EAU Guidelines on Testicular Cancer

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Consultant radiologist: Y. Jain
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1. Introduction

1.1 Aim and objectives
The aim of these guidelines is to present the current evidence for the diagnosis and treatment of patients with cancer of the testis. Testicular cancer (TC) represents 5% of urological tumours affecting mostly younger males. This document addresses post-pubertal testicular germ-cell tumours (TGCTs) in the male including spermatocytic tumour and sex cord/gonadal stromal tumours.

It must be emphasised that clinical guidelines present the best evidence available to the experts but following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions which should also take personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition
The European Association of Urology (EAU) Guidelines Panel on TC consists of a multidisciplinary group of clinicians including, urologists, medical oncologists, a radiation-oncologist and a pathologist. When necessary, consultants from other specialties provide input. Members of this Panel have been selected, based on their expertise, to represent the professionals treating patients with TC. All experts involved in the production of this document have submitted potential conflict of interest statements which can be viewed on the EAU website: http://www.uroweb.org/guideline/testicular-cancer/.

1.3 Available publications
A quick reference document (Pocket guidelines) is available, in print and as an app for iOS and Android devices. These are abridged versions which may require consultation together with the full text version. Several scientific publications are available, as are a number of translations of all versions of the EAU Testicular Cancer Guidelines. All documents are accessible through the EAU website: http://www.uroweb.org/guideline/testicularcancer/.

1.4 Publication history and summary of changes

1.4.1 Publication history
The EAU published the first guidelines on TC in 2001. Since 2008, the TC Guidelines contains a separate chapter on testicular stromal tumours. This document presents a limited update of the 2019 publication. Review papers have been published in the society’s scientific journal European Urology, the latest version dating to 2015 [1].

1.4.2 Summary of changes
For the 2021 Testicular Cancer Guidelines, new references have been added throughout the document. Key changes in this publication include:

- The chapter on stromal tumours has been re-structured and revised under a new heading: “Rare adult testicular tumours”;
- The chapter on epidemiology, aetiology and pathology has been revised;
- Summaries of evidence have been added throughout the text;
- Old citations have been refreshed and replaced with newer references;
- A number of articles identified after the scope search cut-off date have been included as they contain important information pertaining to guidelines recommendations;
- Supporting text and recommendations across the guideline have been rephrased and revised;
- The recent re-validation of the 1997 International Germ Cell Cancer Collaborative Group (IGCCCG) prognostic risk-factor based system for metastatic testicular Germ cell tumours in patients treated with cisplatin-etoposide as first-line chemotherapy has been included in the text replacing the old version;
- New recommendations and supporting text regarding VTE prophylaxis in males with metastatic germ cell tumours (GCTs) receiving chemotherapy have been added.

2. Methods

New and relevant evidence has been identified, collated and appraised through a structured assessment of the literature. The search was limited to studies representing high levels of evidence only (i.e., systematic reviews with meta-analysis, randomised controlled trials (RCTs), and prospective non-randomised comparative studies)
published in the English language. The search was restricted to articles published between June 2019 and April 2020 and included testicular stromal tumours. Databases covered by the search included Pubmed, Ovid, EMBASE and the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews. After deduplication, a total of 1,578 unique records were identified, retrieved and screened for relevance. Ninety-six new and updated references have been included in the 2021 guidelines. A detailed search strategy is available online: http://uroweb.org/guideline/testicular-cancer/?type=appendices-publications.

For each recommendation within the guidelines there is an accompanying online strength rating form, the basis of which is a modified GRADE methodology [2, 3]. Each strength rating form addresses a number of key elements namely:

1. the overall quality of the evidence which exists for the recommendation, references used in this text are graded according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [4];
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact of patient values and preferences on the intervention;
6. the certainty of those patient values and preferences.

These key elements are the basis which panels use to define the strength rating of each recommendation. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences.

Additional information can be found in the general Methodology section of this print, and online at the EAU website: www.uroweb.org/guidelines. A list of associations endorsing the EAU Guidelines can also be viewed online at the above address.

2.1 Review
The 2020 Guidelines document was subjected to peer review following publication. Reviewers comments were incorporated accordingly in the present 2021 Guidelines edition.

2.2 Future goals
- A systematic review on diagnostic accuracy on value of the ultrasound (US) in the diagnostic of small testicular masses in collaboration with the Sexual and Reproductive Health panel is ongoing.
- A review and discussion of the recommendations with patient's associations is ongoing.
- A joint registry project in collaboration with the Sexual and Reproductive Health panel in patients with TC is planned.
- The development of a TC survivorship plan in collaboration with patient's associations is planned.
- An Individual Patient Data (IPD) prognostic factor study on the value of pathological factors in clinical stage I seminoma testis patients under active surveillance has been approved by the Guidelines Office Methods Committee. Five international centres are collaborating on the study. Data analysis and outcomes are expected at the end of 2021.
- A number of care pathways are planned for 2021.

3. EPIDEMIOLOGY, AETIOLOGY & PATHOLOGY

3.1 Epidemiology and Aetiology
Testicular cancer represents 1% of adult neoplasms and 5% of urological tumours, with three to ten new cases per 100,000 males/per year in Western societies [6]. Its incidence has increased during recent decades particularly in industrialised countries [7, 8]. At diagnosis, 1-2% of cases are bilateral and the predominant histology is germ cell tumours (GCT) (90-95% of cases) [6]. Peak incidence is in the third decade of life for non-seminoma (NS) and mixed GCTs, and the fourth decade for pure seminoma. In 5% of TGCT the primary site is at an extragonadal location [9].
There are two fundamental categories of TGCTs based on their development and epigenetic features. Most malignant post-pubertal TGCTs (or type II GCT) originate from the germ cell neoplasia “in situ” (GCNIS). They are clinically and histologically subdivided into seminomas and non-seminomas, the latter encompassing somatic and extra-embryonal elements of embryonal carcinoma, yolk sac, choriocarcinoma and teratoma [10].

Non-related GCNIS tumours include pre-pubertal-type teratoma and yolk sac (Type I), diagnosed at early paediatric age and, spermatocytic tumours (Type III) diagnosed in the elderly. Although there is overlapping histology between the pre-pubertal teratoma/yolk sac and the teratoma and yolk sac elements in the GCNIS-related non- seminomas, they have a separate and independent pathogenesis [10].

Overall, type II TGCT have a low mutational burden and few somatic changes. A specific recurrent genetic marker – an isochromosome of the short arm of chromosome 12 – (i12p) – is over-represented in most invasive GCNIS-related TGCTs [10, 11] but not found in GCNIS [12]. However, some type II TGCTs, mostly seminomas, appear to lack a gain of 12p and present preferential cKIT mutations. Without occurrence of these mutations GCNIS will not progress to invasive GCTs [10]. Other significant chromosomal aberrations in type II TGCTs are gain of 7, 8, 21 and loss of chromosomes 1p, 11, 13 and 18 [13].

Epidemiological risk factors for the development of TC are components of the testicular dysgenesis syndrome, which encompasses cryptorchidism, hypospadias, decreased spermatogenesis and sub- or infertility [14, 15], familial history of TCs among first-degree relatives and the presence of a contralateral tumour or GCNIS [14, 16-21].

**General:**

3.2 **Histological classification**

The recommended pathological classification shown below is based on the 2016 update of the World Health Organization (WHO) pathological classification [22].

1. **Germ cell tumours**
   - Germ cell neoplasia in situ (GCNIS)
2. **Derived from GCNIS**
   - Seminoma
   - Embryonal carcinoma
   - Yolk sac tumour, post-pubertal type
   - Trophoblastic tumours
   - Teratoma, post-pubertal type
   - Teratoma with somatic malignant components
   - Mixed germ cell tumours
3. **Germ cell tumours unrelated to GCNIS**
   - Spermatocytic tumour
   - Yolk sac tumour, pre-pubertal type
   - Mixed germ cell tumour, pre-pubertal type
4. **Sex cord/stromal tumours**
   - Leydig cell tumour
     - Malignant Leydig cell tumour
   - Sertoli cell tumour
     - Malignant Sertoli cell tumour
     - Large cell calcifying Sertoli cell tumour
     - Intratubular large cell hyalinising Sertoli cell neoplasia
   - Granulosa cell tumour
     - Adult type
     - Juvenile type
   - Thecoma/fibroma group of tumours
   - Other sex cord/gonadal stromal tumours
     - Mixed
     - Unclassified
   - Tumours containing both germ cell and sex cord/gonadal stromal
     - Gonadoblastoma
5. **Miscellaneous non-specific stromal tumours**
   - Ovarian epithelial tumours
   - Tumours of the collecting ducts and rete testis
- Adenoma
- Carcinoma

- Tumours of paratesticular structures
  - Adenomatoid tumour
  - Mesothelioma (epithelioid, biphasic)
  - Epididymal tumours

- Cystadenoma of the epididymis
- Papillary cystadenoma
- Adenocarcinoma of the epididymis
- Mesenchymal tumours of the spermatic cord and testicular adnexae

4. STAGING & CLASSIFICATION SYSTEMS

4.1 Staging

The 2016 Tumour, Node, Metastasis (TNM) classification of the International Union Against Cancer (UICC) is recommended to assess the anatomical extent of the disease (Table 4.1) [23].

Table 4.1: TNM classification for testicular cancer (adapted from UICC, 2016, 8th edn.) [23]

<table>
<thead>
<tr>
<th>pT - Primary Tumour</th>
<th>pTX</th>
<th>Primary tumour cannot be assessed (see note 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pT0</td>
<td>No evidence of primary tumour (e.g., histological scar in testis)</td>
<td></td>
</tr>
<tr>
<td>pTis</td>
<td>Intratubular germ cell neoplasia (carcinoma in situ)*</td>
<td></td>
</tr>
<tr>
<td>pT1</td>
<td>Tumour limited to testis and epididymis without vascular/lymphatic invasion; tumour may invade tunica albuginea but not tunica vaginalis*</td>
<td></td>
</tr>
<tr>
<td>pT2</td>
<td>Tumour limited to testis and epididymis with vascular/lymphatic invasion, or tumour extending through tunica albuginea with involvement of tunica vaginalis**</td>
<td></td>
</tr>
<tr>
<td>pT3</td>
<td>Tumour invades spermatic cord with or without vascular/lymphatic invasion**</td>
<td></td>
</tr>
<tr>
<td>pT4</td>
<td>Tumour invades scrotum with or without vascular/lymphatic invasion</td>
<td></td>
</tr>
</tbody>
</table>

N - Regional Lymph Nodes – Clinical

<table>
<thead>
<tr>
<th>N0</th>
<th>No regional lymph node metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1</td>
<td>Metastasis with a lymph node mass 2 cm or less in greatest dimension or multiple lymph nodes, none more than 2 cm in greatest dimension</td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension; or more than 5 nodes positive, none more than 5 cm; or evidence of extranodal extension of tumour</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis with a lymph node mass more than 5 cm in greatest dimension</td>
</tr>
</tbody>
</table>

Pn - Regional Lymph Nodes – Pathological

<table>
<thead>
<tr>
<th>pNX</th>
<th>Regional lymph nodes cannot be assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>pN0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>pN1</td>
<td>Metastasis with a lymph node mass 2 cm or less in greatest dimension and 5 or fewer positive nodes, none more than 2 cm in greatest dimension</td>
</tr>
<tr>
<td>pN2</td>
<td>Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension; or more than 5 nodes positive, none more than 5 cm; or evidence of extranodal extension of tumour</td>
</tr>
<tr>
<td>pN3</td>
<td>Metastasis with a lymph node mass more than 5 cm in greatest dimension</td>
</tr>
</tbody>
</table>

M - Distant Metastasis

<table>
<thead>
<tr>
<th>MX</th>
<th>Distant metastasis cannot be assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis **</td>
</tr>
<tr>
<td>M1a</td>
<td>Non-regional lymph node(s) or lung metastasis</td>
</tr>
<tr>
<td>M1b</td>
<td>Distant metastasis other than non-regional lymph nodes and lung</td>
</tr>
<tr>
<td>Stage grouping</td>
<td>pTis</td>
</tr>
<tr>
<td>----------------</td>
<td>------</td>
</tr>
<tr>
<td>Stage IB</td>
<td>pT2 - pT4</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>Any pT/TX</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>Any pT/TX</td>
</tr>
<tr>
<td>Stage IIIC</td>
<td>Any pT/TX</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>Any pT/TX</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>Any pT/TX</td>
</tr>
<tr>
<td>Stage IIC</td>
<td>Any pT/TX</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>Any pT/TX</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>Any pT/TX</td>
</tr>
<tr>
<td>Stage IIC</td>
<td>Any pT/TX</td>
</tr>
</tbody>
</table>

Stage IA: Patients have primary tumours limited to the testis and epididymis, with no evidence of microscopic vascular or lymphatic invasion by tumour cells on microscopy, no sign of metastases on clinical examination or imaging, and post-orchidectomy serum tumour marker levels within normal limits. Marker decline in patients with CS I disease should be assessed until normalisation.

Stage IB: Patients have a more locally invasive primary tumour, but no sign of metastatic disease.

Stage IS: Patients have persistently elevated (and usually increasing) serum tumour marker levels after orchidectomy, indicating subclinical metastatic disease (or possibly a second GCT in the remaining testis).

In population-based patient series from developed countries, 75-80% of seminoma patients, and about 55%-64% of non-seminomatous germ cell tumour (NSGCT) patients have stage I disease at diagnosis [25, 26]. True stage IS (persistently elevated or increasing serum tumour marker levels after orchidectomy) is found in about 5% of non-seminoma patients [25].
4.3 The International Germ Cell Cancer Collaborative classification for the prognostic-risk groups of metastatic testicular cancer

The 1997 International Germ Cell Cancer Collaborative Group (IGCCCG) defined a prognostic risk-factor system for metastatic GCT based on identification of clinically independent adverse factors. The classification has been revalidated on a contemporary cohort of metastatic testicular GCT treated with cisplatin/etoposide based first-line chemotherapy.

Compared to the 1997 figures, the five-year progression-free survival (PFS) of non-seminoma patients was unchanged for good- and intermediate-risk, but significantly improved for poor-risk patients (from 41% to 54%). The five-year overall survival (OS) was substantially better for all groups. In addition to the traditional components of the IGCCCG risk-prognostic groups previously described, older age (linear association) and lung metastasis were confirmed as negative factors for PFS [27].

In seminoma, the five-year PFS increased to 89% and 79% in good- and intermediate-risk patients with the corresponding OS rates of 95% and 88%. Lactate dehydrogenase (LDH) proved to be an additional adverse prognostic factor. Good-prognosis patients with LDH above 2.5 times the upper limit of normal (ULN) had a three-year PFS of 80% and a three-year OS of 92%, vs. 92% and 97% (in the group with lower LDH) [28].

Table 4.3: Prognostic-based staging system for metastatic germ cell cancer (IGCCCG) [27, 28]*

<table>
<thead>
<tr>
<th>Good-prognosis group</th>
<th>Non-seminoma</th>
<th>Seminoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-year PFS 90%</td>
<td>5-year PFS 89%</td>
<td>5-year PFS 89%</td>
</tr>
<tr>
<td>5-year survival 96%</td>
<td>5-year survival 95%</td>
<td>5-year survival 95%</td>
</tr>
<tr>
<td>All of the following criteria:</td>
<td>All of the following criteria:</td>
<td>All of the following criteria:</td>
</tr>
<tr>
<td>Testis/retro-peritoneal primary</td>
<td>Any primary site</td>
<td>Any primary site</td>
</tr>
<tr>
<td>No non-pulmonary visceral metastases</td>
<td>No non-pulmonary visceral metastases</td>
<td>No non-pulmonary visceral metastases</td>
</tr>
<tr>
<td>AFP &lt; 1,000 ng/mL</td>
<td>Normal AFP</td>
<td>Normal AFP</td>
</tr>
<tr>
<td>hCG &lt; 5,000 IU/L (1,000 ng/mL)</td>
<td>Any hCG</td>
<td>Any hCG</td>
</tr>
<tr>
<td>LDH &lt; 1.5 x ULN</td>
<td>Any LDH</td>
<td>Any LDH</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intermediate-prognosis group</th>
<th>Non-seminoma</th>
<th>Seminoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-year PFS 78%</td>
<td>5-year PFS 79%</td>
<td>5-year PFS 79%</td>
</tr>
<tr>
<td>5-year survival 89%</td>
<td>5-year survival 88%</td>
<td>5-year survival 88%</td>
</tr>
<tr>
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<td>All of the following criteria:</td>
<td>All of the following criteria:</td>
</tr>
<tr>
<td>Testis/retro-peritoneal primary</td>
<td>Any primary site</td>
<td>Any primary site</td>
</tr>
<tr>
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<td>No non-pulmonary visceral metastases</td>
<td>No non-pulmonary visceral metastases</td>
</tr>
<tr>
<td>AFP 1,000 - 10,000 ng/mL or</td>
<td>Normal AFP</td>
<td>Normal AFP</td>
</tr>
<tr>
<td>hCG 5,000 - 50,000 IU/L or</td>
<td>Any hCG</td>
<td>Any hCG</td>
</tr>
<tr>
<td>LDH 1.5 - 10 x ULN</td>
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<table>
<thead>
<tr>
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<th>Seminoma</th>
</tr>
</thead>
<tbody>
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<td>5-year PFS 54%</td>
<td>No patients classified as “poor-prognosis”</td>
</tr>
<tr>
<td>5-year survival 67%</td>
<td>5-year survival 67%</td>
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<tr>
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<tr>
<td>Mediastinal primary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-pulmonary visceral metastases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AFP &gt; 10,000 ng/mL or</td>
<td></td>
<td></td>
</tr>
<tr>
<td>hCG &gt; 50,000 IU/L (10,000 ng/mL) or</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDH &gt; 10 x ULN</td>
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<td></td>
</tr>
</tbody>
</table>

* Pre-chemotherapy serum tumour markers should be assessed immediately prior to the administration of chemotherapy (same day).

PFS = progression-free survival; AFP = alpha-fetoprotein; hCG = human chorionic gonadotrophin; LDH = lactate dehydrogenase.
5. **DIAGNOSTIC EVALUATION**

5.1 **Physical examination**
Testicular cancer usually presents as a unilateral scrotal testicular mass detected by the patient, or as an incidental finding on US. Scrotal pain may be present in 27% of patients [29, 30] and a potential reason for delayed diagnosis in 10% of cases [29]. Around 1% of patients presenting with gynecomastia have a germ cell or sex cord/gonadal tumour of the testes [31] and 11% present with back and flank pain [30]. As such, when there is suspicion of TC, physical examination must include abdominal, chest and supraclavicular exploration.

5.2 **Imaging**

5.2.1 **Ultrasonography of the testes**
High-frequency (>10 MHz) testicular US should be used to confirm a testicular tumour even in the presence of a clinically evident testicular lesion [30, 32].

The use of testicular US can:
1. determine whether a mass is intra- or extra-testicular;
2. determine the volume and anatomical location of the testicular lesion;
3. be used to characterise the contralateral testicle – to exclude other lesions and identify risk factors for GCNIS (see section 5.4.4).

Testicular US is also recommended for all men with retroperitoneal or visceral masses and/or without elevated serum human chorionic gonadotropin (hCG) or alpha-fetoprotein (AFP) in the absence of a palpable testicular mass; and for fertility work-up evaluation [30, 32-34].

A range of modalities of US have been investigated (B-mode, dynamic contrast enhanced, real-time elastography, and shear wave elastography) in small cohorts to determine if these can distinguish between benign and malignant testicular lesions [35-38]. So far, the results are not reliable enough to replace the mandatory histopathological tissue diagnosis.

5.2.2 **Computerised tomography**
Contrast enhanced computerised tomography (CECT) is the most sensitive means to evaluate the thorax, abdomen and pelvis for TC staging [39]. Contrast enhanced computerised tomography is recommended in all patients for staging before orchidectomy but may be postponed until histopathological confirmation of malignancy.

The size of metastases should be described in three dimensions, or at least by the greatest axial diameter. For abdominal staging a recent systematic review reports a median sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy with CECT of 67% (range 37-100%), 92% (range 58-100%), 87% (60-100%), 73% (67-100%) and 83% (range 71-100%), respectively [39]. Sensitivity decreases and specificity increases with increasing lymph node cut-off size. With nodes ≥ 4 mm pooled sensitivity and specificity are 93% and 58% respectively, whereas for nodes ≥ 10 mm sensitivity is 37% and specificity increases to 100% [39]. Using a 10 mm short-axis lymph node diameter as a cut-off yielded a high specificity (97%), a moderate sensitivity (59%) and false-negative rate of 20% in the retroperitoneum [40]. The expected patterns of nodal spread in TC should be considered when evaluating small and borderline nodes.

Chest CT was evaluated in three studies in a systematic review by Pierorazio et al. [39]. This presents a median sensitivity, specificity, PPV, NPV and accuracy of 100% (range 95-100%), 93% (range 89-97%), 68% (range 25-84%), 100% (range 99-100%) and 93% (range 91-97%), respectively. Computerised tomography of the chest is more sensitive but less specific than chest X-ray (CXR) in thoracic staging. Nevertheless, potential harms of chest CT imaging in low-stage seminoma should be taken into consideration [39].

In patients with masses (< 2 cm) in the retroperitoneum or chest and negative tumour markers, restaging after six to eight weeks rather than treatment initiation is advisable (See sections 7.2.2.1. and 7.2.2.2).

Cerebral imaging by CECT is recommended in patients with NSGCT, multiple lung metastases and poor-prognosis IGCCCG risk group (for patients with hCG values > 5,000 UI/L), or if clinical symptoms are present [41].
5.2.3 Magnetic resonance imaging

Magnetic resonance imaging (MRI) of the scrotum provides higher sensitivity and specificity than scrotal US in the diagnosis of TC, but its high cost does not justify its routine use for this purpose [42-44]. However, it may be helpful to distinguish between an intra- and extra-testicular mass when this cannot be confirmed clinically or with US [42, 43].

Magnetic resonance imaging for abdominal staging purposes has similar accuracy to CECT in the detection of retroperitoneal nodal enlargement [39, 45]. A systematic review, however, only identified one study providing granular data on the use of MRI in abdominal staging with a reported sensitivity of 78% to 96% among three radiologists [39]. Magnetic resonance imaging is subject to greater artefacts and is not routinely indicated. If CECT is contraindicated because of allergy to iodine-based contrast media, non-contrast CT may be performed to evaluate nodal size. Currently, there are no indications for routine use of MRI for TC staging.

There is no literature regarding the comparative accuracy of CECT and MRI for the detection and evaluation of cerebral metastases in CGTs. Data from cerebral metastasis detection in other malignancies suggest that MRI is far more sensitive than CECT but requires specific expertise [38, 45, 46]. Therefore, when available, MRI should be preferentially used in the evaluation of cerebral metastases in GCTs [45].

Magnetic resonance imaging of the spine is also advisable in patients with symptoms suggesting metastatic disease or if there is equivocal staging on CECT [46].

5.2.4 Fluorodeoxyglucose-positron emission tomography (FDG-PET)

There is no evidence to support the use of Fluorodeoxyglucose-positron emission tomography (FDG-PET) for initial staging and follow-up of TC [39, 46-48]. Fluorodeoxyglucose-positron emission tomography is only recommended for seminoma patients with post-chemotherapy residual masses > 3 cm (largest diameter) to assess FDG activity [49]. Fluorodeoxyglucose-positron emission tomography should not be performed until at least two months after completion of the last cycle of chemotherapy, as inflammation and the desmoplastic reaction induced by chemotherapy may result in FDG avidity and a false positive result [48]. Whilst the NPV for active disease is > 90% [50, 51], the PPV ranges from 23% to 69% [50-52]. False-positives are common and may occur in up to 80% of lesions [50, 52]. Indicating that necrosis, fibrosis and the consequent inflammation are also associated with FDG activity. Caution is advised on initiating active therapy driven only by positive findings on FDG-PET-CT [52].

5.2.5 Bone scan

There is no evidence to support the use of bone scan for staging of TC.

5.3 Serum tumour markers

5.3.1 Pre-operative serum tumour markers

Alpha-fetoprotein (AFP), beta subunit of human Chorionic Gonadotropin (β-hCG) and LDH should be determined before and after orchidectomy as they support the diagnosis of TC, may be indicative of GCT histology and are used for disease staging and risk stratification (Table 4.3), as well as to monitor treatment response and detect disease relapse [53, 54]. Overall, elevation of any of these three markers is present in up to 60% of patients at diagnosis and in 72% to 93% of those with CS ≥ II in recently reported GCT cohorts [55, 56].

Alpha-fetoprotein and β-hCG increase are detected in 50-72% and in 30-60% of patients with NSGCT, respectively. Up to 90% of NSGCTs present with a rise in either/or both AFP and β-hCG at diagnosis [29, 54, 55]. Up to 30% (9-32%) of pure seminomas may also have modestly elevated β-hCG level at diagnosis [53, 54]. Overall, in a modern GCT cohort, elevation any of these three markers was present in up to 60% of patients at diagnosis and in 72% to 93% of those with CS ≥ II [54]. Its level may be elevated in 80% of patients with advanced disease [55].

Tumour markers have limitations in terms of their low sensitivity as normal levels do not exclude the presence of disease. Lactate dehydrogenase is of limited utility as its serum level is generally proportional to tumour volume, with persistently elevated levels in up of 30% of patients with metastatic disease after complete remission [55].

5.3.2 Serum tumour markers after orchidectomy

Serum levels of AFP, β-hCG and LDH following orchidectomy provide staging and prognostic information [56]. As the serum half-life of AFP and β-hCG are five to seven days and one to three days respectively, it may take several weeks until normalisation occurs [53, 55]. The persistence of, or increase in serum tumour marker
elevation following orchidectomy indicates the likely presence of metastatic disease [54]. Whilst normalisation of marker levels after orchidectomy is a favourable indicator, it does not exclude the possibility of metastatic disease. With metastatic TC, risk stratification is based on serum tumour marker levels immediately before initiation of systemic treatment [56]. Before chemotherapy AFP and LDH levels may act as prognostic factors for OS in non-seminoma intermediate risk group [57].

At relapse, only 25% of patients have elevated AFP and hCG, and LDH may remain persistently elevated in 30% of patients despite cure [54]. Tumour markers should be routinely used for follow-up as indicators of recurrence, although the precise frequency of testing is not well defined [58].

5.3.3 Other tumour markers
Micro RNAs (miRNAs) are emerging as potential new biomarkers for TC. Preliminary evidence suggests higher discriminatory accuracy for miRNAs (most particularly miR-371a-3p) compared to conventional GCT markers in diagnosis, and treatment monitoring, as well as their being predictors of residual or recurrent viable disease [59-65]. Before miRNAs can be considered for use in routine clinical practice, a number of issues including laboratory standardisation and availability of the test need to be resolved.

5.4 Inguinal exploration and initial management
5.4.1 Orchidectomy
Orchidectomy including division of the spermatic cord at the internal inguinal ring represents the standard of care in patients with TC. Scrotal approach should be avoided when TC is suspected as it results in a higher local recurrence rate [66].

5.4.2 Testis-sparing surgery
Testis-sparing surgery (TSS) may be offered in cases with synchronous bilateral tumours, metachronous contralateral tumours or in patients with a solitary testis in order to attempt to preserve fertility and hormonal function [67].

Testis-sparing surgery should only be offered together with frozen section examination (FSE) as FSE has shown to be reliable and highly concordant with final histopathology [68, 69]. Patients should be informed of the risk of completion or the need for subsequent orchidectomy, as there may be discordance between FSE and final pathology.

Patients should also be made aware that limited data exists regarding oncological safety of TSS. They should be made aware that local recurrence rates of around 8% have been reported when TC is present in the specimen [67, 71] with implications for ongoing close surveillance of the testis. They should also be made aware of the role and impact of adjuvant radiotherapy when GCNIS is present, as well as potential infertility and the need for hormonal supplementation despite parenchyma preservation [67, 71].

In cases of small or indeterminate testicular masses with negative tumour markers, patients may be offered TSS when feasible, to avoid overtreatment of potentially benign lesions and to preserve testicular function. Currently there is no evidence supporting any size criteria for a testicular lesion to be safely monitored. Patients should be made aware that cancer can be present even in small (i.e., < 1cm) masses [67, 70, 71], thus obtaining histology is mandatory.

5.4.3 Insertion of testicular prosthesis
Testicular prosthesis should be offered to all patients receiving unilateral or bilateral orchidectomy [72]. The prosthesis can be inserted at orchidectomy or subsequently without adverse consequences, including infection [73].

5.4.4 Contralateral biopsy
Contralateral biopsy has been advocated to exclude the presence of GCNIS [74].

Whilst routine policy in some countries [75], the low incidence of GCNIS and metachronous contralateral testicular tumours (up to 9% and approximately 2.5%, respectively) [76, 77], the morbidity of GCNIS treatment (see section 7.1.), and the fact that most metachronous tumours are low stage at presentation, makes it controversial to recommend routine contralateral biopsy in all patients [78, 79]. Nevertheless, the risks and benefits of biopsy of the contralateral testis should be discussed with TC patients at high risk for contralateral GCNIS, i.e., testicular volume < 12 mL, and/or a history of cryptorchidism. Contralateral biopsy is not necessary in patients older than 40 years without risk factors [80-82]. Patients should be informed that a subsequent TGCT may arise despite a negative biopsy [83]. When indicated, a two-site surgical testicular biopsy is the technical procedure recommended [82].
5.5 Pathological examination of the testis

The recommendations for reporting and handling the pathological examination of a testis neoplasm are based on the recommendations of the International Society of Urological Pathology (ISUP) [84-87].

**Mandatory pathological requirements:**

- **Macroscopic features:** It must indicate radical or partial orchidectomy, side, testis size, number of tumours, and macroscopic features of the epididymis, cord length, and tunica vaginalis.
- **Sampling:** At least a 1 cm² section for every centimetre of maximum tumour diameter including normal macroscopic parenchyma (if present), tunica albuginea and epididymis, with selection of suspicious areas. If the tumour is < 20 mm it should be completely sampled.
- **At least one proximal (base of the cord) and one distal section of spermatic cord plus any suspicious area. Cord blocks should preferably be taken prior to tumour sections to avoid contamination.**
- **Microscopic features and diagnosis:** histological types (specify individual components and estimate amount as percentage) according to WHO 2016 [84]:
  - Presence or absence of peri-tumoural lymph vessels and/or blood vessels invasion. In case of doubt, the use of endothelial markers, such as CD31, are recommended.
  - Presence or absence of GCNIS in non-tumour parenchyma;
  - In case of rete testis invasion attention should be paid to distinguishing between pagetoid involvement and stromal invasion [85].
- **If microscopic findings are not concordant with serum markers further block samples should be taken.**
- **pT category according to TNM 2016 [23]. In a multifocal seminoma the largest nodule should be used to determine pT category.**

**Immune-histochemical markers in cases of doubt are:**

- Seminoma: CD-117 (c-KIT), OCT 3/4, Sall4, PLAP
- GCNIS: CD-117 (c-KIT), OCT 3 / 4, Sall4, PLAP
- Syncytiotrophoblast: β-hCG
- Embryonal carcinoma: CD30
- Yolk sac tumour: Glypican 3
- Sex cord gonadal tumours: Inhibin, calretinin

The search for i12p (FISH or PCR) or gain in Ch9 (spermatocytic tumour) are additional immuno-chemistry techniques, utility confirmation of other molecular markers such as P53, MDM2, KRAS AND HRAS is awaited [88].

In order to facilitate consistent and accurate data collection, promote research, and improve patient care, the International Collaboration on Cancer Reporting has constructed a dataset for the reporting of urological neoplasms. The dataset for testicular tumours encompasses the updated 2016 WHO classification of urological tumours, the ISUP consultation and staging with the 8th edition of the American Joint Cancer Committee (AJCC) [87].

The dataset includes those elements unanimously agreed by the expert panel as “required” (mandatory) and those “recommended” (non-mandatory) that would ideally be included but are either non-validated or not regularly used in patient management [87]. The dataset for handling pathological assessment of TC is shown in Table 5.5.
Table 5.5: Recommended dataset for reporting of neoplasia of the testis (modified from the International Collaboration on Cancer Reporting [87].

<table>
<thead>
<tr>
<th>Elements</th>
<th>Required</th>
<th>Recommended</th>
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<td></td>
<td>- Previous history of testicular cancer</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Previous therapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Other</td>
<td></td>
</tr>
<tr>
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</tr>
<tr>
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<td></td>
<td></td>
<td>- If provided within normal limits</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Specify serum tumour markers used</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Specify levels</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>- Specify date markers were drawn</td>
<td></td>
</tr>
<tr>
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<td>Specify side for partial or radical orchidectomy Specify other</td>
</tr>
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<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>- Orchidectomy radical</td>
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</tr>
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<td></td>
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</tr>
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<td>- Unifocal</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Maximum tumour dimension</td>
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<td>Specify at least maximum diameter of largest tumour Preferably specified 3 dimensions axes*</td>
</tr>
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<td>- Dimensions largest tumour (mm)</td>
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<tr>
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<td></td>
<td>- Invades epididymis</td>
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<td></td>
<td></td>
<td>- Invades tunica vaginalis</td>
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<td></td>
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<td>✓</td>
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<td>✓</td>
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<td>- Tunica albuginea#</td>
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<td></td>
<td></td>
<td>- Tunica vaginalis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Spermatic cord</td>
<td></td>
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<tr>
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<td></td>
<td></td>
<td>- Scrotal wall</td>
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<td></td>
<td></td>
<td>- Present</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>- Other intratubular lesions#</td>
<td></td>
</tr>
</tbody>
</table>
5.6 Screening

There are no high-level evidence studies supporting screening programs. It has not been shown that screening asymptomatic patients has benefit in terms of detecting TC at a more curable stage, despite the fact that stage and prognosis have been shown to be directly related to early diagnosis [89, 90]. In the presence of clinical risk factors, which include family history of TC, family members and the patient should be informed about the importance of physical self-examination [91].

5.7 Impact on fertility and fertility-associated issues

Sperm abnormalities and Leydig cell dysfunction are frequently found in patients with TCs prior to orchidectomy [92, 93]. Up to 24% of TC patients are azoospermic and almost 50% have abnormal sperm counts (oligozoospermic) before treatment [93].

Treatment for TC, including orchidectomy, may have a negative impact on reproductive function [94]. Chemotherapy and radiation treatment (RT) can both impair fertility; although, long-term infertility is rare after radiation therapy and is dose-cumulative-dependent after chemotherapy [95-97]. Spermatogenesis usually recovers one to four years after chemotherapy [98]. In CS I, adjuvant treatment (BEP [cisplatin, etoposide, bleomycin] x1; Carbo x1) does not appear to significantly affect testicular function compared to surveillance, with full recovery after one year [99].

All patients should be offered semen preservation as the most cost-effective strategy for fertility preservation, and pre-treatment fertility assessment (testosterone, luteinizing hormone [LH] and follicle stimulating hormone [FSH] levels) is advised [100].

If cryopreservation is desired, sperm banking should be offered before orchidectomy, maximizing the chances of fertilisation and avoiding the risk of a non-functioning remaining testicle after surgery. If not arranged before orchidectomy, it should be undertaken prior to chemotherapy or RT [95-97, 100, 101].

Long-term testosterone supplementation is necessary in patients who have had bilateral orchidectomy or have low testosterone levels after treatment of GCNIS [102].

| Margin status | √ | - Partial orchidectomy . cannot be assessed . involved . not involved . Radical orchidectomy . cannot be assessed . spermatic cord margin involved . spermatic cord margin not involved . Other margin involved | In partial orchidectomy if margin not involved, distance of tumour from closest margin (mm)# If other margin involved specify |
| Coexisting pathology | √ | - None identified - Hemosiderin-laden macrophages - Atrophy - Other | If other specify |
| Ancillary studies | √ | - Not performed - Performed | If performed specify |
| Response to neoadjuvant therapy | √ | - Present - Absent, - No prior treatment, - Cannot be assessed | Explain reasons if cannot be assessed |
| Pathologic staging* | √ | T classification according to TNM 8th edition (UICC)** | m-multiple primary tumours r-recurrent y-post-therapy |

* Not mandatory. Ideally to be included but either non-validated or no regularly used in patient management.
** TNM 8th edition (AJCC) used in the original publication.
# Recommended, i.p. intratubular seminoma and embryonal carcinoma.
Chemotherapy and RT are both teratogenic. Therefore, contraception must be used during treatment and for at least six months after its completion [103].

For more detailed information, the reader is referred to the EAU Guidelines on Sexual Reproductive Health [104].

### 5.8 Guidelines for the diagnosis and staging of Testicular Cancer

<table>
<thead>
<tr>
<th>Summary of evidence</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor sperm quality is frequently found in TC patients, before and after treatment. Semen preservation is the most cost-effective strategy for fertility preservation.</td>
<td>2b</td>
</tr>
<tr>
<td>Serum tumour markers (AFP, β-hCG and LDH) should be determined before and after orchidectomy and throughout follow-up. They are used for accurate staging, risk stratification, to monitor treatment and to detect relapse.</td>
<td>2b</td>
</tr>
<tr>
<td>For abdominal staging, CECT has a median sensitivity, specificity, PPV, NPV and accuracy of 67%, 95%, 87%, 73% and 83%, respectively. Sensitivity decreases and specificity increases with increasing lymph node size.</td>
<td>2a</td>
</tr>
<tr>
<td>For chest staging, CECT has a median sensitivity, specificity, PPV, NPV and accuracy of 100%, 93%, 68%, 100% and 93%, respectively.</td>
<td>2a</td>
</tr>
<tr>
<td>Contrast enhanced computerised tomography and MRI are key image modalities for the detection of brain metastasis. Magnetic resonance imaging is far more sensitive than CECT, though it does require expertise.</td>
<td>2b</td>
</tr>
<tr>
<td>Fluorodeoxyglucose-positron emission tomography has a limited diagnostic accuracy for staging before chemotherapy.</td>
<td>2b</td>
</tr>
<tr>
<td>There are no high-level evidence studies supporting screening programs.</td>
<td>2b</td>
</tr>
<tr>
<td>In testicular sparing surgery, FSE has shown to be reliable and highly concordant with final histopathology.</td>
<td>1b</td>
</tr>
<tr>
<td>There is no evidence supporting any size criteria for a testicular lesion to be safely followed-up.</td>
<td>2b</td>
</tr>
<tr>
<td>In patients without risk factors, there is low incidence of contralateral GCNIS and of metachronous GCTC.</td>
<td>2b</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Strength rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discuss sperm banking with all men prior to starting treatment for testicular cancer (TC).</td>
<td>Strong</td>
</tr>
<tr>
<td>Perform bilateral testicular ultrasound (US) in all patients with suspicion of TC.</td>
<td>Strong</td>
</tr>
<tr>
<td>Perform physical examination including supraclavicular, cervical, axillary and inguinal lymph nodes, breast and testicles.</td>
<td>Strong</td>
</tr>
<tr>
<td>Measure serum tumour markers both before and after orchidectomy taking into account half-life kinetics.</td>
<td>Strong</td>
</tr>
<tr>
<td>Perform orchidectomy and pathological examination of the testis to confirm the diagnosis and to define the local extension (pT category). In a life-threatening situation due to extensive metastasis, commence chemotherapy prior to orchidectomy.</td>
<td>Strong</td>
</tr>
<tr>
<td>Perform contrast enhanced computerised tomography (CECT) scan (chest, abdomen and pelvis) in patients with a diagnosis of TC. If iodine allergy or other limiting factors perform abdominal and pelvic magnetic resonance imaging (MRI).</td>
<td>Strong</td>
</tr>
<tr>
<td>Perform MRI of the brain (or brain CECT if not available) in patients with multiple lung metastases, or high beta subunit of human Chorionic Gonadotropin (β-hCG) values, or those in the poor-prognosis International Germ Cell Cancer Collaborative Group (IGCCCG) risk group.</td>
<td>Strong</td>
</tr>
<tr>
<td>Do not use positron emission tomography–computed tomography or bone scan for staging.</td>
<td>Strong</td>
</tr>
<tr>
<td>Encourage patients with TC to perform self-examination and to inform first-degree male relatives of the need for self-examination.</td>
<td>Weak</td>
</tr>
<tr>
<td>Discuss testis-sparing surgery with frozen section examination in patients with a high-likelihood of having a benign testicular tumour which are suitable for enucleation.</td>
<td>Strong</td>
</tr>
<tr>
<td>Discuss biopsy of the contralateral testis to patients with TC and who are at high-risk for contralateral germ cell neoplasia ‘in situ’ (GCNIS).</td>
<td>Weak</td>
</tr>
</tbody>
</table>
6. PROGNOSIS

6.1 Risk factors for metastatic relapse in clinical stage I
With stage I seminoma, tumour size and stromal invasion of the rete testis have been identified as predictors for relapse in a pooled analysis of retrospective data [105]. Absence of both factors indicates a low risk of recurrence (6%) [106]. Whilst the original analysis was not supported by a further retrospective report [107], some prospective series [108-110] support the prognostic significance of tumour size and stromal invasion of the rete testis. Two systematic reviews have assessed the prognostic value of these risk factors [111, 112]. While tumour size (continuous or dichotomised) and rete testis invasion are associated with a higher risk of relapse, both systematic reviews highlighted the low quality of the studies included and that the level of evidence is too low to recommend the use of these pathological risk factors to drive adjuvant treatment decisions [111, 112].

For non-seminoma stage I, invasion of the primary tumour into blood or lymphatic vessels (LVI) is the most reliable single predictor of occult metastatic disease [86, 113, 114]; while interobserver agreement is limited, immunohistochemistry might improve detection [115]. The percentage of embryonal carcinoma within a tumour may enhance the PPV and NPV of LVI [113], but there is no definitive prognostic cut-off for percentage [113]. Risk of relapse at five years with LVI is 50% compared to 15% without LVI. The significant prognostic pathological risk factors for stage I TC are listed in Table 6.1.

Table 6.1: Pathological risk-factors for occult metastatic disease in Stage I testicular cancer

<table>
<thead>
<tr>
<th>Histological type</th>
<th>Seminoma [111]</th>
<th>Non-seminoma [85, 114]</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Pathological risk-factors</td>
<td>• Tumour size</td>
<td>• Lympho-vascular invasion in peri-tumoral tissue</td>
</tr>
<tr>
<td></td>
<td>• Invasion of the rete testis</td>
<td></td>
</tr>
</tbody>
</table>

7. DISEASE MANAGEMENT

Chemotherapy results in excellent cure rates in TC due to chemosensitivity to Cisplatin-based regimens [116]. Careful staging at diagnosis, adequate early treatment based on a multidisciplinary approach, rigorous follow-up and adequate initiation of salvage therapies are critical to successful outcomes. Whilst early stages can be successfully treated in a non-specialist centre, relapse rates are higher than in specialist centres [117, 118]. In clinical trials on poor-prognosis patients, OS relates to the number of patients treated at the participating centre (worse if < 5 patients enrolled) [119]. Treatment at high-volume specialist centres is thus strongly encouraged. Establishment of second-opinion clinics for TC patients as well as collaboratively working with specialist centres may also help prevent over- and under-treatment [120].

Initiation of treatment before histopathological confirmation
In cases of life-threatening disseminated disease, chemotherapy should commence immediately, particularly when the clinical picture strongly supports TC, and/or tumour markers are increased. Orchidectomy in these circumstances can be delayed until clinical stabilisation occurs or subsequently in combination with resection of residual lesions.

7.1 Stage I Germ cell tumours

7.1.1 germ cell neoplasia “in situ” (GCNIS)
If GCNIS is diagnosed, local radiotherapy (18-20 Gy in fractions of 2 Gy) should be offered in the case of a solitary testis [97, 121-123]. Testicular radiotherapy in a solitary testis will result in infertility and increased long-term risk of Leydig cell insufficiency [97]. Fertile patients who wish to father children may delay radiation therapy and be followed by regular testicular US [82]. Chemotherapy is significantly less effective, and the cure rates are dose-dependent [121].

If GCNIS is diagnosed and the contralateral testis is healthy, the options or management are orchidectomy or close observation, as the five-year risk of developing TC is 50% [124].

7.1.2 Seminoma clinical Stage I
Despite modern staging procedures, approximately 15% of clinical stage I seminoma patients have subclinical
metastatic disease, usually in the retroperitoneum, and will relapse after orchidectomy alone [107, 110, 125, 126].
The decision regarding adjuvant treatment should always be based on a thorough discussion with the patient,
taking into account the described advantages and disadvantages, as well as the individual situation of the patient.

7.1.2.1 Surveillance
Several prospective non-randomised surveillance studies have been conducted over the past decade. Previous
analysis from four studies showed an actuarial five-year relapse-free rate of 82% [127]. The largest series
(> 1500 patients) reported an overall relapse rate in unselected patients of 17% [127]. The conditional risk
of relapse is of the order of 12% to 20% at five years, with most relapses occurring in retroperitoneal lymph
nodes during the first two years [128-130].

Very low recurrence rates of 6% have been described in patients with low-risk features, including tumour size
< 4 cm and no stromal rete testis invasion. In contrast, others report a five-year conditional risk of relapse of
12% with tumours < 3 cm in size [109, 130].

The cancer-specific survival (CSS) rate reported with surveillance performed by specialist centres is over
99% for clinical stage I seminoma [127-129, 131]. The principal limitation of surveillance is the need for more
intensive follow-up, especially with repeated imaging examinations of the retroperitoneal lymph nodes.

7.1.2.2 Adjuvant chemotherapy
A joint trial by the Medical Research Council (MRC) and the European Organisation for Research and Treatment
of Cancer (EORTC), which compared one cycle of carboplatin reaching area under curve (AUC) of 7 mg/mL/min
(AUC 7) with adjuvant RT, showed no significant difference in relapse-free rate (95% in adjuvant chemotherapy
vs. 96% in adjuvant RT), time to recurrence and survival after a median follow-up of four years [132-134]. For
those patients that received 99% of the carboplatin AUC 7 dose, relapse-free survival increased slightly to 96% [133].
Non-randomised risk-adapted population-based studies using one cycle of carboplatin reported a lower
five-year relapse rate of 3% to 4% vs. 14% to 16% for those patients who underwent active surveillance [128, 129]. Therefore, adjuvant carboplatin therapy using a dosage of one course of AUC 7 is an alternative to RT
or surveillance in clinical stage I seminoma [128, 132, 133]. Retrospective data on patients who relapsed after
adjuvant treatment with carboplatin showed that relapses developed later than those who underwent active
surveillance [135]. Median time to relapse was reported to be nineteen months, with 15% occurring later than three
years after adjuvant treatment. The majority of patients relapsing after adjuvant carboplatin can be successfully
treated with a standard cisplatin-based chemotherapy regimen appropriate to their disease stage [135].

7.1.2.3 Adjuvant radiotherapy
Seminomas are extremely radiosensitive tumours. Adjuvant RT to a para-aortic (PA) field or to a PA and ipsilateral
field (PA and ipsilateral iliac nodes), with a total dose of 20-24 Gy, reduced the relapse rate to 1% to 3% [136-
138]. Adjuvant irradiation of supra-diaphragmatic lymph nodes is not indicated.

With regard to the irradiation dose, a large MRC RCT of 20 Gy vs. 30 Gy PA radiation in clinical stage I seminoma
showed non-inferiority in terms of recurrence rates [137]. The rate of severe radiation induced long-term toxicity
is less than 2%. Moderate chronic gastrointestinal (GI) side-effects were seen in about 5% of patients with
moderate acute GI toxicity in about 60% [136].

The main concern with adjuvant RT is the increase of long-term risk of radiation-induced secondary non-germ cell
malignancies [139-142]. This has limited the role of adjuvant RT in CS I seminoma to those exceptional cases that
are not suitable for adjuvant chemotherapy or surveillance and the elderly. A scrotal shield should be considered
during adjuvant RT in order to prevent scattered radiation toxicity in the contralateral testis [139].

7.1.2.4 Risk-adapted treatment
Using testicular tumour size > 4 cm and stromal rete testis invasion, patients with clinical stage I seminoma
may be subdivided into low- and high-risk groups for relapse following radical orchidectomy. Patients with
and without both risk factors have a 32% and 6% risk of relapse, respectively. These risk factors were
introduced based on an analysis of retrospective trials [92], and then confirmed in subsequent prospective
studies [109, 110]. Two prospective trials based on these risk factors demonstrated the feasibility of a risk-
adapted approach. In a Spanish study including 227 men, patients with no or one risk factor were managed
with surveillance, whilst the group with both risk factors present received two adjuvant courses of carboplatin,
AUC 7 [109]. Although the median follow-up was relatively short (34 months), the relapse rate with adjuvant
treatment was reported at 1.4% [109].

A SWENOTECA trial included 897 patients [110]. Patients with none or one risk factor were offered
surveillance, patients with both risk factors were offered one course of carboplatin, AUC 7. The final decision regarding adjuvant treatment was made by the individual patient. At a median follow-up of 5.6 years, patients without risk factors had a relapse rate of 4% with surveillance compared to 2% with adjuvant carboplatin. Overall, when one or both risk factors were present, 15.5% of the patients under surveillance relapsed whereas 9% of those receiving adjuvant carboplatin relapsed. Thirty-three per cent of relapses in patients who received adjuvant treatment occurred more than three years after orchidectomy and 3% occurred after more than five years [110].

With a risk reduction of 60% in patients with tumours with both risk factors present, the efficacy of one cycle of adjuvant carboplatin seems rather low, although the comparison with two adjuvant cycles of carboplatin is difficult because of small sample size and limited follow-up in the Spanish study [109]. A currently recruiting SWENOTECA-ABC trial compares the efficacy of one cycle of adjuvant carboplatin with one cycle of adjuvant cisplatin, etoposide, bleomycin (BEP) [143].

7.1.2.5 Guidelines for the treatment of stage I seminoma testis tumours

<table>
<thead>
<tr>
<th>Summary of evidence</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary testicular tumour size and rete testis invasion correlate with the risk of relapse in clinical stage I seminoma testis patients. However, the evidence to guide adjuvant treatment decisions is too limited to justify the routine use in clinical practice.</td>
<td>2a</td>
</tr>
<tr>
<td>Active surveillance is a feasible approach in CS I seminoma testis patients. Conditional relapse risk in unselected series is between 12% and 20%.</td>
<td>2a</td>
</tr>
<tr>
<td>In patients without risk factors the five-year relapse rate under surveillance is 4% to 6%, whereas in the presence of one or two risk-factors, five-year relapse rate in contemporary surveillance series is 15% to 20%.</td>
<td>2b</td>
</tr>
<tr>
<td>In non-randomised prospective series five-year relapse rates with adjuvant carboplatin are 2% in patients without risk factors and 9% in patients with one or two risk factors.</td>
<td>2b</td>
</tr>
<tr>
<td>Adjuvant chemotherapy with one course carboplatin AUC 7 is not inferior to adjuvant radiotherapy when pathological risk-factors are taken into account. Relapse rates with both adjuvant treatments are around 5%.</td>
<td>1b</td>
</tr>
<tr>
<td>Adjuvant radiotherapy is associated with an increased risk of developing secondary non-germ cell malignancies.</td>
<td>2b</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Strength rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fully inform the patient about all available management options, including surveillance or adjuvant therapy after orchidectomy, as well as treatment-specific recurrence rates and acute and long-term side effects.</td>
<td>Strong</td>
</tr>
<tr>
<td>Offer surveillance as the preferred management option if facilities are available and the patient is compliant.</td>
<td>Strong</td>
</tr>
<tr>
<td>Offer one course at area under curve (AUC) 7 if carboplatin chemotherapy is considered.</td>
<td>Strong</td>
</tr>
<tr>
<td>Do not perform adjuvant treatment in patients at very low risk of recurrence (no risk factors).</td>
<td>Strong</td>
</tr>
<tr>
<td>Do not routinely perform adjuvant radiotherapy.</td>
<td>Strong</td>
</tr>
<tr>
<td>Adjuvant radiotherapy should be reserved only for highly selected patients not suitable for surveillance and with contraindication for chemotherapy.</td>
<td>Strong</td>
</tr>
</tbody>
</table>

7.1.3 NSGCT clinical stage I

Management options for CS I-NSGCTs comprise surveillance, adjuvant chemotherapy or retroperitoneal lymph node dissection. Overall, approximately 70% of CS I-NSGCTs are cured with orchidectomy alone. In those with high-risk features (LVI) as outlined in Section 6.1 relapse occurs in 50% compared to those without LVI in which relapse occurs in only 15%. Thorough discussion should be undertaken with the patient outlining the potential advantages and disadvantages of the treatment options, as well as their specific circumstances, co-morbidities, disease features and risk factors, alongside their own personal preferences, in order to guide their treatment decision.

7.1.3.1 Surveillance

Improvements in clinical staging and follow-up methods, as well as the availability of effective salvage treatment with cisplatin-based chemotherapy and post-chemotherapy surgery, have led to studies of close surveillance as initial management following orchidectomy in CS I-NSGCT patients. This entails a strict protocol of repeated cross-sectional imaging, monitoring of serum tumour markers and clinical assessment for the early identification of the subset of patients experiencing relapse who must receive salvage treatment.
Overall, 14% to 48% of CS I-NSGCT patients undergoing surveillance recur within two years of orchidectomy. The largest reports of surveillance indicate a cumulative relapse risk in about 30% of CS I-NSGCT (five-year conditional risk of relapse 42% and 17% for high- and low-risk CS I-NSGCT respectively) [126, 127]. Of these, 92% present within the first two years [126, 127].

Approximately 35% of patients have normal levels of serum tumour markers at relapse, with 60% of relapses occurring in the retroperitoneum. Despite rigorous follow-up, 11% of relapsing patients will present with large volume metastatic recurrent disease [126, 144].

Surveillance studies have reported lower relapse rates compared to some series of patients undergoing primary Retroperitoneal lymph node dissection (RPLND) [145]. This is likely related to selection bias with both exclusion of high-risk cases and very early marker relapse precipitating treatment prior to surveillance re-imaging. Based on the overall CSS data, surveillance within a rigorous protocol can safely be offered to patients with non-risk stratified CS I-NSGCT who are compliant and informed about the expected recurrence rate and need for salvage treatment [144, 146, 147].

7.1.3.2 Retroperitoneal lymph node dissection (RPLND)

Primary RPLND for management of CS I-NSGCT evolved prior to the availability of effective systemic treatment for relapsed disease with improved survival following orchidectomy [148]. A large series of 464 unselected cases of CS I-NSGCT commencing within this era reported an overall relapse rate of 14% including 11% with PS1 disease. Of those upstaged to pathological stage II only 36% relapsed. These figures are consistent with more contemporary experience.

Approximately 35% of patients have normal levels of serum tumour markers at relapse, with 60% of relapses occurring in the retroperitoneum. Despite rigorous follow-up, 11% of relapsing patients will present with large volume metastatic recurrent disease [126, 144].

With primary RPLND, approximately 10% of patients with no evidence of nodal involvement (i.e., PS I) will relapse at distant sites [113, 148, 149]. More recent series report lower figures of pN+ patients and relapse possibly reflecting case selection [150]. Following RPLND 18% to 30% of patients have retroperitoneal lymph node metastases on RPLND (i.e., PS II), [149, 151]. Without adjuvant chemotherapy, approximately 31% of those with active nodal malignancy will experience recurrence [149]. Presence of LVI, predominant embryonal carcinoma, pT category and extranodal extensions of involved nodes all appear associated with an increased risk of recurrence with PS II disease without adjuvant chemotherapy. The use of these further parameters has yet to be clearly defined in clinical practice [149, 152].

Strategies to reduce the morbidity of primary RPLND include nerve-sparing and minimally invasive approaches. In a multicentre setting, higher rates of in-field recurrences and complications have been reported with nerve-sparing RPLND [151, 153]. This suggests that primary RPLND, when indicated or chosen, should be performed by an experienced surgeon in a specialist centre. Primary RPLND, laparoscopic or robot-assisted RPLND appears feasible but cannot be recommended outside of a high-volume RPLND centres with appropriate minimally invasive expertise [154, 155].

Follow-up after RPLND is less demanding and costly than other options due to the reduced need for cross-sectional imaging [156]. Nevertheless, in view of the high CSS rates of surveillance with salvage treatment in cases of relapse and the low relapse rates with adjuvant chemotherapy, the role of primary RPLND for CS I-NSGCT has diminished.

7.1.3.3 Adjuvant chemotherapy

Adjuvant chemotherapy has been evaluated with both one and two cycles of BEP in CS I-NSGCT. A prospective MRC trial reported in 1996 in high-risk patients used two cycles of BEP [157]. Subsequently, adjuvant chemotherapy was mainly given to high-risk patients (LVI present) [157-159]. In these series, including 200 patients, some with a median follow-up of nearly 7.9 years [157], a relapse rate of only 2.7% was reported, with minimal long-term toxicity. Two cycles of cisplatin-based adjuvant chemotherapy do not seem to adversely affect fertility or sexual activity [160].

More recently, one cycle of adjuvant BEP has been shown to result in low recurrence rates (2% to 3%) [161, 162]. Reduction from two to one cycle of BEP improves the risk-benefit ratio of adjuvant chemotherapy considerably. A randomised phase III trial has also compared two-year recurrence free survival with adjuvant BEP x 1 to RPLND. Results favoured chemotherapy with recurrence free survival of 99.5% vs. 91% [153]. The hazard ratio to experience a tumour recurrence with surgery compared to BEP x 1 was 8 [153]. No clinically relevant differences in quality of life (QoL) were detected [163].

A community based prospective study of 490 unselected patients with CS I-NSGCT that received BEP x 1, showed a five-year relapse rate of 3% for LVI+ patients and 2% for LVI- patients. After a median follow-up of
eight years the overall relapse rate was 2% comprising 3% and 1% for LVI+, and LVI-, respectively [161, 162]. These numbers imply that > 90% of relapses were prevented by adjuvant chemotherapy and, importantly, no relapses were observed later than 3.3 years.

As such, BEP X 1 is now the recommended strategy if adjuvant chemotherapy is considered [161, 162]. The very-long term (> 20 years) side effects of adjuvant chemotherapy, particularly cardiovascular, are yet to be fully defined which should be taken into consideration with decision-making [164, 165].

7.1.3.4 Risk-adapted treatment
A risk-adapted strategy is an alternative to any single approach for patients with CS I-NSGCT. The advantages and disadvantages of treatment options must be discussed with patients in the context of their specific circumstances including disease risk factors, co-morbidities and personal preference, as well as clinician recommendation in reaching a treatment decision. As outlined in Section 6.1 LVI appears as the strongest predictive risk factor for relapse and should be carefully outlined to the patient in order to assist in their decision-making.

Patients without LVI should be guided to consider surveillance, although some patients with significant co-morbidities or concerns regarding salvage chemotherapy with multicyle cisplatin-based chemotherapy may opt for adjuvant therapy. Those with LVI, should have their high risk of relapse (42% to 50%) highlighted and be guided to consider adjuvant chemotherapy with BEP X 1 as the “preferred” option.

Some patients may wish to consider primary RPLND although they need to be aware of the potential additional requirement of adjuvant chemotherapy if nodes contain active disease, as well as the 10% risk of systemic relapse requiring subsequent chemotherapy treatment (BEP X 3).

Cost-analyses comparing surveillance, RPLND and primary chemotherapy show disparate results in the reported studies, reflecting variabilities in intensity of follow-up protocols and costs in different health-care systems [166]. With lower frequency of retroperitoneal imaging following RPLND, the costs of follow-up may be reduced – although this is an economic rather than clinical consideration [167].

7.1.3.5 Teratoma with somatic malignant component
According to a multi-institutional study analysing retrospective datasets of patients with teratoma with somatic malignant component (TSMC), patients with clinical stage I disease and TSMC had an approximately 10% shorter five-year OS than GCT stage I patients. Moreover, the proportion of those stage I patients undergoing primary RPLND who had nodal metastases (PSII) of TSMC was higher than expected (37.5%). Despite the limitations of this study, this represents the strongest evidence on this issue and supports primary RPLND in clinical stage I patients diagnosed with TSMC in the testis [162].

7.1.3.6 Guidelines for the treatment of clinical stage I non-seminoma testis tumour

<table>
<thead>
<tr>
<th>Summary of evidence</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphovascular invasion increases the risk of relapse in CS I non-seminoma testis.</td>
<td>2a</td>
</tr>
<tr>
<td>The relapse rate in patients under active surveillance is up to 50%, depending on LVI status.</td>
<td>2a</td>
</tr>
<tr>
<td>The relapse rate in patients who receive adjuvant chemotherapy with BEP (x 1 cycle) is less than 3%.</td>
<td>2a</td>
</tr>
<tr>
<td>Adjuvant chemotherapy with BEP is superior to adjuvant RPLND in terms of the risk of relapse.</td>
<td>1b</td>
</tr>
<tr>
<td>A risk-adapted approach, based on LVI, is feasible. Risk of relapse with one cycle adjuvant BEP is about 2% to 3%.</td>
<td>2b</td>
</tr>
<tr>
<td>The acute toxicity of one cycle adjuvant BEP is rather low.</td>
<td>1b</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Strength rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inform patients with stage I non-seminomatous germ cell tumour (NSGCT) about all management options after orchidectomy (surveillance, adjuvant chemotherapy, and retroperitoneal lymph node dissection) including treatment-specific recurrence rates as well as acute and long-term side effects.</td>
<td>Strong</td>
</tr>
<tr>
<td>Offer surveillance or risk-adapted treatment based on lymphovascular invasion in patients with stage I NSGCT (see below).</td>
<td>Strong</td>
</tr>
<tr>
<td>Discuss one course of cisplatin, etoposide, bleomycin as an adjuvant treatment alternative if patients are not willing to undergo or comply with surveillance.</td>
<td>Strong</td>
</tr>
</tbody>
</table>
7.1.3.7 Risk-adapted treatment for clinical stage I non-seminomatous germ cell tumour based on vascular invasion

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Strength rating</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage IA (pT1, no vascular invasion): low risk</strong></td>
<td></td>
</tr>
<tr>
<td>Offer surveillance if the patient is willing and able to comply.</td>
<td>Strong</td>
</tr>
<tr>
<td>Offer adjuvant chemotherapy with one course of cisplatin, etoposide, bleomycin (BEP) in low-risk patients not willing (or unsuitable) to undergo surveillance.</td>
<td>Strong</td>
</tr>
</tbody>
</table>

| **Stage IB (pT2-pT4): high risk** | |
| Offer adjuvant chemotherapy with one course of BEP, or surveillance and discuss the advantages and disadvantages. | Strong |
| Offer surveillance to patients not willing to undergo adjuvant chemotherapy. | Strong |
| Offer nerve-sparing retroperitoneal lymph node dissection (RPLND) to highly selected patients only; those with contraindication to adjuvant chemotherapy and unwilling to accept surveillance. | Strong |
| Primary RPLND should be advised in men with post-pubertal teratoma with somatic-malignant component. | Weak |

*For summary of evidence see 7.1.3.6 Guidelines for the treatment of clinical stage I non-seminoma testis tumour.

**Figure 1: Risk-adapted treatment in patients with clinical stage I non-seminoma NSGCT**

- Discuss all treatment options with individual patients, to allow them to make an informed decision as to their further care.
- In case of PS II, the rate of recurrence is higher and chemotherapy can be administered (max. 2 cycles).
- BEP = cisplatin, etoposide, bleomycin; CS = clinical stage; IGCCCG = International Germ Cell Cancer Collaborative Group; NS = nerve-sparing; RPLND = retroperitoneal lymph node dissection; VIP = etoposide, cisplatin, ifosfamide.
7.2 Metastatic germ cell tumours
The first-line treatment of metastatic GCTs depends on:
• the histology of the primary tumour;
• prognostic groups as defined by the IGCCCG (Table 4.3) [56];
• serum tumour marker decline during the first cycle of chemotherapy in poor-prognosis patients.
In relapsed patients, a prognostic score has been developed including response to first-line therapy which can be used to estimate patient outcome following salvage chemotherapy [170].

7.2.1 CSIS with (persistently) elevated serum tumour markers
If AFP or β-hCG increase or fail to normalise following orchidectomy, US examination of the contralateral testicle must be performed. If a contralateral tumour is excluded, repeated imaging is required if the latter is older than three weeks. This should include extra-abdominal sites in order to detect and define sites of metastasis not evident on initial imaging and to potentially tailor treatment [169].

Some patients may have stable but slightly elevated AFP or β-HCG who can be initially monitored. Treatment should be commenced if markers rise or follow-up imaging demonstrates metastatic disease [169].

The treatment of true CS IS-NSGT should be the same as other good-prognosis metastatic non-seminoma (stage IIa/B). With this, five- and ten- years disease-free survival of 87% and 85%, respectively, have been recently reported [171].

7.2.2 Metastatic disease (stage IIa/B)
7.2.2.1 Stage IIa/B seminoma
Patients with enlarged retroperitoneal lymph nodes < 2 cm and normal markers may be observed for six to eight weeks with repeat staging imaging as these may be non-metastatic. Treatment should not be initiated unless metastatic disease is unequivocal based on biopsy, increasing nodal size/number, or subsequent marker rise [169, 171]. A special case are those patients who can undergo primary RPLND within a trial or institutional study (see below for further details).

Standard historical treatment of stage II A/B seminoma has been radiotherapy, with reported relapse rates of 9% to 24% [172, 173]. Most reports describe large target fields and high doses. Recent studies using more limited fields report similar rates of relapse [174]. The radiation dose recommended in stage IIA and IIB is 30 Gy and 36 Gy, respectively, with the standard field encompassing the PA and ipsilateral iliac nodes. With these, five-year relapse-free survival rates in stage IIA and IIB are 92% and 90%, respectively [172, 173]. Further dose reduction in stage IIA to 27 Gy is associated with a higher relapse rate of 11% [129, 174].

Accumulating data on long-term morbidity, such as an increased risk of cardiovascular events and second malignancies following radiotherapy has raised concerns. One study with a follow-up of 19 years reported a sevenfold higher all-cause mortality rate than mortality due to seminoma [175].

Currently, chemotherapy is the preferred alternative to radiotherapy for stage II seminoma. This entails 3 cycles of BEP as a preferred strategy, or 4 cycles of etoposide and cisplatin (EP) as an alternative in case of contraindications to bleomycin for older patients [176]. There are no randomised studies comparing radiotherapy and chemotherapy. A recent meta-analysis of thirteen high-quality studies, comparing efficacy and toxicity of radiotherapy and chemotherapy in stage IIA/IIB patients [177], shows that radiotherapy and chemotherapy appeared to be similarly effective in both stages, with a non-significant trend towards greater efficacy for chemotherapy (HR: 2.17) in stage IIB seminoma [177]. Acute toxicity was almost exclusively reported following chemotherapy, while long-term toxicity was more frequent following radiotherapy, mainly comprising bowel toxicity and secondary cancers, generally in the irradiated field [177]. Radiation therapy may be considered in highly-selected patients who are either elderly or have contraindications or difficulties tolerating systemic chemotherapy.

Single-agent carboplatin is not an alternative to standard EP or BEP chemotherapy for metastatic disease, with the risk of failure or relapse at the site of initial nodal disease [178].

Specific trials (e.g., including RPLND or involved field radiation combined with a single course of carboplatin chemotherapy) are addressing the role of treatment options with potentially lower toxicity compared to standard options of either radiotherapy or chemotherapy with 3 cycles of BEP.
Figure 2: Treatment options in patients with seminoma clinical stage IIA and B*

**Clinical stage IIA**
- Preferred: Chemotherapy 3 x BEP or 4 x EP if contraindications to bleomycin
- Alternative: Radiotherapy 2 Gy x 15 to a target dose of 30 Gy to para-aortic and ipsilateral iliac field

**Clinical stage IIB**
- Preferred: Chemotherapy 3 x BEP or 4 x EP if contraindications to bleomycin
- Alternative: Radiotherapy 2 Gy x 15 to a target dose of 30 Gy to para-aortic and ipsilateral iliac field and an additional boost to the enlarged lymph nodes of 2 Gy x 3 to 6 Gy.

Follow-up
- Residual tumour to be followed

---

*BEP = cisplatin, etoposide, bleomycin; EP = etoposide, cisplatin.

*When enlarged retroperitoneal lymph nodes are < 2 cm and with normal markers, treatment should not be initiated unless metastatic disease is unequivocal based on biopsy, increasing nodal size/number, or subsequent marker rise.

7.2.2.2 Stage II A/B non-seminoma (NSGCT)

Management of clinical stage II A/B NSGCTs encompasses those patients in which nodal disease is present at diagnosis, as well those in whom this occurs following initial surveillance for stage I disease or marker negative patients with equivocal radiological findings.

All cases of stage II A/B NSGCT with elevated tumour markers at presentation, as well as those in whom nodal disease evolves with a concomitant increase in the tumour marker AFP or β-hCG, require primary chemotherapy according to the treatment algorithm for patients with metastatic disease and according to IGCCCG risk-group (See section 7.2.3).

In clinical stage IIA NSGCT disease without elevated tumour markers, nerve-sparing RPLND when performed by an experienced surgeon in a specialised centre is the recommended initial treatment [179, 180]. Initial surveillance may be considered, when no staging classification is needed, in patients with normal markers and lymph nodes < 2 cm of greatest axial diameter, or non-nodular shape with early re-evaluation at six weeks. A shrinking lesion may be observed further. If the lesion progresses further or fails to adequately resolve it should be regarded as CS II and be managed with chemotherapy or primary RPLND based on marker status as outlined in Figure 3.

After RPLND, those pathologically downstaged to PS I require no further treatment even with LVI in the primary tumour site. With PS II disease RPLND alone may be curative. A recent study from Indiana found that 81% of patients with confirmed pathological stage II disease were cured with RPLND alone without additional adjuvant chemotherapy [181]. A further retrospective report on selected patients with stage II relapse after surveillance for stage I NSGCT confirmed a long-lasting remission in 73% of cases following RPLND alone [144]. Relapse, either in the retro-peritoneum or visceral, occurs in 30% of patients with PS II treated with RPLND alone, requiring systemic treatment according to risk-group. In order to reduce the risk of relapse in PS II adjuvant chemotherapy (BEP maximum two cycles) may be discussed with the patient encompassing the following points:

1. that adjuvant chemotherapy may represent overtreatment in 70% of cases;
2. that relapse may occur at variable time-points, representing a further lengthy period of treatment involving more intensive chemotherapy;
• The individual features of the patient’s disease, including the adequacy of surgery;
• The cure rate with either approach will be close to 98% [182-184].

However, primary RPLND in case of stage IIA/B disease and slightly elevated markers is not recommended outside a specific study in a referral centre [179, 180].

When a marker negative stage II A/B relapse is diagnosed two or more years after initial diagnosis, a CT- or US-guided biopsy should be advised to confirm the diagnosis of GCT relapse before initiating treatment. A RPLND may be an alternative option and certainly considered if biopsy is not feasible or does not provide confirmation of active disease. There is insufficient published data on PET scans in this situation to provide recommendations.

**Figure 3: Treatment options in patients with non-seminoma clinical stage IIA**

In Case of PS II A/B patient can be followed up or receive adjuvant chemotherapy (maximum of 2 cycles). BEP = cisplatin, etoposide, bleomycin; NS = nerve-sparing; RPLND = retroperitoneal lymph node dissection; PS = pathological stage; PD = progressive disease; NC = no change.

**7.2.3 Metastatic disease (stage II C and III)**

**7.2.3.1 Primary chemotherapy**

**7.2.3.1.1 Good-prognosis risk group - seminomatous germ cell tumour**

For metastatic seminoma, only very limited data is available from RCTs, although studies suggest that a cisplatin-based regimen should be preferred to carboplatin chemotherapy [185].

As data from the French Groupe d’Etude des Tumeurs Genito-Urinaires (GETUG) S99 trial indicates that EP x 4 results in cure in almost all cases of good-prognosis SGCTs [186], this regime can also be used; therefore, standard treatment in good-prognosis seminoma should be, BEP x 3 or EP x 4. In the case of contraindications to bleomycin, EP x 4 should be given [187].

Post-chemotherapy masses should be managed as described in Section 7.5.2.

**7.2.3.1.2 Intermediate-prognosis risk group - seminomatous germ cell tumour**

For patients with intermediate-risk seminoma, BEP x 4 or etoposide, cisplatin, ifosfamide (VIP) when contraindications to bleomycin, are recommended options, although no RCT has focused specifically on this rare group of patients.

A risk-adapted approach with EP x 4 for patients with good-prognosis and VIP x 4 for patients with
intermediate-prognosis metastatic seminoma yielded an OS of 99% and 87% for good- and “intermediate-prognosis” patients, respectively [186].

7.2.3.1.3 Good-prognosis risk group - non-seminomatous germ cell tumour
For non-seminoma, the primary treatment of choice for metastatic disease in patients with good-prognosis disease, according to the IGCCCG risk classification, is BEP x 3 (Table 7.1) [56]. This regimen is superior to cisplatin, vinblastine and bleomycin (PVB) in patients with advanced disease [188, 189].

The available randomised controlled data support the equivalence of 3 or 4 cycles of BEP on a three- or five-day regime for projected two-years PFS. However, the group of patients on the three-days regime experienced increased GI toxicity at three months and increased two-years risk of tinnitus (see section 8.3.9). The difference in toxicity between the three- and five-day regimes reached clinical relevance when BEP x 4 was given [190, 191]. Based on these data the BEP x 3 and a five-day regimen is recommended in the good-prognosis risk group.

Table 7.1: cisplatin, etoposide, bleomycin (BEP) regimen (interval 21 days)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Duration of cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>20 mg/m²</td>
<td>Days 1-5*</td>
</tr>
<tr>
<td>Etoposide</td>
<td>100 mg/m²</td>
<td>Days 1-5</td>
</tr>
<tr>
<td>Bleomycin</td>
<td>30 mg</td>
<td>Days 1, 8, 15</td>
</tr>
</tbody>
</table>

*Plus hydration.

Patients with a clear contraindication to bleomycin may receive EP x 4 [190]. In all other cases omission of bleomycin is not recommended.

Two RCTs support the superiority of 3 x BEP over other regimes or schedule intensities [176, 192]. Additionally, the GETUG T93BP RCT suggested that when EP is used the mortality rate is twice that as when BEP is used, although the difference did not reach statistical significance [176]. Furthermore, the incidence of residual active cancer in the post-chemotherapy RPLND group was significantly higher in patients who received EP x 4 compared to BEP x 3 (32% vs. 8%, p < 0.0.01) [193]. The risk of requiring post-RPLND adjuvant chemotherapy could be higher after EP x 4 which could thereby offset the anticipated advantage of reduced toxicity.

A randomised study using a 72-hours infusion vs. bolus bleomycin in order to reduce pulmonary toxicity did not show any significant difference in efficacy or in pulmonary side effects [194].

Therapy should be given without reduction of the doses at 21-day intervals. Delaying a chemotherapy cycle is justified only in cases of fever with granulocytopenia < 1,000/mm³ or thrombocytopenia < 100,000/IU. Neutropenia without fever alone is not a reason to delay the next cycle. As Granulocyte colony-stimulating factor (GCS-F) lowers the risk of neutropenic sepsis, one may consider up-front administration. Granulocyte colony-stimulating factor must be given if infectious complications have occurred during or after chemotherapy, or when a treatment interval is delayed due to myelotoxicity [195].

7.2.3.1.4 Intermediate-prognosis risk group - non-seminomatous germ cell tumour
The intermediate-prognosis group in the IGCCCG is defined as patients with a five-year survival rate of 89% [27]. With this group the available data support BEP x 4 as standard treatment [196]. A RCT showed no significant improvement in OS with BEP x 4 plus paclitaxel (T-BEP) compared to BEP x 4 alone [197]. The overall toxicity with T-BEP was higher than with BEP; therefore, it cannot be recommended as a standard approach.

Patients with intermediate-prognosis treated in recent years (after 1997) are more likely to have a five-year survival of near 90% [198, 199].

7.2.3.1.5 Poor-prognosis risk group - non-seminomatous germ cell tumour
For patients with a poor-prognosis non-seminoma as defined by the IGCCCG, standard treatment consists of BEP x 4 with five-year PFS of 67% [27]. Four cycles of cisplatin, etoposide and ifosfamide (PEI) has similar efficacy, but is more myelotoxic [200]. Several RCTs have shown no advantage in OS for high-dose chemotherapy (HDCT) in the overall poor-prognosis patient group [201, 202].
Patients with a slow tumour marker decline after the first or second cycle represent a prognostically inferior subgroup [202, 203]. There are several ways to calculate slow tumour marker decline with an example available at: https://www.gustaveroussy.fr/calculation-tumor/NSGCT.html.

Recently, an international randomised phase III trial (GETUG 13) conducted in 263 patients with IGCCCG poor-risk NSGCT demonstrated that intensifying treatment with dose-dense chemotherapy improves PFS, but not OS in patients with an early unfavourable tumour marker decline [204]. Based on the results from this trial, patients with an unfavourable tumour marker decline after BEP x 1 can be switched to a more intensive chemotherapy regimen [204]. Further prospective trials/registries are planned to validate this approach.

Additional patient groups that may benefit from up-front dose intensification are those with mediastinal primary non-seminoma and patients with brain metastases at initial diagnosis [205, 206].

As a matched-pair analysis comparing high-dose to conventional treatment resulted in a better survival rate [207], poor-prognosis patients should still be treated in ongoing prospective trials or registries, whenever possible. Patients meeting poor-prognosis criteria should be transferred to a specialist centre, as better outcomes are reported for “intermediate” and poor-prognosis patients treated within a clinical trial at high-volume centres [119, 208]. There are no general recommendations for treatment modifications for patients with poor performance status (Karnofsky < 50%) or extended liver infiltration (> 50%), although two small reports indicate that a first cycle of dose-reduced therapy may reduce acute mortality without compromising long-term outcome. The number of subsequent cycles of full-dose therapy should, however, not be reduced after an initial low-dose induction cycle [209, 210].

Patients with extended pulmonary infiltration are at risk for acute respiratory distress syndrome. Omitting bleomycin with the first cycle of chemotherapy (with inclusion for subsequent cycles) has been suggested to reduce the risk of early death in this setting [210]. Management of patients with advanced disease in high-volume centres is associated with improved survival and is consequently recommended [211].

7.2.3.1.6 Prevention of thromboembolism events during chemotherapy

Thromboembolic events (TEE) occur more frequently in patients with GCT receiving chemotherapy than in young males under chemotherapy for other cancers [212]. In Denmark, comparison of TEE incidence between 5,185 GCT patients and 51,850 men without GCT revealed that GCT patients undergoing BEP chemotherapy had significantly more TEE within the first year: with hazard ratios (HRs) of 6.3, 6.0, and 24.7 for myocardial infarction, cerebrovascular accident, and venous thromboembolism, respectively [213]. Several retrospective studies identified increasing stage, size of retroperitoneal lymph nodes (different cut-off reported e.g. 3.5 cm and 5 cm), as well as Khorana score ≥ 3 and most importantly indwelling venous access device (VAD) as TEE risk factors [214].

The proportion of GCT patients developing a deep vein thrombosis (DVT) is nearly halved by low molecular weight heparin (LMWH) prophylaxis in 9 out of 97 (9.2%) as compared to 9 out of 54 (16.6%) patients undergoing chemotherapy without LMWH [215]. With the exception of one patient with intra-tumour haemorrhage due to progressive brain metastases, no serious adverse events were observed in patients treated with preventive LMWH.

Given the apparent high venous thromboembolism (VTE) incidence and only non-validated VTE risk factors, the Panel opinion was divided between some favouring thromboprophylaxis for all men and others favouring restricting thromboprophylaxis to men with certain risk factors. However, the majority of the panel agreed that a central VAD should be avoided whenever possible, as this represents the only modifiable risk factor which remained significantly associated with VTE in a multivariable risk prediction model [216].

Until RCTs or well-designed cohort studies provide a higher level of evidence, the panel agreed that based on the current literature only a generic statement about the use of thromboprophylaxis should be given until stronger evidence is available. In spite of the lack of strong certainty, the potential benefits and risks of TEE prevention should be considered in GCT patients receiving cisplatin-based chemotherapy for metastatic disease. The benefit of this preventive treatment is expected to be most pronounced in patients with high LDH, retroperitoneal lymph nodes larger than 3.5 cm and those with stage III or poor-risk features [214].
Summary of evidence

<table>
<thead>
<tr>
<th>Evidence</th>
<th>LE</th>
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<tr>
<td>Thromboembolic events occur more frequently in male patients with GCTs receiving chemotherapy than in young males under chemotherapy for other cancers.</td>
<td>2b</td>
</tr>
<tr>
<td>Retrospective studies have identified multiple risk factors for the development of thromboembolic events including: increasing stage, size of retroperitoneal lymph nodes at different cut-offs, Khorana score ≥ 3 and indwelling vascular access device (only modifiable risk factor).</td>
<td>2b</td>
</tr>
</tbody>
</table>

Recommendations

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Strength rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balance the individual patients’ potential benefits and risks of thromboprophylaxis during first-line chemotherapy in men with metastatic germ cell tumours.</td>
<td>Weak</td>
</tr>
<tr>
<td>Avoid use of central venous-access devices during first-line chemotherapy whenever possible.</td>
<td>Weak</td>
</tr>
</tbody>
</table>

7.3 Treatment evaluation and further treatment

7.3.1 Treatment evaluation

Response to treatment should be assessed after the initial induction cycle by repeat imagining and/or re-evaluation of tumour markers. With marker decline and/or radiologically regressing or stable tumour features, the planned chemotherapy, based on prognostic group, should be completed [217, 218]. If markers decline, but metastases progress on imaging, induction therapy must be completed followed by early resection [219].

With initial disease progression following induction (primary cisplatin refractory), patients should be switched to experimental drug trials [220]. Slow marker decline with the initial one to two cycles of chemotherapy warrants consideration for dose intensification (see Section 7.2.3.1.5).

Following completion of treatment, cases with a low-level β-hCG plateau should be observed to determine whether complete normalisation subsequently occurs. In patients with a low plateau serum AFP level after chemotherapy, removal of residual masses should be undertaken, with subsequent AFP monitoring. Salvage chemotherapy is only indicated for documented marker progression [221, 222].

7.3.2 Residual tumour resection

7.3.2.1 Seminoma

A residual mass of seminoma should be monitored with imaging and tumour markers and not primarily resected, irrespective of size [223-226]. Those with AFP elevation should be regarded as mixed GCTs, be managed as NSGCTs and considered for surgical resection. False-positive AFP elevation (e.g., due to liver toxicity after chemotherapy) has to be excluded.

Fluorodeoxyglucose-positron emission tomography has a high NPV in patients with residual masses after treatment of seminoma. False positive results are less frequent when scans are scheduled > two months after chemotherapy. In patients with residual masses > 3 cm, FDG-PET should be performed in order to provide more information on disease viability. In patients with residual masses < 3 cm, the use of FDG-PET is optional [50, 51].

When a post-chemotherapy mass remains positive at reclassification with FDG-PET with no volume increase, repeat FDG-PET should be performed six weeks later. A recent publication shows a low PPV for vital tumours in residual lesions (generally > 3 cm) after chemotherapy in metastatic seminoma (11% to 38% depending on sub-group). Therefore, caution is recommended with FDG-PET as a single parameter to drive clinical decisions in a persistent mass [52]. In patients with progressive disease on radiological criteria (i.e., a growing mass which enhances with CECT or is FDG-PET avid), salvage therapy is indicated (usually chemotherapy or radiotherapy) [227-229]. Surgery may be an option in patients with a residual nodular mass and contraindications to further chemotherapy or irradiation.

Patients with persistently high and/or progressing β-hCG elevation after first-line chemotherapy should proceed to salvage chemotherapy. Progressing patients without β-hCG progression should undergo histological verification (e.g., by percutaneous or surgical biopsy) before salvage chemotherapy is given. When RPLND is indicated, this should be performed in referral centres, as residual seminoma masses may be extremely difficult to remove due to intense fibrosis [228]. Ejaculation may be preserved in some of these cases [230].
7.3.2.2 **Non-seminoma**

Following first-line BEP chemotherapy, only 6% to 10% of residual masses contain active cancer, 50% have post-pubertal teratoma, and 40% comprise of necrotic-fibrotic tissue only [231]. Fluorodeoxyglucose-positron emission tomography is not indicated to re-stage patients following chemotherapy [46-48]. With complete radiological remission, RPLND is not indicated [232, 233].

No diagnostic or risk calculator can accurately predict histology of the residual masses. Thus, resection is mandatory in all patients with a residual mass > 1 cm in greatest axial diameter at cross-sectional CECT imaging until novel predictive models are externally validated [234-237]. Surgery when indicated should be performed within six to eight weeks after the last chemotherapy cycle.

There is uncertainty regarding the role of surgery with residual retroperitoneal lesions < 1 cm. Whilst there is still a risk of cancer or teratoma the vast majority of patients have only fibro-necrotic tissue present [238]. Advocates of post-chemotherapy RPLND for all patients cite the fact that both teratoma and malignant GCTs may still be present in lesions < 10 mm [239]. The alternative option for a residual mass < 1 cm is an observation protocol with recurrence risk of 6% to 9% depending on the follow-up duration [232, 233]. In the series with the longest follow-up of 15.5 years, twelve (9%) of 141 patients relapsed despite a complete response following primary treatment [233]. Eight of the twelve relapsing patients were cured with subsequent treatment. Patients after salvage chemotherapy or HDCT in first or subsequent salvage situations harbour vital tumour at a much higher rate [240]. Surgery is therefore indicated in salvage patients even with residual masses < 1 cm [232, 233].

Bilateral nerve-sparing RPLND is the standard option. Ipsilateral template resection with contralateral preservation of nerves in selected patients has been reported to yield equivalent long-term results compared to bilateral systematic resections. The mere resection of the residual tumour (so called lumpectomy) should not be performed [233, 237, 238, 240-243].

Laparoscopic or robotic RPLND may yield comparable outcomes to open procedures in selected cases with low volume residual disease and when undertaken by very-experienced surgeons. This should only be considered in specialist TC centres with expertise in open RPLND and minimally invasive surgery to ensure appropriate case selection. In this setting, up to 30% of post-chemotherapy RPLND have been reported via a laparoscopic approach [244-246]. Experience with robot-assisted laparoscopic RPLND remains limited [247] and atypical recurrences have been reported, and occur more often, with this approach [155].

7.3.3 **Sequencing of surgery in the case of multiple sites**

In general, surgery should commence at the site with the highest volume of residual disease. The histology of the mass diverges in different organ sites [234]. In cases of residual retroperitoneal and lung masses, the presence of fibro-necrotic tissue in the retroperitoneum is associated with a probability as high as 90% that lung masses contain the same histology [248]. Resection of contralateral pulmonary lesions is not mandatory when pathologic examination of the lesions from the initial site show complete necrosis. Discordant histology between lung sites, however, may occur in up to 20% of cases [249, 250].

7.3.3.1 **Quality and intensity of surgery**

Post-chemotherapy surgery is always demanding. Whilst most post-chemotherapy RPLNDs do not require resection of major vessels or organs, a proportion of patients may require an intervention in which organs affected by the disease are removed (e.g., kidney, psoas muscle or gross vessels), and may potentially also require ad hoc reconstructive surgery (e.g., vascular interventions such as vena cava or aortic prostheses). Patients undergoing adjunctive complex surgery benefit from disease control but have a greater risk of complications [251, 252]. In patients with intermediate- or poor-risk and residual disease > 5 cm, the probability of vascular procedures is as high as 20% [253]. This surgery must therefore be referred to specialised centres capable of interdisciplinary surgery (hepatic resections, vessel replacement, spinal neurosurgery, thoracic surgery). Even with centralisation of treatment, the median number of RPLNDs performed per surgeon/year in the U.K. is six [254]. Nevertheless, patients treated within such centres benefit from a significant reduction in peri-operative mortality from 6% to 0.8% [255]. In addition, specialised urologic surgeons are capable of reducing the local recurrence rate from 16% to 3% with a higher rate of complete resections [256].

7.3.3.2 **Salvage and desperation surgery**

Surgery of resectable disease after salvage treatment remains a potentially curative option in all patients with any residual mass following salvage chemotherapy. Survival after surgery and first salvage chemotherapy improved by 70% at ten years, following taxane-containing regimens [257]. Also, even with extensive salvage
chemotherapy, surgery remains a fundamental tool to achieve durable complete remissions in up to 20% of patients [258, 259].

Desperation surgery refers to resection of non-responsive or progressive (e.g., rising markers) disease following salvage chemotherapy. When the disease is resectable, a significant proportion of these patients can be rendered disease-free in the long term [260].

7.3.3.3 Consolidation chemotherapy after secondary surgery
After resection of necrosis or post-pubertal teratoma, no further treatment is required. In cases of incomplete resection of viable cancer, two adjuvant cycles of conventionally dosed cisplatin-based chemotherapy may be given in certain subgroups (e.g., poor-prognosis patients) [241]. However, caution is required with cumulative doses of bleomycin. After complete resection of ‘vital’ tumour < 10% of the total volume, particularly in patients who initially had a good-prognosis based on IGCCCG criteria, the relapse rate is very low and adjuvant chemotherapy is not beneficial in preventing further relapse [261]. The prognosis is worse if malignant disease is present in masses resected after second- and third-line chemotherapy. In this latter situation, post-operative chemotherapy is not indicated [262].

7.3.4 Systemic salvage treatment for relapse or refractory disease
Cisplatin-based combination salvage chemotherapy will result in long-term remissions in approximately 50% of patients who relapse after first-line chemotherapy. These results are highly dependent on several prognostic factors [263]. The regimens of choice are four cycles of a three-agent regimen including cisplatin and ifosfamide plus a third drug: etoposide (PEI/VIP), paclitaxel (TIP), or potentially gemcitabine (GIP) (Table 7.2) [264, 265]. No RCT has compared these regimens. Due to their potential risk of lethal haematological toxicity, these regimens should be used with G-CSF support and by well-trained oncologists.

The only available RCT comparing standard-dose and HDCT plus transplantation in the salvage setting showed no benefit in OS in patients treated with three cycles of vinblastine, ifosfamide, and cisplatin (VeIP) plus one cycle of consolidation HDCT, compared with VeIP x 4 [266]. For methodological reasons this trial design can no longer be considered state of the art.

Table 7.2: Standard PEI/VIP, TIP and GIP salvage chemotherapy (interval 21 days)

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Chemotherapy agents</th>
<th>Dosage</th>
<th>Duration of cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEI/VIP</td>
<td>Cisplatin*</td>
<td>20 mg/m²</td>
<td>Days 1-5</td>
</tr>
<tr>
<td></td>
<td>Etoposide</td>
<td>75-100 mg/m²</td>
<td>Days 1-5</td>
</tr>
<tr>
<td></td>
<td>Ifosfamide†</td>
<td>1.2 g/m²</td>
<td>Days 1-5</td>
</tr>
<tr>
<td>TIP</td>
<td>Paclitaxel</td>
<td>250 mg/m² ‡</td>
<td>24 hour continuous infusion day 1</td>
</tr>
<tr>
<td></td>
<td>Ifosfamide†</td>
<td>1.5 g/m²</td>
<td>Days 2-5</td>
</tr>
<tr>
<td></td>
<td>Cisplatin*</td>
<td>25 mg/m²</td>
<td>Days 2-5</td>
</tr>
<tr>
<td>Alternative schedule</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Paclitaxel</td>
<td>175 mg/m²</td>
<td>Day 1, 3 hour infusion</td>
</tr>
<tr>
<td></td>
<td>Ifosfamide†</td>
<td>1.2 g/m²</td>
<td>Days 1-5</td>
</tr>
<tr>
<td></td>
<td>Cisplatin*</td>
<td>20 mg/m²</td>
<td>Days 1-5</td>
</tr>
<tr>
<td>GIP</td>
<td>Gemcitabine</td>
<td>1000 mg/m²</td>
<td>Day 1 + 5</td>
</tr>
<tr>
<td></td>
<td>Ifosfamide</td>
<td>1200 mg/m²</td>
<td>Days 1-5</td>
</tr>
<tr>
<td></td>
<td>Cisplatin</td>
<td>20 mg/m²</td>
<td>Days 1-5</td>
</tr>
</tbody>
</table>

* Plus hydration.
† Plus mesna protection.
‡ An MRC schedule uses paclitaxel at 175 mg/m² in a 3 hour infusion [265].

A retrospective analysis by the International Prognostic Factors Study Group (IPFSG) evaluated the risk of relapse in patients in whom this occurred after at least three cisplatin-based cycles and subsequent cisplatin-based conventional-dose or carboplatin-based high-dose salvage chemotherapy [170]. Seven variables - histology, primary tumour location, response, progression-free interval after first-line treatment and level of AFP, hCG and the presence of liver, bone or brain metastasis at salvage treatment were identified as independent prognostic variables of relapse after initial cisplatin-based chemotherapy [170]. Using these factors, five risk-groups: very low risk = -1 points; low risk = 0 points; intermediate-risk = 1-2 points; high risk = 3-4 points; and very high risk > 5 points; were identified with significant differences in PFS and OS. Table 7.3 illustrates these five risk groups and the corresponding two-year PFS and three-year OS rates [170]. Several recent trials
have validated this scoring system [267-270]. As in first-line therapy, the prognostic impact of tumour marker decline applies in the salvage setting [271]. While progression to induction chemotherapy was negative for OS, prior use of paclitaxel was not significantly associated with a negative outcome [272].

A secondary analysis of the IPFSG cohort (n = 1,600 patients) showed an improvement of about 10% to 15% in OS in all prognostic subgroups when treated with high-dose salvage therapy compared to standard dose therapy. To prospectively confirm this finding, an RCT of high-dose vs. conventional dose chemotherapy in patients with first-line relapse is underway (Tiger trial). When HDCT is used as a salvage treatment, sequential treatment cycles of high-dose carboplatin and etoposide (HD-CE) should be preferred to a single high-dose regimen as the former is associated with less toxicity-related deaths [273]. A recent systematic review confirmed the superiority of using at least two high-dose cycles in the salvage setting over a single high-dose cycle [274]. It is clearly of the utmost importance that these rare patients with relapse are treated within clinical trials and at specialised centres.

Table 7.3: The International Prognostic Factors Study Group Score for seminoma and non-seminoma that relapse after cisplatin-based first-line chemotherapy [170]

<table>
<thead>
<tr>
<th>Points</th>
<th>-1</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
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<tr>
<td>Variable</td>
<td></td>
<td>Seminoma</td>
<td>Non-seminoma</td>
<td></td>
<td></td>
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<td>Histology</td>
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<tr>
<td>Primary site</td>
<td></td>
<td>Gonadal</td>
<td>Retroperitoneal</td>
<td>Mediastinal</td>
<td></td>
</tr>
<tr>
<td>Response</td>
<td>CR/PRm-</td>
<td>PRm+/SD</td>
<td>PD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFI</td>
<td>&gt; 3 months</td>
<td>≤ 3 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AFP salvage</td>
<td>Normal</td>
<td>&lt; 1000</td>
<td>1000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>hCG salvage</td>
<td>&lt; 1000</td>
<td>1000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LBB</td>
<td>No</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AFP = alpha-fetoprotein; CR = complete remission; PRm- = partial remission, negative markers; PRm+ = partial remission, positive markers; hCG = human chorionic gonadotrophin; LBB = liver, bone, brain metastases; PD = progressive disease; PFI = progression-free interval; SD = stable disease.

Table 7.4: PFS and OS estimates for all patients according to IGCCCG prognostic score for seminoma and non-seminoma that relapse after cisplatin-based first-line chemotherapy [171]

<table>
<thead>
<tr>
<th>Score (n = 1,435)</th>
<th>N</th>
<th>%</th>
<th>HR</th>
<th>2-years PFS (%)</th>
<th>3-year OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Low</td>
<td>76</td>
<td>5.30</td>
<td>1</td>
<td>75.1</td>
<td>77.0</td>
</tr>
<tr>
<td>Low</td>
<td>257</td>
<td>17.9</td>
<td>2.07</td>
<td>52.6</td>
<td>69.0</td>
</tr>
<tr>
<td>Intermediate</td>
<td>646</td>
<td>45.0</td>
<td>2.88</td>
<td>42.8</td>
<td>57.3</td>
</tr>
<tr>
<td>High</td>
<td>351</td>
<td>24.5</td>
<td>4.81</td>
<td>26.4</td>
<td>31.7</td>
</tr>
<tr>
<td>Very High</td>
<td>105</td>
<td>7.3</td>
<td>8.95</td>
<td>11.5</td>
<td>14.7</td>
</tr>
<tr>
<td>Missing</td>
<td>159</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

HR = hazard ratio; PFS = progression-free survival; n = number of patients; OS = overall survival.

7.3.5 Second relapse

No RCTs have been reported for patients with second relapse and overall conventional therapy does not appear effective. For patients who have received two series of conventionally-dosed therapy (first-line and first-salvage), high-dose chemotherapy with autologous stem cell support should be used [268]. With this the prospect of cure is only 20% to 25%.

Patients relapsing within four to eight weeks after platinum-based therapy, or who are progressing despite platinum-based therapy, as well as those relapsing shortly after high-dose chemotherapy, are considered as cisplatin refractory. Combinations of gemcitabine and oxaliplatin or the triple combination of gemcitabine, oxaliplatin and paclitaxel have resulted in response rates of 25% to 45% in this setting. Cisplatin re-challenge in association with gemcitabine and paclitaxel may be considered in patients with adequate renal function [275]. For patients with a second relapse not responding to the combination of oxaliplatin and gemcitabine or the triple combination, inclusion in clinical trials is encouraged.

Patients with a good response undergoing subsequent resection of residual tumour lesions may still have a 15% to 20% chance of long-term cure [258, 276].
Various targeted agents have generally failed in refractory disease, including immune checkpoint inhibitors [267-274]. Trials combining PD1/PDL-1 and CTLA4 inhibitors are ongoing; however, even for those combinations early results are not encouraging.

7.3.5.1  
**Late relapse (> two years after end of first-line treatment)**

Late relapse is defined as recurrence more than two years after completion of successful primary treatment of metastatic TC [49]. According to a pooled analysis, this occurs in 1.4% and 3.2% of seminoma and non-seminoma patients, respectively [277]. Interestingly, in a population-based study all late-relapsing seminoma patients had viable GCT [278]. These can be treated with chemotherapy and radiotherapy.

In contrast, patients with late-relapsing NSGCT should undergo surgical resection when feasible, alone or in combination with chemotherapy. Some patients, including those with rapidly rising β-hCG, may benefit from induction salvage chemotherapy with subsequent reconsideration of surgery for resection of persisting residual masses [179]. In general, however, surgery represents the mainstay of treatment and it should be performed in most patients when feasible irrespective of the level of their tumour markers in order to completely resect all viable GCT post-pubertal teratoma or TSTC [179, 279]. Survival strongly relates to the histology of the recurrent lesions rather than that of the initial disease. If not completely resectable, biopsies should be obtained for histological evaluation to direct salvage chemotherapy based on the tumour phenotype. Review by an experienced pathologist is critical to avoid misinterpretation of the therapeutic morphological changes that occur with the treatment of GCT [280]. If the patient responds to salvage chemotherapy, secondary surgery should then be undertaken if feasible. With unresectable, but localised refractory disease, stereotactic or conventional radiotherapy may be considered. To avoid excess mortality, late relapses should be treated only at centres experienced in managing such patients [281].

7.3.6  
**Treatment of brain metastases**

Brain metastases occur in the context of initial metastatic disease, systemic relapse and rarely as an isolated site of relapse. Long-term survival of patients presenting with brain metastases at diagnosis is poor (30% to 50%) and even poorer when a site of recurrent disease (five-year survival-rate is 2% to 5%) [282, 283]. A large international database comprising 523 patients reported 48% three-year OS rates in patients with brain metastases at initial diagnosis and 27% three-year OS rates for patients with brain metastases at relapse [41].

Chemotherapy as initial treatment proved effective in a first-line setting (potentially even as dose-intensified therapy upfront) with data also supporting the use of multimodal treatment particularly in relapsed disease [41]. Consolidation RT, even with total response after chemotherapy, should therefore be used in patients with brain metastases at relapse, but must be carefully discussed in a first-line setting [284]. Surgery may be considered in cases with a persistent solitary metastasis, depending on the systemic disease status, histology of the primary tumour and the location of the metastasis.

7.3.6.1  
**Guidelines for the treatment of metastatic testicular germ cell tumours**

<table>
<thead>
<tr>
<th>Summary of evidence</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>In the NSGCT good-prognosis-risk group (IGCCG), BEP x 3 is superior to other chemotherapy regimes. Toxicity is lower when treatment is delivered in five-day regimes rather than three-day regimes.</td>
<td>1b</td>
</tr>
<tr>
<td>In NSGCT intermediate-prognosis-risk group (IGCCCG) BEP x 4 is the standard treatment of choice with a five-year survival of 89% in contemporary series.</td>
<td>1b</td>
</tr>
<tr>
<td>In pathological stage II NSGCT disease, RPLND performed in specialised centres without adjuvant chemotherapy results in 73% to 81% of long-lasting remissions.</td>
<td>2b</td>
</tr>
<tr>
<td>In patients with a poor-prognosis metastatic NSGCT (defined by IGCCCG), treatment with BEP x 4, results in a five-year PFS of 67%. There is no advantage in OS for high-dose chemotherapy.</td>
<td>1b</td>
</tr>
<tr>
<td>Patients with a poor-prognosis metastatic NSGCT and early unfavourable tumour marker decline may benefit from intensification of treatment with dose-dense chemotherapy, with improvement of PFS in spite of no benefit being observed for OS.</td>
<td>1b</td>
</tr>
<tr>
<td>Following first-line BEP chemotherapy, 6% to 10% of NSGCT residual masses contain active cancer, 50% have post-pubertal teratoma, and 40% comprise of necrotic-fibrotic tissue only. Figures regarding persistence of residual active are slightly lower in post chemotherapy residual masses &lt; 1 cm. Currently there is no accurate prognostication method of histology.</td>
<td>2b</td>
</tr>
</tbody>
</table>
In CS IIA/B seminoma radiotherapy and chemotherapy treatment show similar effectiveness, with a non-significant trend towards greater efficacy of chemotherapy in CS IIB. However, risk of second malignancies and cardiovascular events is higher after radiotherapy.

In metastatic seminoma stage ≥ IIC, primary chemotherapy with BEP, tailored to the IGCCCG risk group, has proven superior to Carboplatin based chemotherapy.

Fluorodeoxyglucose-positron emission tomography has a high NPV in patients with post-chemotherapy seminoma residual masses (> 3 cm) when performed > two months after chemotherapy.

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Strength rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treat low-volume non-seminomatous germ cell tumour (NSGCT) stage IIA/B with elevated markers like metastatic good- or intermediate-prognosis risk group IGCCCG with three or four cycles of cisplatin, etoposide, bleomycin (BEP).</td>
<td>Strong</td>
</tr>
<tr>
<td>Nerve-sparing RPLND when performed by an experienced surgeon in a specialised centre is the recommended initial treatment in clinical stage (CS) IIA NSGCT disease without elevated tumour markers.</td>
<td>Weak</td>
</tr>
<tr>
<td>Repeat staging after six weeks before making a final decision on further management should be considered in patients with small volume (CS IIA &lt; 2 cm) marker negative NSGCT.</td>
<td>Weak</td>
</tr>
<tr>
<td>Treat metastatic NSGCT (stage ≥ IIC) with an intermediate-prognosis with four cycles of standard BEP.</td>
<td>Strong</td>
</tr>
<tr>
<td>In metastatic NSGCT with a poor-prognosis, treat with one cycle of BEP (or cisplatin, etoposide and ifosfamide [PEI], in cases with pulmonary dysfunction), followed by tumour marker assessment after three weeks. Continue the same schedule up to a total of four cycles with favourable marker decline. With unfavourable decline, initiate chemotherapy intensification.</td>
<td>Weak</td>
</tr>
<tr>
<td>Perform surgical resection of visible (&gt; 1 cm) residual masses after chemotherapy for NSGCT when serum levels of tumour markers are normal or normalising.</td>
<td>Strong</td>
</tr>
<tr>
<td>Initially offer cisplatin-based chemotherapy according to IGCCCG prognosis groups, or alternatively radiotherapy to seminoma patients with stage II A/B and, inform the patient of potential long-term side effects of both treatment options.</td>
<td>Weak</td>
</tr>
<tr>
<td>Treat seminoma stage IIC and higher, with primary chemotherapy according to IGCCCG classification (BEP x 3 in good-prognosis and BEP x 4 in intermediate prognosis).</td>
<td>Strong</td>
</tr>
</tbody>
</table>

8. FOLLOW UP AFTER CURATIVE THERAPY

8.1 Minimal recommendations for Follow-up

Based on different risks of relapse depending on diagnosis and initial treatment, three major follow-up groups can be defined:

1. patients with seminoma stage I;
2. patients with non-seminoma stage I on active surveillance;
3. all patients having received either adjuvant treatment or curative chemotherapy for “good”- and intermediate-prognosis metastatic disease (according to the IGCCCG) achieving a complete remission with, or without, surgery (for seminoma this includes residual lesions < 3 cm, or residual lesions > 3 cm that are PET-negative).

It is important to note that patients not achieving a complete remission or presenting with poor-prognosis disease should be followed up individually by specialised centres. Tables 8.1-8.3 show the minimal recommendations for follow-up of the three different groups based on recommendations developed at an European Society for Medical Oncology (ESMO) consensus conference [285].

Generally, MRI of the abdomen can be used as an alternative to CECT in experienced centres. Regarding the use of US of the contralateral testis, the majority of the consensus meeting participants did not support repeat US investigation, either with negative biopsy or if no contralateral biopsy has been performed [285].

A very late relapse (VLR) after five years is a rare event occurring in approximately 0.5% of patients based on a population-based analysis [278]. The aim of follow-up beyond five years therefore shifts to detection of late side effects of treatment, and imaging tests are not routinely recommended.
Most patients with VLR are diagnosed due to symptoms, although in up to 50% elevated tumour markers are present in both seminoma and NSGCTs [278, 286]. Patient education regarding relapse symptoms and clinician awareness are important elements of survivorship management. Early use of imaging and tumour markers with suspicion of relapse is encouraged.

Table 8.1: Recommended minimal follow-up for seminoma clinical stage I on active surveillance or after adjuvant treatment (carboplatin or radiotherapy)

<table>
<thead>
<tr>
<th>Modality</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Years 4 &amp; 5</th>
<th>After 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumour markers ± doctor visit</td>
<td>2 times</td>
<td>2 times</td>
<td>2 times</td>
<td>Once</td>
<td>Further management according to survivorship care plan</td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Abdominopelvic computed tomography/magnetic resonance imaging</td>
<td>2 times</td>
<td>2 times</td>
<td>Once at 36 months</td>
<td>Once at 60 months</td>
<td></td>
</tr>
</tbody>
</table>

Table 8.2: Recommended minimal follow-up for non-seminoma clinical stage I on active surveillance

<table>
<thead>
<tr>
<th>Modality</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4 &amp; 5</th>
<th>After 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumour markers ± doctor visit</td>
<td>4 times**</td>
<td>4 times</td>
<td>2 times</td>
<td>1-2 times</td>
<td>Further management according to survivorship care plan</td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>2 times</td>
<td>2 times</td>
<td>Once, in case of LVI+</td>
<td>At 60 months if LVI+</td>
<td></td>
</tr>
<tr>
<td>Abdominopelvic computed tomography/magnetic resonance imaging</td>
<td>2 times</td>
<td>At 24 months***</td>
<td>Once at 36 months*</td>
<td>Once at 60 months*</td>
<td></td>
</tr>
</tbody>
</table>

LVI+ = Lymphovascular invasion present

* Recommended by 50% of the consensus group members.

** In case of high-risk (LVI+) a minority of the consensus group members recommended six times.

*** In case of high-risk (LVI+) a majority of the consensus group members recommended an additional CT at eighteen months.

Table 8.3: Recommended minimal follow-up after adjuvant treatment or complete remission for advanced disease (excluded: poor-prognosis and no remission)

<table>
<thead>
<tr>
<th>Modality</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4 &amp; 5</th>
<th>After 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumour markers ± doctor visit</td>
<td>4 times</td>
<td>4 times</td>
<td>2 times</td>
<td>2 times</td>
<td>Further management according to survivorship care plan**</td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>1-2 times</td>
<td>Once</td>
<td>Once</td>
<td>Once</td>
<td>-</td>
</tr>
<tr>
<td>Abdominopelvic computed tomography/CT tomography/magnetic resonance imaging</td>
<td>1-2 times</td>
<td>At 24 months</td>
<td>Once at 36 months</td>
<td>Once at 60 months</td>
<td></td>
</tr>
<tr>
<td>Thorax CT</td>
<td>1-2 times*</td>
<td>At 24 months*</td>
<td>Once at 60 months*</td>
<td>Once at 60 months*</td>
<td></td>
</tr>
</tbody>
</table>

* In conjunction with abdominopelvic CT/MRI in case of pulmonary metastases at diagnosis.

** In case of teratoma in resected residual disease: the patient should remain with the uro-oncologist.

8.2 Quality of life and long-term toxicities after cure of testicular cancer

The vast majority of patients will be cured with five-year relative survival rates of approximately 95% in Western Europe. Testicular cancer patients are usually between 18 and 40 years of age at diagnosis and life expectancy after cure extends over several decades [287]. Patients should be informed before treatment of common long-term toxicities, which are avoided or minimised by adherence to international guidelines.

Treatment of stage I TC is controversial, with some experts advocating surveillance for all, thereby avoiding unnecessary adjuvant chemotherapy [147], whereas others highlight the importance of patient autonomy and consider the prospect of avoiding salvage treatment with long-term toxicities appealing [288].
Unfortunately, it is not known which treatment spares most patients from long-term toxicities, which so far seem to be absent or mild after adjuvant chemotherapy [158, 165, 289].

During follow-up, patients should be screened and treated for known risk factors such as hypertension, hyperlipidaemia and testosterone deficiency. When follow-up by the TC clinician is terminated, a written cancer survivorship plan addressing late toxic effects, lifestyle recommendations, recurrence risk, and cancer-specific follow-up may be helpful [49, 290]. Whilst the following overview is not complete, those interested may consider review articles on this topic [287, 290, 291].

8.2.1 Second malignant neoplasms (SMN)
Treatment-induced second malignant neoplasms (SMNs) usually occurs after the first ten years [290]. Testicular cancer belongs to the group of cancers commonly diagnosed in adolescents and young adults (AYA), which have a higher absolute risk of developing a subsequent primary neoplasm than survivors of childhood or adult cancer [292]. In a comprehensive study on second cancers in AYA cancer survivors (aged 15-39 years at AYA cancer diagnosis) 24,309 TC survivors with 1,435 second cancers were registered as opposed to 808 expected second cancers, yielding a standardised incidence ratio of 1.8. The second cancer incidence increased with time resulting in remarkably high and accelerating 35-year cumulative incidence rate of 20% (95% CI: 18–9–21·5) [292].

The risk for solid SMN increases with younger age at radio- or chemotherapy [290]. Radiotherapy-related SMN are primarily localised within, or close to, the radiotherapy field (colon, stomach, pancreas, bladder and the urinary tract) [290]. A remarkably clear radiation-dose relationship to gastric- and pancreatic cancer has been demonstrated [293].

Modern cisplatin-based chemotherapy has been found to be associated with a 40% increased risk of a solid SMN [294]. A relationship between cumulative dose of cisplatin and second SMN, especially in the GI tract has been noted [295]. As few studies have observation times beyond 25 years, the cumulative incidence of SMN may be underestimated. An increase from 6.5% after 25 years to 20% after 35 years has been reported [292]. Second malignant neoplasms were identified in 9.4% of Swedish TC survivors, with half these cancers considered uncommon in men in their 40s [296]. Survival was 40% in TC survivors with a SMN as opposed to 80% in those without [296].

The European Society for Blood and Marrow Transplantation (EBMT) reported SMN in 59 of the 5,295 TC patients registered after receiving HDCT within a median follow-up of 3.8 years. Of them, 39% developed a hematologic SMN and 58% a solid SMN. Twenty-year cumulative incidence of solid and hematologic SMN was 4.2% and 1.4% respectively, with median OS shorter after diagnosis of hematologic vs. solid SMN (8.6 vs. 34.4. months). Age ≥ 40 years at the time of HDCT was significantly associated with hematologic, but not with solid SMNs [297].

8.2.2 Leukaemia
In a series of 40,576 TC survivors, the observed ratio for developing leukaemia, mostly acute myeloid (AML) and lymphoblastic leukaemia was 2.6 [298]. The risk of AML seems to be related to both the dose of cisplatin and etoposide. Doses of etoposide exceeding 2 g/m² have been shown to increase the subsequent risk of AML [299]. The majority of TC patients receive much lower doses of etoposide than this so that the absolute risk of AML after three to four courses of BEP is very low. In patients requiring HDCT with cumulative etoposide doses exceeding this threshold, less than 1.5% have been reported to develop AML. There is a cumulative dose disease risk relationship with cisplatin and AML. Chemotherapy-induced leukaemia is usually diagnosed within the first ten years after treatment for TC and has a poor-prognosis [300].

8.2.3 Infections
Chemotherapy-treated TC survivors (TCSs) have a higher risk of dying from infections than the general population (standard mortality ratio 2.48, 95%; CI: 1.70-3.5) [301]. This is possibly due to long-term bone marrow suppression, as well as complications of subsequent salvage treatment (which was not reliably registered). Alternatively, extensive or subsequent surgical treatment may be contributory. Furthermore, asymptomatic pulmonary fibrosis by mediastinal radiotherapy and/or bleomycin may render TCSs vulnerable to respiratory infections long after treatment.

8.2.4 Pulmonary complications
Chemotherapy exposed TCSs have a nearly three-fold increased risk of dying of pulmonary diseases than the normal population [301]. Bleomycin-induced lung toxicity may affect 7% to 21% of patients in the long term, resulting in death in 1% to 3% [302]. Chemotherapy-treated TC survivors treated with high cumulative cisplatin doses and/or pulmonary surgery, have a poorer pulmonary function than those cured with surgery alone [292].
Intriguingly, long-term pulmonary complications were associated with the cumulative cisplatin doses but not with the dose of bleomycin [303]. The data contrasts with a meta-analysis on chemotherapy for TC including 6,498 patients showing a significant effect of bleomycin administration on all-grade pulmonary toxicity [304]. In a Danish cohort of 565 TC survivors, Lauritsen et al., found pulmonary function recovered with repeated assessments over five years in almost all patients [305]. Pulmonary function was not associated with reduced renal function, age, tobacco-smoking, and cumulative chemotherapy, but rather pulmonary embolism, lung surgery, and poor IGCCCG risk group [305]. In 234 good risk TCSs patients the inclusion of bleomycin did not seem to influence pulmonary morbidity, operative difficulty, or non-pulmonary post-operative complications after post-chemotherapy RPLND [306].

A Canadian study on 212 TC patients receiving bleomycin-containing chemotherapy revealed bleomycin-induced pneumonitis (BIP) in 73 patients (34%) with the majority of these (75%) asymptomatic [307]. Granulocyte colony stimulating factor use was not associated with increased risk of BIP in multivariable analyses nor was it associated with increased severity of symptomatic BIP. There was a non-statistically significant trend towards greater risk of BIP in patients that developed renal impairment during chemotherapy treatment [307].

8.2.5 Cardiovascular toxicity
Thromboembolic events (mostly venous) occur more frequently in patients with GCT receiving chemotherapy than in other young male adults treated with chemotherapy for other cancers [212]. Low-dose heparins used during the course of chemotherapy may prevent the onset of thromboembolic events [215], though level 1 evidence is lacking. Mortality from cardiovascular disease (CVD) is higher in TCSs than in the general population (OR: 5) [213, 308, 309]. Furthermore, CVD is more common in chemotherapy-treated TCSs than in those who underwent surgery only [164, 310]. Feldman et al. applied the Framingham Risk Score (FRS) on 787 TC survivors and compared the results with controls [311]: FRS did not differ by chemotherapy regimen (BEP 3 vs. EP 4) nor between control and TCSs, although the latter were three times less likely to smoke and generally more physically active. However, less educated and less vigorously active TCSs had higher FRS representing a high-risk subgroup for intense follow-up and counselling [311].

Most of the above studies are registry-based and thus limited. Lauritsen et al., took advantage of the comprehensive prospective registration of cancer, diagnoses and drug prescription in Denmark comparing outcomes between 5,185 GCT patients and 51,850 men without GCT [213].

Cisplatin, etoposide, bleomycin (BEP) chemotherapy, applied in 1,819 GCT patients increased the risks of hypertension and hypercholesterolemia and thus CVD within one year after initiation of BEP: with hazard ratios (HRs) of 6.3, 6.0, and 24.7 for myocardial infarction, cerebrovascular accident, and venous thromboembolism, respectively. One year after BEP treatment, the risk of CVD decreased to normal levels, but after 10 years, increasing risks were found for myocardial infarction (HR: 1.4; 95% CI: 1.0 to 2.0) and cardiovascular death (HR: 1.6; 95% CI: 1.0 to 2.5) [213].

Metabolic syndrome, a strong risk factor for CVD and its components, hypertension, obesity and hypercholesterolaemia, increases with treatment intensity (OR: 9.8) [308, 312, 313]. Hypogonadism increases the risk of insulin resistance, a proxy for metabolic syndrome, and an inherent risk of CVD. Bogefors et al., showed, however, that most associations between TC treatment and metabolic parameters became statistically non-significant after adjustment for hypogonadism, indicating that hypogonadism might be the mediator of several toxicities which are usually attributed to the applied TC treatment [314]. Circulating residual serum platinum might exert endothelial stress and thereby possibly lead to hypertension [315]. Furthermore, exposure to circulating platinum is associated with paraesthesia, hypogonadism, and hypercholesterolaemia as well as major vascular events [215].

Physical activity reduces the risk of metabolic syndrome and CVD. High-intensity aerobic interval training (HIIT) for twelve weeks improved cardiorespiratory fitness, multiple pathways of CVD risk, and surrogate markers of mortality in TCSs as compared to standard care, i.e., no supervised training [316]. However, HIIT during cisplatin-based chemotherapy might be harmful as a planned study on 94 patients closed early after recruiting nineteen patients and the finding of severe CVD complications among three out of nine patients undergoing HIIT [317]. Two patients developed a pulmonary embolism (respectively at days seven and nine of BEP cycle 2) and the remainder a myocardial infarction (at day seven of BEP cycle 3). It is difficult to draw firm conclusions from such small patient numbers, but the observed CVD was well above the expected 5% risk of thromboembolic complications during or shortly after cisplatin-based chemotherapy such that the authors discourage HIIT during cisplatin-based chemotherapy for TC.
8.2.6 Raynaud-like phenomena
Chemotherapy-related Raynaud-like phenomena were reported before the introduction of cisplatin and are usually attributed to bleomycin [318, 319]. Cisplatin is believed to contribute to cold-induced vasospasms. Vogelzang et al. reported that the incidence of Raynaud's phenomenon was higher after treatment with CVB than with vinblastine and bleomycin only, 41% vs. 21%, respectively [320].

8.2.7 Neurotoxicity
Cisplatin induces a symmetric dose-dependent sensory, distal, length-dependent glove and stocking paraesthesia, affects 29% of TCSs who received cisplatin-based chemotherapy as opposed to 10% after orchidectomy alone [309, 321]. Treatment with five or more cycles increases the frequency of this symptom to 46%. Paclitaxel-induced acute neuropathy consists of an acute pain syndrome, which usually develops within three to seven days following its administration. Platinum is measurable in the serum of TCSs many years after its application with the intensity of paraesthesia more strongly associated with platinum serum level than with the cumulative dose of applied cisplatin [315]. Patients who experience a larger decline in circulating residual serum platinum during follow-up are at reduced risk of worsening of tinnitus or hand paraesthesia [322].

8.2.8 Cognitive function
There are concerns that chemotherapy may reduce the cognitive function leading to “chemo-brain”. Amidi et al., could show an alteration of brain structural networks after cisplatin-based chemotherapy for TC [323]. Impaired brain networks may underlie poorer performance over time on both specific and nonspecific cognitive functions in TC survivors following chemotherapy.

8.2.9 Ototoxicity
Cisplatin-induced ototoxicity comprises tinnitus and hearing impairment, particularly frequencies of 4,000 Hz and higher, and is caused by damage to the outer hair cells in the inner ear [309, 324-326]. Both hearing impairment and tinnitus are considerably increased after application of 50 mg/m$^2$ cisplatin over two days as compared to 20 mg/m$^2$ over five days (OR: 5.1 and 7.3, respectively), indicating a higher impact of serum peak concentrations than cumulative doses [321]. A significant association between Glutathione S-transferases (GST) genotypes and the risk of cisplatin-induced ototoxicity has been demonstrated [327, 328]. Understanding the pathogenesis of, and susceptibility to, this complication will lead to more individualised treatment in the future.

8.2.10 Nephrotoxicity
Cisplatin-based chemotherapy may lead to long-term renal dysfunction in 20% to 30% of TCSs [215, 310, 312]. In TC patients, reduced renal excretion of cisplatin and bleomycin might increase the risk of other toxicities, e.g., bleomycin-related pneumonitis [329, 330]. A comprehensive assessment of 1,206 Danish TCSs, however, did not associate a significant association between chemotherapy-induced impaired renal function and other toxicities [308]. Renal recovery was poor after five or more cycles of BEP as compared to after BEP x 3 [313]. The estimation of glomerular filtration rate (eGFR) depends on whether creatinine or cystatin is applied, with the latter substance leading to an overestimation of eGFR in cisplatin treated TCSs, whereas this discrepancy was not found in patients with chronic kidney failure due to medical disease [331].

8.2.11 Hypogonadism
Testicular endocrine dysfunction comprises insufficient testosterone production and/or compensatory increased LH levels. Subnormal testosterone levels have been reported in TCSs treated with chemotherapy, when compared to those treated with surgery only or the general population [289, 309, 329, 332]. Compensated Leydig cell dysfunction in TCSs (testosterone within normal limits & increased LH values) was not associated with symptoms of depression, anxiety, sexual dysfunction, fatigue or impaired overall self-evaluated QoL, such that testosterone substitution seems not to be indicated in these patients [333].

Hypogonadism increases the risk of insulin resistance and hence the risk of metabolic syndrome, which, in turn, might lead to CVD in the long term [314]. Wiechno et al., could show a decline in testosterone and an increase in LH and FSH within one year after treatment for unilateral TC [334]. Although there are clear indications of hypogonadism-related complications, and despite an established association between low testosterone and metabolic syndrome, no clear association between Leydig cell dysfunction and the risk of metabolic syndrome during a median ten-year follow-up could be established [335].

Walsh et al., reported a RCT demonstrating a benefit of testosterone replacement therapy in young male survivors of testicular cancer, lymphoma, and leukaemia aged 25–50 years who had low morning serum testosterone. Under the six months of replacement therapy, cancer survivors that received testosterone
experienced a decrease in trunk fat mass and whole-body fat mass and an increase in lean body mass, but no effect on reported physical functioning or other QoL scores when compared to those that received a placebo gel [336]. The absence of improved QoL and the issue of rendering TCSs sub- or infertile by testosterone replacement therapy is the reason why the TC panel does not recommend this strategy until more compelling endpoints are reported. An ongoing Danish RCT might yield new level 1 evidence [337].

Erectile dysfunction (OR: 4.2) has been significantly associated with chemotherapy in a recent multicentre study [309]. Of 481 North American TCSs treated with modern cisplatin-based chemotherapy, 38% were hypogonadal (defined as on testosterone substitution or serum testosterone level $\leq 3.0$ ng/mL) [338]. Hypogonadism was associated with the number of adverse health outcomes and its risk increased with age and obesity [339].

8.2.12 Fatigue
Chronic fatigue (CF) is described as a subjective feeling of emotional, physical and/or cognitive tiredness that is not relieved by rest and persists for more than six months. Significantly higher levels of C-reactive protein and interleukin-1 receptor antagonist are measured in TCSs with CF [338]. Also, a significantly higher frequency of CF (16%) was reported in a cross-sectional Norwegian study of long-term TCSs at a median of twelve years after treatment for TC when compared with the age-matched Norwegian population (10%) [191]. Of note, the prevalence of CF increased from 15% to 27% during a 10-year period in long-term TCSs [340].

8.2.13 Quality of life
Quality of life is transiently reduced by chemotherapy, during which patients experience a loss of appetite, increased fatigue, increased dyspnoea and reduced social- and physical function [191]. When comparing three or four cycles of BEP in good-risk patients, all outcomes favour treatment with three courses [190]. After one and two years, one-third of patients reported an improvement in global QoL after chemotherapy, while one-fifth of patients reported deterioration, with no difference between treatment groups. After adjuvant treatment of non-seminoma stage I patients, there was no difference in short-term or long-term (five years) QoL between RPLND, or one course of BEP [163].

Anxiety, depression, fear of cancer recurrence (FCR), and distress may impair the health-related quality of life (HRQoL) in TCSs. A recent review identified a considerable variation in both severity and prevalence of each of these issues, probably due to use of different questionnaires and also cultural variations [341]. Clinically significant anxiety is reported in approximately one out of five TCSs and distress in one out of seven; therefore, it is more frequent among TCS than in the general population. Depression was not uniformly found to be more frequent, whereas every third TCSs reported fear of recurrence. Importantly, poorer psychological outcomes were more common among single, unemployed TCSs with a low socio-economic status and co-morbidities, as well as those experiencing worse symptoms/side effects, and those using passive coping strategies.

A German study found clinically significant anxiety in 6.1% and depression present in 7.9% of TC patients, with both a higher number of physical symptoms and the prospect of having children being related to higher levels of anxiety and depression [342].

Among 2,479 Danish long-term TCSs higher anxiety was reported by those who experienced bilateral TC as compared to unilateral TC [343]. For a subset of approximately 11% of TSCs, the diagnosis of TC was traumatic. This subset was found to suffer from post-traumatic stress disorder in the long term, which resulted in significant QoL reduction [344]. The authors recommend that healthcare professionals explore stress symptoms at follow-up visits in order to timely identify TSCs requiring support.

Sexual function and satisfaction were assessed in 2,260 Danish TCSs. Erectile dysfunction was found in men who underwent radiotherapy, BEP chemotherapy with subsequent surgical resection of residual masses, or more than one line of treatment. The latter group also reported orgasmic dysfunction. After radiotherapy, significantly more men reported overall decreased sexual satisfaction, whereas all other groups reported no difference in overall satisfaction, intercourse satisfaction, and sexual desire [345].

Testicular cancer survivors were more likely to have high level of stress compared to the reference population with a prevalence ratio of 1.56 (95% CI: 1.40 – 1.73), according to a big cohort study with 2,252 patients, with a median of 19 years from diagnosis [346].
9. RARE ADULT TESTICULAR TUMOURS

Less than 5% of testicular cancers are unrelated to GCNIS and lack 12p alterations [347]. These tumours are rare with available literature based on case reports and small retrospective series. As a result of publication bias related to these types of study the risk of metastatic disease may be less than that reported in the literature.

9.1 Classification

These testicular tumors have a similar presentation as TC and are only identified after histopathologic examination. They are classified according to the WHO Classification of Tumours of the Urinary System and Male Genital Organs [84].

9.2 Spermatocytic Tumours

Spermatocytic tumours are GCTs unrelated to GCNIS. They show a unique amplification of chromosome 9 corresponding to the DMRT1 gene and are never associated with other forms of germ cell tumours [84].

Spermatocytic tumours are extremely rare, occur exclusively in the testis and do not normally show elevated tumour markers [84]. Due to a morphological overlap to classic seminoma, they were previously named as “spermatocytic seminomas” but reclassified as spermatocytic tumours more recently [84]. As those tumours cannot be differentiated from seminomatous GCT by frozen section analysis, radical orchiectomy represents the standard treatment option and outcomes after testis sparing surgery or adjuvant treatment is unknown and therefore not recommended [348]. Metastatic disease is very rare and, if occurring, it presents early after initial diagnosis with limited survival [348].

9.3 Sex cord-stromal tumours

Sex cord–stromal tumours are relatively uncommon but represent the second largest group of primary testicular tumours after germ cell tumours [349]. As a small minority of these tumours are clinically malignant, a thorough evaluation of those morphological features associated with malignancy should be performed to ensure proper management. Two or more of the following features correlate with malignant potential: size > 5 cm, infiltrative borders, cytological atypia, three or more mitotic figures per ten high-power fields, vascular invasion and necrosis [349].

9.3.1 Leydig cell tumours

Leydig cell tumours comprise about 4% of adult testicular tumours and mainly present as localised tumours of which only 2.5% have metastatic potential [350]. They may present with hormonal manifestations, including gynecomastia and more rarely accompanied by Cushing’s Syndrome [349]. After testis sparing surgery a local recurrence rate of 7% has been reported and no adjuvant treatment options can be recommended [351]. Several risk factors for metastatic disease have been proposed which may guide image guided follow-up intensity [351]. Survival of men with metastatic disease is poor but response to surgical and systemic treatment have been reported in several cases [351].

9.3.2 Sertoli cell tumours

Sertoli cell tumours are even less common than Leydig cell tumours and account for approximately 1% of all testicular neoplasms [349]. The risk of metastatic potential remains unclear. After testis sparing surgery a local recurrence rate of < 1% has been reported and no adjuvant treatment options can be recommended [352]. Several risk factors for metastatic disease have been proposed which may guide image guided follow-up intensity [352]. Survival of men with metastatic disease is poor but response to surgery has been reported in a few cases [352].

9.3.3 Granulosa cell tumour

Granulosa cell tumours include adult and juvenile variants and are very infrequent [349]. The risk of metastatic potential remains unclear. After testis sparing surgery a local recurrence rate of 5% has been reported and no adjuvant treatment options can be recommended [353]. Whereas metastatic disease has never been reported in juvenile granulosa cell tumours, men with adult type rarely present with metastatic disease [353]. Survival of men with metastatic disease is poor but response to surgical or systemic treatment has been reported in a few cases [353].

9.3.4 Thecoma/fibroma group of tumours

These tumours derive from the testicular parenchymal stroma or from the tunica albuginea. They seem to be uniformly benign [349, 354].
10. REFERENCES


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11. CONFLICT OF INTEREST

All members of the Testicular Cancer Guidelines working group have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publicly accessible through the European Association of Urology website: http://www.uroweb.org/guidelines.

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