EAU Guidelines on
Testicular Cancer

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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 references/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 2021 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 2022 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 para- and testicular tumours";
- All the chapters have been reviewed and supporting text and recommendations across the guideline have been rephrased and 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;
- 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 with the corresponding references;
- New supporting text regarding VTE prophylaxis in males with metastatic germ cell tumours (GCTs) receiving chemotherapy has 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 April 2020 and June 2021 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 1,959 unique records were identified, retrieved and screened for relevance. Fifty-eight new and updated references have been included in the 2022 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 represented by the words 'strong' or 'weak' [5]. 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.

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 has been produced and is under peer-review.
- A review and discussion of the recommendations with patient associations is ongoing.
- The development of a TC survivorship plan in collaboration with patient 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 approved by the Guidelines Office Methods Committee and including data from with five international centres is presently in the analysis phase.
- Care Pathways on diagnostic, treatment CS I, and treatment of metastatic disease and Cheat Sheets on TC are being prepared in collaboration with the EAU GO.

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], and continues to rise. At diagnosis, 1-2% of cases are bilateral and the predominant histology is germ cell tumours (GCT) (90-95% of cases) [6]. The peak incidence is in the third decade of life for non-seminoma testis (NST) and mixed GCT patients, and in the fourth decade for seminoma testis (ST) patients. In 5% of TGCT patients 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 later 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 impaired fertility [14-16] or disorders/differences of sex development [17]. Additional risk factors include family history of TC among first-degree relatives and the presence of a contralateral testicular tumour or GCNIS [14, 18-24]. Recent genome-wide association studies revealed detectable susceptibility loci leading to an increased relative risk to develop TC [25].

3.2 Histological classification

General:
The recommended pathological classification shown below is based on the 2016 update of the World Health Organization (WHO) pathological classification [26].

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) [27].

Table 4.1: TNM classification for testicular cancer (adapted from UICC, 2016, 8th edn.) [27]

pT - Primary Tumour[1]		
pTX	Primary tumour cannot be assessed (see note[1])	
pT0	No evidence of primary tumour (e.g., histological scar in testis)	
pTis	Intratubular germ cell neoplasia (carcinoma *in situ*)+	
pT1	Tumour limited to testis and epididymis without vascular/lymphatic invasion; tumour may invade tunica albuginea but not tunica vaginalis*	
pT2	Tumour limited to testis and epididymis with vascular/lymphatic invasion, or tumour extending through tunica albuginea with involvement of tunica vaginalis**	
pT3	Tumour invades spermatic cord with or without vascular/lymphatic invasion**	
pT4	Tumour invades scrotum with or without vascular/lymphatic invasion	
N - Regional Lymph Nodes – Clinical		
NX	Regional lymph nodes cannot be assessed	
N0	No regional lymph node metastasis	
N1	Metastasis with a lymph node mass 2 cm or less in greatest dimension or multiple lymph nodes, none more than 2 cm in greatest dimension	
N2	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	
N3	Metastasis with a lymph node mass more than 5 cm in greatest dimension	
Pn - Regional Lymph Nodes – Pathological		
pNX	Regional lymph nodes cannot be assessed	
pN0	No regional lymph node metastasis	
pN1	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	
pN2	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	
pN3	Metastasis with a lymph node mass more than 5 cm in greatest dimension	
M - Distant Metastasis		
MX	Distant metastasis cannot be assessed	
M0	No distant metastasis	
M1	Distant metastasis **	
	M1a Non-regional lymph node(s) or lung metastasis	
	M1b Distant metastasis other than non-regional lymph nodes and lung	

S - Serum Tumour Markers (Pre chemotherapy)			
SX	Serum marker studies not available or not performed		
S0	Serum marker study levels within normal limits		
	LDH (U/l)	**hCG (mIU/mL)**	**AFP (ng/mL)**
S1	< 1.5 x N and	< 5,000 and	< 1,000
S2	1.5-10 x N or	5,000-50,000 or	1,000-10,000
S3	> 10 x N or	> 50,000 or	> 10,000

N indicates the upper limit of normal.

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

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

[+] *The current "Carcinoma in situ" nomenclature is replaced by GCNIS.*

[*] *AJCC eighth edition subdivides T1 Pure Seminoma by T1a and T1b depending on size no greater than 3 cm or greater than 3 cm in greatest dimension [28].*

[**] *AJCC eighth edition considers the hilar soft tissue invasion as pT2, while the discontinuous involvement of the spermatic cord is considered as pM1 [28].*

4.2 The Union for International Cancer Control prognostic groups
According to the 2016 TNM classification, the following prognostic groups are defined:

Table 4.2: Prognostic groups for testicular cancer (UICC, 2016, 8th edn.) [28]

Stage grouping	T	N	M	S
Stage 0	pTis	N0	M0	S0
Stage I	pT1-T4	N0	M0	SX
Stage IA	pT1	N0	M0	S0
Stage IB	pT2 - pT4	N0	M0	S0
Stage IS	Any pT/TX	N0	M0	S1-3
Stage II	Any pT/TX	N1-N3	M0	SX
Stage IIA	Any pT/TX	N1	M0	S0
	Any pT/TX	N1	M0	S1
Stage IIB	Any pT/TX	N2	M0	S0
	Any pT/TX	N2	M0	S1
Stage IIC	Any pT/TX	N3	M0	S0
	Any pT/TX	N3	M0	S1
Stage III	Any pT/TX	Any N	M1a	SX
Stage IIIA	Any pT/TX	Any N	M1a	S0
	Any pT/TX	Any N	M1a	S1
Stage IIIB	Any pT/TX	N1-N3	M0	S2
	Any pT/TX	Any N	M1a	S2
Stage IIIC	Any pT/TX	N1-N3	M0	S3
	Any pT/TX	Any N	M1a	S3
	Any pT/TX	Any N	M1b	Any S

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 [29, 30]. True stage IS (persistently elevated or increasing serum tumour marker levels after orchidectomy) is found in about 5% of non-seminoma patients [29].

4.3 The International Germ Cell Cancer Collaborative classification for the prognostic-risk groups of metastatic testicular cancer

The 1997 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 [31].

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) [32].

Table 4.3: Prognostic-based staging system for metastatic germ cell cancer (IGCCCG) [31, 32]*

Good-prognosis group	
Non-seminoma 5-year PFS 90% 5-year survival 96%	*All of the following criteria:* • Testis/retro-peritoneal primary • No non-pulmonary visceral metastases • AFP < 1,000 ng/mL • hCG < 5,000 IU/L (1,000 ng/mL) • LDH < 1.5 x ULN
Seminoma 5-year PFS 89% 5-year survival 95%	*All of the following criteria:* • Any primary site • No non-pulmonary visceral metastases • Normal AFP • Any hCG • Any LDH
Intermediate-prognosis group	
Non-seminoma 5-year PFS 78% 5-year survival 89%	*Any of the following criteria:* • Testis/retro-peritoneal primary • No non-pulmonary visceral metastases • AFP 1,000 - 10,000 ng/mL or • hCG 5,000 - 50,000 IU/L or • LDH 1.5 - 10 x ULN
Seminoma 5-year PFS 79% 5-year survival 88%	*All of the following criteria:* • Any primary site • Non-pulmonary visceral metastases • Normal AFP • Any hCG • Any LDH
Poor-prognosis group	
Non-seminoma 5-year PFS 54% 5-year survival 67%	*Any of the following criteria:* • Mediastinal primary • Non-pulmonary visceral metastases • AFP > 10,000 ng/mL or • hCG > 50,000 IU/L (10,000 ng/mL) or • LDH > 10 x ULN
Seminoma	No patients classified as "poor-prognosis"

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

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

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 [33, 34] and a potential reason for delayed diagnosis in 10% of cases [33]. Around 1% of patients presenting with gynaecomastia have a germ cell or sex cord/gonadal tumour of the testes [35] and 11% present with back and flank pain [34]. 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 [34, 36].

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 [34, 36-38].

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 [39-42]. 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 [43]. 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 [43].

Sensitivity decreases and specificity increases with increasing lymph node cut-off size. With nodes $\geq$ 4 mm pooled sensitivity and specificity are 93% and 58% respectively, whereas for nodes $\geq$ 10 mm sensitivity is 37% and specificity increases to 100% [43]. 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 [44]. 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.,* [43]. 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 [43].

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 [45].

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 [46-48], It should only be considered when US is inconclusive, as local staging for testis-sparing surgery (TSS) planning, to differentiate between paratesticular and intratesticular lesions and/or to characterise intratesticular masses (e.g., distinctive features of Leydig tumours) [46, 47, 49].

Magnetic resonance imaging of the abdomen may be used for staging in case of allergy to iodine-based contrast media with similar accuracy to CECT in the detection of retroperitoneal nodal enlargement [43].

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 [42, 50, 51]. Therefore, when available, MRI should be preferentially used in the evaluation of cerebral metastases in GCTs [51]. Magnetic resonance imaging of the spine is also advisable in patients with symptoms suggesting metastatic disease or if there is equivocal staging on CECT [50].

5.2.4   *Fluorodeoxyglucose-positron emission tomography*

There is no evidence to support the use of Fluorodeoxyglucose-positron emission tomography (FDG-PET) for initial staging and follow-up of TC [43, 50, 52, 53]. Fluorodeoxyglucose-positron emission tomography is only recommended for seminoma patients with post-chemotherapy residual masses > 3 cm (largest diameter) to assess FDG activity [54]. 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 [53]. Whilst the NPV for active disease is > 90% [55, 56], the PPV ranges from 23% to 69% [55-57]. False positives are common and may occur in up to 80% of lesions [55, 57], 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 [57].

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*

Alphafetoprotein 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 [58, 59].

In a recently reported cohort, the three markers (AFP, β-hCG and LDH) are simultaneously elevated in 7.1% of patients. The elevation of any of these three markers is seen in up to 60% of patients at diagnosis [50.2% (44-56%) in CS I and 93% in CS III (75.8-98.8%)] [59].

Both alphafetoprotein and β-hCG increase is detected in 39% of patients with NSGCT [59], and up to 90% of NSGCTs present with a rise in either AFP or β-hCG at diagnosis [33, 59, 60]. Pure seminomas may also have modestly elevated β-hCG level at diagnosis in up to 30% (9-32%) of cases [58, 59].

Tumour markers have limitations due to their low sensitivity as normal levels do not exclude the presence of disease [60].

5.3.2   *Serum tumour markers after orchidectomy*

Serum levels of AFP, β-hCG and LDH following orchidectomy provide staging and prognostic information [61]. 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 [58, 60]. The persistence of, or increase in, serum tumour marker elevation following orchidectomy indicates the likely presence of metastatic disease [59]. 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 [61]. Before chemotherapy AFP and LDH levels may act as prognostic factors for OS in non-seminoma intermediate risk group [62].

At relapse, only 25% of patients have elevated AFP and β-hCG, and LDH may remain persistently elevated in 30% of patients despite cure [59]. Tumour markers should be routinely used for follow-up as indicators of recurrence, although the precise frequency of testing is not well defined [63].

5.3.3 Other tumour markers
Micro RNAs (miRNAs) are emerging as potential new biomarkers for TC. A number of studies suggest higher discriminatory accuracy for miRNAs (particularly miR-371a-3p) compared to conventional GCT markers in diagnosis, treatment monitoring, and predicting of residual or recurrent viable disease [64-71]. Furthermore, they may differentiate between GCT and other (stromal/non-germ cell originated) tumours [71]. However, before miRNAs can be considered for use in routine clinical practice, several issues including laboratory standardisation, availability of the test and, importantly, prognostic validation [70] 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 [72].

5.4.2 Testis-sparing surgery
Testis-sparing surgery is a valid treatment option in men with interstitial cell or benign testicular tumours and may prevent hypogonadism, lifelong testosterone supplementation and infertility in young men.

In men with TGCTs orchiectomy represents the standard of care as pathological studies describe multifocal and/or adjacent GCNIS in 20-30% of patients [73, 74]. However, TSS when feasible, is indicated in synchronous bilateral tumours or in tumours in solitary testis [75]. Importantly, when indicated in this setting, besides enucleation of the testicular lesion, at least two additional testicular biopsies should be taken to exclude GCNIS [76].

Testis-sparing surgery can also be offered in cases of small or indeterminate testicular masses with negative tumour markers in the presence of a normal contralateral testis in order to avoid the over-treatment of potentially benign lesions and to preserve testicular function [75, 77].

Patients should be informed that cancer can be present even in small (i.e., < 1 cm) masses [75, 78, 79], thus obtaining histology is mandatory.

In both settings, TSS should only be offered together with frozen section examination (FSE). Frozen section examination has shown to be reliable and highly concordant with final histopathology, with a 99% and 96% of sensitivity and specificity respectively and 98% and 97% of PPV and NPV, respectively [77, 80, 81]. In cases of discordance between FSE and final pathology delayed orchiectomy might be needed.

Whether history of GCT or indeterminate small testicular lesion, patients should be made aware on the following issues regarding TSS practice: that limited data exists regarding oncological safety of TSS; that local recurrence rates have been reported (overall 0-26.9%), when TC is present in the specimen [75, 79, 82] and that TSS has implications for ongoing surveillance of the testis. Similarly, patients should be informed about the role and impact of adjuvant radiotherapy when GCNIS is present, on the potential infertility, the need for hormonal supplementation despite parenchyma preservation [75, 79, 83], and that possible discordance between FSE and final pathology may drive the need for a delayed orchidectomy.

5.4.3 Insertion of testicular prosthesis
Testicular prosthesis should be offered to all patients receiving unilateral or bilateral orchidectomy [83]. The prosthesis can be inserted at orchidectomy or subsequently without adverse consequences, including infection [84].

5.4.4 Contralateral biopsy
Contralateral biopsy has been advocated to exclude the presence of GCNIS [85]. Whilst routine policy in some countries [86], the low incidence of GCNIS and metachronous contralateral testicular tumours (up to 9% and approximately 2.5%, respectively) [87, 88], the morbidity of GCNIS treatment (see section 7.1.1), and the fact that most metachronous tumours are low stage at presentation, makes it controversial to recommend routine contralateral biopsy in all patients [89, 90]. 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 [76, 91, 92]. Patients should be informed that a subsequent TGCT may arise despite a negative biopsy [93]. When indicated, a two-site surgical testicular biopsy is the technical procedure recommended [76].

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) [94-97].

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 cm^2 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 [94]:
  - 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 [95].
- If microscopic findings are not concordant with serum markers further block samples should be taken.
- pT category according to TNM 2016 [27]. In a multifocal seminoma the largest nodule should be used to determinate 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 [98].

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) [97].

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 [97]. 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) [97]**.**

Elements	Required	Recommended*	Content	Remarks
Clinical information		√	- Not provided - Previous history of testicular cancer - Previous therapy - Other	Specify each
Serum tumour markers		√	- Not provided - If provided within normal limits or - Specify serum tumour markers used - Specify levels - Specify date markers were drawn	Select all that apply: Serum tumour markers: LDH (IU/L), AFP (ug/L), β-hCG (IU/L)
Operative procedure	√		- Not specified - Orchidectomy partial - Orchidectomy radical - Other	Specify side for partial or radical orchidectomy. Specify other
Tumour focality	√		- Cannot be assessed - Indeterminate - Unifocal - Multifocal	If multifocal specify number of tumours in specimen.
Maximum tumour dimension	√		- Cannot be assessed - Dimensions largest tumour (mm) - Dimensions additional tumour nodules#	Specify at least maximum diameter of largest tumour. Preferably specified 3 dimensions/axes.#
Macroscopic extent of invasion	√		- Cannot be assessed - Confined to testis - Invades epididymis - Invades tunica vaginalis - Invades hilar structures - Invades spermatic cord - Invades scrotum - Other	Select all that apply. If other specify.
Block identification key		√	N/A	List overleaf or separately with indication of nature and origin of all tissue blocks.
Histological tumour type	√		- Germ cell tumour: type and percentage - Other	Use WHO classification (2016). If other specify.
Microscopic extent of invasion	√		- Rete testis of stromal/ interstitial type - Epididymis - Hilar fat - Tunica albuginea# - Tunica vaginalis - Spermatic cord - Scrotal wall	For all: - not submitted - not involved - involved
Lymphovascular extension	√		- Not identified - Present	If present specify type.#
Intratubular lesions (GCNIS)	√		- Not identified - Present - Other intratubular lesions#	If other intratubular lesions present identify type.#

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.

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 [99, 100].

Until clinical data supporting or refuting self-examination in the general population becomes available, TC patients and their family members should be informed about the importance of physical self-examination, particularly in the presence of clinical risk factors including family history of TC [101].

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 [102, 103]. Up to 24% of TC patients are azoospermic and almost 50% have abnormal sperm counts (oligozo-ospemic) before treatment [103].

Treatment for TC, including orchidectomy, may have a negative impact on reproductive function [104]. 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 [105-107]. Spermatogenesis usually recovers one to four years after chemotherapy [108]. 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 [109].

All patients should be offered semen preservation as the most cost-effective strategy for fertility preservation, and pre-treatment fertility assessment (testosterone, luteinising hormone [LH] and follicle stimulating hormone [FSH] levels) is advised [110].

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 [105-107, 110, 111].

Long-term testosterone supplementation is necessary in patients who have had bilateral orchidectomy or have low testosterone levels after treatment of GCNIS [112].

Chemotherapy and RT are both teratogenic. Therefore, contraception must be used during treatment and for at least six months after its completion [113].

For more detailed information, the reader is referred to the EAU Guidelines on Sexual Reproductive Health [114].

5.8 Guidelines for the diagnosis and staging of Testicular Cancer

Summary of evidence	LE
Poor sperm quality is frequently found in TC patients, before and after treatment. Semen preservation is the most cost-effective strategy for fertility preservation.	2b
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.	2b
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.	2a
For chest staging, CECT has a median sensitivity, specificity, PPV, NPV and accuracy of 100%, 93%, 68%, 100% and 93%, respectively	2a
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.	2b
Fluorodeoxyglucose-positron emission tomography has a limited diagnostic accuracy for staging before chemotherapy.	2b
There are no high-level evidence studies supporting screening programs.	2b
In testicular sparing surgery, FSE has shown to be reliable and highly concordant with final histopathology.	1b
There is no evidence supporting any size criteria for a testicular lesion to be safely followed-up.	2b
In patients without risk factors, there is low incidence of contralateral GCNIS and of metachronous GCTC.	2b

Recommendations	Strength rating
Discuss sperm banking with all men prior to starting treatment for testicular cancer (TC).	Strong
Perform bilateral testicular ultrasound (US) in all patients with suspicion of TC.	Strong
Perform physical examination including supraclavicular, cervical, axillary, and inguinal lymph nodes, breast, and testicles.	Strong
Measure serum tumour markers both before and after orchidectomy taking into account half-life kinetics.	Strong
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.	Strong
Perform contrast enhanced computerised tomography (CECT) scan (chest, abdomen, and pelvis) in patients with a diagnosis of TC. In case of iodine allergy or other limiting factors perform abdominal and pelvic magnetic resonance imaging (MRI).	Strong
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.	Strong
Do not use positron emission tomography–computed tomography or bone scan for staging.	Strong
Encourage patients with TC to perform self-examination and to inform first-degree male relatives of the need for self-examination.	Weak
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.	Strong
Discuss biopsy of the contralateral testis to patients with TC and who are at high-risk for contralateral germ cell neoplasia "*in situ*".	Strong

6.   PROGNOSIS

6.1   Risk factors for metastatic relapse in clinical stage I testicular cancer

With stage I seminoma, primary testicular tumour size and stromal invasion of the rete testis have been identified as predictors for relapse in a pooled analysis of retrospective data [115]. Absence of both factors indicates a low risk of recurrence (6%) [116]. Whilst the original analysis was not supported by a further retrospective report [117], some prospective series [118-120] 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 [121, 122]. 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 [121, 122].

For non-seminoma stage I, invasion of the primary tumour into blood or lymphatic vessels, lymphovascular invasion (LVI), is the most reliable single predictor of occult metastatic disease [96, 123, 124]; while interobserver agreement is limited, immunohistochemistry might improve detection [125]. The percentage of embryonal carcinoma within a tumour may enhance the PPV and NPV of LVI [123], but there is no definitive prognostic cut-off for percentage [123]. 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

Histological type	Seminoma [121]	Non-seminoma [95, 124]
• Pathological risk factors	• Tumour size • Invasion of the rete testis	• Lympho-vascular invasion in peri-tumoral tissue

7.   DISEASE MANAGEMENT

The availability of cis-platin based chemotherapy to which TC is exquisitely sensitive, in combination with surgery and in highly selected cases, radiotherapy, has resulted in the high cure rates seen with this disease [126]. 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 [127, 128]. In clinical trials on poor-prognosis patients, OS relates to the number of patients treated at the participating centre (worse if < 5 patients enrolled) [129]. 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 [130]. This will ensure that patients are neither subjected to unnecessary or inappropriate treatment and associated toxicities or denied early management options which may subsequently compromise their long-term quality of life or survival.

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 be performed 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 in a patient with a solitary testis, local radiotherapy (18-20 Gy in fractions of 2 Gy) should be considered [107, 131-133]. Chemotherapy is significantly less effective, and the cure rates are dose-dependent [131]. Radiotherapy to a solitary testis will result in infertility and increased long-term risk of Leydig cell insufficiency [107]. Fertile patients who wish to father children may delay radiation therapy and be monitored with regular testicular US [76].

If GCNIS is diagnosed and the contralateral testis is normal, management options include orchidectomy or close observation, as the five-year risk of developing TC is 50% [134].

7.1.2 *Seminoma germ cell tumour clinical stage I (SGCT CS I)*
Approximately 15% of clinical stage I SGCT patients have subclinical metastatic disease, usually in the retroperitoneum, and will relapse after orchidectomy alone [117, 120, 135, 136]. Adjuvant treatment decisions should be based on thorough discussions with the patient, incorporating potential advantages and disadvantages, as well as individual patient circumstances.

7.1.2.1 *Surveillance*
Several prospective non-randomised surveillance studies have been conducted over the past decade. These have shown an overall risk of relapse in unselected CS I patients of 12-20% at five years with 17% in the largest series of over 1,500 patients [137]. Most occur in the retroperitoneal lymph nodes during the first two years [138-140].

Risk of relapse is 12% with small size (tumours < 3 cm) as a single parameter [119, 139]. With both small tumour size (< 4 cm) and absence of stromal rete testis invasion even lower recurrence rates of 6% have been described.

The cancer-specific survival (CSS) rate reported with surveillance for CS I seminoma performed by specialist centres is over 99% [137, 138, 140, 141]. Whilst cost effective compared to other management strategies [142], surveillance can represent a burden to the patient due to the need for repeated imaging of the retroperitoneum and clinic visits. These may impact patient compliance which is crucial to an active surveillance strategy.

7.1.2.2 *Adjuvant chemotherapy*
A trial compared one cycle of carboplatin reaching area under curve of 7 mg/mL/min (AUC 7) with adjuvant RT. This showed no difference in relapse free rates (95% and 96%), time to recurrence and survival after a median follow-up of four years [143-145]. Non-randomised risk-adapted population-based studies using one cycle of carboplatin reported a lower five-year relapse rate of 3%-4% compared to 14-16% with active surveillance [138, 140]. Adjuvant carboplatin (AUC 7) is therefore an alternative to RT or surveillance in CS I seminoma [138, 143, 144]. Retrospective data shows a median time to relapse after Carboplatin of nineteen months , with 15% of relapses occurring beyond three years. Time to relapse after after Carboplatin is longer than with active surveillance. Most patients relapsing after adjuvant carboplatin can be successfully treated with a standard cisplatin-based chemotherapy regimen appropriate to their disease stage [146].

7.1.2.3 *Adjuvant radiotherapy*
Seminomas are extremely radiosensitive tumours. Adjuvant RT to a para-aortic (PA) field or a PA and ipsilateral field (PA and ipsilateral iliac nodes), with a total dose of 20-24 Gy, reduces the relapse rate between 1-3% [147-149]. A large MRC RCT of 20 Gy vs. 30 Gy PA radiation in CS I seminoma showed non-inferiority in terms of recurrence rates [148]. A scrotal shield should be considered during adjuvant RT in order to prevent scattered radiation toxicity in the contralateral testis [150]. Adjuvant irradiation of supra-diaphragmatic lymph nodes is not indicated.

Whilst moderate acute gastrointestinal side effects occur in up to 60% of patients, moderate chronic gastrointestinal side-effects are present in about 5% of patients. Severe radiation induced long-term toxicity is seen in less than 2% of patients.

The main concern with adjuvant RT is the long-term risk of radiation-induced non-germ cell malignancies [150-153]. This has limited its role in CS I seminoma to elderly patients and those unfit for chemotherapy.

7.1.2.4 *Risk-adapted treatment*
Tumour size > 4 cm and stromal rete testis invasion may stratify patients into low- and high-risk groups. These risk factors were introduced based on an analysis of retrospective trials [102], and then confirmed in subsequent prospective studies [119, 120]. Patients with both risk factors have a 32% of relapse compared to 6% with neither. Prospective trials based on these risk factors have demonstrated the feasibility of a risk-adapted approach to CS I seminoma.

A large study in 744 patients with CS I seminoma managed with a risk-adapted policy (low risk [0-1 factors] receiving active surveillance and high risk [1-2 factors] treated with two adjuvant courses of carboplatin, AUC 7) with a median follow-up of 67 months showed 12% of low-risk cases relapsed on active surveillance

whilst 3% of those with one or both risk factors relapsed with adjuvant chemotherapy. The patterns and outcome of relapse was similar in the two groups [119, 154].

A trial of 897 patients offered surveillance to patients with no or one risk factor whilst patients with both risk factors were offered one dose of carboplatin, AUC 7 [120]. The 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. When one or both risk factors were present, 15.5% of surveillance patients relapsed whereas 9% receiving adjuvant carboplatin relapsed. Thirty-three per cent of relapses who received adjuvant carboplatin occurred more than three years after orchidectomy with 3% occurring after five years [120].

7.1.2.5   Guidelines for the treatment of clinical stage I seminoma testis tumours

Summary of evidence	LE
Primary testicular tumour size and stromal rete testis invasion correlate with the risk of relapse. The evidence to guide adjuvant treatment decisions is, however, too limited to justify its routine use in clinical practice.	2a
Active surveillance is a feasible approach with conditional relapse risk in unselected series of between 12% and 20%.	2a
In patients without risk factors the five-year relapse rate under surveillance is 4-6%, whereas in the presence of one or two risk factors, five-year relapse rate in contemporary surveillance series is 15-20%.	2b
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 both risk factors.	2b
Adjuvant chemotherapy with one course carboplatin AUC 7 is not inferior to adjuvant radiotherapy when pathological risk factors are considered. Relapse rates with both adjuvant treatments are around 5%.	1b
Adjuvant radiotherapy is associated with an increased risk of developing secondary non-germ cell malignancies.	2b

Recommendations	Strength rating
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.	Strong
Offer surveillance as the preferred management option if resources are available and the patient is compliant.	Strong
Offer one dose of carboplatin at area under curve (AUC) 7 if adjuvant chemotherapy is considered.	Strong
Do not perform adjuvant treatment in patients at very low-risk of recurrence (no risk factors).	Strong
Do not routinely perform adjuvant radiotherapy.	Strong
Adjuvant radiotherapy should be reserved only for highly selected patients not suitable for surveillance and with contraindication for chemotherapy.	Strong

*7.1.3   **Non-seminomatous germ cell tumours clinical stage I (CS I-NSGCT)***
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 orchiectomy alone. In those with the high-risk feature of LVI, relapse occurs in 50% compared to 15% in those without LVI. A thorough discussion should be undertaken with the patient outlining the potential advantages and disadvantages of treatment options, as well as individual co-morbidities, disease features, risk factors, specific circumstances, and personal preferences, to guide their treatment decision.

7.1.3.1   Surveillance
Surveillance for CS I-NSGCT 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.

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) [136, 137]. Of these, 92% present within the first two years [136, 137].

Serum tumour markers alone are an unreliable indicator of relapse. In a systematic review of CS I-NSGCT patients undergoing surveillance, the rate of marker elevation at time of relapse varied between 28 and 75% [155]. Approximately 60% of relapses occur in the retroperitoneum and 11% have large volume metastatic recurrent disease reinforcing the need for cross-sectional imaging [136, 156].

Surveillance studies have reported lower relapse rates compared to some series of patients undergoing primary Retroperitoneal lymph node dissection (RPLND) [157]. This is likely related to both 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 [156, 158, 159].

7.1.3.2 Retroperitoneal lymph node dissection (RPLND)
Prior to the availability of effective systemic therapy for relapsed disease primary RPLND for CS I-NSGCT evolved as a strategy which improved survival following orchidectomy [160]. A large series of 464 unselected cases of CS I-NSGCT commencing within this era reported an overall relapse rate of 14%. Of PS (pathological stage) II cases 36% relapsed. With PS I cases 11% relapsed – which is consistent with more contemporary series reporting approximately 10% of patients with no evidence of nodal involvement at RPLND (i.e., PS I) relapsing at distant sites [123, 160, 161]. More recent series report lower relapse rates possibly reflecting case selection [162].

Since the introduction of platin based chemotherapy the role of adjuvant primary RPLND in men with stage I GCT has decreased. The few indications in stage I disease include men with Teratoma with somatic malignant transformation, interstitial cell tumours with an increased risk of metastases or patients who are not willing or suitable to undergo chemotherapy in case of a later recurrence.

With RPLND 18-30% of patients have active nodal malignancy (i.e., PS II), [161, 163]. Without further treatment approximately 30% of these will recur [161]. The presence of LVI, predominant embryonal carcinoma and pT stage of the primary as well as histologically extranodal tumour extension all appear associated with an increased risk of recurrence. The use of these further parameters has yet to be clearly defined in clinical practice [161, 164]. However, following RPLND, presence and extent of lymph-node involvement (specifically lymph-node ratio), may represent stronger predictive factors of recurrence and could be adopted for subsequent decision making [161, 162].

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 [163, 165]. This suggests that primary RPLND, when indicated or chosen, should be performed by an experienced surgeon in a specialist centre. Minimally invasive (laparoscopic or robot-assisted) primary RPLND, appears feasible and safe (e.g., low-complication rate) in experienced hands. However, most of the series have only a short follow-up precluding definitive conclusions regarding oncological outcomes when compared to open primary RPLND. At present, it cannot be recommended outside of a high-volume RPLND centres with appropriate minimally-invasive expertise [166-173].

Follow-up after RPLND is less demanding and costly than other options due to the reduced need for cross-sectional imaging [174]. Nevertheless, in view of the high CSS rates of surveillance with salvage treatment in cases of relapse, the low relapse rates with adjuvant chemotherapy, and the lower reproducibility of primary RPLND on a large scale, its role 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 trial from 1996, as well as subsequent studies, used two cycles of BEP in high-risk patients (LVI present) [175-177]. In these series, including 200 patients, some with a median follow-up of nearly 7.9 years [175], a relapse rate of only 2.7% was reported, with minimal long-term toxicity. Two cycles of cisplatin-based adjuvant chemotherapy also do not seem to adversely affect fertility or sexual activity [178].

More studies have shown one cycle of adjuvant BEP results in similar very low recurrence rates (2-3%) [179, 180]. 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% [165]. The hazard ratio to experience a tumour recurrence with surgery compared to BEP x 1 was 8 [165]. No clinically relevant differences in quality of life (QoL) were detected [181].

A community based prospective study of 490 unselected patients with CS I-NSGCT that received adjuvant single cycle BEP had five-year relapse rates of 3% and 2% for LVI+ and LV- patients, respectively. After a median follow-up of eight years these rates were sustained, no relapses were observed beyond 3.3 years [179, 180]. These numbers imply that > 90% of relapses are prevented by single cycle BEP which is now the recommended strategy if adjuvant chemotherapy is considered [179, 180]. The very-long term (> 20 years) side effects of adjuvant chemotherapy, particularly cardiovascular, are yet to be fully defined which should be considered with decision-making [182, 183].

Limited data are available on outcomes with relapse after adjuvant BEP. A retrospective analysis indicated that about one third of these relapses were late and that the outcome may be slightly worse compared to those presenting with *de novo* metastatic disease [184].

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. Lymphovascular invasion 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 multicycle cisplatin-based chemotherapy may opt for adjuvant therapy. Those with LVI should have their high risk of relapse (up to 50%) highlighted and be guided to consider adjuvant management, and 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 (pN1), as well as the 10% risk of systemic relapse, even if pN0, requiring subsequent chemotherapy treatment (BEP X 3).

7.1.3.5 Post Pubertal Teratoma with somatic malignant component
According to a multi-institutional study analysing retrospective datasets of CS I patients with post-pubertal teratoma with somatic malignant component (TSMC), these patients had inferior five-year OS of approximately 10% compared to other CS I-GCT patients. Furthermore, CS I TSMC cases undergoing primary RPPLND had a much higher proportion of nodal metastases (PS II) than expected (37.5%). Despite its limitations this study provides the strongest evidence on this issue and supports primary RPLND in CS I-NSGCT with TSMC [185].

For patients presenting with CS I pure post-pubertal teratoma without a somatic malignant component, surveillance provides comparable survival outcomes to primary RPLND [186]. However, subtype discrepancies in primary diagnostic of post-pubertal teratoma are not infrequent. When present they consist in addition of subtype and involve secondary somatic type of malignancy in 83% of cases. As such, central review by expert genitourinary pathologist is recommended when teratoma is diagnosed in the orchidectomy specimen [187].

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

Summary of evidence	LE
Lymphovascular invasion increases the risk of relapse.	2a
The relapse rate with active surveillance is up to 50%, depending on LVI status.	2a
The relapse rate in patients who receive adjuvant chemotherapy with BEP (x 1 cycle) is up to 3%.	2a
Adjuvant chemotherapy with BEP is superior to adjuvant RPLND in terms of the risk of relapse.	1b
A risk-adapted approach, based on lymphovascular invasion is feasible.	2b
The acute toxicity of one cycle adjuvant BEP is low.	1b

Recommendations	Strength rating
Inform patients 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.	Strong
Offer surveillance or risk-adapted treatment based on lymphovascular invasion (see below).	Strong
Discuss one course of cisplatin, etoposide, bleomycin as an adjuvant treatment alternative in patients with stage I non-seminomatous germ cell tumour if patients are not willing to undergo or comply with surveillance.	Strong

7.1.3.7   Risk-adapted treatment for clinical stage I non-seminomatous germ cell tumour based on vascular invasion

Recommendations	Strength rating
Stage IA (pT1, no vascular invasion): low-risk	
Offer surveillance if the patient is willing and able to comply.	Strong
Offer adjuvant chemotherapy with one course of cisplatin, etoposide, bleomycin (BEP) in low-risk patients not willing (or unsuitable) to undergo surveillance.	Strong
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 to highly selected patients only; those with contraindication to adjuvant chemotherapy and unwilling to accept surveillance.	Strong
Primary retroperitoneal lymph node dissection should be advised in men with post-pubertal teratoma with somatic malignant component.	Weak

Figure 1: Risk-adapted treatment in patients with clinical stage I non-seminoma NSGCT [188]*
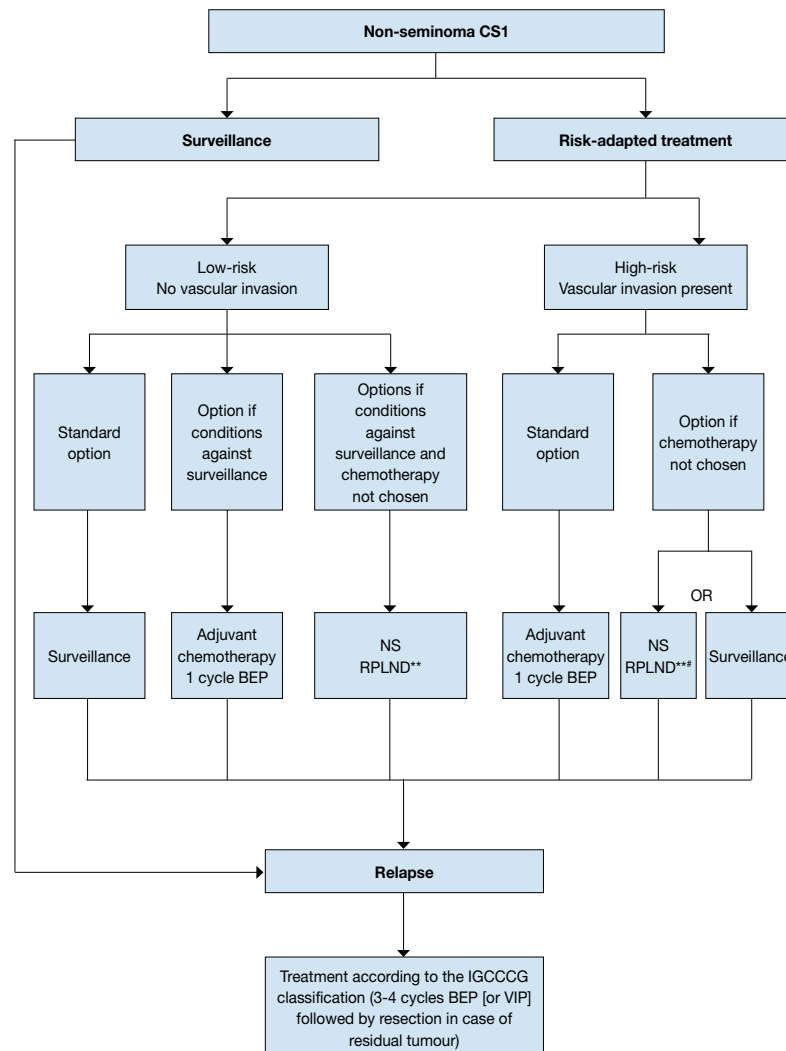
*   *Discuss all treatment options with individual patients, to allow them to make an informed decision as to their further care.*
** *In case of PS II, the rate of recurrence is higher and chemotherapy can be administered (max. 2 cycles).*
# *Primary retroperitoneal lymph node dissection should be advised in men with post-pubertal teratoma with somatic malignant component.*
BEP = cisplatin, etoposide, bleomycin; CS = clinical stage; IGCCCG = International Germ Cell Cancer Collaborative Group; NS = nerve-sparing; RLNPD = 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) [61];
*   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 [189].

7.2.1 Clinical stage I 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, repeat staging four weeks after orchidectomy is required [188].

Some patients may have stable but slightly elevated AFP or β-HCG and can be initially monitored. Treatment should be commenced if markers rise or when follow-up imaging demonstrates metastatic disease [188].

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-year disease-free survival of 87% and 85%, respectively, have been recently reported [190].

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 [188, 190]. 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 9-24% [191, 192]. Most reports describe large target fields and high doses. Further studies using more limited fields report similar rates of relapse [193]. 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 [191, 192]. Further dose reduction in stage IIA to 27 Gy is associated with a higher relapse rate of 11% [140, 193].

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 nineteen years reported a sevenfold higher all-cause mortality rate than mortality due to seminoma [194].

Currently, chemotherapy is the preferred alternative to radiotherapy for stage II seminoma. This entails three cycles of BEP as a preferred strategy, or four cycles of etoposide and cisplatin (EP) as an alternative in case of contraindications to bleomycin, or for older patients [195]. 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 [196], showed 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 [196]. 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 [196]. Radiation therapy may be considered in highly selected patients who are either elderly or have contraindications or difficulties tolerating systemic chemotherapy.

Single agent carboplatin, using three to four cycles at AUC 7 is not an alternative to standard EP or BEP chemotherapy for metastatic disease, due to the risk of failure (19%) or subsequent relapse (13%) at the site of initial nodal disease [197]. The same strategy utilising a higher dose of carboplatin, AUC 10, has also been reported in a trial [198] and a subsequent multi-institutional analysis [199]. The latter study comprised 216 patients and reported three-year PFS of 96.5% and five-year DSS of 98.3% comparable to standard regimens. Myelosuppression was the principal toxicity with 37% and 27% experiencing grade 3 or higher neutropenia and thrombocytopenia, respectively.

Primary RPLND has also been reported for CS II seminoma [200, 201]. Data from the National Cancer Data Base identified 155 men who underwent primary RPLND for CS II A/B reporting five-year OS of 92%. Specific trials are addressing the role of primary RPLND compared to standard options.

Figure 2: Treatment options in patients with seminoma clinical stage IIA and B*
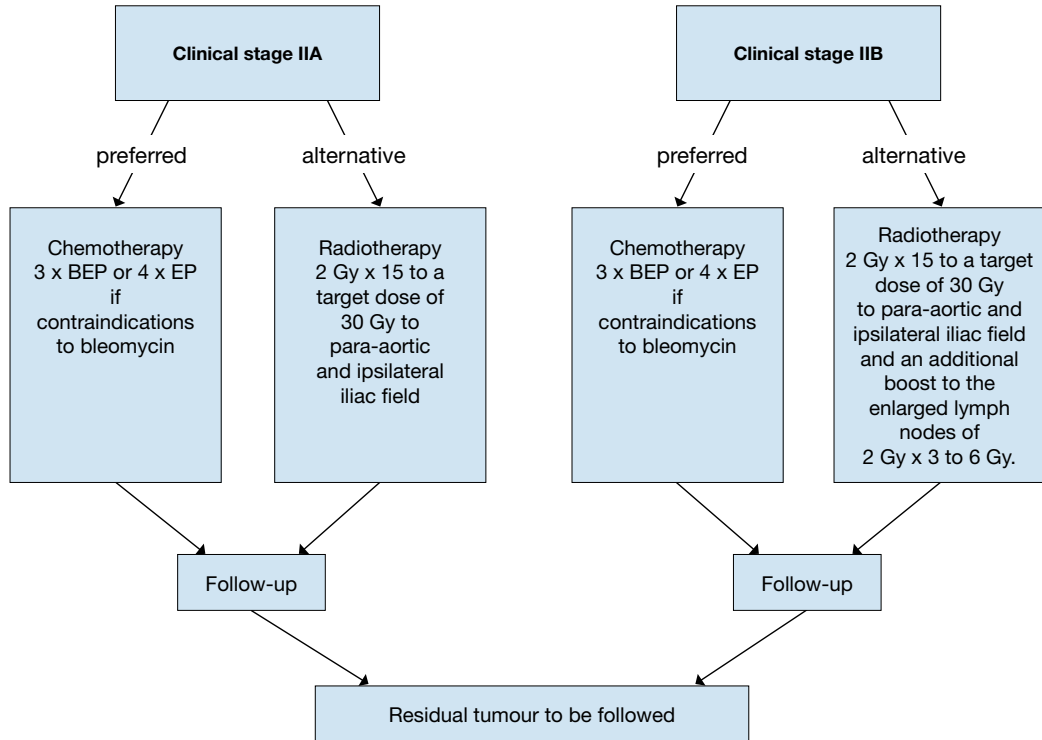
When enlarged retroperitoneal lymph nodes are < 2 cm and with normal markers, treatment should not be initiated unless metastatic disease is unequivocal based on biopsy, increasing nodal size/number, or subsequent marker rise.
BEP = cisplatin, etoposide, bleomycin; EP = etoposide, cisplatin.

7.2.2.2   Stage II A/B non-seminoma (NSGCT)
Management of CS II A/B NSGCTs encompasses patients in which retroperitoneal nodal disease is present at diagnosis, or appears with relapse following initial surveillance for stage I disease, or marker negative patients with equivocal radiological findings.

All cases of CS 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 CS 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 [202, 203]. Initial surveillance may be considered, 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.

Patients down-staged 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 PS II disease were cured with RPLND alone without additional adjuvant chemotherapy [204]. 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 [156]. Relapse, usually outside the retroperitoneum, occurs in 30% of patients with PS II treated with RPLND alone, requiring systemic treatment according to risk-group.

However, adjuvant chemotherapy to reduce the risk of relapse in PS II may be discussed with the patient. Key issues include the risk of overtreatment in about 70% of cases, the need of adequate follow-up to monitor the usually predictable pattern of relapse with minimal but not absent risk of late relapses, the higher relative risk of more intensive therapy in case of relapse, and the possibility of considering quality of surgery and extent of disease (positive lymph node-ratio) as a predictive factor to orient decision. When the choice is for adjuvant chemotherapy, standard treatment is BEP for a maximum of two cycles, but a recent single-centre study of 150 patients undergoing two cycles EP following RPLND and PS II disease reported excellent outcomes with a ten-year relapse-free survival of 98% [205].

Primary RPLND for CS IIA/B disease with elevated markers is not recommended outside a specific study in a referral centre [202, 203].

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 should be performed 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
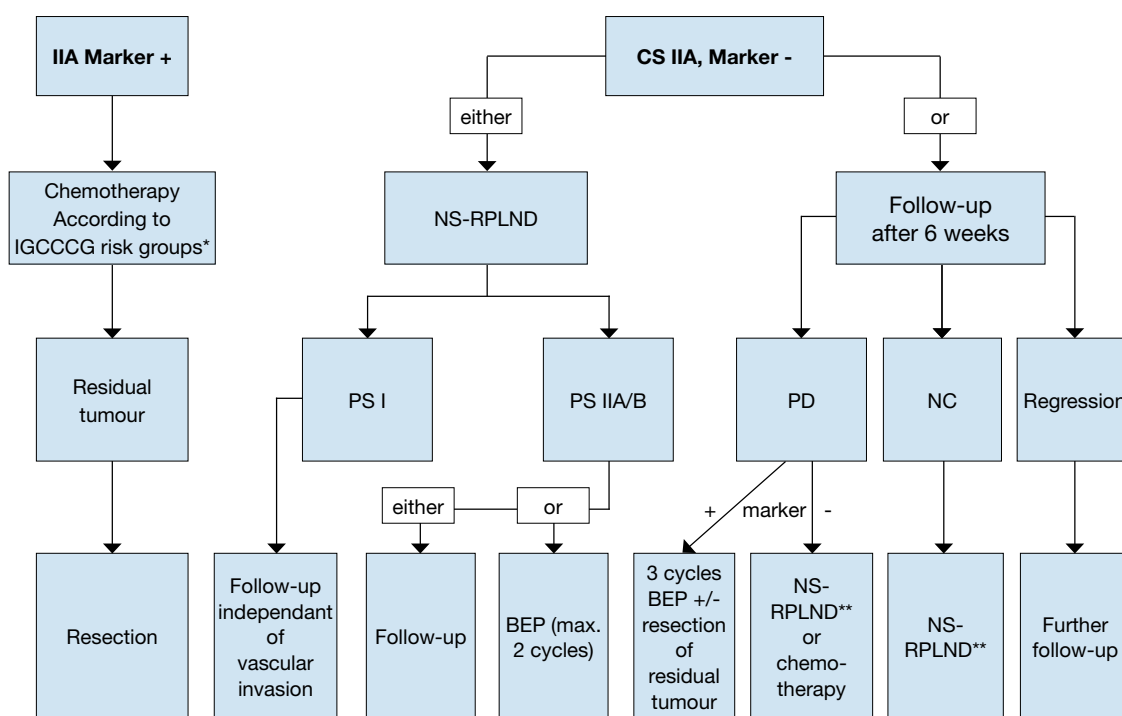
* Most of the patients will be good prognostic group (BEP x3 or PE x4).
** In case of PS II A/B patient can be followed-up or receive adjuvant chemotherapy (maximum of 2 cycles).
BEP = cisplatin, etoposide, bleomycin; NS = nerve-sparing; RPLND = retroperitoneal lymph node dissection;
PS = pathological 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, studies available suggest that a cisplatin-based regimen should be preferred to carboplatin chemotherapy [206].

As data from the GETUG S99 trial indicates that EP x 4 results in cure in almost all cases of good-prognosis SGCTs [207], 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 [208].

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 the recommended options, although no RCT has focused specifically on this rare group of patients (see Table 4.3).

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 (Table 4.3.), is BEP x 3 (Table 7.1) [61]. This regimen is superior to cisplatin, vinblastine, and bleomycin (PVB) in patients with advanced disease [208].

The available randomised controlled data support the equivalence of three or four 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 8.2.6). The difference in toxicity between the three- and five-day regimes reached clinical relevance when BEP x 4 was given [209, 210]. Based on these data the BEP x 3 and a five-day regimen is strongly recommended in the good-prognosis risk group.

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

Drug	Dosage	Duration of cycles
Cisplatin	20 mg/m^2	Days 1-5*
Etoposide	100 mg/m^2	Days 1-5
Bleomycin	30 mg	Days 1, 8, 15

Plus, hydration.

Patients with a clear contraindication to bleomycin may receive EP x 4 [209]. 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 [195, 211]. Additionally, a RCT has 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 [195]. 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) [212]. 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.

Therapy should be given without reduction of the doses at 21-day intervals. Cytopenias on day fifteen of BEP are common; however, Bleomycin on day fifteen should be given irrespective of neutropenia or thrombocytopenia. Delaying a chemotherapy cycle is justified only in the presence of severe granulocytopenia < 500/mm^3 or thrombocytopenia < 50,000/IU. Mild 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 [213].

7.2.3.1.4   Intermediate-prognosis risk group - non-seminomatous germ cell tumour
With this group the available data support BEP x 4 as standard treatment [214].

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, one standard treatment consists of BEP x 4. Four cycles of cisplatin, etoposide and ifosfamide (PEI) has similar efficacy, but is more myelotoxic [215]. Several RCTs have shown no advantage in OS for upfront high-dose chemotherapy (HDCT) in the overall poor-prognosis patient group [216, 217].

Patients with a slow tumour marker decline after the first or second cycle represent a prognostically inferior subgroup [217, 218]. There are several ways to calculate slow tumour marker decline with an example available at: https://www.gustaveroussy.fr/calculation-tumor/NSGCT.html.

A trial in poor prognosis NSGCT demonstrated that intensifying treatment with dose-dense chemotherapy improves PFS in patients with an early unfavourable tumour marker decline [219]. The trial was not powered

to estimate overall survival. 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 (dose-dense) chemotherapy regimen [219]. Further prospective trials/registries are planned to validate this approach. Additional patient groups with an unfavourable prognosis on standard treatment are mediastinal primary non-seminoma and patients with brain metastases at initial diagnosis [220, 221]. These may also be candidates for upfront intensified treatment, preferably in a prospective study.

As a matched-pair analysis comparing high-dose to conventional treatment resulted in a better survival rate [222], 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 [129, 223]. 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 an initial 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 [223, 224].

Patients with extended pulmonary infiltration are at risk for acute respiratory distress syndrome (ARDS). They should receive only two to three days of EP, followed by standard chemotherapy when the risk of ARDS has passed (typically after ten days). Management of patients with advanced disease in high-volume centres is associated with improved survival and is consequently recommended [225].

Table 7.2: Level of evidence for prognostic group and treatment

Prognostic group IGCCCG	Treatment	LE
Good (SGCT and NSGCT)	BEP x 3 or PE x 4	1b
Intermediate (SGCT and NSGCT)	BEP x 4 or PEI x 4	1b
Poor (NSGCT)	BEP x 4 or PEI x 4 if favorable marker decline	1b
	Dose escalation in selected cases with slow marker decline	1b

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 [226]. 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 [227]. Indwelling venous access devices (VADs) have been identified as TEE risk factors [228].

Recent RCTs have assessed the risks and benefits of thromboprophylaxis in ambulatory cancer patients receiving chemotherapy and report a relative risk reduction of 30-60% in venous thromboembolic events (VTE) but a doubling of bleeding risk [229-232]. Based on these results, the most recent ASCO Clinical Practice Guideline Update recommends thromboprophylaxis with apixaban, rivaroxaban, or low molecular weight heparin (LMWH) to cancer patients with a high risk of VTE and low risk of bleeding [233]. Metastatic germ cell tumour (mGCT) patients were under-represented in all trials and; thus, it is not clear whether this recommendation applies to this group although retrospective data suggests a similar efficacy of VTE prophylaxis [234].

Several retrospective cohort studies published mGCT specific VTE and bleeding risks as well as potential VTE risk factors. In the largest multi-centre cohort study, men with mGCT showed a cumulative VTE incidence of 11% and < 1% were fatal [235]. Nearly all VTEs occurred shortly prior to or during the first 90 days of commencing chemotherapy [235]. Bleeding was observed in 0.5% (95% CI: 0.02–1%) of men not on thromboprophylaxis, 2.5% (95% CI: 0.3–8.8%) of men on thromboprophylaxis and 3.6% (95% CI: 1.2–8.3%) of patients fully anticoagulated because of VTE [235]. A cumulative VTE incidence of 5% during or after chemotherapy occurred in men without any risk factors for VTE. This would translate to a number needed to treat of 32-55 depending on the assumed efficacy of thromboprophylaxis [228]. If thromboprophylaxis resulted in a similar VTE risk reduction and bleeding risk increase observed in other cancers [229-232], VTE may decrease by a relative risk of 30-60%. This would translate to an absolute risk reduction from 5-10% to 2-5% with the absolute risk of bleeding increasing from <1% to approximately 2-3% [228].

Critics of thromboprophylaxis in mGCT argue that the interobserver reliability of detecting incidental asymptomatic VTEs on staging scans is poor and some asymptomatic VTEs may only represent artifact. Nevertheless only <1% mGCT have asymptomatic VTEs detected on staging scans [228]. Furthermore, incidental VTEs may not truly be asymptomatic as affected patients may have mild symptoms such as cough and fatigue which may be misinterpreted because of the underlying cancer or its associated treatment.

Advocates of thromboprophylaxis contend that reduction of VTE risk may improve outcomes as VTE can be fatal directly or indirectly in <1% of cases. An immediate initial consequence of VTE is the need for therapeutic anticoagulation which is associated with a higher risk of clinically significant bleeding [228, 236] including critical areas particularly intracerebral and complicate post chemotherapy surgery. Venous thromboembolic events may also result in long term complications including post-thrombotic syndromes leading to venous leg ulceration and chronic pain. Similarly, pulmonary embolism can impair right ventricular function and pulmonary arterial pressure that does not resolve in 10-30% of patients, with up to 4% ultimately developing chronic symptomatic pulmonary hypertension [237]. These complications all reduce QoL and increase lifetime healthcare costs.

Based on disease specific VTE risk assessments in numerous retrospective cohort studies and the long life-expectancy of mGCT patients, the European Association of Urology Testis Cancer Guideline panel has discussed a recommendation regarding thromboprophylaxis. All members agreed that men with mGCTs undergoing chemotherapy are at high-risk for VTE and low-risk of bleeding. Although several mGCT specific VTE risk factors have been described in the literature [238] only data from retrospective cohorts is available, VTE outcome definitions are heterogeneous and, in most of the studies, only univariable analyses without external validation were performed. Given the apparent high VTE incidence and only non-validated VTE risk factors, the panel preferences were divided between those panel members that favoured thromboprophylaxis in all men and those panel members that restricted thromboprophylaxis to men with certain risk factors. For the final guideline recommendation, 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. Therefore, RCTs or well conducted prospective cohort studies with an adequate sample size allowing adjusting for potential confounders and numerous risk factors are needed to clarify the indication for thromboprophylaxis.

However, no randomised trials are underway to answer those questions and the only two retrospective studies analysed the risk benefits of thromboprophylaxis reported contradictory results [234, 239]. Both studies only had a limited number of men with VTE limiting the ability to account for known confounders which limits the conclusion from both studies.

A generic statement in the TC Guideline should remind clinicians about the high VTE incidence and to prescribe thromboprophylaxis after balancing the risk and benefits. Additionally, the majority of the panel agreed that a central venous-access device 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 [228].

Thromboprophylaxis includes either LMWH or oral thromboprophylaxis (apixaban 2.5 mg bid or rivaroxaban 10 mg qd) starting before chemotherapy and continued for at least 90 days. Thromboprophylaxis should only be prescribed if no drug interactions or significant risk factors for bleeding are present. Although GCT patients specific risk factors for bleeding are ill-defined the personal experience of panel members and case reports suggest that men with organ infiltration, cerebral metastases and/or significantly elevated β-hCG levels suggestive of choriocarcinoma are at a higher risk of bleeding.

Summary of evidence	LE
Thromboembolic events occur more frequently in male patients with GCTs receiving chemotherapy than in young males under chemotherapy for other cancers.	2b
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).	2b

Recommendations	Strength rating
Balance the individual patients' potential benefits and risks of thromboprophylaxis during first-line chemotherapy in men with metastatic germ cell tumours.	Weak
Avoid use of central venous-access devices during first-line chemotherapy whenever possible.	Weak

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 [240, 241]. If markers decline, but metastases progress on imaging, induction therapy must be completed followed by early resection [242].

With initial disease progression following induction (primary cisplatin refractory), patients should be switched to experimental drug trials [243]. 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 [244, 245].

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 [246-249]. 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 more than 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 may be useful, but it is optional [55, 56].

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 [57]. 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) [250-252]. 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 [251]. Ejaculation may be preserved in some of these cases [253].

7.3.2.2 Non-seminoma

Following first-line BEP chemotherapy, only 6-10% of residual masses contain active cancer, 50% have post-pubertal teratoma, and 40% comprise of necrotic-fibrotic tissue only [254]. Fluorodeoxyglucose-positron emission tomography is not indicated to re-stage patients following chemotherapy [50, 52, 53]. With complete radiological remission, RPLND is not indicated [255, 256].

Usual timing for restaging is three to four weeks after the beginning of the last cycle. 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 [257-260]. 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. It is difficult to distinguish between a true residual node below 10 mm and a complete remission, and many authors consider these situations as equivalent. Residuals containing cancer or teratoma are possible, but the vast majority of patients have fibro-necrotic tissue only [261]. So far, post-chemotherapy RPLND in case of residuals < 10 mm

or complete remission is an option [262], but the alternative option is an observation protocol with recurrence risk of 6-9% depending on the follow-up duration [255, 256]. 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 [256]. Eight of the twelve relapsing patients were cured with subsequent treatment. These cases should be discussed on individual basis taking into account the orientation and expectations of the patient.

Patients after salvage chemotherapy or HDCT in first or subsequent salvage situations harbour vital tumour at a much higher rate [263]. Surgery is therefore indicated in salvage patients even with residual masses < 1 cm [255, 256].

When resection is indicated bilateral nerve-sparing RPLND is the standard option. Ipsilateral template resection avoids contralateral nerve dissection and leads to improved functional results together with favourable clinical results although mapping studies describe the risk of missed contralateral disease [264].

In men with post-chemotherapy residuals with a residual diameter < 5 cm [265], as well as unilateral lymph node metastases on pre- and post-chemotherapy CT scans, left-sided tumours only require para-aortic resection whereas right-side tumours need paracaval and interaortocaval resection down to the iliac arteries [266, 267].

Indications for ipsilateral template resection after first-line chemotherapy represent men with a residual tumour volume < 5 cm and ipsilateral metastatic disease on pre- and post-chemotherapy scans. The mere resection of the residual tumour (so called lumpectomy) should not be performed [256, 260, 261, 263, 265, 267, 268].

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 [269-271]. Experience with robot-assisted laparoscopic RPLND remains limited [272] and atypical recurrences have been reported, and occur more often, with this approach [167].

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 [257]. 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 [273]. Resection of contralateral pulmonary lesions is not mandatory when pathologic examination of the lesions from the initial side show complete necrosis. Discordant histology between lung sites, however, may occur in up to 20% of cases [274, 275].

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 in order to achieve radical resection (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 [276, 277]. In patients with intermediate- or poor-risk and residual disease > 5 cm, the probability of vascular procedures is as high as 20% [278]. This "maximal" 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 [279]. Nevertheless, patients treated within such centres benefit from a significant reduction in peri-operative mortality from 6-0.8% [280]. In addition, specialised urologic surgeons are capable of reducing the local recurrence rate from 16-3% with a higher rate of complete resections [281].

7.3.3.2 *Salvage and desperation surgery*

Surgery of resectable disease after salvage treatment remains a potentially curative option in 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 [282]. Also, even with extensive salvage chemotherapy, surgery remains a fundamental tool to achieve durable complete remissions in up to 20% of patients [283, 284].

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 [285].

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) [268]. 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 [286]. 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 [287].

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 [288]. 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 7.3) [289, 290]. 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 [291]. For methodological reasons, this trial design can no longer be considered state of the art.

Table 7.3: Standard PEI/VIP, TIP and GIP salvage chemotherapy (interval 21 days)

Regimen	Chemotherapy agents	Dosage	Duration of cycles
PEI/VIP	Cisplatin*	20 mg/m^2	Days 1-5
	Etoposide	75-100 mg/m^2	Days 1-5
	Ifosfamide†	1.2 g/m^2	Days 1-5
TIP	Paclitaxel	250 mg/m^2 xx	24 hour continuous infusion day 1
	Ifosfamide†	1.5 g/ m^2	Days 2-5
	Cisplatin*	25 mg/m^2	Days 2-5
	Alternative schedule		
	Paclitaxel	175 mg/m^2	Day 1, 3 hour infusion
	Ifosfamide†	1.2 g/m^2	Days 1-5
	Cisplatin*	20 mg/m^2	Days 1-5
GIP	Gemcitabine	1000 mg/m^2	Day 1 + 5
	Ifosfamide	1200 mg/m^2	Days 1-5
	Cisplatin	20 mg/m^2	Days 1-5

* Plus, hydration.
† Plus, mesna protection.
xx An MRC schedule uses paclitaxel at 175 mg/m^2 in a 3 hour infusion [290].

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 [189]. 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 cisplatinum-based chemotherapy [189]. 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 7.4 illustrates these five risk groups and the corresponding two-year PFS and three-year OS rates [189]. Several recent trials have validated this scoring system [292-295]. As in first-line therapy, the prognostic impact of tumour marker decline applies in the salvage setting [296]. While progression to induction chemotherapy was negative for OS, prior use of paclitaxel was not significantly associated with a negative outcome [297].

A secondary analysis of the IPFSG cohort (n = 1,600 patients) showed an improvement of about 10-15% 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 [292]. 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 [298]. It is clearly of the utmost importance that these rare patients with relapse are treated within clinical trials and at specialised centres.

Table 7.4: The International Prognostic Factors Study Group Score for seminoma and non-seminoma that relapse after cisplatin-based first-line chemotherapy [189]

Points	-1	0	1	2	3
Variable					
Histology	Seminoma	Non-seminoma			
Primary site		Gonadal	Retroperitoneal		Mediastinal
Response		CR/PRm-	PRm+/SD	PD	
PFI		> 3 months	≤ 3 months		
AFP salvage		Normal	< 1000	1000	
hCG salvage		< 1000	1000		
LBB		No	Yes		

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 7.5: 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 [190]

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

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 [293]. 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 25-45% in this setting. Cisplatin re-challenge in association with gemcitabine and paclitaxel may be considered in patients with adequate renal function [299]. 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 15-20% chance of long-term cure [283, 300].

Various targeted agents have generally failed in refractory disease, including immune checkpoint inhibitors [292-298, 301]. 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 (more than 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 [54]. According to a pooled analysis, this occurs in 1.4% and 3.2% of seminoma and non-seminoma patients, respectively [302]. Interestingly, in a population-based study all late-relapsing seminoma patients had viable GCT [303]. 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 [202]. 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 [202, 304]. 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 [305]. 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 [306].

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 (30-50%) and even poorer when a site of recurrent disease (five-year survival-rate is 2-5%) [307, 308]. 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 [45].

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 [45]. 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 [309]. 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

Summary of evidence	LE
In the NSGCT good-prognosis-risk group (IGCCG), BEP x 3 is superior to other chemotherapy regimens. Toxicity is lower when treatment is delivered in five-day regimes rather than three-day regimes.	1b
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.	1b
In pathological stage II NSGCT disease, RPLND performed in specialised centres without adjuvant chemotherapy results in 73-81% of long-lasting remissions.	2b
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.	1b
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 despite no benefit being observed for OS.	1b
Following first-line BEP chemotherapy, 6-10% 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 < 1 cm. Currently there is no accurate prognostication method of histology.	2b
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.	2a
In metastatic seminoma stage ≥ IIC, primary chemotherapy with BEP, tailored to the IGCCCG risk group, has proven superior to Carboplatin based chemotherapy.	1b
Fluorodeoxyglucose-positron emission tomography has a high NPV in patients with post-chemotherapy seminoma residual masses (> 3 cm) when performed more than two months after chemotherapy.	2b

Recommendations	Strength rating
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).	Strong
Nerve-sparing retroperitoneal lymph node dissection 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.	Weak
Repeat staging after six weeks before making a final decision on further management should be considered in patients with small volume (CS IIA < 2 cm) marker-negative NSGCT.	Weak
Treat metastatic NSGCT (stage ≥ IIC) with an intermediate prognosis with four cycles of standard BEP	Strong
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.	Weak
Perform surgical resection of visible (> 1 cm) residual masses after chemotherapy for NSGCT when serum levels of tumour markers are normal or normalising.	Strong
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.	Weak
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).	Strong

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 a European Society for Medical Oncology (ESMO) consensus conference [310].

Both CT and MRI can be used to evaluate the retroperitoneum, pelvis and inguinal regions for sites of metastatic disease from TC [311]. Magnetic resonance imaging benefits from an absence of ionising radiation but is more time consuming and less readily available than CT [312]. Given the frequency of follow-up, over a number of years some studies have estimated a risk of up to 1 in 300 of second malignancy related to CT imaging follow-up alone [51], although more recent dose saving protocols and limitations on field of view will have mitigated this somewhat. Nevertheless, this risk could be excluded by the use of MRI for follow-up.

Both CT and MRI rely predominantly on size cut-offs for evaluation given the excellent spatial resolution of both modalities, with morphological assessment for features such as necrosis and irregular shape an adjunct. Sensitivity and specificity vary according to the size cut-off used [311]. However, studies have shown comparable excellent results between CT and MRI with up to 98% sensitivity on MRI for the detection of retroperitoneal nodal metastases in TGCT [313]. It has, however, been demonstrated that reader experience is important when interpreting images [314]. In the setting of TGCT, one study demonstrated decreased sensitivity for detection of retroperitoneal nodal disease on MRI when reported by a trainee radiologist with sensitivity of detection of 80% [51]. However, experienced radiologists in the same study again achieved sensitivity for detection of nodal disease of 97% with good interobserver agreement. It was therefore suggested that if MRI is

to be used instead of CT for follow-up this be done in centres/units with oncological radiologists who routinely report CT and MRI in patients with TGCT rather than general radiologists who may only occasionally see such imaging. Consequently, MRI of the abdomen can be used as an alternative to CECT in experienced centres [315].

Regarding the use of US examination 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 [310].

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 [303]. 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 up to 50% elevated tumour markers are present in both seminoma and NSGCTs [303, 316]. 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)

Modality	Year 1	Year 2	Year 3	Years 4 & 5	After 5 years
Tumour markers ± doctor visit	2 times	2 times	2 times	Once	Further management according to survivorship care plan
Chest X-ray	-	-	-	-	
Abdominopelvic computed tomography (CT)/magnetic resonance imaging	2 times	2 times	Once at 36 months	Once at 60 months	

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

Modality	Year 1	Year 2	Year 3	Year 4 & 5	After 5 years
Tumour markers ± doctor visit	4 times*	4 times	2 times	1-2 times	Further management according to survivorship care plan
Chest X-ray	2 times	2 times	Once, in case of LVI+	At 60 months if LVI+	
Abdominopelvic computed tomography (CT)/magnetic resonance imaging	2 times	At 24 months**	Once at 36 months***	Once at 60 months***	

*   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.
*** Recommended by 50% of the consensus group members.
LVI+ = Lymphovascular invasion present

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

Modality	Year 1	Year 2	Year 3	Year 4 & 5	After 5 years
Tumour markers ± doctor visit	4 times	4 times	2 times	2 times	Further management according to survivorship care plan**
Chest X-ray	1-2 times	Once	Once	Once	
Abdominopelvic computed tomography (CT)/magnetic resonance imaging (MRI)	1-2 times	At 24 months	Once at 36 months	Once at 60 months	
Thorax CT	1-2 times*	At 24 months*	Once at 60 months*	Once at 60 months*	

*	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 [317]. 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 [159], whereas others highlight the importance of patient autonomy and consider the prospect of avoiding salvage treatment with long-term toxicities appealing [318]. 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. This observation is confirmed by the absence of excess mortality or late toxicities between stage I non-seminoma patients randomised to either primary RPLND or one cycle of adjuvant BEP [319].

During follow-up, patients should be screened and treated for known risk factors such as hypertension, hyperlipidaemia, and testosterone deficiency. Adverse health outcomes (AHOs) are more commonly found in TC patients who received chemotherapy than those cured by surgery alone. Further, modifiable risk factors do contribute to AHOs like hypertension and noise exposure to hearing impairment or smoking to Raynaud phenomenon [320]. Therefore, a healthy lifestyle should be promoted during the follow-up consultations. Adverse health outcomes are associated with unemployment, which is found clearly increased in TCSs as compared to a male normative population [321]. 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 [54, 322].

### 8.2.1	*Second malignant neoplasms (SMN)*

Metachronous contralateral TC represents a particular SMN as it consists of a GCT. Further, cisplatin-based chemotherapy approximately reduces the risk of a subsequent contralateral TC as compared to surgery only [323, 324]. Second malignant neoplasms of different histologic origin usually occur after the first ten years and are considered to be induced by chemo- and/or radiotherapy [322]. Testicular cancer is 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 [325]. 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) [325].

The risk for solid SMN increases with younger age at radio- or chemotherapy [322]. Radiotherapy-related SMN are primarily localised within, or close to, the radiotherapy field (colon, stomach, pancreas, bladder, and the urinary tract) [322]. A remarkably clear radiation-dose relationship to gastric- and pancreatic cancer has been demonstrated [326].

Modern cisplatin-based chemotherapy has been found to be associated with a 40% increased risk of a solid SMN [327]. A relationship between cumulative dose of cisplatin and second SMN, especially in the GI tract, has been noted [328]. 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 [325]. Second malignant neoplasms were identified in 9.4% of Swedish TC survivors, with half these cancers considered uncommon in men in their 40s [329]. Survival was 40% in TC survivors with a SMN as opposed to 80% in those without [329].

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 [330]. Among 24,900 US TCSs, one out of six (16.9%) developed a solid SMN after 30 years of observation time [331].

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 [332]. Among 24,900 US TCSs, the risk of developing leukaemia, mostly AML, after chemotherapy was 2.7 fold increased [331]. The risk of AML seems to be related to both the dose of cisplatin and etoposide. Doses of etoposide exceeding 2 g/m^2 have been shown to increase the subsequent risk of AML [333]. 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, fewer 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 [334].

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) [335]. 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 [335]. Bleomycin-induced lung toxicity may affect 7-21% of patients in the long term, resulting in death in 1-3% [336]. Testicular cancer survivors who received high cumulative cisplatin doses and/ or pulmonary surgery, have a poorer pulmonary function than those cured with surgery alone [325]. Intriguingly, long-term pulmonary complications were associated with the cumulative cisplatin doses but not with the dose of bleomycin [337]. 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 [338]. 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 [339]. 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 [339]. 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 [340].

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 [341]. 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 [341].

8.2.5 Cardiovascular toxicity
Thromboembolic events (mostly venous) occur more frequently in GCT patients receiving chemotherapy than in other young male adults treated with chemotherapy for other cancers [226]. Low-dose heparins used during the course of chemotherapy may prevent the onset of thromboembolic events [234], though level 1 evidence is lacking. Mortality from cardiovascular disease (CVD) is higher in TCSs than in the general population (OR: 5) [227, 342, 343]. Furthermore, CVD is more common in chemotherapy-treated TCSs than in those who underwent surgery only [182, 344]. Feldman et al., applied the Framingham Risk Score (FRS) on 787 TC survivors and compared the results with controls [345]: 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 [345].

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 [227].

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 ten 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) [227].

Metabolic syndrome, a strong risk factor for CVD and its components, hypertension, obesity and hypercholesterolaemia, increases with treatment intensity (OR: 9.8) [343, 346, 347]. 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 [348]. Circulating residual serum platinum might exert endothelial stress and thereby possibly lead to hypertension [349]. Furthermore, exposure to circulating platinum is associated with paraesthesia, hypogonadism, and hypercholesterolaemia as well as major vascular events [234].

In a 30-year follow-up, chemotherapy treated TCSs used more often anti-hypertensive or lipid-lowering medications as controls. The TCSs' diastolic heart function was impaired as compared to the controls, whereas no difference was found regarding systolic- or valvular function or prevalence of arrhythmias [350]. The finding of increased vascular stiffness of TCSs more than 20 years after chemotherapy suggests accelerated vascular aging; thus, highlighting the need for intensive cardiovascular risk management [351].

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 [352]. However, HIIT during cisplatin-based chemotherapy might be harmful as a planned study on 94 patients was closed early after recruiting nineteen patients and the finding of severe CVD complications among three out of nine patients undergoing HIIT [353]. 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, Neurotoxicity & Ototoxicity
Chemotherapy-related Raynaud-like phenomena were reported before the introduction of cisplatin and are usually attributed to bleomycin [354, 355]. 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 [356].

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 [343, 357]. 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 [349]. 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 [358].

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 [343]. Encouragingly, hearing impairment deteriorated not considerably after the first decade after chemotherapy and quite normal speech perception tests 30 years after treatment indicated a limited clinical relevance of the high-frequency hearing

loss [359, 360]. 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 [357]. A significant association between Glutathione S-transferases (GST) genotypes and the risk of cisplatin-induced ototoxicity has been demonstrated [361, 362].

A comprehensive clinical and genome-wide analysis of multiple severe cisplatin-induced neurotoxicities has revealed a correlation between neurotoxicity, ototoxicity, and Raynaud phenomena in TCSs [363]. Of particular interest was the observation that certain TCSs seem to be particularly vulnerable to develop multiple and serious neuro-otological toxicities. TCSs without toxicities comprised the 196 controls and TCSs with two to three severe toxicities represented the 104 cases. Only three controls (1.5%) reported fair/poor health as compared to 18 (17.5%) of the cases.

Patients with multiple severe neurotoxicities were also more likely to report symptoms of peripheral motor neuropathy. Current smoking had a clearly negative impact on severe neurotoxicities. No genome-wide significant SNPs for developing severe cisplatin-induced neurotoxicities were identified. The authors concluded that metastatic TC patients with good-risk features should preferably be treated with 3 x BEP instead of 4 x EP in order to avoid neurotoxicities by the fourth cycle of cisplatin [363].

8.2.7 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 [364]. Impaired brain networks may underlie poorer performance over time on both specific and non-specific cognitive functions in TC survivors following chemotherapy.

8.2.8 Nephrotoxicity
Cisplatin-based chemotherapy may lead to long-term renal dysfunction in 20-30% of TCSs [234, 344, 346]. In TC patients, reduced renal excretion of cisplatin and bleomycin might increase the risk of other toxicities, e.g., bleomycin-related pneumonitis [365, 366]. A comprehensive assessment of 1,206 Danish TCSs, however, did not reveal a significant association between chemotherapy-induced impaired renal function and other toxicities [342]. Renal recovery was poor after five or more cycles of BEP as compared to after BEP x 3 [347]. 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 [367]. Genomic markers are related to the risk of cisplatin-induced nephrotoxicity [368]. How these results will impact selection and/or modification of chemotherapy remains to be seen.

8.2.9 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 [343, 365, 369, 370]. 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 [371].

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 [348]. Wiechno *et al.*, could show a decline in testosterone and an increase in LH and FSH within one year after treatment for unilateral TC [372]. 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 [373].

Walsh *et al.*, reported a RCT demonstrating a benefit of testosterone replacement therapy in young male survivors of TC, 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 [374]. 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 [375].

Erectile dysfunction (OR: 4.2) has been significantly associated with chemotherapy in a recent multicentre study [343]. Of 481 North American TCSs treated with modern cisplatin-based chemotherapy, 38% were hypogonadal (defined as on testosterone substitution or serum testosterone level ≤ 3.0 ng/mL) [376]. Hypogonadism was associated with the number of adverse health outcomes and its risk increased with age and obesity [377].

8.2.10 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 [377]. 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%) [210]. Of note, the prevalence of CF increased from 15-27% during a ten-year period in long-term TCSs [378].

8.2.11 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 [210]. When comparing three or four cycles of BEP in good-risk patients, all outcomes favour treatment with three courses [209]. 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 [181].

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 [379]. 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 [380].

Among 2,479 Danish long-term TCSs, higher anxiety was reported by those who experienced bilateral TC as compared to unilateral TC [381]. For a subset of approximately 11% of TCSs, 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 [382]. Kreiberg *et al.,* recommend stress symptoms at follow-up visits in order to timely identifyTCSs requiring support [383]. This recommendation is supported by the finding of an increased mental health service utilisation as compared to healthy controls [384]. Testicular cancer survivors who developed bilateral TC had a higher degree of anxiety compared to survivors of unilateral TC but did not report otherwise impaired QoL [385].

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 [385].

Testicular cancer survivors were more likely to have high levels 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 nineteen years from diagnosis [383].

9. RARE ADULT PARA- AND TESTICULAR TUMOURS

Less than 5% of testicular cancers are unrelated to GCNIS and lack 12p alterations [386, 347]. These tumours are rare with available literature based on case reports and small retrospective series. Given the rarity of non-germ cell para-/testicular cancers, referral of these cases to specialist units for multidisciplinary discussion including central image and pathology review is highly recommended. 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 tumours 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 [387].

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 [387].

Spermatocytic tumours are rare, occur exclusively in the testis and do not normally show elevated tumour markers [387]. Previously named "spermatocytic seminomas" they have been recently reclassified as spermatocytic tumours [387]. As those tumours cannot be differentiated from seminoma GCT by frozen section analysis, radical orchiectomy is the standard treatment option. Outcomes after testis-sparing surgery or adjuvant treatment is unknown and therefore not recommended [388]. Metastatic disease is very rare and typically presents at or soon after initial diagnosis with limited survival [388].

9.3 Sex cord-stromal tumours
Sex cord–stromal tumours are relatively uncommon but represent the second largest group of primary testicular tumours after GCT's [389]. As a small subset of these tumours are clinically malignant, a thorough evaluation of those morphological features associated with malignancy should be performed to guide management. Two or more of the following features are associated with malignant potential: size > 5 cm, infiltrative borders, cytological atypia, three or more mitotic figures per ten high-power fields, vascular invasion and necrosis [389].

9.3.1 Leydig cell tumours
Leydig cell tumours comprise about 4% of adult testicular tumours. These mainly present as localised tumours with metastases occurring in only 2.5% [390]. They may present with hormonal manifestations, including gynaecomastia and more rarely are accompanied by Cushing's Syndrome [389]. With testis-sparing surgery a local recurrence rate of 7% has been reported although no adjuvant treatment options can be recommended [391]. Several risk factors for metastatic disease have been proposed which may guide image-guided follow-up intensity [391]. Survival of men with metastatic disease is poor but occasional responses to surgical and systemic treatment have been reported [391].

9.3.2 Sertoli cell tumours
Sertoli cell tumours account for approximately 1% of testicular neoplasms [389]. The risk of metastases is unclear. With testis-sparing surgery a local recurrence rate of < 1% has been reported although no adjuvant treatment options can be recommended [392]. Several risk factors for metastatic disease have been proposed which may guide image guided follow-up intensity [392]. Survival of men with metastatic disease is poor although response to surgery has been occasionally reported [392].

9.3.3 Granulosa cell tumour
Granulosa cell tumours, which include adult and juvenile variants, are extremely rare and metastatic potential is unclear [389]. With testis-sparing surgery a local recurrence rate of 5% has been reported although no adjuvant treatment options can be recommended [393]. Whereas metastatic disease has never been reported in juvenile granulosa cell tumours, men with adult type may occasionally present with metastatic disease [393]. Survival of men with metastatic disease is poor although rare instances of response to surgical or systemic treatment has been reported [393].

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 [389, 394].

9.3.5 ***Paratesticular tumours of the epididymis or spermatic cord***
The majority of epididymal masses are benign cystic or inflammatory conditions. Solid epididymal tumours are rare and comprise numerous benign and neoplastic lesions. In the only population-based analyses [395], the majority of neoplastic lesions of the epididymis or spermatic cord were sarcomas, metastases from other organs or primary adenocarcinomas similar to proportions reported in institutional studies [396, 397]. Benign lesions, which may comprise the majority in clinical practice include lipomas, adenomatoid tumours leiomyomas and papillary cystadenomas.

Robust criteria to differentiate between neoplastic benign lesions have not been defined although ultrasonography with or without fine needle aspiration [398] MRI [49, 399] or surgical exploration with frozen section analyses or histopathological confirmation can be considered. No clear recommendation can be provided regarding surgical approach, extent of resection and neo- or adjuvant treatment can be given.

9.4   Mesothelioma of the tunica vaginalis testis
Mesothelioma of the tunica vaginalis testis is a rare but aggressive disease [400]. Beside older age, larger tumour size, presence of necrosis, angiolymphatic invasion or a high mitotic index the only modifiable risk factors represents local recurrence. Therefore, aggressive local treatment with hemiscrotectomy is recommended. No clear recommendation can be given regarding adjuvant treatment. In case of metastatic disease, the median overall survival is a few months only and multimodal treatment could be considered.

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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.

This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

12. CITATION INFORMATION

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EAU Guidelines. Edn. presented at the EAU Annual Congress Amsterdam 2022. ISBN 978-94-92671-16-5.

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