 patients treated with two cycles of carboplatin (45). The dosing strategy for carboplatin used in this study was 400mg/m^2. However, a more contemporary practice is carboplatin dosing based on an area under the curve of seven (AUC7), which is typically around 15% greater than using a per metre square-dosing regimen (46). This dosing schedule was used in MRC TE19 and the Spanish Germ Cell Cancer Cooperative Group trials (15,23). Aparicio reported on the prospective treatment of patients with risk factors for recurrence (tumours > 4 cm and/or rete testis invasion) with two cycles of AUC7 carboplatin and the five-year relapse rate was 3.8% (23). As observed in the MRC TE19 study, most relapses were retroperitoneal, thus necessitating ongoing abdominopelvic CT imaging. When giving a single dose of carboplatin at an AUC7, it is important to calculate the dose based on an accurate measurement of the glomerular filtration rate and not rely on a calculation of the creatine clearance based on the serum creatinine level (46).

One major unanswered question about carboplatin chemotherapy in this setting is whether there are late effects of treatment. Like radiation, cisplatin-based chemotherapy has been associated with an increased risk of cancer and heart disease. Although the total dose of the chemotherapy used in the treatment of stage I seminoma is low compared to the chemotherapy given for more advanced stage disease, only long-term follow-up studies will inform us whether there are long-term health issues associated with one or two doses of carboplatin (47).

The relapse pattern after adjuvant single-agent carboplatin mandates that continued cross-sectional imaging of the retroperitoneal lymph nodes is required (similar to surveillance). The vast majority of relapses occur within the first three years and follow-up efforts should thus concentrate on this time period with less frequent visits thereafter.

2.2.4 Consensus recommendations

Level II Evidence	Grade of Recommendation
1. Patients should be informed of all treatment options, including the potential benefits and side effects of each treatment. This discussion should include discussion of the possible salvage treatment effects.	B
2. In a patient willing and able to adhere to a surveillance program, this should be considered as the management option of choice (assuming facilities are available for suitable monitoring).	B
3. A risk-adapted approach with surveillance for low-risk patients and treatment for those at higher risk of relapse cannot be recommended at the present time – the prognostic model on which this approach is based has not been validated and also has poor discriminative ability.	B
4. When adjuvant therapy is chosen, both RT and adjuvant carboplatin are reasonable options.	B
5. Patients with inflammatory bowel disease or horseshoe or pelvic kidney should be managed with surveillance or carboplatin rather than radiation.	B
6. If either RT or carboplatin is chosen, the patient should be advised to consider sperm banking to preserve fertility.	B
7. If RT is recommended patients must be made aware of the potential long term risks of cardiovascular disease and induction of second malignancy.	B
8. RT should be given to a dose of 20 Gy/10f/2 weeks (or biologically equivalent dose).	B

Level I Evidence	Grade of Recommendation
1. If para-aortic strip RT is given, ongoing pelvic surveillance should be performed.	A
2. If adjuvant carboplatin is used, ongoing retroperiteonal surveillance is necessary.	A
If carboplatin is recommended, patients must be made aware of the potential for late effects from chemotherapy with regard to cardiovascular disease and second malignancy.	

2.3 Management of Stage II Testicular Seminoma

At work-up after orchiectomy, about 15 to 20% of patients have radiologically-involved para-aortic lymph nodes (70% have small bulk disease, lymph nodes < 5 cm – stage IIA/B). The number of patients with stage II disease is too small to mount phase three studies of management, and treatment decisions must be based on reports from single institutions where patients have been treated in a uniform fashion.

The most important prognostic factor in stage II seminoma is the bulk of retroperitoneal tumour. Lymph node size was the only factor that predicted recurrence in 95 patients with stage II seminoma treated with RT at the PMH between 1981 and 1999 (48). The five-year relapse-free rate in 79 patients with nodal disease of less than 5 cm (stage IIA/B) was 91% (7 of 79 patients), compared to 44% (9 of 16 patients) in patients with bulkier disease (stage IIC). Thirteen patients were treated with chemotherapy at relapse, and nine were free of disease at last follow-up. Two patients had salvage RT in the early 1980s (they would now be treated with salvage chemotherapy) and one was free of disease at follow-up. These five patients plus one additional patient who refused salvage RT died of progressive seminoma. Thirty-one patients (23 with stage IIC) received initial chemotherapy for stage II disease with two relapses, one of whom was salvaged by second-line chemotherapy. These results are similar to other series in the literature (Table 2) and support the continued use of primary RT in stage II patients with small bulk lymphadenopathy (49–52). However, the high failure rate following RT in patients with bulky retroperitoneal disease, the fact that not all patients with recurrence were salvaged, and the apparently better outcome of similar patients who were treated with chemotherapy at diagnosis, mandates primary chemotherapy instead of radiation in this population.

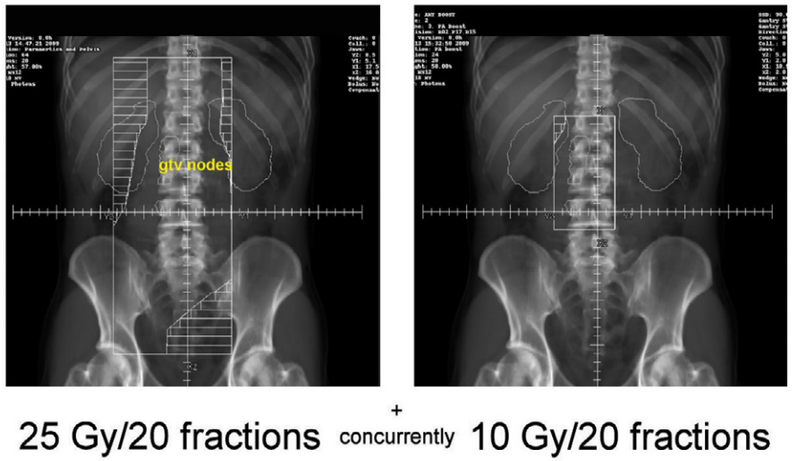
TABLE 2 Results of Retroperitoneal RT in Stage IIA/B Seminoma

Author	No. of Patients	Years of Study	No. of Relapses (%)	Cause-Specific Survival
Bayens *et al.* 1992 (49)	29	1975–1985	7 (24%)	93%
Zagars *et al.* 2001 (51)	37	1984–1999	5 (13.5%)	100%
Chung *et al.* 2004 (48)	79	1981–1999	7 (8.8%)	97.5%
Classen *et al.* 2003 (52)	87	1991–1994	4 (4.6%)	100%
Vallis *et al.* 1995 (50)	48	1974–1989	3 (6%)	98%

Staging should not be the only parameter used to decide on treatment of retroperitoneal disease in patients with stage II seminoma. Tumour bulk must also be considered. For example, a patient with nodal disease extending from 8–9 cm from L1 to L5 in the retroperitoneum with a maximum transverse diameter of 3.5 cm would be classified as having stage IIB disease. In patients with bulky disease such as this, chemotherapy rather than RT should be used (48). Other patient and tumour-related factors should also be taken into account. Lymph node masses that are situated laterally may necessitate irradiating a large volume of one or both kidneys or the liver in order to adequately encompass the tumour. The same situation may arise in cases of abnormal anatomy, such as with horseshoe or pelvic kidney. These patients are better treated with chemotherapy because of an unacceptably high-risk of radiation toxicity.

The technique of radiation in stage II seminoma is similar to that used in stage I disease. The treatment volume includes the gross tumour as well as the para-aortic and ipsilateral common and external iliac lymph nodes. The radiation dose is typically 25 Gy in 20 daily fractions plus a boost of a further 10 Gy to the gross lymphadenopathy (given either concurrently over 20 fractions or subsequently in five to eight fractions) (Fig. 3) (48).

FIGURE 3
RT fields for stage II A/B disease



The use of combination carboplatin and radiation therapy in stage IIA/B seminoma has been suggested by Gilbert *et al.* (53). He and his colleagues described a series of 62 patients treated with one to two courses of carboplatin four to six weeks prior to radiation therapy. Since 1997, 29 patients have been treated with one course of carboplatin prior to radiotherapy to the para-aortic nodes alone and no relapses have been observed. This approach is attractive in that it offers the potential of reducing the treatment volume with RT (and thereby likely decreasing the risks of late effects) while at the same time improving the results, as compared to RT alone (and avoiding the need for more aggressive chemotherapy regimens). However, this approach cannot be accepted as routine practice without further studies, especially as the use of combined-modality therapy has been shown to increase the risk of second non-germ cell malignancies and cardiovascular disease in long-term survivors (13,39).

If chemotherapy is recommended as primary treatment (or for relapse after RT), three cycles of bleomycin, etoposide and cisplatin (BEP) or four courses of etoposide and cisplatin (EP) should be considered as standard options. The need for bleomycin has not been clearly proven so consideration should be given to omitting it in older patients and those with poor pulmonary function.

2.3.1 Residual mass following radiotherapy or chemotherapy

Following treatment, patients with stage II disease require follow-up imaging of the abdomen after treatment until complete regression of disease has occurred. A stable persistent mass often represents fibrosis or necrosis and only the minority contains active tumour. However, the possibility of a non-seminomatous component to explain the residual mass needs to be kept in mind even in patients whose primary tumours show pure seminoma. In addition, surgical extirpation of retroperitoneal nodes in the setting of seminoma is technically challenging and associated with a higher acute morbidity (54). Therapeutic options for patients with residual masses after treatment include observation, surgical removal or biopsy. If the mass grows or biopsy confirms viable malignancy, second-line chemotherapy or, very rarely, RT can be considered. The value of positron emission tomography (PET) scanning is controversial and the decision to perform surgical resection of the residual mass should not be based exclusively on a positive PET image since false-positive results appear to be common (55–58). However, false-negative results are less frequent in this setting and it is reasonable to consider observing patients with masses of more than 3 cm and who have negative PET scans (58).

A small number of centres have reviewed their experience with surgery for residual masses in the setting of seminoma. The Memorial Sloan-Kettering Cancer Centre (MSKCC) group published their data in 55 of 104 patients who demonstrated residual masses post-chemotherapy (59). Of these 55 patients, 32 (58%) had a formal RPLND and 23 (42%) had multiple intraoperative biopsies performed, as the residual mass was deemed unresectable. Among patients with a mass of more than 3 cm (n = 27), eight (30%) had residual viable tumour. Interestingly two of the eight recurrences were teratoma and six were seminoma. No patients with tumours of less than 3 cm had viable tumour at final pathology. Among the eight patients with pre-operative tumour masses of more than 3 cm and positive pathological findings, six remained with no evidence of disease (NED) at 47–month follow-up. Two patients, both with poorly defined masses observed on CT, died of disease. Given this high proportion of persistent malignancy, MSKCC investigators have recommended resection or biopsy of masses of 3 cm or larger. In contrast, Culine and Droz have suggested that as long as the retroperitoneal mass continues to decrease in size after treatment, then continued observation is a reasonable strategy (60).

The use of RT in patients with post-chemotherapy masses is often mentioned as a therapeutic option. Horwich and colleagues published their experience with both observation and RT for these masses and found that the recurrence rate was similar whether RT or observation was performed (61). The MRC Testicular Tumour Working Party published a retrospective pooled analysis assessing the role of RT for post-chemotherapy residual mass among men with seminoma (62). Among the 123 patients with a residual abdominal residual mass, 56% received consolidative RT. There was no significant difference in outcome among patients who did or did not receive RT. Given these data, it was concluded that routine RT is not indicated for a post-chemotherapy residual mass.

It is clear that patients with a residual mass of 3 cm or less can safely be observed. For patients with bulkier disease, upfront surgery or observation can be performed, with treatment reserved for masses that increase in size.

2.3.2 Consensus recommendations

Level II Evidence	Grade of Recommendation
1. In Stage IIA disease, RT should be considered standard treatment if there are no contraindications. Otherwise, chemotherapy is an option.	B
2. In Stage IIB disease, chemotherapy or RT are reasonable treatment approaches.	B
3. In Stage IIC disease, chemotherapy should be considered the standard treatment approach.	B
4. For patients with residual mass after chemotherapy: ▪ The usefulness of PET scanning is controversial ▪ Masses < 3 cm in diameter can likely be safely observed ▪ Patients with residual masses > 3 cm in diameter can be considered for immediate surgery or close observation	B
5. Surgery in this setting is technically challenging and associated with a higher morbidity	B

2.4 Summary

Adjuvant radiation, chemotherapy and surveillance are acceptable treatment options in stage I seminoma. However, in a compliant patient, surveillance should be considered as the management approach of choice. If RT is chosen as the management strategy, then a dose of 20 Gy in 10 daily fractions over 2 weeks to the para-aortic ± upper pelvic nodes is appropriate. Patients should be advised that there are potential carcinogenic and cardiovascular risks with this approach. If the para-aortics alone are treated then, ongoing post-radiation surveillance of the pelvis should be performed. If adjuvant carboplatin is chosen as the management strategy, then one to two courses of treatment can be given.

In stage II seminoma, radiation therapy is the treatment of choice for low tumour volume stage IIA/B cases, with chemotherapy being preferred for more advanced disease.

Long-term follow-up of patients with testicular seminoma is recommended to deal with issues of screening for and treating side effects of treatment as well as assessing the true rate of second malignancies in patients managed by surgery alone. Consideration should be given to enhanced screening for both treatment-induced second malignancies and cardiovascular disease as part of a patient's ongoing management.

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C3

Clinical Practice Guidelines on the Management of Low-Stage Non-Seminomatous Germ Cell Tumours of the Testis

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Committee 3

CONTENTS

Clinical Practice Guidelines on the Management of Low-Stage Non-Seminomatous Germ Cell Tumours of the Testis

3.1 Introduction

Approximately 50% of patients with non-seminomatous germ cell testicular cancer (NSGCT) have low-stage disease at diagnosis (clinical stage [CS] I, IIA and IIB). Clinical stage I is defined as normal post-orchiectomy serum levels of alpha-fetoprotein (AFP), human chorionic gonadotrophin (hCG), and lactate dehydrogenase (LDH) without evidence of metastatic disease on imaging studies of the chest, abdomen and pelvis (1,2). Clinical stage IIA-B patients have non-bulky retroperitoneal adenopathy (< 2 cm for IIA, 2–5 cm for IIB), with or without elevated serum tumour markers (STM), without evidence of distant metastasis. While there is consensus that CS I patients with elevated STM (classified as CS IS), CS IIC (retroperitoneal adenopathy > 5 cm) and CS III (distant metastasis) should receive primary chemotherapy, the optimal management of low-stage NSGCT is controversial. Surveillance, retroperitoneal lymph node dissection (RPLND), and primary chemotherapy are established treatment options for CS I and all are associated with long-term survival rates of 97% or greater. For CS IIA-B, long-term survival rates of 95% or greater have been reported for approaches that employ either induction chemotherapy or RPLND as the initial intervention.

3.2 Data Acquisition

A literature search was performed on MEDLINE to identify fully published English language reports from 1980 to 2009 on outcomes of adult human subjects with CS I, IS, IIA, and IIB NSGCT from randomized controlled trials (RCTs), meta-analyses, clinical practice guidelines, prospective or retrospective cohort studies, case-control studies, or case series. Meeting abstracts, letters, editorials, commentaries, editorials, case reports, studies with sample sizes smaller than 50 patients, and studies limited to pediatric germ cell tumours were excluded. Search terms included “testicular neoplasms”, “neoplasms, germ cell and embryonal”, “lymph node excision”, “retroperitoneum”, “chemotherapy”, “surveillance”, “alpha-fetoprotein”, “human chorionic gonadotrophin”, “lactate dehydrogenase”, “neoplasm staging”, and “prognosis”. Additional articles were also obtained from the bibliography of select articles.

Primary outcome measures included: overall survival, cancer-specific survival, recurrence, treatment-related toxicities, health-related quality of life (HRQOL), and need for additional therapy. The committee met twice to review the results of the systematic review and formulate guideline recommendations. The hierarchy of evidence in support of the panel’s recommendations was defined according to the Modified Oxford Center for Evidence-Based Medicine Grading System for Guideline Recommendations used by the International Consultation on Urological Disease. Given the excellent long-term cancer-specific survival of low-stage NSGCT with appropriate therapy, the committee’s recommendations attempt to minimize serious long-term treatment-related sequelae without compromising survival. Patients with low-stage NSGCT should be assessed and have management plans developed at institutions with expertise in the diagnosis, staging, pathological assessment, and treatment of testicular cancer (Grade B [4-9]). A randomized control trial (RCT) in advanced germ cell tumours showed that patients treated in centres of excellence had improved survival compared to those treated in community centres (4).

3.3 Clinical Stage I NSGCT

An estimated 20%–30% of patients with CS I NSGCT have occult metastasis, with the retroperitoneum being the most common site. As such, any treatment after orchiectomy represents over-treatment for the majority of patients. Long-term cancer-specific survival approaches 100% for all patients, regardless of the initial treatment strategy. Thus, efforts to reduce treatment-related toxicity are paramount in the management of these patients.

3.3.1 Risk stratification

CLINICAL QUESTION: What clinical and histopathological parameters should be used to risk-stratify patients with CS I NSGCT for the presence of occult metastasis?

2009 Recommendations for Risk Stratification	Grade
1. The committee recommends the use of lymphovascular invasion (LVI) (10–21) to risk-stratify patients for the presence of occult metastatic disease. Predominance of embryonal carcinoma (EC) and MIB–1 staining may also be used as prognostic factors (10–21). There is insufficient evidence for the use of these markers to risk-stratify patients for the presence of systemic versus retroperitoneal metastasis.	B
2. The committee recommends the assessment of primary tumour specimens for histopathological prognostic factors by pathologists with expertise in testicular cancer (22).	B
3. There is no role for the use of pre-orchiectomy STM in the risk-stratification of CS I NSGCT.	B
4. For staging purposes, abdominal-pelvic imaging with computed tomography (CT) with intravenous and oral contrast is recommended.	B
5. Magnetic resonance imaging (MRI) is a less well-established alternative to CT if contraindications to CT exist.	B
6. A size cut-off of 10 mm is insufficient to rule out the presence of retroperitoneal metastasis (23,24) and lymph nodes less than 10 mm should be considered "suspicious" if they are located in the appropriate primary landing zone.	C
7. Computed tomography and plain radiography are acceptable modalities for imaging the thorax. There is no proven role of positron emission tomography (PET) in CS I NSGCT (25,26).	B

Literature review and analysis

Numerous studies have attempted to identify risk factors for the presence of occult metastasis in patients with CS I NSGCT. The most commonly reported risk factors for occult metastasis are the presence of lymphovascular invasion (LVI) and a predominant component of embryonal carcinoma (EC). Embryonal carcinoma predominance is, however, not clearly defined and published cut-off values range from 45%–90%. The reported rate of occult metastasis for CS I patients with LVI and EC predominance varies from 45%–90% and 30%–80%, respectively (10–19). In the absence of these two risk factors, the reported rate of occult metastasis is less than 20%. Other identified risk factors include advanced pT stage, absence of mature teratoma, absence of yolk sac tumour, presence of EC, percentage of MIB–1 staining, increasing primary tumour size, and older patient age. In a pooled analysis of 23 studies assessing factors associated with occult metastasis in CS I NSGCT, Vergouwe *et al.* identified LVI (odds ratio [OR] 5.2), MIB–1 staining > 70% (OR 4.7), and EC predominance (OR 2.8) as the strongest predictors (19).

Numerous risk groups and prognostic indices have been proposed based on the presence/absence of several of these risk factors, most commonly on the basis of LVI and EC predominance (10–14,16,17,20,21). Only one of these prognostic models has been prospectively validated, and none have incorporated the results of abdominal-pelvic CT imaging (20,21).

The committee recommends review of primary tumour specimens by pathologists with expertise in testicular cancer prior to finalization of treatment recommendations. In a RCT examining treatment for CS I NSGCT, 5 of 382 specimens (1.3%) were re-classified as seminomas by centralized pathological review (22).

Despite improvements in CT imaging, the retroperitoneum continues to be the most difficult anatomic site to stage clinically. There is no consensus regarding size criteria for retroperitoneal lymph nodes that constitutes a "normal" abdominal CT scan. A size cutoff of 10 mm is frequently used to identify enlarged lymph nodes, but false-negative rates up to 63% have been reported when this size criterion is used. An understanding of the primary drainage sites for left- (para-aortic) and right-sided tumours (inter-aorto-caval and para-caval) has led to efforts to increase the sensitivity of abdominal CT imaging by decreasing the size criteria for clinically positive lymph nodes in the primary landing zone, and a size criterion as small as 4 mm has been proposed. Leibovitch *et al.* showed that using a size cut-off of 4 mm in the primary landing zone and 10 mm outside this region was associated with a sensitivity and specificity for pathologic stage II disease of 91% and 50%, respectively (23). In a similar study, Hilton *et al.* reported a sensitivity and specificity of 93% and 58%, respectively, using a cut-off of 4 mm for lymph nodes in the primary landing zone that were anterior to a horizontal line bisecting the aorta (24).

Fluorodeoxyglucose-positron emission tomography (FDG-PET) imaging has not been shown to improve staging sensitivity compared to CT alone (25,26).

3.3.2 Treatment selection

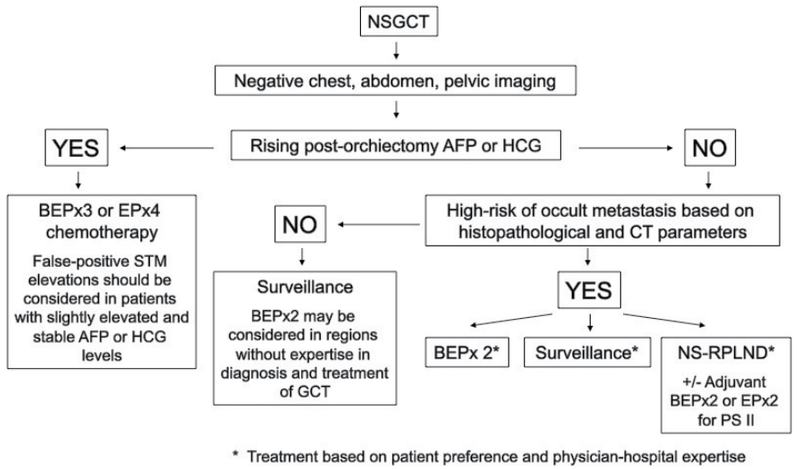
CLINICAL QUESTION: What is the preferred treatment for CS I NSGCT?

2009 Recommendations for Treatment Selection	Grade
1. The committee recommends that patients should be made aware of all treatments (surveillance, primary chemotherapy, and RPLND), potential short- and long-term treatment-related toxicity, as well as the risk and nature of any additional treatments. The panel recommends that patients be informed of their risk of occult metastasis based on the presence of known risk factors (as listed above) and a risk-adapted approach should be employed.	B
2. The committee recommends active surveillance for patients at low-risk of occult metastasis unless this approach is not feasible (16,20,21,27–33).	B
3. For patients at high risk for occult metastasis, active surveillance, RPLND, and primary chemotherapy with two cycles of a cisplatin-based chemotherapy are all acceptable treatment options (13,14,22,33–46).	B

For patients who desire active treatment, the use of primary chemotherapy or RPLND should be based on the specific expertise of the treating physician and institution. Primary chemotherapy is the preferred option for patients without access to a surgeon experienced in RPLND, as the outcome is less reliant on the expertise of the treating physician and facility.

An algorithm for the management of CS I NSGCT is illustrated in Figure 1.

FIGURE 1
Treatment algorithm for clinical stage I NSGCT



Literature review and analysis

There are no RCTs that compare the standard treatment approaches for CS I NSGCT. The only published RCT compared one cycle of bleomycin-etoposide-cisplatin (BEPx1) chemotherapy versus modified-template RPLND (with BEPx2 for patients with pathological stage II disease) (22). Primary chemotherapy with BEPx1 reduced the risk of relapse compared to RPLND, but no cancer-specific deaths were reported in either arm. This trial has been criticized as it compared two non-standard treatment approaches for CS I NSGCT and was confounded by suboptimal pre-treatment staging (47).

Long-term cancer-specific survival approaches 100% when CS I NSGCT patients are treated by active surveillance, RPLND, and primary chemotherapy. Thus, it is inappropriate to recommend against any specific treatment option as patient preferences may vary and there are relative advantages and disadvantages of each approach in terms of treatment-related toxicity, the need for subsequent treatment, and intensity of surveillance testing and imaging.

The rationale for surveillance is based on the following:

- Majority of patients with CS I NSGCT are cured of their cancer following orchiectomy (thus avoiding unnecessary treatment-related morbidity and cost).
- The ability to salvage patients who relapse based on the more than 90% cure rates in patients with good-risk advanced disease treated with cisplatin-based chemotherapy.

The disadvantages of surveillance are that it is associated with the highest risk of relapse, the need for long-term (at least five years) surveillance, the potential for small malignant neoplasms (SMNs) due to intensive surveillance CT imaging, and the fact that relapsing patients may require more intensive therapy at the time of relapse than if they had received treatment at diagnosis. Compliance with the follow-up protocol represents a prerequisite for the early detection of relapse and success of surveillance. Published surveillance series have reported results on over 2,500 men, with a mean relapse risk of 28% and 1.2% cancer-specific mortality. The 10 largest series are summarized in Table 1 (16,20,21,27–33). More than 90% of relapses occur within the first two years but very late relapses (> 5 years) are seen in up to 1% of patients (as many as 5% in some reports) (28). In older surveillance series, relapse at systemic sites or with elevated (STMs) was common and only 30%–40% of relapses were restricted to the retroperitoneum. In a more contemporary series, 65%–75% of relapses are contained in the retroperitoneum, with or without elevated serum tumour markers (33).

TABLE 1 Surveillance Series for Clinical Stage I NSGCT

Author	Patients (Total)	Relapses (%)	Median Follow-Up (months)	Time to Relapse (months)	% Systemic Relapse†	GCT Deaths (%)
Read *et al.* (21)	373	100 (27)	60	3 (1.5–20)	39%	5 (1.3)
Daugaard *et al.* (28)	301	86 (29)	60	5 (1–171)	66%	0
Freedman *et al.* (20)	259	70 (32)	30	NR	61%	3 (1.2)
Colls *et al.* (27)	248	70 (28)	53	NR	73%	4 (1.6)
Francis *et al.* (29)	183	52 (28)	70	6 (1–12)	54%	2 (1)
Gels *et al.* (30)	154	42 (27)	72	4 (2–24)	71%	2 (1)
Sharir *et al.* (32)	170	48 (28)	76	7 (2–21)	79%	1 (0.5)
Sogani *et al.* (16)	105	27 (26)	136	5 (2–24)	37%	3 (3)
Tandstad *et al.* (33)	350	44 (13)	56	8	27%	0
Kollmannsberger *et al.* (31)	223	59 (26)	52	NR	NR	0

† Systemic relapse defined as relapse with elevated serum tumour markers and/or relapse in tissue other than retroperitoneal lymph nodes. Abbreviation: NR = not reported

The rationale for RPLND for CS I NSGCT is based on several factors:

1. The retroperitoneum is the most common site of occult metastatic disease and the risk of systemic disease is low,
2. 15%–25% incidence of retroperitoneal teratoma (which is resistant to chemotherapy) in those with occult metastasis,
3. Low risk of abdominal-pelvic recurrence after full, bilateral RPLND thereby obviating the need for routine surveillance CT imaging,
4. High cure rates after RPLND alone for patients with low-volume retroperitoneal metastasis and teratoma,
5. Avoidance of chemotherapy in more than 75% of patients if adjuvant therapy is restricted to those with extensive retroperitoneal metastases,
6. High salvage rate of relapses with good-risk induction chemotherapy,
7. Low short- and long-term morbidity when a nerve-sparing RPLND is performed by experienced surgeons.

The disadvantages of RPLND include: since all patients undergo major abdominal surgery, it requires the availability of experienced surgeons and thus may not be deliverable to all patients; and it is associated with the highest rate of double therapy. A summary of the seven largest RPLND series for CS I NSGCT are listed in Table 2 (13,14,22,34–37).

The rate of pathologic stage II in these series ranges from 19%–28% and an estimated 66%–81% of these patients were cured after RPLND alone (where adjuvant chemotherapy was not dictated by protocol) (13,14,17,18,34,36,48). The long-term cancer-specific survival with RPLND (± adjuvant chemotherapy) approaches 100% and the risk of late relapse is negligible. Most RPLND series have reported retroperitoneal recurrences in less than 2% of patients, demonstrating its efficacy for control of the retroperitoneum (13,34,36). Published results are generally from high-volume hospitals and the morbidity of RPLND in less experienced hands is poorly characterized.

TABLE 2 Summary of Published Series of RPLND for Clinical Stage I NSGCT

Author	Patients (Total)	PS II (%)	% Teratoma in Retro-peritoneum	% Relapse PS I	% Relapse PS II	% Adjuvant Chemo-therapy	GCT Deaths (%)
Donohue *et al.* (34)	378	113 (30)	15%	12%	34%	13%	3 (0.8)
Hermans *et al.* (13)	292	67 (23)	NR	10%	22%	12%	1 (0.3)
Nicolai *et al.* (14)	322	61 (19)	NR	NR	27%	NR	4 (1.2)
Stephenson *et al.* (36)	297	83 (28)	15%	6%	19%	15%	0
Williams *et al.* (37)	76	37 (49)	NR	5%	11%	NR	0
Albers *et al.* (22)	173	31 (19)	NR	9%	–	19%	0
Richie *et al.* (35)	99	35 (35)	NR	6%	15%	15%	0

Abbreviations: PS = pathologic stage; NR = not reported

The rationale for primary chemotherapy for CS I NSGCT is based on:

1. Low risk of relapse in pathological stage II patients receiving two cycles of adjuvant cisplatin-based chemotherapy after RPLND,
2. Need for chemotherapy in up to 25% of patients who undergo RPLND, and
3. Favourable short-term toxicity of two cycles of chemotherapy.

The advantages of primary chemotherapy are that it is associated with the lowest risk of relapse of any modality and it can be delivered at community-based institutions. One disadvantage of primary chemotherapy is that it does not eradicate retroperitoneal teratoma, thus exposing patients to the potential for late relapse. However, not all patients with microscopic teratoma in the retroperitoneum are destined to progress after chemotherapy. Another disadvantage of chemotherapy is the potential for increased long-term risk of cardiovascular complications and SMN, as reported for patients receiving higher doses of chemotherapy. Furthermore, long-term surveillance with CT imaging of the retroperitoneum is necessary as it is the most common site of relapse. The risk of these complications after two cycles is unknown, though there appears to be no safe lower limit. Primary chemotherapy has been investigated in 11 published series, the majority of which have used BEPx2 (Table 3) (22,33,38–44,46,49). In men with LVI and/or EC predominance, it is possible to reduce the recurrence rate from 30%–60% down to about 2%–3%. In 7 of the 11 series, no deaths from GCT have been observed over an average median follow-up of five years. In the other four studies comprising a total of 406 patients, 13 relapses (3%) have been observed and 6 (46%) of these relapsing patients have died from GCT. Thus, while primary chemotherapy is associated with the lowest risk of relapse, these relapses are less amenable to salvage therapy as they are selected for chemoresistance.

TABLE 3 Published Series of Primary Chemotherapy for Clinical Stage I NSGCT

Author	Patients (Total)	Regimen	Median Follow-Up (months)	Relapses	Time to Relapse (months)	GCT Deaths (%)
Abratt *et al.* 1994 (38)	20	BEPx2 (E: 360)	31	0	–	0
Cullen *et al.* 1996 (42)	114	BEPx2 (E: 360)	48	2	7,18	2 (1.8)
Pont *et al.* 1996 (46)	29	BEPx2 (E: 500)	79	2	8,27	1 (3.5)
Ondrus *et al.* 1998 (49)	18	BEPx2 (E: 360)	36	0	–	0
Amato *et al.* 2004 (39)	68	CEBx2 (E: 360)	38	1	21	0
Bohlen *et al.* 1999 (40)	58	BEPx2 (E: 360) PVBx2 (20 pts)	93	2	22, 90	0
Chevreau, *et al.* 2004 (41)	40	BEPx2 (E: 360)	113	0	–	0
Oliver *et al.* 2004 (44)	148	BEPx1 (n=28); BEPx2 (n=46), BOPx2 (n=74). (E: 360)	33	6	NR	2 (1.4)

E: 360 refers to an etoposide dose of 360 mg/m²/cycle, E: 500 refers to an etoposide dose of 500 mg/m²/cycle.
Abbreviation: NR=not reported

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TABLE 3 Published Series of Primary Chemotherapy for Clinical Stage I NSGCT, *Cont'd*

Author	Patients (Total)	Regimen	Median Follow-Up (months)	Relapses	Time to Relapse (months)	GCT Deaths (%)
Dearnaley *et al.* 2005 (43)	115	BOPx2	70	3	3, 6, 26	1 (0.9)
Albers *et al.* 2008 (22)	191	BEPx1 (E: 500)	56	2	15, 60	0
Tandstad *et al.* 2009 (33)	382	BEPx1 (n=312), BEPx2 (n=70) (E: 500)	56	7	Range: 8-36	0

E: 360 refers to an etoposide dose of 360 mg/m²/cycle, E: 500 refers to an etoposide dose of 500 mg/m²/cycle.
Abbreviation: NR=not reported

3.3.3 Treatment-specific issues

Active surveillance

CLINICAL QUESTION: What is the appropriate surveillance schedule and treatment approach for relapses on active surveillance?

2009 Recommendations for Active Surveillance	Grade
1. Patients on active surveillance should undergo frequent evaluations in years 1–2 with chest imaging, CT abdominal-pelvic imaging, STM determinations, and clinical assessment. There is wide variation in the number of recommended CT scans in published guidelines with inadequate data available to make a firm recommendation.	D
2. Continued surveillance beyond five years with chest imaging, STM determinations, and clinical assessment is recommended. Patients should be informed of the risks of non-compliance in terms of the potential impact on the efficacy and intensity of salvage therapy. Surveillance is not recommended to those who are anticipated to be poorly compliant.	C
3. The standard treatment of relapse is induction chemotherapy though primary RPLND may be considered for patients with non-bulky (<5 cm) retroperitoneal disease, normal serum AFP and hCG, and availability of experienced surgeons (22,33,36,38-46,50).	B

Literature review and analysis

The surveillance schedule employed in published series is highly variable and no schedule has been demonstrated to be superior to another in terms of survival. All studies noted that about 90% of relapses occur within the first two years of follow-up, with about half of all relapses occurring within the first six months, 76%–90% occurring in the first year and 87%–100% occurring within two years. This finding supports a more frequent surveillance schedule early on with gradually increasing intervals between examinations over time. About 1% of relapses will occur more than five years

after (although one study reported 5% of relapses occurring more than five years after) (28). The frequency of abdominal-pelvic CT imaging varies across multiple series from 2 to 13 or more scans within the first five years of follow-up. A randomized trial of two versus five CT scans in years one to two reported no significant differences in survival, International Germ Cell Cancer Collaborative Group (IGCCCG) risk category at relapse, or clinical stage at relapse (51). However, this result has not changed the practice of many investigators as the control arm was not considered a "gold standard" and follow-up was short. Roughly 60%–80% of patients relapse in the retroperitoneum with or without elevated STM, 10%–20% have normal imaging but elevated STM, and 10%–20% relapse at systemic sites (most commonly pulmonary metastasis). In most surveillance series, relapses are treated with induction chemotherapy according to the IGCCCG risk category at relapse. However, satisfactory outcomes with primary RPLND (+/– adjuvant BEPx2 or EPx2) have been reported from centres of excellence for relapsing patients with non-bulky (< 5 cm) retroperitoneal disease and normal AFP and hCG (50). Non-compliance with the prescribed surveillance schedule has been reported in 35%–80% of patients in published series (52,53). These patients are at risk for advanced disease at relapse and might require more intensive therapy (with associated treatment-related sequelae) compared to compliant patients.

Retroperitoneal lymph node dissection

CLINICAL QUESTIONS: What is the optimal technique for performing RPLND? What is the role of adjuvant chemotherapy? What is the appropriate surveillance of patients after RPLND?

2009 Recommendations for RPLND	Grade
1. The committee recommends a full, bilateral template RPLND with nerve-sparing in patients who desire future paternity (54–56). Attempts at nerve-sparing should not compromise the completeness of resection.	B
2. The committee cites insufficient evidence to support laparoscopic RPLND as a therapeutic procedure (57–60).	D
3. Adjuvant chemotherapy and observation are acceptable treatment options for patients with pathological stage II disease and patients should be informed of the risk of relapse after RPLND and the potential benefits and risks of these approaches (61).	A
4. The routine use of CT abdominal-pelvic imaging is not recommended for the surveillance of patients after RPLND if a full, bilateral template dissection is performed by an experienced surgeon (13,34,36).	B
5. The committee emphasizes that RPLND should be performed by experienced surgeons (22).	B

Literature review and analysis

A full, bilateral template dissection is associated with lowest risk of abdominal-pelvic recurrence (< 2%) and a high rate of antegrade ejaculation (> 90%) when nerve-sparing techniques are employed (36,54–56,62,63). The development of nerve-sparing techniques has obviated the need for modified template dissections which are associated with inferior rates of antegrade ejaculation (51%–88%) and an increased risk of abdominal-pelvic recurrence (3%–23%) (35,55,64,65). Attempts at nerve-sparing should not compromise the completeness of resection. If a modified template is employed, removal of all para-caval and inter-aorto-caval nodes and para-aortic nodes above the inferior mesenteric artery is mandatory for right-sided tumours. For left-sided tumours, modified dissections should remove all para-aortic nodes and inter-aorto-caval nodes above the inferior mesenteric artery. Laparoscopic RPLND has been investigated at select institutions with extensive experience in minimally-invasive procedures. The therapeutic efficacy of this procedure has yet to be proven as the procedures were frequently performed for staging purposes only without therapeutic intent and the vast majority of patients with positive lymph nodes received adjuvant chemotherapy. Ipsilateral template dissections have been employed due to the difficulty in performing a full, bilateral dissection without intra-operative repositioning of the patient (59,60,66,67).

RPLND is a curative procedure in 60%–90% of patients with pathological stage N1 disease (five or fewer lymph nodes involved, size 2 cm or less, no extranodal extension) and up to 100% of patients with retroperitoneal teratoma regardless of pathological stage (36,61,68). The risk of relapse in patients with pathologic stage N2-N3 disease (more than five lymph nodes involved, size > 2 cm, extranodal extension) is greater than 50% (36,61,69). With two cycles of adjuvant cisplatin-based chemotherapy (most commonly BEPx2 or EPx2), the risk of relapse after RPLND is generally less than 1% (10, 70, 71). A randomized trial of adjuvant chemotherapy versus observation for pathologic stage II NSGCT showed a significant reduction in the rate of relapse (6% vs. 49%), but no difference in overall survival (61).

The risk of abdominal-pelvic recurrence after a full, bilateral RPLND performed by experienced surgeons is less than 2% (13,34,36). The RCT of BEPx1 versus modified RPLND reported an 11% local recurrence rate among patients with pathological stage I (22). It is noteworthy that the 191 patients undergoing RPLND in this trial were treated by 61 centres in Germany. Thus, patients who opt for RPLND should be referred to an experienced surgeon in order to achieve comparable results.

Primary chemotherapy

CLINICAL QUESTIONS: What is the optimal number of cycles and agents used for primary chemotherapy for CS I NSGCT? What is the role of surveillance CT abdominal-pelvic imaging following chemotherapy?

2009 Recommendations for Primary Chemotherapy	Grade
1. The committee recommends two cycles of cisplatin-based primary chemotherapy for CS I NSGCT (22,38–46).	B
2. Routine abdominal-pelvic CT should be included in the surveillance of patients after chemotherapy.	C

Literature review and analysis

The rationale for two cycles of primary chemotherapy for CS I NSGCT is based on the low risk of relapse after RPLND (1% or less) in patients with pathological stage II disease who receive adjuvant BEPx2 or EPx2 (10,22,70,71). As primary chemotherapy, the majority of studies have used two cycles of cisplatin-based chemotherapy (BEPx2 in five and bleomycin-vincristine-cisplatin (BOP) x 2 in two) (39–44,46). The durable efficacy and safety of these studies have established two cycles of chemotherapy as the standard regimen when given as primary treatment for CS I NSGCT and as adjuvant treatment after RPLND for pathological stage II. A recent RCT and a population-based study have investigated the use of BEPx1 as primary chemotherapy for CS I NSGCT (22,33). Over a median follow-up of less than five years in both studies, the risk of relapse after BEPx1 ranged from 1%–3% and the short-term cancer-specific survival approached 100% in both studies. BEPx1 needs to be compared to BEPx2 in a RCT to verify the safety and efficacy of this approach. Such a study has been initiated by the German Testicular Cancer Study Group.

Though relapses after primary chemotherapy for CS I NSGCT are uncommon (0%–7%), virtually all occur within the retroperitoneum. As such, abdominal-pelvic CT imaging should be used in the routine surveillance of patients after chemotherapy. The optimal timing of surveillance CT imaging is poorly defined.

Clinical stage IS NSGCT with elevated serum tumour markers

CLINICAL QUESTION: What is the preferred treatment for patients with elevated AFP or hCG after orchiectomy without evidence of metastasis on staging by chest-, abdomen- and pelvic-imaging studies?

2009 Recommendations for Clinical Stage IS NSGCT	Grade
1. Patients with no clinical evidence of metastatic NSGCT after orchiectomy other than persistently elevated or rising AFP or hCG should receive chemotherapy for advanced disease, usually with either BEPx3 or EPx4 (72–74). The committee recommends caution when interpreting slightly elevated and stable AFP and hCG levels after orchiectomy, as these may not necessarily stem from disseminated NSGCT.	B

Literature review and analysis

Studies of primary RPLND for CS IS NSGCT have reported that 37%–100% of patients subsequently required chemotherapy for retroperitoneal metastasis, persistently elevated STM, or relapse (72–74). There is general consensus that these patients should receive induction chemotherapy. The cancer-specific survival following chemotherapy for CS IS is greater than 90% (74,75).

Slightly elevated and stable STM levels after orchiectomy in patients without clinical evidence of disease should be interpreted cautiously as they may represent false positives for disseminated NSGCT. False-positive AFP elevations may occur in the setting of hepatobiliary diseases; further hereditary elevations of AFP have been reported. False-positive hCG elevations may occur with marijuana use and hypogonadism. In uncommon cases, minor stable and unexplained elevations of AFP or hCG are seen but are not clinically significant. However, such cases require close monitoring. Given the poor specificity of LDH elevations for GCT, elevated LDH levels unaccompanied by elevations in AFP or hCG or clinical evidence of disease should be interpreted cautiously.

An elevated STM level at a single point in time after orchiectomy does not necessarily indicate stage IS disease (particularly when pre-orchiectomy levels are not available). In this situation, the marker may be falling according to its expected biological half-life and levels should be repeated to clarify the situation.

3.4 Clinical Stage IIA and IIB NSGCT

CLINICAL QUESTION: What is the preferred treatment for CS IIA and IIB NSGCT?

2009 Recommendations for Clinical Stage IIA and IIB NSGCT	Grade
1. Patients with elevated post-orchiectomy AFP or hCG should receive induction chemotherapy (36,48). The committee considers induction chemotherapy and primary RPLND to be acceptable treatment options for patients with CS IIA with normal post-orchiectomy AFP and hCG levels (45,50,65,76–84).	B
2. For patients with CS IIB and normal post-orchiectomy AFP and hCG levels, induction chemotherapy is the preferred approach, although RPLND may be considered for select CS IIB patients with limited nodal involvement (45,50,65, 76–84).	B
3. Whereas patients should be informed of both treatments including the potential short- and long-term treatment-related toxicity, and the risk and nature of any additional treatment, the decision to proceed with induction chemotherapy or RPLND should be based on patient preference and the specific expertise of the treating physician and institution. Surveillance may be considered for patients with equivocal CT retroperitoneal findings who are otherwise considered low-risk for occult metastatic disease.	B

A treatment algorithm for clinical stage IIA and IIB NSGCT is outlined in Figure 2.

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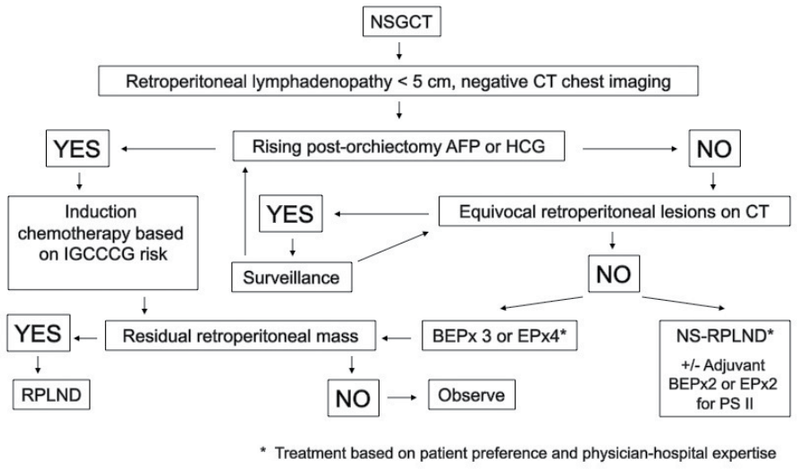
2009 Recommendations for Clinical Stage IIA and IIB NSGCT	Grade
4. Patients treated with induction chemotherapy should receive regimens appropriate to the IGCCCG risk and those with residual masses should undergo post-chemotherapy RPLND.	A
5. As with CS I NSGCT, the committee's recommendations for the technique of RPLND, the use of adjuvant chemotherapy, and the requirement of surgeon experience apply to RPLND for CS IIA and IIB NSGCT.	B
6. All patients with retroperitoneal adenopathy on staging by CT imaging studies should undergo staging by CT chest imaging prior to a treatment decision, although lesions less than 10 mm may represent false-positives and should be interpreted cautiously.	C
7. Patients with indeterminate lesions on staging by abdominal-pelvic CT imaging, who are otherwise considered low-risk for metastatic disease, may be observed closely to clarify subsequent treatment decisions.	C
8. Patients undergoing RPLND should have normal AFP and hCG levels confirmed preoperatively before proceeding with surgery.	B

A treatment algorithm for clinical stage IIA and IIB NSGCT is outlined in Figure 2.

FIGURE 2
Treatment algorithm for clinical stage IIA and IIB NSGCT



Literature review and analysis

The risk of systemic disease in patients with CS IIA and IIB NSGCT is substantially higher than in those with CS I. The identification of pulmonary metastasis may significantly influence treatment decisions. Given the increased sensitivity of CT imaging for pulmonary metastasis, the committee recommends staging by CT chest imaging in patients with retroperitoneal adenopathy. Approximately 13%–35% of CS II patients have pathologically negative lymph nodes at RPLND (50,65,76,77). Thus, patients with indeterminate lesions on staging by abdominal-pelvic CT imaging may be observed closely, with RPLND reserved for evidence of interval growth, or primary chemotherapy for evidence of rising STM.

The long-term cancer-specific survival of CS IIA and IIB patients treated by induction chemotherapy and RPLND should exceed 95%. There are no RCTs comparing these treatment approaches. A prospective, multicentre, nonrandomized trial of RPLND and two cycles of adjuvant chemotherapy versus induction chemotherapy did not demonstrate significant differences in recurrence (7% for RPLND vs. 11% for chemotherapy) or overall survival (65). A single-institution, non-randomized, retrospective comparison of RPLND (and two cycles of adjuvant chemotherapy for pathological stage II) and induction chemotherapy reported a significant reduction in the risk of recurrence with induction chemotherapy (98% vs. 79%), but with similar cancer-specific survival figures with both approaches (100% vs. 98%) (50). Furthermore, RPLND patients received fewer cycles of chemotherapy (mean 4.2 vs. 1.4), and 51% of RPLND patients avoided chemotherapy (50).

In two retrospective studies of patients with low-stage NSGCT treated by RPLND, the presence of elevated post-orchiectomy AFP or hCG levels were associated with a high risk of relapse (36, 48). In the largest series, persistent STM elevation was a significant and independent predictor of relapse (HR 5.6; 95% CI: 2.4–12.8; $P < 0.001$) (36). In two other series, results analyzed by univariate analysis showed that a persistently elevated AFP or hCG levels were associated with an increased risk of relapse (48). These data support the concept that persistent elevation of AFP or hCG after orchiectomy identifies patients with low-stage NSGCT who are unlikely to be cured by RPLND. Thus, the patients should receive induction chemotherapy.

The arguments in favour of RPLND for CS IIA-B are:

1. About 13%–35% of patients have pathologically negative retroperitoneal lymph nodes (50,65,76,77),
2. Approximately 30% have retroperitoneal teratoma which is resistant to chemotherapy (50,85),
3. Long-term cancer-specific survival is 98%–100% with RPLND (+/– adjuvant chemotherapy) (50 65,76,77),
4. Between 10%–52% avoid any chemotherapy (50,65,76,77), and
5. Ejaculatory function is preserved in 70%–90% of patients (65,76,86)

The disadvantage of RPLND is that additional chemotherapy is required in 50% or more of patients: 13%–15% have persistence of disease after RPLND and require a full induction chemotherapy regimen, and high-quality RPLND may not be deliverable at all institutions (50,65).

The arguments in favour of induction chemotherapy is the fact that 60%–78% of patients achieve a complete response and avoid post-chemotherapy surgery, and cancer-specific survival rates of 96%–100% are reported (45,50,65,78–84). The disadvantages of chemotherapy are that all patients are exposed to the risk of long-term toxicity of chemotherapy and those who do not undergo post-chemotherapy RPNLD require surveillance by abdominal-pelvic CT imaging and are potentially at risk of relapse with chemo-refractory GCT due to unrecognized, unresected, small-volume teratoma in retroperitoneal lymph nodes.

3.5 Summary

Recommendations

- The committee recommends the treatment of NSGCT in centres with medical, surgical and diagnostic expertise in testicular cancer.
- Cancer-specific survival for CS I and CS IIA-B should approach 100% and 95%-100%, respectively.
- CS I patients should be made aware of all treatments (surveillance, primary chemotherapy, and RPLND) and potential side-effects.
- For CS I patients at low risk for occult metastasis, surveillance is preferred.
- For patients at high-risk for occult metastasis, all three options may be considered.
- For immediate treatment, the choice between primary chemotherapy and RPLND should be based on patient preference and the specific expertise of the treating institution.
- Patients with rising post-orchiectomy serum AFP or hCG (CS IS and CS IIA-B) should receive induction chemotherapy.
- Induction chemotherapy or RPLND may be considered for CS IIA-B patients with normal post-orchiectomy AFP and hCG.
- Surveillance may be considered for patients with equivocal CT retroperitoneal findings who are otherwise considered low-risk for metastatic disease.

3.6 Other Guidelines and Consensus Statements

The European Society of Medical Oncology (87), European Germ Cell Cancer Consensus Group (88,89), European Association of Urology (90), National Comprehensive Cancer Network (91), Cancer Care Ontario Program in Evidenced-Based Care (92), and Canadian professional societies of urology, medical oncology and radiation oncology (93) have all recently published guidelines or consensus statements on managing low-stage NSGCT. The committee has evaluated these sources' recommendations and found them to be generally consistent with the ICUD-SIU clinical practice guidelines for low-stage NSGCT. The major difference between the European organizations and the committee's recommendations is the exclusion of RPLND as a standard treatment approach for high-risk CS I NSGCT and CS IIA and IIB NSGCT.

3.7 Conclusion

These clinical practice guidelines are designed to improve clinical practice based on the available evidence and expert opinion of the committee. The committee's recommendations attempt to maximize cure and minimize treatment-related morbidity. As such, deviation from these recommendations should be based on sound clinical judgment considering the unique situation of the patient and the expertise of the treating physician and institution.

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C4

Testicular Cancer: Treatment of Advanced Disease

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Testicular Cancer: Treatment of Advanced Disease

Committee 4

4.1 Introduction

Historical background: from cisplatin and PVB to BEP

Introduction of cisplatin

The introduction of cisplatin in the mid-1970s revolutionized the systemic treatment of germ cell tumour (GCT) patients with advanced disease. The landmark study conducted at Indiana University by Einhorn and colleagues (1), reported in 1977, showed that the so-called PVB chemotherapy regimen followed by maintenance vinblastine resulted in a markedly improved clinical outcome in patients with disseminated testicular cancer. Cisplatin-based chemotherapy, either alone or in combination with surgical resection of postchemotherapy residual masses, resulted in complete responses in 85% and potential cure in the majority of patients with newly diagnosed metastatic testicular cancer. The toxicity of PVB chemotherapy consisting of four cycles of cisplatin 20 mg/m^2 daily for five days every three weeks, vinblastine every three weeks, and bleomycin weekly was distinct but moderate and acceptable. Since severe neurotoxicity was commonly associated with the use of vinblastine, a randomized study was performed by the performed by the European Organization for Research and Treatment of Cancer (EORTC) Genito-Urinary Group in 214 metastatic non-seminomatous testicular cancer patients comparing the vinblastine dose of 0.4 mg/kg/cycle in the PVB regimen with a reduced vinblastine dose of 0.3 mg/kg/cycle (2). Complete response (CR) rates to both regimens were identical (68% and 71%, respectively) and there was no significant difference in disease-free and overall survival, demonstrating that the use of reduced dose vinblastine was as effective and less toxic. It was subsequently shown that maintenance therapy was not necessary to maintain the efficacy of the PVB regimen (3,4).

The Southeastern Cancer Study Group (SECSG) performed a randomized study to assess the value of maintenance therapy and randomized between cisplatin, vinblastine, and bleomycin (PVB) versus PVB plus doxorubicin induction chemotherapy, with a second randomization comparing maintenance vinblastine versus no further therapy. The results reported in 1988 indicated that maintenance therapy was of no additional value with respect to treatment outcome (3). An Australian study also investigated the role of 6 months maintenance therapy with vinblastine in 253 advanced testicular cancer patients treated with cisplatin, vinblastine, and bleomycin followed by surgical resection of residual masses if possible. This study also failed to demonstrate a benefit of vinblastine maintenance therapy (4).

In the late 1970s, etoposide was identified as an active agent for patients with cisplatin-refractory advanced GCT demonstrating that the combination of etoposide and cisplatin (EP) resulted in a favourable response and outcome in one fourth of patients failing on PVB (5). Peckham *et al.* reported substituting etoposide for vinblastine (BEP) as first-line treatment of patients with advanced GCT and BEP was shown to result in an 86% long-term relapse-free survival rate (6).

PVB and BEP were directly compared in a multicenter randomized trial including 261 men with disseminated GCT; in 1987, Williams *et al.* (7) reported the results of a randomized trial which compared four courses of BEP with four courses of PVB (in a poor-prognostic patient group). Both regimens were equally myelosuppressive and had similar pulmonary toxicity, but BEP was associated with less neurotoxicity. Patients receiving BEP had a higher rate of complete clinical response (83%

vs. 74%), but the two-year survival rate was similar (80%) in both groups. In a subset of 157 men with bulky disease, BEP was associated with significantly better survival and a higher rate of becoming disease-free (77% vs. 61%).

Based on this randomized trial, etoposide in a dose of 100 mg/m²/d for 5 consecutive days (E_{500}) replaced vinblastine in first-line chemotherapy regimens and four cycles of BEP became the standard regimen for men with advanced GCT.

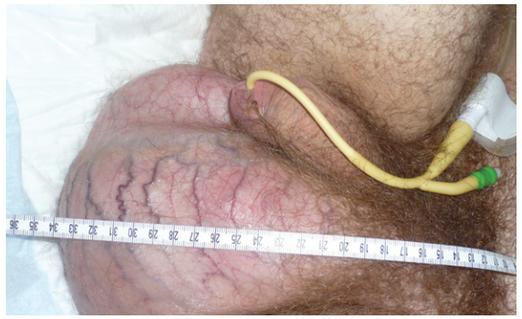
4.2 Risk-Group Stratification

The clinical success of cisplatin-based chemotherapy allowed the development of algorithms to categorize advanced testicular cancer patients based on clinical features in order to stratify patients into prognostic groups and predict the likelihood of response to standard chemotherapy regimens.

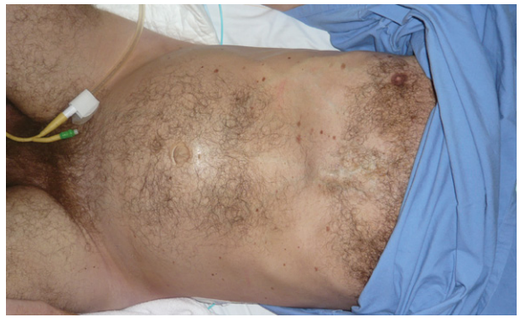
The International Germ Cell Cancer Collaborative Group (IGCCCG) prepared a risk-group stratification system which separated patients into good-, intermediate-, and poor-prognostic groups according to predicted outcome to cisplatin-combination chemotherapy, based on histology, primary site, sites of metastasis, and serum tumour marker elevation (Table 1). A pooled analysis of 5202 patients was used for defining the consensus classification of the IGCCCG (8). Patients with advanced testicular cancer are classified into those with a pure seminoma tumour and non-seminoma tumours which may consist of a mixture of non-seminoma and seminoma elements. In advanced testicular cancer good-risk patients, the 5–year overall survival (OS) rate is approximately 90% for non-seminoma and seminoma.

Poor-risk clinical features are a non-seminoma histology with very high serum tumour markers, extrapulmonary metastases to liver, bone, or brain and the primary tumour originating in the mediastinum. This prognostic classification system has been validated and has been shown to be extremely useful. This classification system is used worldwide and allows for modification of chemotherapy for the patient based on risk and comparison of treatment outcomes in different clinical trials. Factors associated with long-term survival after first-line chemotherapy are now reasonably well established.

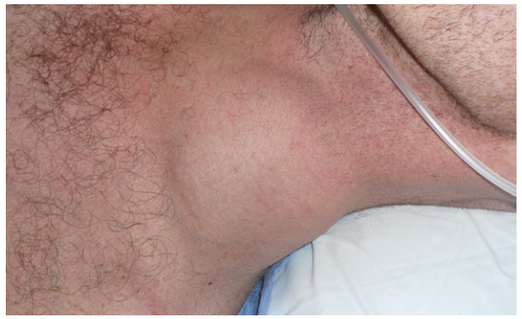
If the patient presents with metastatic disease at initial diagnosis, first a diagnostic radical orchiectomy will be performed (Fig. 1). Moreover, since the testis is considered a sanctuary site, removal of the testis before the start of chemotherapy in case of metastatic disease at presentation, is also preferred. However, in case of a life-threatening situation due to massive tumour load, immediate start of chemotherapy is mandatory. Serum markers can be helpful to make the diagnosis in particular if they are markedly elevated. Malignancies other than germ cell tumours of the testis or primary extragonadal GCT can also lead to an elevation of serum AFP, hCG or LDH.



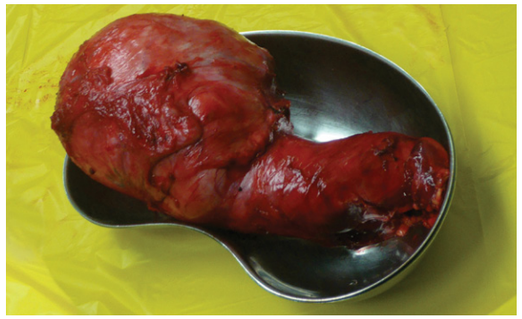
A Left testicle with tumour



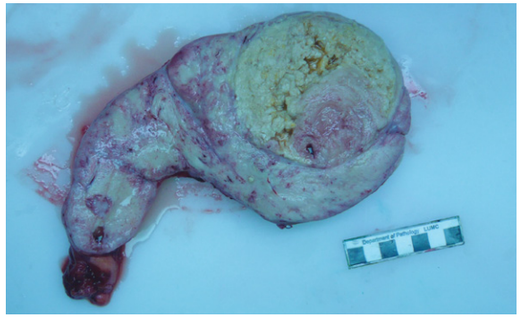
B Abdominal mass



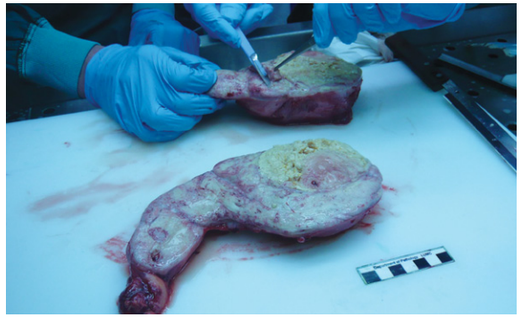
C Mass in left neck



D Resection specimen



E Resected specimen



F Resected specimen

FIGURE 1

A 38-year old male with a clinically manifest 21cm enlargement of the left testis (A), an abdominal mass (B) and mass in the left neck (C) compatible with metastatic testicular cancer at initial presentation.

There was a patient delay of several months. Two percutaneous nephrostomy catheters were placed since the abdominal mass had caused obstruction of both ureters and renal insufficiency. A diagnostic radical orchiectomy was performed via an inguinal incision and the left testis and the tumour surgically removed (D). He was classified as having a poor-prognosis non-seminoma and was scheduled to receive four cycles of BEP chemotherapy. The first chemotherapy cycle was started two days after orchiectomy

(Courtesy Prof. S. Osanto)

TABLE 1 Risk Groups in Advanced Germ Cell Tumours
(Definition International Germ Cell Cancer Collaborative Group, IGCCCG, 1997)

Prognostic Classification System		
GOOD PROGNOSIS		
Non-Seminoma	(56% of the non-seminomas; 5–year PFS 89%, 5–year survival rate of 92%).	
		Testis or retroperitoneal primary No non-pulmonary visceral metastases AFP < 1,000 ng/mL, hCG < 5,000 IU/L (<1,000 ng/mL), and LDH < 1.5 times upper normal limit
Seminoma	(90% of the seminomas, 5–year PFS 82%, 5–year survival rate 86%).	
		Any primary site No nonpulmonary visceral metastases Normal AFP, any hCG or LDH
INTERMEDIATE PROGNOSIS		
Non-Seminoma	(28% of the non-seminomas, 5–year PFS 75%, 5–year survival rate of 80%).	
		Testis or retroperitoneal primary No nonpulmonary visceral metastases Any of: AFP 1,000–10,000 ng/mL, hCG 5,000–50,000 IU/L (1,000–10,000 ng/mL) LDH 1.5 to 10 times upper normal limit
Seminoma	(10% of the seminomas, 5–year PFS 67%, 5–year survival rate 72%).	
		Testis or retroperitoneal site Nonpulmonary visceral metastasis Normal AFP, any hCG or LDH
POOR PROGNOSIS		
Non-Seminoma only	(16% of the non-seminomas, 5–year PFS 41%, 5–years survival 48%).	
		Any of the following: Mediastinal primary Nonpulmonary visceral metastases AFP>10,000 ng/mL, or hCG>50,000 IU/L (>10,000 ng/mL), or LDH>10 fold upper normal limit

AFP = alpha-fetoprotein; hCG = human chorionic gonadotrophin; LDH = lactate dehydrogenase.

*In case of an elevated AFP, treatment according to non-seminoma. In case of a markedly elevated hCG, consider presence of non-seminoma and revision of primary tumour histology required. If the diagnosis remains seminoma, for instance the variant with syncytiotrofoblastic giant cells, treatment should be given according to treatment for seminoma.

4.3 Chemotherapy for the Initial Management of Advanced Disease (Non-Seminoma and Seminoma): Good-Prognosis Testicular Cancer

The good-risk group comprises about 60% of patients with metastatic GCT and has an excellent outcome with a 5–year relapse-free and overall survival rate of about 90%. High complete response rate achieved in the majority of patients with advanced testicular cancer following standard first-line cisplatin-based chemotherapy as evidenced by CT scan and normalization of serum tumour markers was associated with moderately severe toxic effects.

Because of this excellent prognosis, a number of approaches have been explored to maintain the favourable long-term outcome of BEP whilst reducing chemotherapy toxicity.

Various modification of the use of four cycles of BEP in good-risk patients have been evaluated, including decreasing the number of cycles of BEP from four to three. Other modifications of BEP chemotherapy explored in good-risk GCT patients included omitting bleomycin and treating with four cycles of EP instead of BEP. This has been accepted by some centres, but not adopted as preferred regimen in others. Other modifications explored in good-risk GCT patients were reduction of the dose of bleomycin to circumvent pulmonary toxicity, and etoposide to reduce haematological toxicity respectively, which has led to reduced outcome (and not to equivalence of treatment outcome) and thus been rejected. Another approach was substituting the less toxic platinum analogue, carboplatin, for cisplatin, which has been rejected due to a higher relapse rate and lower survival.

The various randomized trials in seminoma and non-seminoma patients, discussed hereunder and summarized in Table 2, led to three cycles of BEP as established standard of care in patients with a good prognosis.

4.3.1 Number of cisplatin-based chemotherapy cycles

In good-risk patients, Einhorn and colleagues tested whether the number of cycles could be safely reduced from four to three without compromising on treatment efficacy, and demonstrated that three cycles of bleomycin, etoposide and cisplatin (BEP, i.e. $B_{90}E_{500}P$) were less toxic and equivalent in terms of efficacy in comparison to four cycles of BEP ($B_{90}E_{500}P$). In 1989, they reported a similar disease-free and overall survival for patients treated with four or three courses of BEP with 92% of patients randomized to four and 92% of patients randomized to three cycles being continuously disease-free (9). Three cycles of $BE_{500}P$ became the standard treatment in patients with a favourable risk.

4.3.2 Omitting or reducing bleomycin

Because of the association of bleomycin with serious and in some cases, fatal pulmonary toxicity, various prospective randomized trials investigated whether bleomycin could be omitted (EP) or the bleomycin dose reduced in men with good-risk GCT.

Two-drug EP regimen: EB versus VAB–6

In the Memorial Sloan Kettering Cancer Center (MSKCC), an alternative regimen, the so-called VAB–6 regimen – consisting of cyclophosphamide, vinblastine, bleomycin, dactinomycin, and cisplatin – had been explored in advanced GCT patients. Bosl *et al.* (10) in 1986, reported the results of their study aimed to assess the value of maintenance chemotherapy. VAB–6 resulted in an overall CR rate of 78% (i.e., 67% to chemotherapy alone, and 11% after chemotherapy and resection of viable residual cancer). The overall relapse rate was 12%. Maintenance chemotherapy did not prolong either relapse-free or total survival.

Subsequently, it was investigated whether the toxicity of the VAB–6 regimen could be avoided in advanced patients of good-prognosis. Four cycles of the less intense regimen, EP, was compared with their standard three cycles of VAB–6 (Table 2, Bosl *et al.*, 1988) (11). A total of 164 patients were randomized. Complete remission rates with or without surgery were similar after four courses of EP compared to three courses of VAB–6 (93% vs. 96%). Similar proportions of patients in both arms were found at surgery to have necrosis, fibrosis or mature teratoma. The total, relapse-free survival was similar in the two groups. Four cycles of etoposide and cisplatin ($E_{500}P$) were shown to be equivalent but less toxic as compared with three cycles of the VAB–6 regimen, indicating that four cycles of EP could be safely used in advanced good-prognosis patients.

Two-drug regimen: PV versus PVB

Levi *et al.* (12) reported the results of an Australian trial in which 218 patients were randomly assigned to either four courses of cisplatin and vinblastine (PV) or four courses of PVB. Toxicities encountered in this study were greater for those patients who received bleomycin, with significantly more leukopenia, thrombocytopenia, anemia, alopecia, and renal and pulmonary toxicities. The proportion of patients who achieved a CR and had no evidence of disease (resection of all viable malignancy) was similar for PV versus PVB (89% vs. 94%, P = 0.29) but at follow-up, more relapses have occurred in patients who received PV than those who received PVB. Despite the toxicities encountered with bleomycin in cisplatin-based combination chemotherapy for these patients, omitting bleomycin seemed to compromise therapeutic efficacy.

Two-drug regimen: EP versus BEP

Three other trials compared the EP regimen to the BEP regimen in patients with a good prognosis.

In 1995, a randomized study reported by Loehrer *et al.* (13) compared three cycles of EP ($E_{500}P$) to three cycles of BEP ($B_{90}E_{500}P$) in 166 patients (Table 2). There were significantly more deaths in the EP arm compared to the BEP arm (14 vs. 4). Both disease-free survival (DFS) and overall survival (OS) were better in patients who received bleomycin. Three courses of EP was thus inferior, but since only three courses of EP were given, no conclusions regarding the efficacy of four courses of EP versus three courses of BEP could be made.

TABLE 2 Randomized Trials of First-Line Chemotherapy Regimens in Patients With Good-Risk Metastatic Germ Cell Tumours

Author	No. of Eligible Patients	No. of Cycles	Regimen	Response Rate %	P Value	Outcome
Bosl *et al.*, 1988 (11)	164	3	VAB–6	96	NS	4xEP has equal efficacy, less toxicity
		4	EP	93		
Einhorn *et al.*, 1989 (9)	184	4	BEP	97	NR	3xBEP has equal efficacy, less toxicity
		3	BEP	98		
Levi *et al.*, 1993 (12)	218	4	PVB	87	NR	4xPVB more effective
		4	PV	82		
Bajorin *et al.*, 1993 (17)	265	4	EP	90	0.02	4xEP more effective
		4	EC	88		
Loehrer *et al.*, 1995 (13)	166	3	BEP	94	0.01	3xBEP more effective
		3	EP	88		
Bokemeyer *et al.*, 1996 (18)	54	3	BEP	97	0.02	3xBEP more effective
		4	$BE_{360}C$	96		
de Wit *et al.*, 1997 (14)	395	4	$BE_{360}P$	95	NR	4x$BE_{360}P$ more effective
		4	$E_{360}P$	87		
Horwich *et al.*, 1997 (19)	598	4	rdBEP	94	<0.001	4xBEP more effective
		4	CEB	87		
Horwich *et al.*, 2000† (20)	130	4	EP	95	NS	4xEP more effective
		4	C	91		
de Wit *et al.*, 2001 (21)	792	3	$BE_{360}P$ 5– or 3–days	90	0.02	3xBEP has equal efficacy and toxicity as 4xBEP ((3– and 5– day equal efficacy but 3– day more toxic)
		4	$BE_{360}P$ 5– or 3–days	90		

† seminoma only

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TABLE 2 Randomized Trials of First-Line Chemotherapy Regimens in Patients With Good-Risk Metastatic Germ Cell Tumours, *Cont'd*

Author	No. of Eligible Patients	No. of Cycles	Regimen	Response Rate %	P Value	Outcome
Toner *et al.*, 2001 (15)	166	3	BEP	88	0.08	3x BEP has equal efficacy but less toxicity
		4	BEP	87		
Culine *et al.*, 2007 (16)	270	3	BEP	95	NS	3xBEP and 4xEP have equivalent efficacy and toxicity
		4	EP	97		

† seminoma only

4.3.3 Reducing bleomycin and reducing etoposide

The EORTC performed a larger trial which compared the efficacy of EP with reduced-dose etoposide plus cisplatin ($E_{360}P$) versus BEP with reduced-dose etoposide ($B_{90}E_{360}P$) chemotherapy in patients with good-prognosis metastatic non-seminomatous testicular cancer (Table 2) (14). A total of 419 patients with good-prognosis non-seminomatous testicular cancer were randomized to receive four cycles of cisplatin 20 mg/m² on days 1 to 5 plus etoposide 120 mg/m² on days 1, 3, and 5, with or without bleomycin 30 mg weekly (four cycles of EP [$E_{360}P$] or four cycles of BEP [$B_{90}E_{360}P$]). Acute and late pulmonary toxicity and neurotoxicity were significantly greater in patients who received BEP, while only those patients who received BEP developed Raynaud's syndrome vascular toxicity. Four cycles of BEP and four cycles of EP, with both regimens using a reduced dose of etoposide in each cycle (360 mg/m²), resulted in a higher CR rate following BEP (95% vs. 87%), and a slightly higher death rate in the EP arm. Both regimens used an inferior dose of etoposide (360 mg/m²), which could have led to a superiority of BEP.

Another randomized trial in 166 good-risk patients, reported in 2001 by Toner *et al.* (15), assessed whether the dose of bleomycin and etoposide could be reduced. Conventional BEP was dosed according to the standard US dose of etoposide (500mg/m²). Randomizing between three courses of $B_{90}E_{500}P$ and four courses of $B_{30}E_{360}P$ resulted in equal response rates of 88% vs 87% but one versus nine cancer-specific deaths were reported, respectively, suggesting that reducing the dose of bleomycin and diluting the dose density of etoposide (despite same cumulative dose) translates in poorer outcome.

In 2007, the Genito-Urinary Group of the French Federation of Cancer Centre (GETUG) investigated whether bleomycin dose can be safely omitted (Table 2, Culine *et al.*, 2007) (16). Good-risk patients were randomized between four courses of EP ($E_{360}P$) and three courses of BEP ($B_{90}E_{500}P$) (Table 2, Culine *et al.*). GETUG used an equivalency design to directly compare four cycles of EP with three cycles of BEP using optimal etoposide doses. Equal response rates of 95% versus 97% were obtained but 5 versus 12 cancer-specific deaths were reported. The four-year event-free survival rates obtained after four cycles of EP (86% vs. 91%, respectively; P = 0.14) and the higher mortality (12 vs. 5 deaths, respectively; P = 0.01) did not reach the level of statistical significance. Response rates were statistically not significantly different, but the trial was underpowered for survival analyses, and the authors concluded that bleomycin should not be omitted and that three cycles of BEP was the preferred regimen for good-risk patients with metastatic non-seminomatous germ cell tumours (NSGCT).

In summary, three courses of BEP has less toxicity due to its shorter duration and less cumulative toxicity than four courses of EP. Bleomycin-related pulmonary toxicity does not occur frequently; risk factors include the cumulative dose of bleomycin, older age, and renal impairment, as bleomycin is rapidly excreted by the kidney. EP may be preferred over three cylces of BEP because of bleomycin-related pulmonary toxicity. Randomized studies did not demonstrate therapeutic superiority of four cycles of EP over three cycles of BEP. Other studies support the value of bleomycin, suggesting equivalence or superiority of bleomycin-containing regimens. Bleomycin, etoposide and cisplatin for three cycles remained the most widely accepted and commonly preferred (standard) regimen in the treatment of advanced good-risk patients. Four cycles of EP may be the preferred regimen in patients who are at risk for bleomycin toxicity (e.g., for patients older than 50 years, heavy smokers and patients with poor renal function).

4.3.4 Substituting carboplatin for cisplatin

In 1993, Bajorin of the MSKCC and colleagues reported the results of a randomized trial which compared four cycles of EP ($E_{500}P$) with four cycles of etoposide, carboplatin (EC) ($E_{500}C_{500}$) in 270 patients with good-risk GCTs (Table 2, Bajorin *et al.*, 1993) (17). The etoposide dose in all patients was 100 mg/m² on days 1 through 5. For EC patients, the carboplatin dose was 500 mg/m² on day 1 of each cycle and the EC recycling interval was longer, namely 28 days, whereas EP was given every 21 days. There was no significant difference in CR rate between EC and EP (88% vs. 90%). A significantly higher percentage of patients treated with carboplatin had an incomplete response or a relapse: 32 patients (24%) compared with only 17 of 134 patients (13%). Relapse-free survival were significantly inferior for patients treated with carboplatin (EC) (P = 0.005), but there was no significant difference in overall survival (P = 0.52). The two-drug carboplatin regimen EC, using this dose and schedule, was inferior to the two-drug cisplatin regimen, EP. Cisplatin remained the standard platinum analogue in the treatment of patients with good-risk GCTs.

In 1996, Bokemeyer *et al.* published the results of a small study of 54 patients, comparing three courses of cisplatin, etoposide and bleomycin (referred to as PEB, $B_{30}E_{360}P$) at the conventional doses, with four courses of carboplatin, etoposide and bleomycin (CEB, $B_{90}E_{360}C$) in good-risk metastatic non-seminoma patients (Table 2) (18). Four cycles of CEB were given, but bleomycin was omitted in the fourth cycle. Thus, the cumulative doses of etoposide and bleomycin applied in the two treatment arms were comparable. No significant difference in response to chemotherapy was seen between the two arms; with a CR rate of 81% versus 76%, respectively favouring BEP (albeit not significantly different). However, more patients treated with CEB (32% vs. 13%) had relapsed after therapy, and four patients had died of disease progression after CEP in contrast to one after PEB therapy. The trial was stopped early, since the first interim analysis showed a significantly higher rate of adverse events after CEB than after PEB therapy.

In the larger randomized Medical Research Council (MRC)/EORTC trial reported in 2001 by Horwich *et al.* (19) (Table 2), the efficacy of carboplatin plus etoposide and bleomycin (CEB or BEC) versus cisplatin plus etoposide and bleomycin (BEP) was tested in first-line chemotherapy of 598 patients with good-risk non-seminoma. In this trial, four cycles of $B_{30}E_{360}P$ was compared with four cycles of $B_{30}E_{360}C$ (AUC = 5). In each cycle, the etoposide dose was 120 mg/m² on days 1, 2, and 3. BEP patients received cisplatin at 20 mg/m²/d on days 1 to 5 or 50 mg/m² on days 1 and 2. A significantly higher percentage of patients allocated to BEP (94.4%) achieved a complete response, compared with patients allocated to receive CEB (87.3%). The one-year relapse-free survival in the BEP arm was 91% in the BEP arm and only 77% in the CEB arm, respectively. In the BEP group, 10 patients died compared to 27 patients in the CEP group and the 3–year survival rate was 97% in the BEP and only 90% in the carboplatin-containing CEB group, clearly favouring the cisplatin-containing regimen.

Horwich *et al.* (20) reported their randomized study in 130 seminoma-only patients, comparing four cycles of EP versus single-agent carboplatin, in which inferiority of carboplatin to the cisplatin-containing regimen, EP, in advanced seminoma patients was shown.

4.3.5 Three versus four cycles of BEP and shortening of days of cisplatin and etoposide administration

A large trial performed by the EORTC GU Group together with the MRC reported in 2001, tested the equivalence of three versus four cycles of bleomycin, etoposide, and cisplatin (BEP) and of the 5–day schedule versus 3 days per cycle in good-prognosis germ cell cancer in a 2 x 2 factorial design (21). A cycle of BEP consisted of etoposide 500 mg/m², administered at either 100 mg/m² on days 1 through 5 or 165 mg/m² on days 1 through 3, cisplatin 100 mg/m², administered at either 20 mg/m² on days 1 through 5 or 50 mg/m² on days 1 and 2. Bleomycin 30 mg was administered on days 1, 8, and 15 during cycles 1 through 3.

A total of 812 patients were randomized to receive three or four cycles of standard BEP ($B_{90}E_{500}P$). Of these, 681 were randomly assigned to the 5–day or the 3–day schedule. The study showed equivalence of three versus four cycles in terms of DFS in both groups of patients (PFS 90.4% vs. 89.4%) and also in the 5– versus 3–day comparison. In addition, the incidence of hematologic and non-hematologic toxicities were essentially similar. Quality of life was maintained better in patients receiving three rather than four cycles. The 3–day schedule increased gastrointestinal (GI) toxicity (at 3 months) and risk of tinnitus (at 2 years), with clinical relevance demonstrated after four cycles, more than those receiving the 5–day regimen (22). Three cycles of BEP, with etoposide at 500 mg/m², is sufficient therapy in good-prognosis germ cell cancer. Administration of the chemotherapy in three days has no detrimental effect on the efficacy of the BEP regimen. Because of the increased acute GI toxicity with nausea and vomiting at three months and long-term tinnitus after the 3–day regimen, the 5–day regimen was recommended if four cycles of BEP are planned. If only three cycles are to be given, the 3–day regimen is considered acceptable.

4.4 Chemotherapy for the Initial Management of Advanced Disease (Non-Seminoma and Seminoma): Intermediate- and Poor-Risk Testicular Cancer

In 1987, Williams *et al.* (7) had already established four courses of BEP as standard of care based on their results of the randomized trial BEP versus PVB in 72 poor-risk testicular cancer patients. Further efforts to improve outcome in intermediate- and poor-risk GCT patients have thus far been unsuccessful.

4.4.1 Dose-intensified cisplatin

In an early study, Ozols and colleagues at the National Cancer Institute (NCI) explored whether a high-dose cisplatin could improve the results of cisplatin-based combination chemotherapy in poor-risk patients (23). The regimen called PVeBV, comprising of cisplatin [P] (at twice the dose used in previous combination chemotherapy regimens), vinblastine [Ve], bleomycin [B], plus VP–16 [V] with cisplatin administered in hypertonic saline whilst maintaining hyperhydration, did result in a higher complete remission rate (87%) for PVeBV compared to (62%) for PVeB. PVeBV resulted in greater toxicity; in particular, more severe myelosuppression, but there was no significant increase in survival in the patients receiving the four-drug regimen with higher cisplatin dosage. The results of this trial suggested a steep dose-response relationship for cisplatin that might improve survival in poor-risk GCT patients.

Based upon these results, the Southeastern Cancer Study Group and Southwest Oncology Group performed a randomized trial and compared standard dose BEP to BEP with double-dose platinum (BEP_{200}, Nichols *et al.*, 1991, Table 3) in 153 men with poor-risk GCTs. Patients treated with higher-dose cisplatin experienced considerably more toxicity without any improvement in overall survival (74% in both groups) or cancer-specific survival (63% vs. 61%) (24).

4.4.2 Alternative regimens

Alternating PVB and BEP

In 1995, the EORTC GU Group reported the results of their study investigating whether an alternating induction chemotherapy regimen of four courses of alternating PVB/BEP is superior to four courses of BEP in 234 patients with poor-prognosis testicular non-seminoma (25). The complete response (CR) rates to PVB/BEP and BEP were similar, 76% and 72%, respectively (P = 0.58). In addition, there was no significant difference in relapse rate, disease-free and overall survival at an average follow-up of 6 years. The 5–year PFS and survival rates in both treatment groups were approximately 80%. The PVB/BEP regime was more toxic with regard to hematological toxicity and neurotoxicity. Neuropathy occurred more often in the PVB/BEP arm: 47% versus 25% (P = 0.001). This study demonstrated that an alternating regimen of PVB/BEP is not superior to BEP and that it is more myelo- and neurotoxic. Based on this EORTC study, the standard regimen for poor-risk GCT patients is four cycles of BEP.

TABLE 3 Randomized Trials of First-Line Chemotherapy Regimens in Patients With Intermediate- and/or Poor-Risk Metastatic Germ Cell Tumours

Author	Risk Group	No. of Eligible Pts	No. of Cycles	Regimen	Response %	P Value	Results
Williams *et al.*, 1987 (7)	Poor	72	4	BEP	63	NR	4xBEP more effective, less toxic
			4	PVB	38		
Nichols *et al.*, 1991 (24)	Poor	153	4	BEP	73	NS	4xBEP equal efficacy, less toxicity
			4	BEP_{200}	68		
de Wit *et al.*, 1995 (25)	Poor	208	4	BEP	72	NR	4xBEP equal efficacy, less toxicity
			4	PVB/BEP	76		
de Wit *et al.*, 1998 (26)	Intermediate	84	4	BEP	82	NS	4xBEP equal efficacy, less toxicity
			4	VIP	80		
Kaye *et al.*, 1998 (28)	Poor	371	4 2	BEP+ EP	65	NR	4xBEP 2xEP equal efficacy, less toxicity
			3 3	BOP+ VIP–B	61		
Nichols *et al.*, 1998 (27)	Poor	286	4	BEP	60[b]	NS	4xBEP equal efficacy, less toxicity
			4	VIP	63		
Culine *et al.*, 2008 (28)	Intermediate + poor	185	4	BEP	65	NS	4xBEP equal efficacy, less toxicity
			4–6	CISCA/VB	56		

4.4.3 Regimens which investigated the utility of ifosfamide

Exchange of bleomycin by ifosfamide (VIP/PEI regimen)

Two trials compared BEP with VIP in which etoposide was exchanged for ifosfamide (Table 3).

In the EORTC trial, a total of 84 intermediate-risk patients were randomized to receive four cycles of etoposide, ifosfamide, cisplatin (VIP), or four cycles of bleomycin, etoposide, cisplatin (BEP) (26). The CR rates to VIP and BEP were similar, 74% and 79%, respectively. Including the cases in whom viable cancer was completely resected with post-chemotherapy debulking surgery, the percentages of patients who achieved a no-evidence-of-disease (NED) status were 80% on VIP and 82% on BEP. In addition, there were no differences in relapse rate, DFS and OS after a median follow-up of 7.7 years. The VIP regimen was more myelotoxic. The sample size in this study was small as the study was prematurely discontinued when data became available from a competing study that showed no improved effectiveness of VIP compared with BEP.

In 1998, Nichols and colleagues reported a much larger randomized study comparing four cycles of BEP with four cycles of VIP (etoposide, ifosfamide plus cisplatin) in 286 poor-risk patients. VIP resulted in a similar DFS and OS, but increased hematological toxicity of the VIP regimen (27). In both trials, the efficacy and toxicity of four courses of cisplatin and etoposide with either bleomycin or ifosfamide (BEP versus VIP chemotherapy) was studied. This regimen called VIP or PEI, is more toxic given in four cycles when compare to four courses of standard BEP, but of similar efficacy (CR rates).

BOP-VIP

In another study reported in 1998 by Kaye *et al.* (28), an alternative regimen which included the use of ifosfamide was explored and compared with BEP. In this large randomized trial performed in 371 poor-risk GCT patients, men received either four cycles of BEP plus two cycles of EP or three cycles of BOP plus three cycles of VIP–B (BOP–VIP–B). The sequential treatment BOP–VIP–B combination was equally effective as BEP–EP but was more toxic.

CISCA/VB

The French GETUG randomized 185 intermediate- and poor-risk metastatic non-seminomatous GCT patients between four cycles of BEP or four to six alternating cycles of CISCA/VB (cyclophosphamide, doxorubicin, cisplatin 100 mg/m^2 d3, vinblastine and bleomycin) (29). The CISCA/VB regimen induced more significant hematologic and mucous toxicities compared with the BEP arm. Favourable responses did not differ statistically between the two arms: 49% in the CISCA/VB arm and 56% in the BEP arm. The 5–year event-free survival rates were 37% and 47% in CISCA/VB and BEP arms, respectively. With a median follow-up of 7.8 years, the 5–year OS rates were 59% and 69% in CISCA/VB and BEP arms, respectively. Based on this outcome, four cycles of BEP chemotherapy remained the standard for intermediate and poor-risk patients because of equivalent efficacy and lesser toxicity of BEP.

4.5 High-Dose Chemotherapy as First-Line Treatment in Intermediate- and Poor-Risk Testicular Cancer

The role of upfront first-line high-dose chemotherapy with autologous stem-cell support has been investigated in intermediate- and poor-risk metastatic GCT in attempts to improve outcome, and also in patients who relapsed after standard-dose chemotherapy. The advantage of high-dose therapy in first-line may be that it is better tolerated when used as first-line compared to its use as a salvage regimen, and its use before chemoresistance develops (as induced by standard first-line chemotherapy).

In 1986, Einhorn and co-workers had started treating patients with carboplatin-based high-dose chemotherapy with autologous hematopoietic stem cell transplantation to rescue the bone marrow from the myeloablative effects of chemotherapy (30). Initially, they used autologous bone marrow cells for hematopoietic rescue after high-dose chemotherapy. In 1996, this was changed into the use of peripheral-blood stem cells, which rapidly engrafted, thereby permitting a second course of high-dose chemotherapy with fewer delays. High-dose chemotherapy consisted of two cycles of carboplatin plus etoposide, intravenously five, four and three days before the infusion of peripheral-blood stem cells. Provided a clinical response was observed following the first course and recovery of granulocyte and platelets had occurred, the second cycle of high-dose chemotherapy was given. Most patients who achieved a complete or partial remission after the two cycles of high-dose chemotherapy and who had normal serum levels of hCG and AFP received a maintenance oral etoposide for 21 consecutive days every four weeks for three cycles. During a median follow-up of 48 months (range, 14 to 118), 116 of 184 patients (63%) were continuously disease-free. Of these 116 patients, 104 (90%) were disease-free for more than two years. Six additional patients had complete remission of disease after chemotherapy (paclitaxel plus gemcitabine) or subsequent surgery.

In 2003, Schmoll *et al.* (31) reported the results of the German Testicular Group phase I/II study in which 221 patients received high-dose chemotherapy with stem-cell support as first-line therapy for advanced, poor-risk, testicular cancer patients. After a 4–year median follow-up, PFS and disease-specific survival rates in the poor-prognosis subgroup were 69% and 79% at two years and 68% and 73% at 5 years, respectively. Severe toxicity included treatment-related death (4%), treatment-related acute myeloid leukemia (1%), long-term impaired renal function (3%), chronic renal failure (1%), and persistent grade 2–3 neuropathy (5%). This long-term study suggested a favourable outcome in these patients given high-dose chemotherapy, when compared with historical control of poor-risk patients treated with conventional-dose therapy. Treatment-related toxicity was considerably worse as anticipated, compared with standard therapy consisting of four cycles of BEP.

Various clinical studies were performed aiming at improving survival in this category of patients but faced difficulties in patient accrual rates for various reasons. These include the lower incidence of poor-risk patients and the difficulty in performing a trial comparing upfront first-line high-dose chemotherapy to standard chemotherapy with the option of second-line possibility of high-dose chemotherapy (HDCT).

An intergroup phase III randomized trial reported by Motzer *et al.* in 2007 randomly assigned 219 intermediate- or poor-risk GCT patients to four cycles of BEP or two cycles of BEP followed by two cycles of high-dose carboplatin, etoposide, and cyclophosphamide with stem-cell support in intermediate- and poor-risk patients (Table 4) (32). The 1–year durable CR rate was 52% after two courses of BEP followed by two courses of HDCT and 48% after four courses of BEP alone (P = 0.53). Patients with slow serum tumour marker decline (AFP and/or hCG) during the first two cycles of chemotherapy had a significantly shorter PFS and OS compared with patients with satisfactory marker decline. Interestingly, among the subgroup of 67 patients with unsatisfactory marker decline, the 1–year durable complete response proportion was 61% for patients who received HDCT versus 34% for patients receiving BEP alone (P = 0.03). The conclusion from this first-line HDCT versus standard chemotherapy trial was that HDCT did not improve the clinical outcome for intermediate- and poor-risk GCT patients.

The French GETUG also performed a randomized trial to assess the impact on survival of high-dose chemotherapy with hematopoietic support in patients with poor-risk metastatic GCT (Table 4) (33). A total of 114 intermediate- and poor-risk patients were randomized to receive either four cycles of PveBV (cisplatin, vinblastine, bleomycin and etoposide) or two cycles of PveBV plus HDCT. A total of 115 patients were randomized to receive either four cycles every 21 days of vinblastine, etoposide, cisplatin (40 mg/m^2/d on days 1 through 5), and bleomycin, or a slightly modified regimen followed by a high-dose chemotherapy including etoposide, cisplatin (40 mg/m^2/d on days 1 through 5), and cyclophosphamide.

This trial demonstrated equal efficacy for PveBV, but less toxicity than the HDCT arm. In the standard arm, there were 28% intermediate-risk and 68% poor-risk, and in the experimental arm, there were 32% intermediate- and 60% poor-risk patients. Complete remission rates were significantly higher, namely 56% in standard-dose PveBV versus 42% in the PveBV HDCT arm (P = 0.099). When subgroups based on risk category were analysed, the 5–year OS was 88% versus 82% in the intermediate-risk subgroup and 69% and 44% in the poor-risk subgroup, for patients receiving the standard chemotherapy versus the HDCT (P = 0.045). This study of first-line HDCT with hematopoietic support failed to demonstrate a favourable impact on response and survival in patients with intermediate- and poor-risk metastatic non-seminomatous testicular cancer.

The phase I/II trial by Schmoll *et al.* (31) provided the rationale for the investigational arm used in a phase III trial performed by the European Organisation for Research and Treatment of Cancer (EORTC 30974). In this first-line phase III trial of high-dose VIP, poor prognosis GCT patients were randomly assigned to four cycles of BEP or one cycle of standard-dose VIP (cisplatin, etoposide, and ifosfamide), followed by three cycles using high doses of the same agents with stem-cell support (Table 4). The study had to be closed prematurely due to poor patient accrual with only 131 patients evaluable (34). The difference in failure-free survival, which is the primary endpoint of the study, was not statistically significant at one or two years (48% vs. 66% and 45% vs. 58%, respectively). There also was no significant difference in overall survival (83% vs. 86% at one year, and 66% vs. 73% percent at two years). Toxicity was more severe with the high-dose regimen. There was thus no significant difference in outcome between the two treatment arms., although a clear trend for improved DFS and OS by upfront HDCT.

The results of these three randomized trials comparing first-line treatment of HDCT with standard-dose chemotherapy in intermediate- and poor-risk patients with germ-cell tumours (US Intergroup and French study) and in poor-risk patients are disappointing. The studies may all have been underpowered to detect a modest difference in complete remission and OS benefit. Since no clear advantage for HDCT in first-line has been demonstrated, four courses of BEP remains the standard of care in intermediate- and poor-risk patients. Overall, approximately 20%–30% of advanced GCT patients either relapse or achieve an incomplete response to cisplatin-based chemotherapy. There is a clear need to establish more effective treatment and increase cure rates, particularly in first-line treatment of poor-risk patients and in second- or even third-line for relapsing patients.

TABLE 4 Randomized Trials for Intermediate- and Poor-Prognosis Germ Cell Tumour Patients Comparing Standard Dose with High-Dose Chemotherapy (HDCT) as First-Line Chemotherapy Regimens

Author	Risk Group	No. of Eligible Pts	No. of Cycles	Regimen	Response %	P Value	Outcome
			4	VIP	63		
Motzer *et al.*, 2007 (32)	Poor	219	4	BEP	55	0.53	4xBEP equal efficacy, less toxicity
			2 2	BEP+ HDCT	56		
Droz *et al.*, 2007 (33)	Intermediate + poor	114	4	PveBV	75	NR	4xPveBV equal efficacy, less toxicity
			2 2	PveBV + HDCT	67		
Daugaard *et al.*, 2011 (35)	Poor	131	4	BEP	33	NS	HD chemo not superior
			1 3	VIP HD–VIP	46		

4.6 Supportive Care

The value of supportive care using granulocyte colony-stimulating factor (G–CSF) was investigated in patients with metastatic poor-prognosis GCT who received full dose-intensity combination chemotherapy consisting of six cycles of BEP/EP or six cycles of BOP/VIP–B (35). A subset of patients was secondarily randomized to receive or not receive filgrastim. Eighty-five percent of 120 patients randomized to filgrastim received at least six chemotherapy cycles compared with 70% of 130 patients randomized to not receive filgrastim. Neutropenic fever occurred more frequently in the non-filgrastim-treated patients (30%) than in the filgrastim-treated patients (20%) ($P = 0.052$) and dose-intensities were significantly higher in patients on filgrastim. Twelve and three toxic deaths occurred in the non-filgrastim- and filgrastim-arms, respectively, and most toxic deaths were associated with febrile grade 4 neutropenia.

Clinical outcomes, DFS and OS, were similar in both arms. Although the use of filgrastim was associated with a clinically relevant reduction in toxic deaths, this was confined to the experimental intensified-chemotherapy schedule. The study therefore does not support the routine use of G–CSF during standard chemotherapy with BEP.

4.7 Centralized Treatment of High-Risk Testicular Cancer Patients

An analysis was performed on 380 patients in 1 of 49 institutions participating in the EORTC/MRC randomized trial of four cycles of BEP followed by two cycles of EP versus three cycles of BOP followed by three cycles of VIP–B, both treatment regimens given with or without filgrastim (G–CSF). Institutions were divided into four groups based on the total number of patients entered in the trial. Patients treated in institutions which entered fewer than five patients into the trial appeared to have poorer survival than those treated in institutions that entered a larger number of patients with poor-risk non-seminoma GCT (36).

4.8 Assessment of Tumour Response and Response Evaluation for Metastatic Disease

4.8.1 Post-chemotherapy management

The majority of metastatic GCT patients will achieve a complete remission following first-line chemotherapy with normalization of serum markers and regression to normal size of radiographically detectable metastatic masses. Approximately 30% of patients with advanced GCT have either persistent serum tumour marker elevation or persistent radiographic disease (partial remission). In these cases, surgery should be considered in order to achieve cure with combined-modality treatment. Surgical resection of residual masses will provide both a more accurate evaluation of the effect of systemic treatment as well as potential for cure by post-chemotherapy surgery. In the resected masses, necrosis and/or fibrosis can be found, but also viable GCT tumour cells, teratoma (Figs 2 and 3) or in rare cases, another malignancy resulting from de-differentiated teratoma. Figure 4 illustates RPLND following first-line chemotherapy for residual peritoneal mass.

FIGURE 2
Retroperitoneal mass before and after chemotherapy

A Abdominal CT-scan showing a large retroperitoneal mass before chemotherapy

B Same patient after 4 BEP: partial response suggesting remnant teratoma
(Courtesy of Prof. H. van Poppel)

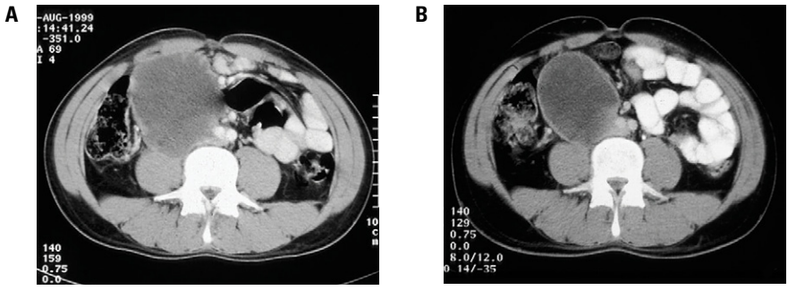
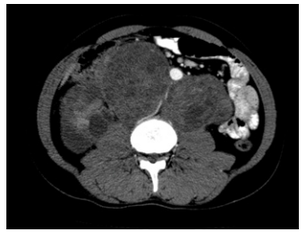


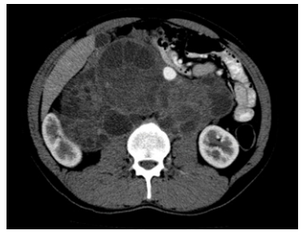
FIGURE 3
Residual teratoma masses in abdomen, mediastinum and neck following first-line BEP chemotherapy
(Courtesy of Prof. S. Osanto)

A



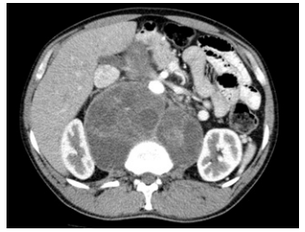
Abdomen

B



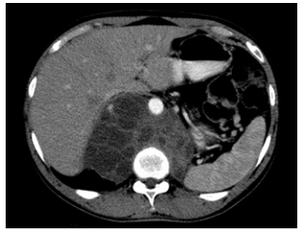
Abdomen

C



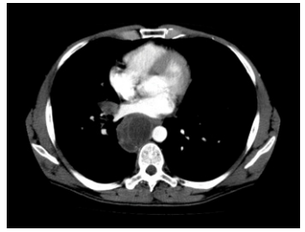
Abdomen

D



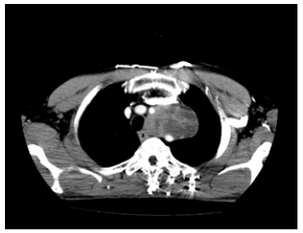
Abdomen

E



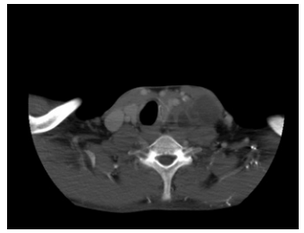
Mediastinum

F



Mediastinum

G

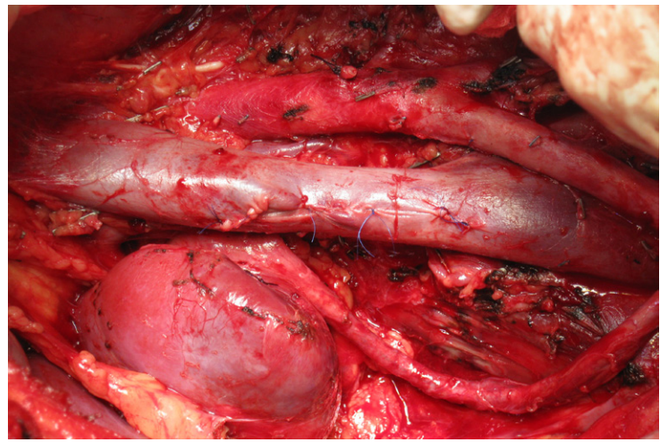


Left neck

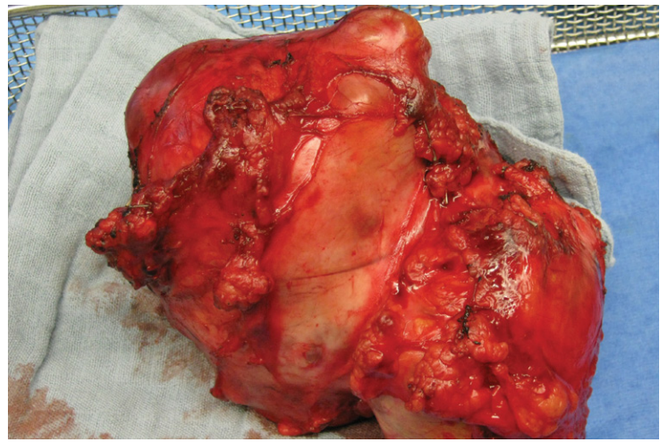
A young male refugee presented with an intermediate-risk advanced non-seminoma and received 4 cycles of T-BEP accompanied by normalization of the AFP marker. After first-line chemotherapy he still had large painful masses of histology-proven differentiated mature teratoma in the abdomen (A-D), mediastinum (E-F) and neck (G). Surgical removal of all these residual masses was technically not feasible. The patient refused further treatment and infrequently came for visits. Radiotherapy of the painful mass in the neck resulted in slow shrinkage of this mass, local irradiation of parts of the abdominal mass also resulted in transient relief of the pain. A gradual rise in AFP more recently indicated a relapse of the malignant tumour (embryonal cell carcinoma).

FIGURE 4
RPLND following first-line chemotherapy for residual retroperitoneal mass

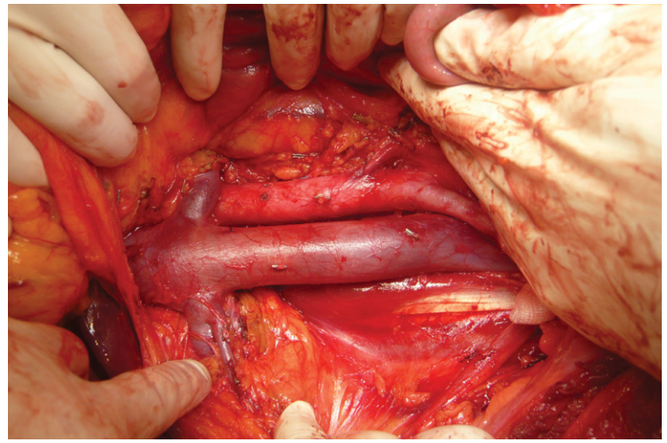
A Resection of remnant mass after chemotherapy with template retroperitoneal lymph node dissection, exposure of the large vessels, the kidney and the ureter



B Resection specimen after RPLND



C Template RPLND
Resection of remnant mass after chemotherapy with template retroperitoneal lymph node dissection, exposure of the large vessels, the kidney and the ureter
(Courtesy of Prof. H. van Poppel)



In the past, persistent serum tumour marker elevation after chemotherapy was considered to be an absolute contraindication for post-chemotherapy surgery, since elevated markers were perceived as reflecting persistent active GCT disease requiring the institution of second-line salvage chemotherapy. Usually elevated tumour markers indeed indicate residual disease and if surgery is performed, this will most likely be incomplete.

Advanced Seminoma

Post-chemotherapy surgical resection of seminoma is often technically more demanding and carries a higher morbidity due to treatment-induced reactive changes in the sites of metastases (37). The chance of residual viable GCT in the surgical specimen is lower in pure seminomas as compared to non-seminoma. PET scan is considered to be of some value to decide whether or not to pursue resection (38).

Advanced Non-Seminoma

Approximately 70% of metastatic GCT patients will achieve a complete remission following first-line chemotherapy with normalization of serum markers and resolution of radiographic disease. In the remaining 30% who have negative or residual marker levels and persistent radiographic disease (partial remission), surgery should be considered in order to achieve cure with combined-modality treatment. Pathology at post-chemotherapy retroperitoneal lymph node dissection (PC–RPLND) in patients with marker normalization after first-line chemotherapy reveals fibrosis/necrosis in 40% to 50%. Approximately 35% to 40% of patients display mature or immature teratomatous elements, with active germ-cell cancer identified in fewer than 10% of patients. In contrast, in patients with elevated serum tumour markers at time of surgery, the reported incidence of active germ-cell cancer is much higher (40%–81%).

In patients with residual lesions of less than 1 cm, there is an increased risk of residual teratoma if teratoma was present in the initial histology; therefore, these patients have been in the past, considered for PC–RPLND. The rationale to resect even small residual masses with mature teratomas lies in their disposition for progressive local growth, their risk of malignant transformation, and their risk of late relapse. However, recent data show that relapses are rare in these cases, which can be removed safely even at time of relapse.

Except in select cirumstances (39,40), tumour-marker normalization is a prerequisite to postchemotherapy surgery; elevated markers imply residual systemic disease and predict a high likelihood of incomplete resection or recurrence (41,42). Persistent serum tumour marker elevation after chemotherapy was therefore perceived as an absolute contraindication for post-chemotherapy surgery, since the patients supposedly have persistent systemic disease and should be treated systemically with salvage second-line chemotherapy. More recently, some centres have explored surgery in this setting, indicating that cure can be obtained in this situation by post-chemotherapy surgery alone (43).

However, a marker plateau with resistant markers can remain for six weeks up to several months and might indicate progressive resorption of necrotic mass; in these cases, in particular with large masses and/or multiple lesions, the spontaneous course of the markers should be followed by definitive surgery or salvage chemotherapy.

Full bilateral post-chemotherapy RPLND is not always required, and it should be considered as surgical approach of choice only in patients with extensive residual masses, inter-aorta-caval location, or a location of the residual mass not corresponding to the site of the primary testis tumour. In well-defined small masses of less than 5 cm, only local resection of residual tumour should be performed with less chance of morbidity. An algorithm for post-chemotherapy treatment procedure is given in Table 7 [4C].

4.8.2 Resection in multiple metastatic sites

The management of patients with residual masses after first-line chemotherapy poses a difficult task to clinicians. Various groups have studied the optimal sequence of lymph-node dissection and resection of other sites. Steyerberg *et al.* (44) performed a retrospective study in 159 patients who underwent a RPLND and a thoracotomy following cisplatin-based induction chemotherapy for metastatic testicular non-seminomatous germ cell tumour. Necrosis was found more often at RPLND, if the primary tumour did not contain teratoma, the residual mass was small or the decrease in size was great.

In a small series of 27 patients with metastatic non-seminomatous germ cell tumours who underwent multiple resections for residual masses at different localizations after first-line cisplatin-based chemotherapy, eight (30%) showed dissimilar histological findings at sequential or one-stage resections (45). Five of these demonstrated less favourable pathological features (mature teratoma or undifferentiated tumour) at the second operation, while only necrosis (n = 3) or teratoma (n = 2) had been found following the first operation. Tumour necrosis was documented more frequently at thoracotomy (n = 15/21) compared to RPLND (n = 17/27). By univariate analysis, completeness of surgery (R0 resection) and the histological finding of necrosis or differentiated teratoma were associated with improved relapse-free and overall survival. After a median follow-up period of 33 months (range 1–167), 19 of 26 (73%) evaluable patients are alive; 18 of 27 (67%) patients have continuous NED (one patient with recurrent disease was lost to follow-up). The authors are in favor of excision of all present tumour masses if technically feasible, because the histological findings in post-chemotherapy residuals may vary between different anatomical sites and no prediction seems possible. In agreement with findings of others, they noted a trend that the retroperitoneum harbours unfavourable histological findings more frequently than mediastinum.

The French group (46) reported a retrospective study in 71 patients with thoracic residual masses (39 patients had bilateral lung metastases) after first-line cisplatin-based chemotherapy for disseminated non-seminomatous GCT. Pathologic findings in post-chemotherapy residual masses included complete necrosis, teratoma, and viable cancer in 31%, 55%, and 14% of patients, respectively. Discordant pathologic findings were evidenced between retroperitoneal lymph node and thoracic (lung or mediastinal lymph nodes) residual masses in 27% of patients. When a bilateral pulmonary resection was performed, only 2 (5%) of 39 patients had discordant histologic findings between the two lungs. Among patients who had necrosis only in residual masses from their first lung (n = 20), 19 (95%) also had necrosis only in contralateral lesions. Thus, a high rate (95%) of pathologic concordance between the residual masses in two lungs was observed, and thus contralateral lung surgery could therefore be considered when complete necrosis is found in the first lung after induction chemotherapy for non-seminomatous germ cell tumour.

In conclusion, there is evidence to go forward, if possible, with retroperitoneal resection, followed by lung metastases resection; however, the decision is dependent on the individual situation (Level of evidence IV/Grade of recommendation C–D).

4.8.3 Post-surgery chemotherapy

Patients who underwent post-chemotherapy surgical resection of residual mass have been treated in the past mostly with post-surgery chemotherapy, in case of presence of viable tumour cells in the surgical specimen. No prospective study has been performed to assess the value of post-surgery chemotherapy versus wait and see (i.e., watchful waiting), in case of complete resection of residual mass(es) containing viable tumour cells. Fizazi *et al.* (43) performed a retrospective analysis of the prognostic factors and role of post-surgery chemotherapy. In all 238 patients studied, tumour markers had normalized before resection. The 5–year PFS rate was 64% and the 5–year OS rate was 73%. Three factors were independently associated with both PFS and OS: complete resection ($P < 0.001$), less than 10% of viable malignant cells ($P = 0.001$), and a good IGCCC group ($P = 0.01$).

Patients were assigned to one of three risk groups: those with no risk factors (favourable group), those with one risk factor (intermediate group), and those with two or three risk factors (poor-risk group). The 5–year OS rate was 100%, 83%, and 51%, respectively ($P < 0.001$). After adjustment on the three prognostic factors, postoperative chemotherapy was associated with a significantly better PFS ($P < 0.001$) but not with better OS. Patients in the favourable-risk group had a 100% 5–year OS, with or without postoperative chemotherapy. Postoperative chemotherapy appeared beneficial in both PFS ($P < 0.001$) and OS ($P = 0.02$) in the intermediate-risk group but was not statistically beneficial in the poor-risk group (Level of evidence IV/Grade of recommendation C–D).

However, this concerns a retrospective study with a limited number of patients, indicating that no firm conclusion can be drawn based on this report as to the value of postsurgical chemotherapy in patients with a limited percentage of viable tumour cells present in their surgical specimen. The analysis only suggests that perhaps those patients with less than 10% viable tumour cells in the resection specimen may be cured by post-chemotherapy surgery alone, but clearly prospectively collected data are needed before decision making can be made based on evidence.

4.9 Follow-Up and Risk of Recurrence

The recommended follow-up schedules are very pragmatic and have never been validated. Table 5 gives an exemplary programme. The risk of development of early or late relapse may vary according to initial risk-group classification at the time of metastatic disease.

Post-chemotherapy teratoma has been considered a low risk for disease progression, although removal of (chemoresistant) teratoma can be considered as therapeutic. Svatek *et al.* (47) have investigated the long-term outcome of 97 patients with pure teratoma within the PC–RPLND specimen. At a median follow-up of 7.4 years, 21 patients (22%) developed recurrent disease after PC–RPLND.

The 5–year and 10–year probabilities (± standard error) of freedom from disease recurrence were 81% ± 4% and 76% ± 5%, respectively. In patients with pure teratoma histology at PC–RPLND, mediastinal involvement at presentation and the presence of an elevated AFP level before PC–RPLND predicted an unfavourable outcome. Patients who had teratoma at the time of PC–RPLND remained at considerable risk for disease progression because of the unpredictable nature of teratoma and the presence of unrecognized, active germ-cell disease outside the retroperitoneum.

TABLE 5 Standard Chemotherapy Regimens for Patients with Advanced Germ Cell Tumour

Drug/Combination	Dose and Schedule
BEP	
Bleomycin	30 IUS–P IV bolus, days 2, 9 and 16
Etoposide	100 mg/m² IV (30–60 min), days 1–5
Cisplatin	20 mg/m² IV (30–60 min), days 1–5 (plus hydration)
Repeat cycle every 21 days for 3 or 4 cycles†	
EP	
Etoposide	100 mg/m² IV (30–60 min), days 1–5
Cisplatin	20 mg/m² IV (30–60 min), days 1–5 (plus hydration)
Repeat cycle every 21 days for 4 cycles†	
VIP	
Ifosfamide	1.2 g/m² IV days 1–5
Etoposide	75 mg/m² IV (30–60 min), days 1–5
Cisplatin	20 mg/m² IV (30–60 min), days 1–5 (plus hydration)
Mesna	400 mg IV bolus prior to the 1st ifosfamide dose, then 1.2 g/m² IV infused continuously on days 1–5
Repeat cycle every 21 days for 4 cycles†	

† Note: Therapy should be given preferably every 21 days on schedule without reduction of the doses at 21–day intervals; There is no indication for prophylactic application of hematopoietic growth factors such as, for example, granulocyte colony-stimulating factor (G–CSF). However, if infectious complications have occurred during chemotherapy, prophylactic administration of G–CSF is recommended for the following cycles.

4.10 Level of Evidence and Recommendations

Levels of evidence [I–IV] and Grades of Recommendation [A–D] are provided (See pp. XXII-XXIV.)

SUMMARY AND RECOMMENDATIONS

For all patients with advanced germ cell tumours (GCTs), stratification into good-, intermediate-, or poor-risk categories, based upon their histology, primary tumour site, anatomic staging, and levels of serum markers, is necessary prior to treatment. Platinum-based chemotherapy is the foundation of therapy. The four courses of BEP regimen has equal efficacy but less toxicity than PVB in poor-risk patients and subsequently BEP was the standard arm in many randomized studies in good-, intermediate- and poor-risk metastatic patients.

4.10.1 Level of evidence and recommendations in the good-prognosis group

Standard regimen for good-risk patients

Level of Evidence I: Three courses of BEP was equivalent to four courses of BEP with respect to treatment outcome. Treatment with three cycles of BEP chemotherapy results in a high complete remission rate and overall survival.

Grade of Recommendation A: Three courses of BEP is the regimen of choice in good-risk patients with advanced disease.

Increased risk of bleomycin lung toxicity

Level of Evidence I: Four cycles of BEP administered at standard doses of bleomycin and etoposide was compared to four cycles of EP (standard dose of etoposide) in good-risk patients and most trials indicated equal efficacy, although most trials suggested a trend for superiority of three cycles of BEP.

Grade of Recommendation A: In good-risk GCT patients at a significantly increased risk of bleomycin lung toxicity and thus a contraindication for bleomycin, four cycles of chemotherapy with etoposide and cisplatin (EP) is the therapy of choice.

Three courses of EP should not be used

Level of Evidence I: Three courses of EP has been shown to be less effective than three courses of BEP.

Grade of Recommendation A: Good-risk patients should not be treated with three cycles of EP. In cases where bleomycin is contraindicated, patients should NOT be treated with three courses of EP.

Lowering the dose of bleomycin and/or etoposide

Level of Evidence I: BEP regimens with lower doses of etoposide (360 mg/m^2 vs 500 mg/m^2 per cycle), bleomycin (30 IUS–P versus 90 IUS–P per cycle), demonstrated lower relapse-free and overall survival rates than conventional dosing.

Grade of Recommendation A: The dose of etoposide should not be lowered from 500 mg/m^2 per cycle to 360 mg/m^2 per cycle and the dose of bleomycin should not be lowered from 90 IUS–P per cycle to 30 IUS–P per cycle.

Three-day versus five-day regimen

Level of Evidence I: 3–day BEP

Data support a 3–day regimen of administering BEP combination chemotherapy to be equally effective as a 5–day regimen, but the three–day regimen is associated with increased toxicity.

Grade of Recommendation A: The primary treatment of choice for good-risk (IGCCCG risk classification) patients is the 5–day regimen, BE$_{500}$P, combination chemotherapy. Based on the increased toxicity of the 3–day BEP regimen, the 5–day BEP regimen is recommended in good-risk patients although for these patients, the 3–day regimen can be considered as an alternative. For intermediate- and poor-risk patients the four cycles should be administered only as a 5–day regimen, not a 3–day regimen.

Less than 3 cycles of BEP?

Level of Evidence I: Efforts to further reduce toxicity by administering less intensive chemotherapy than three cycles of BEP and four cycles of EP have been unsuccessful.

Grade of Recommendation A: No less than three cycles of BEP should be administered in good-risk patients.

Substituting cisplatin with carboplatin

Level of Evidence I: Substituting cisplatin with carboplatin results in less favourable outcome. Two trials that substituted the potentially less toxic carboplatin for cisplatin in these regimens showed poorer relapse-free survival rates, with one study also showing an overall lower survival rate.

Grade of Recommendation A: Substitution of cisplatin by carboplatin in combination chemotherapy regimens is NOT recommended. Single-agent carboplatin should not be used in the treatment of good-risk seminomas.

4.10.2 Level of evidence and recommendations in the intermediate- or poor-prognosis group

Level of Evidence I: None of the randomized trials performed in intermediate- and poor-risk patients have shown superiority of the investigational arm over four courses of BEP.

Grade of Recommendation A: The primary treatment of choice for advanced disease is four cycles of BEP (also called PEB) combination chemotherapy in intermediate-risk (IGCCCG risk classification) metastatic GCT patients.

Intensified cisplatin

Level of Evidence I: Double-dose cisplatin (BEP$_{200}$) is equally effective but associated with markedly increased toxicity.

Grade of Recommendation A: Cisplatin dose should not be doubled to 200 mg/m^2 in week 1.

Increased risk of bleomycin lung toxicity: ifosfamide-containing regimen, VIP

Level of Evidence I: Four courses of BEP is equally effective, but less toxic than four courses of VIP.

Grade of Recommendation A: Four cycles of BEP remains the regimen of choice, but for those at a significantly increased risk of bleomycin lung toxicity, four cycles of etoposide, ifosfamide and cisplatin (VIP), should be considered as the regimen of choice.

High-dose chemotherapy

Level of Evidence I: Randomized trials have shown no significant advantage of HDCT for the overall group of intermediate- and poor-prognosis patients. However, patients with a slow marker decline may represent a prognostically inferior subgroup.

Grade of Recommendation A: Dose intensification strategies or HDCT with peripheral-blood stem-cell support should not be used as first-line treatment, except in the context of a clinical trial.

Modification for patients with a poor general condition

There are no general recommendations for treatment modifications for patients with a poor general condition (Karnofsky < 50%), extended liver infiltration (> 50%), or extended pulmonary infiltration (no level of evidence).

4.10.3 Referral to expert centres

Level of Evidence III: Metastatic testicular cancer is a rare but treatable cancer and it has been shown that optimal treatment of these patients is provided in experienced centres, thus providing patients with their best chance of cure. Analysis of the clinical outcome of poor-risk patients in a randomized clinical trial indicated that outcome is better in centres with experience in treatment of testicular cancer patients. Since post-chemotherapy surgery may also be quite challenging and requires the setting of an experienced centre, this report on the outcomes in poor- and intermediate-risk patients supports the notion that GCT patients should be referred to centres experienced in management of GCT patients and performing clinical trials.

Grade of Recommendation B-C: Whenever possible, men with advanced testicular germ cell tumours should be referred to centres with expertise in the management of such tumours. Poor-risk patients should be referred to expert centres.

4.10.4 Level of evidence and recommendations for post-chemotherapy resection

SUMMARY AND RECOMMENDATIONS

Patients with intermediate- or poor-risk disease often have residual tumours seen on imaging studies at the completion of chemotherapy. The current standard of care is to resect all residual disease following chemotherapy if technically feasible, unless serum tumour markers are rising. With possible rare exceptions, resection of residual masses is only performed when all residual masses can be resected. No randomized trials were performed, all series are retrospective and concern non-comparative studies. The level of evidence is thus III or IV and recommendations are C, including expert opinions from the committee expert panel members.

4.10.5 Level of evidence for conclusions for post-chemotherapy surgery

Recommendations for post-chemotherapy surgery

No randomized trials were performed; all were retrospective series. The algorithms for post-chemotherapy treatment procedure are given in Tables 6 and 7 (Level of Evidence IV; Grade of Recommendation C).

TABLE 6 Treatment Algorithm for Advanced Seminoma Stage CSIIc/ III

IGCCCG Prognosis Group	Treatment	Status After Treatment	Result/ Further Management	
Good	3 cycles of BEP (3– or 5–day schedule) If arguments against bleomycin: 3 cycles of VIP (or PEI)	▪ CR		FUp
		▪ Residual tumour <3 cm: PET optional	▪ No PET done:	FUp
			▪ PET done and negative:	FUp
			▪ PET done and positive:	Consider resection or alternatively FUp
Intermediate	4 cycles of BEP If arguments against bleomycin: 4 cycles of VIP (or PEI)	▪ Residual tumour >3 cm: PET recommended	▪ No PET done:	Fup or resection
			▪ PET done and negative:	FUp
			▪ PET done and positive:	Consider resection or alternatively FUp

FUp = Follow-up

TABLE 7 Treatment Algorithm for Advanced Non-Seminoma

IGCCCG Prognosis Group	Treatment	Result	Further Treatment	Result	Further Treatment
Good	BEP x 3 cycles (3– or 5–day schedule) Arguments against bleomycin: PE x 4 cycles	Marker normalized and no residual tumour			FUp
		Marker normalized and residual, but resectable tumour	Resection	▪ $R^{1}/_{2}$:	Salvage CT
				▪ R0, no viable tumour:	FUp
				▪ R0, viable tumour <10%:	FUp
Intermediate or Poor	BEP x 4 cycles Arguments against bleomycin: VIP (or PEI) x 4 cycles			▪ R0, teratoma:	FUp
				▪ R0, viable tumour >10%:	Consolidation CT (e.g. VIP 2 cycles)
				▪ R?, unclear resection margins:	
		Marker not normalized and residual tumour, but potentially resectable	FUp q 6–12 weeks	▪ Markers normalized or plateau:	Resection
				▪ Markers increased	Salvage CT
		Marker normalized, but irresectable and/or multiple residual tumour	FUp q 8 weeks		
				▪ In case of progression	Salvage CT

FUp = Follow-up; CT = Chemotherapy

Advanced Seminoma

Level of Evidence IV/Grade of Recommendation C: In case of complete response, follow-up only is required. In case of post-chemotherapy residual tumour larger than 3 cm, a PET scan (a minimum of 6 weeks after chemotherapy) is recommended, whereas it is only optional in residual lesions less than 3 cm (in lesions < 3 cm, predictive value is less proven). If PET scan is positive, there is strong evidence for residual active tumour and resection should be considered. If PET scan is negative, follow-up only without active treatment is needed. If no PET is done, lesions greater than 3 cm can be either resected or followed only until resolution or progression. The treatment effect must be monitored by appropriate measures (chest X-ray, CT scan and markers) at one month after the end of treatment (Table 6).

Advanced Non-Seminoma

Level of Evidence III/Grade of Recommendation C: Approximately 70% of metastatic GCT patients will achieve a complete remission following first-line chemotherapy with normalization of serum markers and resolution of radiographic disease. Patients with normalized serum tumour markers and complete resolution of all metastatic disease do not need to undergo PC–RPLND since less than 3% of these men will relapse when undergoing active surveillance. In the remaining 30% who have negative or residual marker levels and persistent radiographic disease (partial remission), surgery should be considered in order to achieve cure with combined-modality treatment. Full bilateral post-chemotherapy RPLND is required in patients with extensive residual masses. In well-defined small masses of less than 5 cm, only local resection of residual tumour should be performed as it is associated with less chance of morbidity.

4.10.6 Level of evidence for conclusions for post-surgery chemotherapy

Patients who have undergone post-chemotherapy surgical resection of residual mass, and viable tumour cells have been found in the surgical specimen, should receive two additional cycles of ("consolidation") chemotherapy. No prospective study has been performed to assess the value of post-surgery chemotherapy versus wait-and-see, in case of complete resection of residual mass(es) containing viable tumour cells.

Based on the results of a retrospective series, post-surgical chemotherapy could perhaps be omitted in patients with favourable prognostic factors and less than 10% viable cells (Level of Evidence IV/Grade of Recommendation C–D). In case of more than 10% viable tumour in the resected specimen, consolidation chemotherapy is certainly indicated (Table 7, e.g. two cycles of VIP).

4.11 Treatment Schedule Logistics

STANDARD AND MODIFICATION OF DOSE/SCHEDULE

4.11.1 Choice of platinum/etoposide schedule

In case of three cycles of BEP, efficacy and toxicity is equivalent if cisplatin is divided over two days instead of five days, and etoposide fractionated over three instead of five days. Therefore, for the treatment of patients with good prognosis, two options for BEP are available: short- and long-course treatment with equal efficacy (Table 6).

However, for intermediate and poor prognosis with four cycles of BEP, the 5–day BEP schedule should be applied since due to the additional cycle in comparison to good-prognosis patients, the toxicity increases with the 3–day BEP schedule. For intermediate- and poor-prognosis patients the 5–day schedule therefore remains standard.

4.11.2 Treatment interval

Level of Evidence III/Grade of Recommendation C: Treatment cycles should be repeated every three weeks, regardless of leukocyte count. However, in case of apparent infection or other physical or medical reasons, the treatment should be delayed until recovery. The reason is that the original data which led to the use of four cycles of BEP, have been generated with 3–week intervals, and dose intensity analysis has shown that the outcome is associated with dose intensity and treatment schedule every three weeks. However, a formal comparison of three or four intervals has never been done and cannot be expected in the future. There is common agreement that for good-prognosis patients the cycle interval is of less importance, since the early EORTC trials as well as the MRC have used 4–week intervals. However, since dose intensity is very likely to be relevant for outcome, a 3–week schedule should be standard, if toxicity allows.

4.11.3 Supportive care

Adequate anti-emetic prophylaxis with a double regimen of a combination of a 5–HT3 antagonist plus dexamethasone, or a triple regimen including a NK1 receptor antagonist to this combination, is standard to reduce, prevent or eliminate platinum-associated nausea and vomiting. Addition of a NK1 receptor antagonist may be useful to prevent delayed nausea and vomiting associated with emetogenic cisplatin chemotherapy. Infectious complications are most relevant and dangerous particularly in this patient population with high likelihood of cure. Although, infection-associated mortality in a prospective comparative trial of the EORTC/MRC (35) was not significantly different, any risk of infection-associated severe toxicity or even mortality should be eliminated. Therefore, prophylactic measures with either G–CSF or prophylactic antibiotics should not be routinely applied, but considered in patients with a high risk for severe infection.

4.11.4 Modification of dose according to bone marrow toxicity in the previous cycle

Patients should be treated on schedule regardless of blood counts. Low blood cell counts at the beginning of a scheduled subsequent course of chemotherapy do not mandate dose reductions or treatment delays unless the previous cycle was complicated by febrile neutropenia or some other significant clinical event. Preferably, full doses should be administered at the scheduled time, regardless of the white blood cell count in order not to compromise the chance for cure.

4.11.5 Prophylactic hematopoietic growth factors

Level of Evidence III: There is no indication for prophylactic application of hematopoietic growth factors such as, for example, G–CSF. However, if infectious complications have occurred during chemotherapy, prophylactic administration of G–CSF is recommended for the following cycles.
Recommendation: Prophylactic hematopoietic growth factors (eg, G–CSF) are only recommended to prevent dose attenuation or treatment delay after febrile neutropenia has occurred. However, the routine use of G–CSF during standard chemotherapy with BEP is not recommended.

4.11.6 Modification of dose or schedule in patients with poor performance status

Level of evidence IV/Grade of Recommendation C: In patients with poor-performance status, massive tumour load or an expected risk of bleeding, (e.g. in the lung or brain, reduced pulmonary function with dyspnea or haemoptoe), the first cycle should be given in a reduced dose. Substitution of cisplatin by carboplatin is particularly important in cases of reduced renal function (GFR < 50 ml/min) or postrenal occlusion. It is recommended to give two days of cisplatin/etoposide (or carboplatin/etoposide, in case of GFR < 50 ml/min) with or without bleomycin in full doses, followed by a break, and start a full-dose cycle after recovery, (e.g. days 8 to 10). If the patient has complete renal failure or needs respiratory assistance, chemotherapy can also be given in these patients with adapted doses to overcome the acute situation.

4.11.7 Treatment of brain metastases

Ten percent of patients with poor-prognosis germ cell tumours have synchronous CNS-metastases. Chemotherapy is standard treatment; however, it is not proven whether additional concurrent radiotherapy is necessary. Since no prospective trial is performed, and retrospective analysis from large patient series are ambiguous, most patients currently receive additional brain irradiation or stereotactic local irradiation, if applicable, in parallel to chemotherapy (single dose 2 Gy, total dose 45–50 Gy).
Level of Evidence III/Grade of Recommendation C: The role of surgical resection of solitary metastases is even less clear; however, given the high efficacy of chemotherapy with or without irradiation, a surgical approach should only be done in case of risk or presence of bleeding.

4.11.8 Duration of chemotherapy, follow-up and secondary measures

Treatment duration with induction chemotherapy is three cycles for good- and four cycles for intermediate- and poor-prognosis patients. If there is progressive disease during the first two cycles with increasing tumour markers and size and number of metastases, treatment must be stopped and salvage chemotherapy instituted.

This is an extremely rare event; however, more often, tumour markers are falling despite increasing tumour mass, which is indicating a "pseudoprogression" based on a growing teratoma ("growing teratoma syndrome"). This is the case most likely in patients with large retroperitoneal mass, however, it can also occur in lung and even brain locations. In this case, further chemotherapy is not helpful, and surgical resection must be instituted early (**Level of Evidence IV/Grade of Recommendation C**).

In most patients the tumour marker falls. However, in about 20% of the patients, markers initially rise, followed by delayed decline. This "marker surge" is prognostic, and patients with delayed marker decline have a higher risk for impaired survival. However, since a change of chemotherapy based on marker surge is not proven to be more efficacious, the measurement of the marker surge is not indicated (**Level of Evidence IV/Grade of Recommendation C**).

Marker determination must be done directly before the next cycle and not between cycles since marker release from a necrotic tumour can lead to false positive increase of the marker. In patients with large tumour mass and high hCG levels, even in the case of complete necrosis of residual mass, hCG can remain elevated up to several months. This "pseudo-plateau" should be known, and salvage chemotherapy not initiated as long as the residual marker is not increasing. Rather, the metastases and marker levels should be followed until normalization and/or resolution of the residual mass (**Level of Evidence IV/Grade of Recommendation C**).

4.12 References

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C5

Salvage Therapy

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CONTENTS

Salvage Therapy

5.1 Introduction

Patients with germ cell tumours (GCTs) who relapse are a heterogeneous group. Depending on the histology and initial presenting stage, this relapse may occur while on surveillance for stage I disease, after either abdominal radiation therapy or limited chemotherapy as adjuvant for stage I disease, after retroperitoneal lymph node dissection (RPLND) for stage I or stage II non-seminoma, or after chemotherapy for metastasis. This section of the guidelines discusses "salvage" therapy of germ cell cancers and we restrict this term to disease progressing after combination chemotherapy for metastatic disease. Patients who relapse on surveillance for stage I non-seminoma should undergo RPLND or chemotherapy. Those after first-line radiotherapy for stage I or early stage II seminoma should receive cisplatin-based chemotherapy comparable to the first-line treatment strategy in advanced seminoma which has a cure rate of more than 90%. Those with recurrent disease after surgery alone also have cure rates of more than 90% after cisplatin-based chemotherapy as for the first-line treatment strategy in metastatic non-seminoma. A decrease in the rate of marker decline during the later cycles of primary chemotherapy is not evidence of failure and should not lead to a change to salvage chemotherapy. Thus, this chapter on salvage therapy after first-line chemotherapy includes patients who are progressing while on chemotherapy as well as any patients who relapse after having shown response to one or several lines of chemotherapy. Additionally, we will consider patients in special categories (e.g., late relapse). The sensitivity to further treatment will be different in these groups, ranging from slight to profound chemotherapy resistance. Other distinct relapse subtypes include the "growing teratoma" syndrome (GTS), comprising a slow benign enlargement of an often cystic teratoma (Figures 1a and 1b) (1), and the syndrome of malignant transformation of a teratoma to a non-germ cell tumour (2).

Late relapse is defined as any disease recurrence more than two years after completion of first-line chemotherapy (3,4). Prognosis in general is worse with earlier relapse, especially if disease progresses during previous chemotherapy (5,6), but late relapse of non-seminoma is rarely curable by chemotherapy alone (4,7). A pooled analysis of a larger series published between 1989 and 2006 showed a crude late relapse incidence of 3.2% and 1.4% for patients with non-seminoma and seminoma, respectively. [Level of evidence: II]

5.1.1 Methods

These international guidelines were assembled initially by an expert and a multidisciplinary writing committee based on consensus guidelines produced by The European Association of Urology (8), the recommendations from the European Consensus Conference on Diagnosis and Treatment of Germ Cell Cancer (9), by a Canadian Germ Cell Consensus 2007 conference and from ESMO Minimum Clinical Recommendations (10). The principles of evidence-based medicine were scored using a modified version of the Oxford levels of evidence as presented earlier in this book (see pp. XXII–XXIV). Draft guidelines were presented at an International Consensus in Urological Disease (ICUD) meeting in Shanghai in November of 2009 (Shanghai, November 2009). The writing committee compiled the results of the discussion.

5.2 Diagnosis and Assessment

The incidence of relapse after first-line chemotherapy depends on the pathological subtype, and on the extent of disease at presentation, usually classified as "good", intermediate" or "poor" according to the International Germ Cell Cancer Consensus Group (IGCCCG) (11); for non-seminoma, the relapse risk by five years is 11%, 25% and 59%, respectively, whereas for seminoma, there are only two prognostic groups (good and intermediate) with relapse risks by five years of 18% and 33% (11). [Level of evidence: II]

Timing of relapse is different for seminoma and non-seminoma. Almost all seminoma recurrences occur within five years with no clear differences in biology between early and later relapse. For non-seminomas, most malignant relapses will occur within two years, and later relapses are mainly a consequence of residual teratoma. Late relapse is estimated to occur in about 2.6% of testicular tumours (3,4). [Level of evidence II]

Detection of relapse is influenced by the detail of the post-treatment follow-up. Most early relapses are identified by routine tumour marker assays, especially human chorionic gonadotrophin (hCG) and alfa-fetoprotein (AFP) since they are more specific than LDH, or by routine follow-up radiology. Growing teratoma is often seen on follow-up computed tomography (CT) scans or occasionally even on standard chest X-ray. If neglected, growing teratoma can cause obstructive symptoms or may undergo malignant transformation, and should therefore be resected. Late malignant change in residual teratoma may be detected by serum tumour marker assays, characteristically by a raised serum AFP, but often, late relapse is marker-negative and patients may present with advanced symptomatic malignant disease. [Level of evidence: IV]

Assessment of the relapsed patient should include full restaging with CT scans of the brain, thorax, abdomen, pelvis as well as tumour marker assays. Bone involvement is rare especially in non-seminomas. The skeletal system can be assessed by the routine spiral CT scans as well as by conventional radionuclide scans. All patients with relapsed non-seminoma should have a brain scan (CT or MRI) even in the absence of neurological symptoms, especially if there is evidence of high hCG levels or the presence of multiple lung metastases. It is important to assess organ function to determine tolerance of possible further treatments. In view of previous chemotherapy, the assessment should include measurements of renal and lung functions, and assessment of neuropathy. If fertility has recovered, sperm banking may be considered. [Level of evidence IV]

Patients with late relapse after chemotherapy are particularly difficult to treat and should be managed differently from all other groups. If technically feasible, all patients with late relapse after chemotherapy should undergo immediate radical surgical resections of all lesions irrespective of the level of their tumour markers in order to completely resect all undifferentiated germ-cell tumour, teratoma or secondary non-germ cell cancer. If the lesions are not completely resectable, biopsies should be obtained for histological assessment and salvage chemotherapy should be initiated according to the histological results. If the patient responds to salvage chemotherapy, secondary surgery should be conducted whenever possible. To avoid excess morbidity and mortality, late relapses should only be treated at centres experienced in managing such patients. [Level of evidence: IV]

5.3 Prognosis and Prognostic Factors in the Salvage Setting

Prognostic factors have long been recognized to strongly impact the results of first-salvage chemotherapy and have been the focus of several retrospective analyses (5,6,12,13). In the first-salvage setting, the importance of prognostic factors is even greater than at initial diagnosis of the tumour. In contrast, patients who suffer further relapses and require second or even third salvage treatment have a uniformly poor prognosis, in particular, if they have rapidly progressing, multifocal disease. Yet, cures can still be achieved in any of these subsets (14,15). [Level of evidence: IV]

Although consistent prognostic variables have been identified, previous analyses suffered from substantial limitations. All have been too small to identify but a few variables reliably; some databases contained only incomplete information and were without source-data verification; often external or internal validation of the results were missing; many analyses were based on outdated treatments that would no longer be considered standard today (16). Many of these obstacles have been overcome by a recent large international collaboration that included more than 1,500 patients in an analysis of prognostic factors for first salvage treatment (Table 1) (15). Seminoma histology was identified as a good prognostic factor. The adverse prognostic factors were:

1. Extragonadal primary tumours, in particular primary mediastinal non-seminomas
2. Less than complete remission or less than tumour-marker negative partial remission to first-line treatment
3. A progression-free interval of three months or less
4. Elevation of AFP at salvage, particularly if more than 1000 ng/ml
5. Elevation of hCG at salvage to more than 1000 U/l
6. The presence of liver, bone or brain metastases.

TABLE 1 Prognostic Factors for First Salvage Treatment

TIT	Poor	Good
Primary Tumour	extragonadal, particularly mediastinal non-semioma	gonadal primary
Histology	non-seminoma	seminoma
First-Line Response	PRm+, SD or PD	CR, NED, or PRm–
Salvage Attempt	second or subsequent	first
Response Duration	≤ 3 months	> 3 months
AFP or hCG Level	high (e.g. > 1000)	low (e.g. ≤ 1000)
Metastatic Location	liver, bone, or brain	lymph nodes and/or lung

Legend: CR = complete remission
NED = no evidence of disease after surgery;
PRm+ = partial remission, positive tumour markers
PRm– = partial remission, negative tumour markers
AFP = alpha-fetoprotein
hCG = human chorionic gonadotrophin

The results of the analysis confirmed the large variation in survival in patients relapsing after at least three cycles of cisplatin-based first-line treatment. Patients relapsing with seminoma and no other risk factors had a projected progression-free survival rate of more than 75% at two years. In contrast, patients relapsing with seminoma or non-seminoma and who have one or several of the above mentioned risk factors had an increasingly dismal prognosis with a progression-free survival rate of less than 10% at two years in the most unfavourable risk group. [Level of evidence: II]

The challenge will be to exploit these results in clinical practice, in particular, to use them to adjust the intensity of the salvage strategy according to the risk of failure. However, the availability of the recent robust analysis makes this a timely enterprise. International efforts are now needed to study risk-adapted salvage strategies prospectively.

5.4 Role of Surgery in Salvage

5.4.1 In the setting of residual disease after salvage chemotherapy

In patients who normalize or achieve a low-level plateau in their markers but have residual disease radiographically, all residual masses should be resected within 4–6 weeks or when the patient has recovered sufficiently to consolidate systemic treatment. Residual viable disease in the mass(es) is associated with a worse prognosis and adjuvant chemotherapy does not appear to improve outcomes after complete resection (17,18). [Level of evidence: II]

The term "desperation surgery" has been used for salvage surgery in the setting of the occasional patients who have exhausted chemotherapy options, who have rising tumour markers, and in whom, complete resection of all tumour appears feasible. This will often require a multidisciplinary surgical team and should be performed by surgeons skilled in these operations who work in specialized centres. Surprisingly, long-term survival is about 25% of these patients. Late relapse patients with moderately elevated AFP and localized (mainly retroperitoneal) metastatic deposits do better. Salvage surgery is not recommended in the face of rapidly progressing disease, multiple metastatic sites or a rapidly increasing hCG level. [Level of evidence: III]

5.4.2 In the setting of late relapse

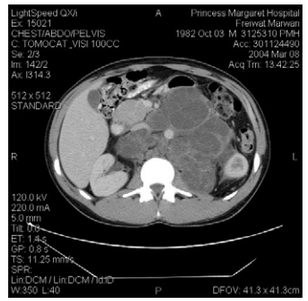
It is generally accepted that the term, "late relapse", refers to patients with relapse of more than two years after primary therapy. The overall risk of late relapse at diagnosis is approximately 1.5% for seminoma and 3% for non-seminoma patients. These patients are more chemotherapy-resistant so if the relapsed disease is resectable, whether or not a previous RPLND has been performed, they should be managed by immediate surgery if complete resection is feasible, even if tumour markers are elevated (3,4,19,20). If unresectable, biopsy should be obtained and appropriate salvage chemotherapy given with the intent of subsequent salvage surgery. [Level of evidence: III]

5.4.3 Growing teratoma syndrome

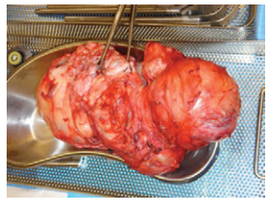
The rare GTS was described in 1982 by Logothetis *et al.* (1) as enlarging residual mass(es) observed on or after chemotherapy for NSGCT that at resection, contained mature chemorefractory teratoma only (1). The chemotherapy refractory mass growth was attributed to secretion into expansile cysts in some cases (Figures 1a and 1b), but others were solid. The masses are most commonly in the retroperitoneum or mediastinum. Markers are usually normal. Growth rates can vary and most importantly, surgery is effective with long-term local control and a low risk of progression. Further salvage chemotherapy should not be given when GTS is suspected. [Level of evidence: III]

FIGURE 1

A



B



5.5 Salvage Chemotherapy

Patients who relapse after cisplatin-based chemotherapy can be treated with either further standard-dose chemotherapy or high-dose chemotherapy and autologous stem-cell transplantation (HDCT with ASCT).

Various regimens have been explored but superiority of one treatment regimen over another has not yet been shown. Conventional salvage chemotherapy has almost exclusively been tested in retrospective studies or small phase II studies, which included a limited number of patients accrued over long periods, as well as very heterogenous patient populations . These factors make definitive assessment of these treatment options difficult. However, tailoring the intensity of salvage treatment according to the estimated risk of chemotherapy resistance and the risk of salvage failure has often been the intention. Consensus participants have noted that many of the phase II trials of conventional-dose chemotherapy were conducted in "good-risk" patients, making it difficult to extrapolate the results to the "poor-risk" subgroup. At present, it is unclear whether conventional-dose cisplatin-based combination chemotherapy is sufficient as first-salvage treatment or whether early intensification of first-salvage treatment with HDCT should be attempted. It is therefore important that these rare patients are treated within clinical trials and at experienced centres.

In recurrent seminoma, conventional-dose cisplatin-based salvage chemotherapy after first-line therapy with bleomycin, etoposide and cisplatin (BEP) or etoposide and cisplatin (EP), will result in long-term remissions in the majority of patients without adverse prognostic factors. The regimens of choice are four cycles of vinblastine, ifosfamide and cisplatin (VeIP/VIP) or of paclitaxel, ifosfamide and cisplatin (TIP) (Table 2). So far, no conventional-dose salvage regimen has shown unequivocal superiority over another conventional-dose cisplatin-containing salvage regimen. [Level of evidence: III]

TABLE 2 Standard PEI /VIP, TIP and VeIP chemotherapy (interval 21 days)

	Dosage	Duration	No. of cycles
PEI/IPE (VIP in the past)			**4 cycles every 21 days**
Cisplatin*	20 mg/m²	Days 1–5	
Etoposide	75–100 mg/m²	Days 1–5	
Ifosfamide†	1.2 g/m²	Days 1–5	
TIP‡			**4 cycles every 21 days**
Paclitaxel	250 mg/m²	Day 1, 24h infusion	
Ifosfamide†	1.5 g/m²	Days 2–5	
Cisplatin†	25 mg/m²	Days 2–5	

Legend: PEI/IPE = cisplatin, etoposide, ifosfamide
TIP = paclitaxel, ifosfamide, cisplatin
* Plus hydration, † Plus mesna protection
‡ UK MRC regimen (24) paclitaxel 175mg/m² over 3 hours on day 1, ifosfamide 1 g/m² days 1–5; cisplatin 20 mg/m² days 1–5

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TABLE 2 Standard PEI /VIP, TIP and VeIP chemotherapy (interval 21 days), *Cont'd*

	Dosage	Duration	No. of cycles
VeIP (VIP)			**4 cycles every 21 days**
Vinblastine	0.11 mg/kg	Days 1 + 2	
Ifosfamide†	1.2 g/m²	Days 1–5	
Cisplatin*	20 mg/m²	Days 1–5	

Legend: VeIP/VIP = vinblastine, ifosfamide, cisplatin
* Plus hydration
† Plus mesna protection

Similarly, in recurrent non-seminoma, conventional-dose salvage treatment after first-line chemotherapy for metastatic disease should comprise four cycles of VIP, or TIP (21–24). Etoposide may replace vinblastine in patients with less prior exposure or with neuropathy (Table 2). Paclitaxel has shown single-agent activity in patients refractory to conventional cisplatin-based chemotherapy. In addition, a high response rate of more than 50% to TIP was observed in good prognosis patients (23,24). Results from randomized trials specifically addressing the role of paclitaxel are not yet available. Conventional-dose cisplatin-based salvage chemotherapy can achieve long-term remissions in 15%–60% of patients, depending on individual risk factors. In the absence of randomized trials, no conventional-dose salvage regimen has shown unequivocal superiority. The use of more than three drugs in salvage chemotherapy increases toxicity without improving overall treatment outcome. [Level of evidence: III]

The results of salvage therapy after first-line cisplatin-based treatment are unsatisfactory overall. No advantage from HDCT was observed according to the results of the randomized IT 94 trial. Therefore at present, patients with good prognostic features should be offered conventional-dose salvage chemotherapy as first-salvage treatment. In patients with poor prognostic features, several phase II trials as well as one retrospective matched-pair analysis have suggested an improvement in survival with early intensification of first-line salvage treatment using HDCT. Yet, no consensus exists for the role of HDCT as first-salvage treatment. HDCT still represents a curative option for patients with second or subsequent relapses, albeit with long-term disease-free survival rates of less than 20% (14). Options for palliative chemotherapy include monotherapy with oral etoposide, paclitaxel, gemcitabine, oxaliplatin or combinations of these drugs. However, in individual patients, even third-line combinations incorporating new agents and multimodality treatment can still result occasionally in long-term remissions or even cure. Therefore, all patients with relapsed seminoma and non-seminoma as well as patients undergoing palliative treatment should be treated at experienced centres and preferably within prospective randomized trials. [Level of evidence: IV]

5.5.1 Role of high-dose chemotherapy in GCT salvage

Carboplatin and etoposide have remained the backbone of every salvage HDCT regimen to date. The dosages of these two agents have varied with different regimens. Some regimens include a third drug, mostly ifosfamide or cyclophosphamide. However, the use of more than three drugs has increased toxicity without improving survival rates and should therefore no longer be pursued. The use of peripheral blood stem cells has become standard. [Level of evidence: II]

In a German randomized phase III study (25), a comparison between single versus sequential HDCT as first or subsequent salvage treatment in patients with relapsed or refractory germ cell tumours was performed. No difference in survival probabilities was observed between the single HDCT arm containing carboplatin etoposide and cyclophosphamide and sequential HDCT using only carboplatin and etoposide at slightly lower doses. The study was discontinued prematurely after the recruitment of 216 patients as a result of excess treatment-related mortality in the arm containing the single HDCT. In this study sequential HDCT was better tolerated and resulted in fewer treatment-related deaths. [Level of evidence: II]

One randomized study has been published, with HDCT in first relapse. A total of 280 patients with cisplatin-sensitive disease were randomized to four cycles of VIP (or VelP) (cisplatin, ifosfamide and etoposide (or vinblastine)) or three cycles of this treatment followed by HDCT with carboplatin, etoposide and cyclophosphamide with stem cell rescue (26). All patients included into this study had previously achieved a complete or partial remission from platinum-combination chemotherapy as first-line treatment and thereby belonging to a prognostic favourable group. Patients with cisplatin-refractory disease were excluded from the study. Only a single high-dose cycle was given compared with sequential high-dose cycles in other studies. Patients who received HDCT at relapse had no benefit compared to patients treated with salvage therapy in conventional doses (26). Overall complete response and partial response rates were 41% and 17% in the standard arm and 44% and 18% in the HDCT arm, respectively. The three-year overall survival rate was 53% in both of the two arms (26). [Level of evidence: II]

Einhorn *et al.* (14) performed a retrospective review of treatment results in 184 patients treated with HDCT as second line, third line or later therapy. The majority of patients had two cycles of HDCT. A prognostic scoring algorithm was developed, which included timing of HDCT (second, third or subsequent line), platinum refractory disease and IGCCCG poor-prognosis group. A score of 3 was given for third-line chemotherapy, 2 for platinum refractoriness and 2 for poor-prognosis risk group. For patients in the low-risk group (0 points), intermediate-risk group (2–3 points) and high-risk group (4–7 points), the five-year survival was around 80%, 60% and 40%, respectively (14). [Level of evidence: III]

The poor results achieved with salvage chemotherapy especially in second- and third-line salvage therapy, has prompted the increased use of HDCT since the end of the 1980s. Several retrospective and phase II studies have been undertaken. Nichols *et al.* (27) first reported in 1989 a very promising response rate of 44% and long-term remissions in 12% of 32 patients with therapy-refractory testicular cancer using high-dose carboplatin and etoposide. A number of subsequent studies have

reproduced these results and confirmed responses and long-term survival for patients with second or third relapses as well as for selected patients with cisplatin-refractory disease. In the German randomized phase III study (25) comparing three cycles of VIP chemotherapy followed by a single high-dose cycle with a sequential HDCT regimen, 10% of patients even with cisplatin-refractory disease achieved long-term survival after HDCT. [Level of evidence: III]

5.6 Conclusions

It is clear that complete remission and long-term disease free survival can be obtained in selected patients after both second- and third-line HDCT. Based on a recent robust prognostic factor analysis, an international collaborative group is working on the definition of favourable or unfavourable classification for relapsing patients. This could have a significant impact on the success of choosing patients for conventional- or high-dose salvage chemotherapy strategies to treat first relapse in the future. Further clarification of the role of HDCT in germ cell tumours can only be achieved in well-designed clinical trials. For this endeavour, international collaboration will be very important.

In patients who failed to be cured with a standard-dose option and who are well enough to tolerate it, HDCT with transplantation should be offered before declaring the relapsed disease incurable. To maintain the highest chance of cure, patients with a poor prognosis or relapse should be transferred to a specialized centre without any delay to benefit from optimal interdisciplinary management and supportive care.

5.7 Summary

In stage I disease, the consensus conference recommended that patients should be informed of all treatment options, including the potential benefits and side effects of each treatment. It was agreed that this discussion should include the possible salvage treatment effects. Additionally, in patients willing and able to adhere to a surveillance program, this should be considered as the management option of choice (assuming facilities are available for suitable monitoring).

In stage IIA disease, the consensus conference recommended that radiotherapy (RT) should be considered standard treatment if there were no contraindications. In stage IIB disease, chemotherapy or RT were considered to be reasonable treatment approaches and in stage IIC disease, chemotherapy should be considered the standard treatment approach. For patients with residual mass after chemotherapy, the consensus conference noted that patients with masses less than 3 cm in diameter could likely be safely observed while patients with residual masses of more than 3 cm in diameter could be considered for immediate surgery or close observation. It was also noted that surgery in this setting is technically challenging and could be associated with a higher morbidity than in patients with non-seminomatous tumours.

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The Société Internationale d'Urologie

The Société Internationale d'Urologie is the world's only truly international professional organization serving the global urological community. Founded in Paris in 1907, the SIU now serves its members from its Central Office facilities in Montreal, Canada.

SIU members represent the full spectrum of clinicians and investigators from all subspecialties that come together to diagnose, treat and support patients with urological disease.

The Society's mission is to enable urologists in all nations, through international cooperation in education and research, to apply the highest standards of urological care to their patients. The SIU is unique in its international scope and its commitment to effecting positive and sustainable change in nations across the world.

The SIU promotes its mission objectives through annual world congresses, training scholarships, equipment donation and maintenance in training centres, donation of teaching materials, and support of the International Consultation on Urological Diseases (ICUD).

Previous SIU congresses have addressed the following topics: Urogenital Trauma (2002), Bladder Cancer (2004), Congenital Genital Anomalies (2006), Stone Disease (2007), Penile Cancer (2008, Testicular Cancer (2009), Vesicovaginal Fistula (2010), Urethral Strictures (2010). Planned for the near future are Prostate Cancer (2011) and Male Lower Urinary Tract Symptoms (2012).

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It is now time to share this textbook with our readers, in the hope that the concepts discussed herein will prove useful in caring for their patients, as well as inspiring further studies and research into this disease.

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