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 germ-cell tumours (GCTs) and sex cord/gonadal stromal tumours.

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

1.2 Panel composition

The EAU Guidelines Panel on Testicular Cancer consists of a multidisciplinary group of clinicians including, urologists, oncologists, a radio-oncologist and a pathologist. Members of this Panel have been selected, based on their expertise, to represent the professionals treating patients suspected of having 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 European Association of Urology (EAU) published the first guidelines on TC in 2001. Since 2008, the Testicular Cancer Guidelines contains a separate chapter on testicular stromal tumours. This document presents a limited update of the 2019 publication. Review papers have been published in the society's scientific journal European Urology, the latest version dating to 2015 [1].

*1.4.2 **Summary of changes***

For the 2020 Testicular Cancer Guidelines, new references have been added throughout the document. Key changes in this publication include:

- A table on minimal sets for pathology reports of neoplasia of the testis has been included in the 2020 version.
- Citations relating to a number of low quality papers (SEER database on epidemiology retrospective biased fluorodeoxyglucose-positron emission tomography [FDG-PET] scan and non-validated prognostic models) have been removed from the text. As per previous versions of the text, some small phase II studies in the relevant text section on second relapse are included since there are few publications addressing this rare and desperate clinical scenario.
- Several old citations have been replaced with newer reports.
- Beyond the Scope search, a few relevant articles identified in the months after the search have been included.
- Text and tables throughout the guideline have been rephrased and revised.
- The panel is aware that a new International Germ Cell Cancer Collaborative Group (IGCCCG) classification for metastatic tumours has recently been presented. This new classification stratifies more accurately the population of patients with metastatic TC than the one proposed in 1997 and used in these guidelines. However, as of December 2019, there is no "peer reviewed" publication or external validation of the proposed new classification. Once published, these will be incorporated into the 2021 version of the guideline.
- Recommendations on abdominal, thorax and brain imaging at diagnostic and staging have been reviewed by a consultant radiologist.

2. METHODS

For the GCT section, new and relevant evidence has been identified, collated and appraised through a structured assessment of the literature. The search was limited to studies representing high levels of evidence only (i.e. systematic reviews with meta-analysis, randomised controlled trials (RCTs), and prospective non-randomised comparative studies) published in the English language. The search was restricted to articles published between June 2018 and April 2019 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 1,256 unique records were identified, retrieved and screened for relevance. Fifty-four new references have been included in the 2020 print. 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

This document was subjected to peer review prior to publication in 2015. The 2020 guidelines will be peer-reviewed following publication with reviewer comments forming the basis for the 2021 revision.

2.2 Future goals

- A new chapter on "Incidentally diagnosed testicular masses" will be included in the 2021 revision of the Guidelines.
- A systematic review on the topic of "Quality of care of testicular cancer" will be explored by the panel. The main research question will investigate the quality of care for patients undergoing post-chemotherapy retroperitoneal lymph node dissection (RPLND).
- A preliminary literature search will be performed to explore the evidence on minimally invasive RPLND.
- An Individual Patient Data (IPD) prognostic factor study on the value of pathological factors in clinical stage I seminoma testis patients under active surveillance has been approved by the Guidelines Office Methods Committee. Five international centres are collaborating on the study. Data analysis and outcomes are expected in 2021.

3. EPIDEMIOLOGY, AETIOLOGY & PATHOLOGY

3.1 Epidemiology and Aetiology

Testicular cancer represents 1% of male neoplasms and 5% of urological tumours, with three to ten new cases per 100,000 males/per year in Western societies [6]. Its incidence has increased during recent decades particularly in industrialised countries [7, 8]. At diagnosis, 1-2% of cases are bilateral and the predominant

histology is GCT (90-95% of cases) [6]. Peak incidence is in the third decade of life for non-seminoma and mixed GCTs, and fourth decade for pure seminoma.

Genetic changes have been described in patients with TC. A specific genetic marker – an isochromosome of the short arm of chromosome *12 – (i12p)* – is pathognomonic of all types of adult GCTs [9] as well as germ cell neoplasia *in situ* (GCNIS). Alterations in the *p53* locus have been identified in 66% of cases of GCNIS [10] and an association between genetic polymorphism in the PTEN tumour suppressor gene and the risk of TC have recently been described [11]. A deregulation in the pluripotent programme of foetal germ cells (identified by specific markers, *M2A, C-KIT* and *OCT4/NANOG*) is likely to be responsible for the development of GCNIS and germ cell neoplasia. In line with this, genome-wide association studies (GWAS) have revealed several single nucleotide polymorphisms (SNPs) markers associated with an increased risk of developing TC, in particular at 15q21.3 [12]. That said, current genomic studies do not show evidence for a major single high-penetrance TC susceptibility gene [13]. There is overlap in the development to seminoma and embryonal carcinoma, as shown by genome-wide expression analysis and detection of alpha-fetoprotein (AFP) mRNA in some atypical seminoma [14, 15].

Epidemiological risk factors for the development of TC are components of the testicular dysgenesis syndrome, which encompasses cryptorchidism, hypospadia, decreased spermatogenesis evidenced by sub- or infertility [16, 17], familial history of testicular tumours among first-grade relatives and the presence of a contralateral tumour or GCNIS [9, 16, 18-22].

3.2 Histological classification

The recommended pathological classification shown below is based on the 2016 update of the World Health Organization (WHO) pathological classification [23].

1. **Germ cell tumours**
   - Germ cell neoplasia *in situ* (GCNIS)
2. **Derived from germ cell neoplasia *in situ* (GCNIS)**
   - Seminoma
   - Embryonal carcinoma
   - Yolk sac tumour, post-pubertal type
   - Trophoblastic tumours
   - Teratoma, post-pubertal type
   - Teratoma with somatic-type malignancies
   - 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) [24].

Table 4.1: TNM classification for testicular cancer (adapted from UICC, 2016, 8th edn.) [24]

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 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 greatest dimension; or more than 5 nodes positive, none more than 5 cm; or evidence or 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 [25].*
*** AJCC eighth edition considers the hilar soft tissue invasion as pT2, while the discontinuous involvement of the spermatic cord is considered as pM1 [25].*

4.2 UICC 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.) [24]

Stage grouping				
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 of 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 [26, 27]. True stage IS (persistently elevated or increasing serum marker levels after orchiectomy) is found in about 5% of non-seminoma patients [26].

4.3 The International Germ Cell Cancer Collaborative Classification for metastatic Testicular Cancer

In 1997, the International Germ Cell Cancer Collaborative Group (IGCCCG) defined a prognostic factor-based staging system for metastatic TC based on identification of clinically independent adverse factors. This widely-used classification uses histology, location of the primary tumour, location of metastases and pre-chemotherapy serum tumour marker levels as prognostic factors to categorise patients into 'good', 'intermediate' or 'poor' prognosis (Table 4.3) [28].

Table 4.3: Prognostic-based staging system for metastatic germ cell cancer (IGCCCG) [26]*

Good-prognosis group	
Non-seminoma (56% of cases) 5-year PFS 89% 5-year survival 92%	*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 (90% of cases) 5-year PFS 82% 5-year survival 86%	*All of the following criteria:* • Any primary site • No non-pulmonary visceral metastases • Normal AFP • Any hCG • Any LDH
Intermediate-prognosis group	
Non-seminoma (28% of cases) 5-year PFS 75% 5-year survival 80%	*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 (10% of cases) 5-year PFS 67% 5-year survival 72%	*All of the following criteria:* • Any primary site • Non-pulmonary visceral metastases • Normal AFP • Any hCG • Any LDH
Poor-prognosis group	
Non-seminoma (16% of cases) 5-year PFS 41% 5-year survival 48%	*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).*

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

5. DIAGNOSTIC EVALUATION

5.1 Physical examination

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

5.2 Imaging

5.2.1 ***Ultrasonography of the testes***

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

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

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

In order to distinguish between benign and malignant lesions, diverse modalities of US have been used (B-mode, dynamic contrast enhanced, real time elastography, and shear wave elastography) in an investigational mode in small cohorts [35-38]. So far, the results are preliminary and not sufficiently mature to provide clinical recommendations.

5.2.2 ***Computerised tomography (CT)***

Contrast enhanced computerised tomography (CECT) is the most sensitive means to evaluate the thorax, abdomen and pelvis for TC staging [39]. Contrast enhanced CT 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 of 66.7% (range 37-100%), 95.2% (range 58-100%, 87.4% (60-100%), 73.4% (67-100%) and 83% (range 71-100%), respectively [39].

Sensitivity decreases and specificity increases with increasing lymph node size. As such, pooled sensitivity decreases to 37% and specificity increases to 100% for nodes ≥ 10 mm. For nodes ≥ 4 mm pooled sensitivity is 93% and specificity 58% [39]. Using a 10 mm short-axis lymph node diameter as a cut-off yielded a high specificity (97%), a moderate sensitivity (59%) and false-negative rate of 20% in the retroperitoneum [40]. Note should be taken of the expected patterns of nodal spread in TC when evaluating small and borderline nodes.

Chest CT was evaluated in three studies in the systematic review by Pierorazio *et al.* [39]. It presents a median sensitivity, specificity, PPV, NPV and accuracy of 100% (range 95-100%), 92.7% (range 89-97%), 67.7% (range 25-84%), 100% (range 99-100%) and 93% (range 91-97%), respectively. Computerised tomography of the chest is more sensitive but less specific than chest X-ray (CXR) in thoracic staging. Nevertheless, potential harms of chest CT imaging in low-stage seminoma should be taken into consideration [39].

In patients with equivocal masses (< 2 cm) in the retroperitoneum (doubts on stage I) or chest and negative tumour markers, restaging after 6-8 weeks rather than treatment initiation is advisable.

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

5.2.3 ***Magnetic resonance imaging (MRI)***

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

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

Magnetic resonance imaging has a primary role in the detection of brain metastasis. Whilst both CECT and MRI are key image modalities for the detection of brain metastasis, MRI is far more sensitive than CECT, though it does requires some expertise [39, 46, 47]. In the absence of specific reports on comparative accuracy of TC brain metastasis by CECT or MRI, extrapolation of data from other cancer-related brain metastases indicates that if available, or when CECT is contraindicated (e.g. iodine contrast allergy), MRI should be used to screen for brain metastases [46].

Magnetic resonance imaging of spine is advisable in patients with symptoms or equivocal staging on CT [47].

*5.2.4 **Fluorodeoxyglucose-positron mission tomography (FDG-PET)***

There is no evidence to support the use of FDG-PET for initial staging and follow-up of TC [39, 48-50].

Fluorodeoxyglucose-positron emission tomography is only recommended for seminoma patients with post-chemotherapy residual masses > 3 cm (largest diameter) to assess FDG activity [51]. However, it should not be performed before two months after completion of the last cycle of chemotherapy. The NPV for active tumours is > 90% [52, 53]; however, the PPV ranges from 23% to 69% [52-54]. Thus, for a positive FDG-PET the possibility of residual seminoma is of the order of 20%, and false-positive results are common (up to 80% of lesions are only-necrotic tissue) [52, 54]. Given the low PPV (necrosis, fibrosis, inflammation and benign tumours were also associated with positive FDG activity) caution is advised on initiating active therapy driven by positive findings in FDG-PET-CT [54].

*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 lactate dehydrogenase LDH should be determined before and after orchidectomy as they predict germ cell cancer histology supporting the diagnosis of TC [55]. Alphafetoprotein and β-hCG are increased in 50-70% and in 40-60% of patients with NSGCT, respectively, and about 90% of NSGCT present with a rise in either AFP or β-hCG at diagnosis [29, 56]. Only 30% of pure seminomas can present or develop an elevated β-hCG level during the course of the disease [55]. Overall serum tumour markers have a low sensitivity and high false positive rates and normal marker levels do not exclude the diagnosis of GCT [56]. Lactate dehydrogenase is a less specific marker, its serum level being proportional to tumour volume. Its level may be elevated in 80% of patients with advanced TC [56].

Recent interest has been given to miRNAs as potential new biomarkers for TC diagnosis. The preliminary evidence revealed higher discriminatory accuracy than conventional markers [57-60]. Before miRNAs can be considered for use in routine clinical practice, issues around laboratory standardisation and availability of the test need to be resolved.

*5.3.2 **Serum tumour markers after orchidectomy***

Serum levels of AFP, β-hCG and LDH are used for TC prognostic stratification after orchidectomy [28]. 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 [55, 56] The persistence or increase of elevated serum tumour markers following orchidectomy indicates the likely presence of metastatic disease. 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 markers levels immediately before initiation of systemic treatment [28].

Tumour markers should be routinely used for follow-up as indicators of recurrence, although the precise frequency of testing is unclear [61].

Following orchiectomy, preliminary results suggest that miRNAs may indicate metastatic disease. Further studies are required to verify its value in the detection of occult metastases [59, 62, 63].

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.

*5.4.2 **Testis-sparing surgery***

Testis sparing surgery (TSS) may be attempted in patients with a solitary testis and is often used to preserve fertility and hormonal function. Testis sparing surgery should only be offered together with frozen section examination (FSE) because FSE has shown to be reliable and highly concordant with final histopathology [64, 65]. Nevertheless, patients should be informed about the risk of completion orchidectomy in case of incorrect FSE. Patients should be aware that only limited data about the oncological safety of TSS is available when TC is present [66].

In cases of small or indeterminate testicular masses with negative tumour markers, where possible patients should be offered TSS when feasible, to avoid overtreatment of potentially benign lesions and to preserve testicular function. Currently, there is no evidence supporting any size cut-off for a testicular lesion to be safely followed-up. Patients should be informed and the physician must be aware that cancer can be found even in sub-centimetre masses [67, 68], thus obtaining histology is mandatory.

*5.4.3 **Insertion of testicular prosthesis***

Testicular prosthesis should be offered to all patients receiving unilateral or bilateral orchiectomy [69]. The prosthesis can be inserted during the follow-up or at orchidectomy without adverse consequences, including infection [70].

*5.4.4 **Contralateral biopsy***

Contralateral biopsy has been advocated to rule out the presence of GCNIS [71].

Whilst routine policy in some countries [72], the low incidence of GCNIS and contralateral metachronous testicular tumours (up to 9% and approximately 2.5%, respectively) [73, 74], the morbidity of GCNIS treatment, and the fact that most metachronous tumours are low stage at presentation, it is controversial to recommend routine contralateral biopsy in all patients [75, 76]. 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 [77-79]. Patients should be informed that a testicular tumour may arise despite a negative biopsy [80]. When indicated, a two-site surgical testicular biopsy is the technical procedure recommended [79].

5.5 Pathological examination of the testis

The recommendations for reporting and handling the pathological examination of a testis neoplasia are based on the recommendations of the International Society of Urological Pathology (ISUP) [81-84].

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 [81]:
  - Presence or absence of peri-tumoural venous and/or lymphatic invasion;
  - 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 [82].
- If microscopic findings are not concordant with serum markers further block samples should be taken.
- pT category according to TNM 2016 [24]. In a multifocal seminoma the largest nodule should be used to determinate pT category.

Advisable immunohistochemical markers in cases of doubt are:

- Seminoma: CD-117 (c-kit), OCT ¾, Sall 4, PLAP
- GCNIS: CD-117 (c-kit), OCT ¾, Sall 4, PLAP
- Syncytiotrophoblast: β-hCG
- Embryonal carcinoma: CD30
- Yolk sac tumour: Glypican 3
- Sex cord gonadal tumours: Inhibin, calretinin

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 AJCC [84].

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 [84]. The dataset for handling pathological assessment of TC is shown in table 5.5.

Table 5.5: Recommended data set for reporting of neoplasia of the testis (modified from the International Collaboration on Cancer Reporting [84]**.**

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), b-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 maximun 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

5.6 Screening

There are no high-level evidence studies supporting screening programs. It has not been shown that screening asymptomatic patients has greater accuracy for detecting TC at more curable stages; stage and prognosis have been shown to be directly related to early diagnosis [85, 86].

In the presence of clinical risk factors, and especially in patients with a family history of TC, family members and the patient should be informed about the importance of physical self-examination [87].

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 [88, 89]. Up to 24% of TC patients are azoospermic and almost 50% have abnormal sperm counts (oligozoospermic) before treatment [89].

Treatment for TC, including orchidectomy, may have a negative impact on the reproductive function [90]. Chemotherapy and radiation treatment can both impair fertility; although, long-term infertility is rare after radiation therapy and is dose-cumulative-dependent after chemotherapy [91-93]. Spermatogenesis usually recovers one to four years after chemotherapy [94]. In CSI, 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 [95].

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 [96].

If cryopreservation is desired, sperm banking should be offered before orchidectomy, maximising the chances of fertilisation and avoiding the risk of having a non-functioning remaining testicle after surgery. If not offered before orchidectomy, it should be undertaken prior to chemotherapy or RT [91-93, 96-98].

In patients with bilateral orchidectomy or low testosterone levels after treatment of GCNIS, life-long testosterone supplementation is necessary [99].

Chemotherapy and radiation therapy are both teratogenic. Therefore, contraception must be used during treatment and for at least six months after its completion [100].

For more detailed information, the reader is referred to the EAU Guidelines on Sexual Reproductive Health [101].

5.8 Guidelines for the diagnosis and staging of testicular cancer

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 orchiectomy taking into account half-life kinetics.	Strong
Perform orchiectomy 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 (CT) scan (chest, abdomen and pelvis) in patients with a diagnosis of TC. If iodine allergy or other limiting factors perform abdominal and pelvic magnetic resonance imaging (MRI).	Strong
Perform MRI of the brain (or brain CT 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.	Strong
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
Offer biopsy of the contralateral testis to patients with TC and at high-risk for contralateral germ cell neoplasia *in situ*.	Strong

6. PROGNOSIS

6.1 Risk factors for metastatic relapse in clinical stage I

With stage 1 seminoma, tumour size and stromal invasion of the rete testis have been identified as predictors for relapse in a pooled analysis of retrospective data [102]. Absence of both factors indicates a low risk of recurrence (6%) [103]. Whilst the original analysis was not supported by a further retrospective report [104], some prospective series [105-107] 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 [108, 109]. 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 [108, 109].

For non-seminoma stage I, invasion of the primary tumour into blood or lymphatic vessels (LVI) is the most reliable single predictor of occult metastatic disease [82, 110]. The percentage of embryonal carcinoma within a tumour may enhance the positive- and negative predictive value of LVI [110]. 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** [108]	**Non-seminoma** [82]
• Pathological risk-factors	• Tumour size • Invasion of the rete testis	• Lympho-vascular invasion in peri-tumoral tissue

7. DISEASE MANAGEMENT

Chemotherapy results in excellent cure rates in TC due to their chemosensitivity, particularly with cisplatin based regimens [111]. 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 [112, 113]. In clinical trials poor prognosis patients, overall survival (OS) relates to the number of patients treated at the participating centre (worse if < 5 patients enrolled) [114]. 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 [115].

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

7.1 Stage I Germ cell tumours

7.1.1 ***GCNIS***

If GCNIS is diagnosed, local radiotherapy (18-20 Gy in fractions of 2 Gy) should be offered in the case of a solitary testis [93, 116-118]. Testicular radiotherapy in a solitary testis will result in infertility and increased long-term risk of Leydig cell insufficiency [93]. Fertile patients who wish to father children may delay radiation therapy and be followed by regular testicular US [79]. Chemotherapy is significantly less effective and the cure rates are dose-dependent [116].

If GCNIS is diagnosed and the contralateral testis is healthy, the options for management are orchidectomy or close observation, as the five-year risk of developing TC is 50% [119].

7.1.2 ***Seminoma clinical Stage***

Despite modern staging procedures, approximately 15% of clinical stage I seminoma patients have subclinical metastatic disease, usually in the retroperitoneum, and will relapse after orchiectomy alone [104, 107, 120, 121].

The decision regarding adjuvant treatment should always be based on a thorough discussion with the patient, taking into account the described advantages and disadvantages, as well as the individual situation of the patient.

7.1.2.1 Surveillance

Several prospective non-randomised surveillance studies have been conducted over the past decade. Previous analysis from four studies showed an actuarial five-year relapse-free rate of 82.3% [122]. The largest series (> 1500 patients) reported an overall relapse rate in unselected patients of 16.8% [122]. The conditional risk of relapse is of the order of 12.2% - 20.3% at five years, with most relapses occurring in retroperitoneal lymph nodes during the first two years [123-125].

Very low recurrence rates of 6% have been described in patients with low-risk features, including tumours size < 4 cm and no stromal rete testis invasion. In contrast, others report a five year conditional risk of relapse of 12.2% with tumours < 3 cm in size [106, 125].

The cancer-specific survival (CSS) rate reported with surveillance performed by specialist centres is over 95% for clinical stage I seminoma [122-124, 126]. The principal limitation of surveillance is the need for more intensive follow-up, especially with repeated imaging examinations of the retroperitoneal lymph nodes.

7.1.2.2 Adjuvant chemotherapy

A joint trial by the Medical Research Council (MRC) and the European Organisation for Research and Treatment of Cancer (EORTC), which compared one cycle of carboplatin area under curve (AUC) 7 with adjuvant RT, showed no significant difference in recurrence rate, time to recurrence and survival after a median follow-up of four years [127-129]. Therefore, adjuvant carboplatin therapy using a dosage of one course of AUC 7 is an alternative to RT or surveillance in clinical stage I seminoma [123, 127, 128]. Retrospective data on patients who relapsed after adjuvant treatment with carboplatin showed that these seem to be later than those with active surveillance [130]. Median time to relapse was reported to be 19 months, with 15% occurring later than three years after adjuvant treatment. The majority of patients relapsing after adjuvant carboplatin can be successfully treated with a standard cisplatin-based chemotherapy regimen appropriate to their disease stage [130].

7.1.2.3 Adjuvant radiotherapy

Seminomas are extremely radiosensitive tumours. Adjuvant radiotherapy to a para-aortic (PA) field or to a PA and ipsilateral field (PA and ipsilateral iliac nodes), with a total dose of 20-24 Gy, reduced the relapse rate to 1-3% [131-133]. Adjuvant irradiation of supra-diaphragmatic lymph nodes is not indicated.

With regard to the irradiation dose, a large MRC RCT of 20 Gy versus 30 Gy PA radiation in clinical stage I seminoma showed non-inferiority in terms of recurrence rates [132]. The rate of severe radiation induced long-term toxicity is less than 2%. Moderate chronic gastrointestinal (GI) side-effects were seen in about 5% of patients with moderate acute GI toxicity in about 60% [131]. The main concern with adjuvant radiotherapy is the increased long term risk of radiation-induced secondary non-germ cell malignancies [134-137].

A scrotal shield should be considered during adjuvant radiotherapy in order to prevent scattered radiation toxicity in the contralateral testis [134].

7.1.2.4 Risk-adapted treatment

Using testicular tumour size > 4 cm and stromal rete testis invasion, patients with clinical stage I seminoma may be subdivided into low- and high-risk groups for relapse following radical orchidectomy. Patients with and without both risk factors have a 32% and 6% risk of relapse, respectively. These risk factors were introduced based on an analysis of retrospective trials [88], and then confirmed in subsequent prospective studies [106, 107]. Two prospective trials based on these risk factors demonstrated the feasibility of a risk-adapted approach. In a Spanish study including 227 men, patients without or with one risk factor were managed with surveillance, whilst the group with both risk factors present received two adjuvant courses of carboplatin, AUC 7 [106]. Although the median follow up was relatively short (34 months), the relapse rate with adjuvant treatment was reported at 1.4% [106].

A SWENOTECA trial included 897 patients [107]. Patients with no or one risk factor were offered surveillance, patients with both risk factors were offered one course of carboplatin, AUC 7. The final decision regarding adjuvant treatment was made by the individual patient. At a median follow up of 5.6 years patients without risk factors had a relapse rate of 4% with surveillance compared to 2.2% with adjuvant carboplatin. Overall, when one or both risk factors were present, 15.5% of the patients under surveillance relapsed whereas 9.3% of those receiving adjuvant carboplatin relapsed. Thirty-three per cent of relapses in patients who received adjuvant treatment occurred more than three years after orchidectomy and 3% more than five years [107].

With a risk reduction of 60% in patients with tumours with both risk factors present, the efficacy of one cycle of adjuvant carboplatin seems rather low, although the comparison with two adjuvant cycles of carboplatin is difficult because of small sample size and limited follow up in the Spanish study [106]. A currently recruiting SWENOTECA ABC trial compares the efficacy of one cycle of adjuvant carboplatin with one cycle of adjuvant cisplatin, etoposide, bleomycin (BEP) [138].

7.1.2.5 Guidelines for the treatment of stage I seminoma

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 a management option if facilities are available and the patient is compliant.	Strong

Offer one course at area under curve 7, if carboplatin 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. This option should be reserved for selected patients not suitable for surveillance and with contraindications to chemotherapy.	Strong

*7.1.3 **NSGCT clinical stage I***

Depending on risk factors, up to 50% of NSGCT patients with CS1 disease have subclinical metastases and will relapse during surveillance [110, 121, 125, 139]. This raises the issue of adjuvant chemotherapy, which should be considered on the basis of discussion with each patient about advantages and disadvantages of the options, as well as their individual circumstances and concerns.

7.1.3.1 Surveillance

Improvements in clinical staging and follow-up methods, as well as the availability of effective salvage treatment with cisplatin-based chemotherapy and post-chemotherapy surgery, have led to studies of close surveillance only after orchiectomy in CS1 NSGCT patients.

Overall, 14-48% of CS1-NSGCT patients undergoing surveillance recur within two years of orchidectomy. The largest reports of surveillance indicate a cumulative relapse risk in about 30% of CS1-NSGCT (five-year conditional risk of relapse 42.4% and 17.3 for high- and low-risk CS1-NSGCT respectively) [121, 122]. Of these, 92% present within the first two years [121, 122].

Approximately 35% of patients have normal levels of serum tumour markers at relapse, with 60% of relapses occurring in the retroperitoneum. Despite rigorous follow-up, 11% of relapsing patients will present with large-volume metastatic recurrent disease [121, 139].

The somewhat lower relapse rates reported from surveillance studies, compared with some series of patients staged by RPLND [140], may relate to selection bias with exclusion of high-risk cases or very early marker relapse 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 CSI non-seminoma as long as they are compliant and informed about the expected recurrence rate as well as the salvage treatment [139, 141, 142].

7.1.3.2 Adjuvant chemotherapy

Adjuvant chemotherapy with two courses of BEP was evaluated in a prospective MRC trial reported in 1996 [143]. Subsequently, adjuvant chemotherapy was mainly given to high-risk patients (LVI present) [143-145]. In these series, including 200 patients, some with a median follow-up of nearly 7.9 years [143], a relapse rate of only 2.7% was reported, with minimal long-term toxicity. Two cycles of cisplatin-based adjuvant chemotherapy do not seem to adversely affect fertility or sexual activity [146].

More recently, use of one cycle of adjuvant BEP has also resulted in low recurrence rates (2-3%) [147, 148]. Reduction from two to one cycle of BEP improves the risk-benefit ratio of adjuvant chemotherapy considerably. In light of equivalent CSS rates, including salvage strategies in large prospective trials with sufficient follow-up, one cycle of BEP is now the recommended strategy if adjuvant chemotherapy is considered [147, 148]. The very-long term (> 20 years) side effects of adjuvant chemotherapy, particularly cardiovascular, are yet to be fully defined which should be taken into consideration with decision making [149, 150].

7.1.3.3 Retroperitoneal lymph node dissection

In view of the high CSS rates of surveillance with salvage treatment in cases of relapse and the low relapse rates if adjuvant chemotherapy is chosen, the role of primary RPLND has diminished.

A randomised phase III trial compared two-year recurrence free survival with adjuvant BEP x 1 to RPLND favoured chemotherapy with recurrence free survival of 99.5% versus 91% [151]. The hazard ratio to experience a tumour recurrence with surgery compared to BEP x 1 was 8 [151]. No clinically relevant differences in quality of life (QoL) were detected [152].

In a multicentre setting, higher rates of in-field recurrences and complications have been reported with nerve sparing RPLND [151, 153]. This suggests that primary RPLND, when indicated or chosen, should be performed by an experienced surgeon in a specialist centre.

If retroperitoneal metastases are not found at RPLND (PS1), approximately 10% of patients will relapse at distant sites [110, 154], although more recent series report lower figures of pN+ cases and relapse [155]. Following RPLND about 18-30% of patients are found to have retroperitoneal lymph node metastases on RPLND, corresponding to pathological stage II (PS2) disease [153, 154]. In patients with active malignancy who are not treated with adjuvant chemotherapy, approximately 31% will experience recurrence [154].

Presence of LVI, predominant embryonal carcinoma, pT category and extranodal extensions of involved nodes all appear associated with an increased risk of recurrence with PS2 disease without adjuvant chemotherapy. The use of these further parameters, however, has yet to be clearly defined in clinical practice [154, 156].

Follow-up after RPLND is less demanding and costly than with surveillance due to the reduced need for CECT [157]. With primary RPLND, laparoscopic or robot-assisted RPLND appears feasible but cannot be recommended outside of a high-volume RPLND centres with appropriate minimally invasive expertise [158].

7.1.3.4 Risk-adapted treatment

A risk-adapted strategy is an alternative to universal surveillance patients with CS1 NSGCT. Risk-stratification is based on the presence of LVI. If a risk-adapted policy is applied, patients with LVI receive adjuvant chemotherapy with BEP whereas patients without LVI are recommended surveillance. A community based prospective study of 490 patients that received BEP x 1, showed a five-year relapse rate of 3.2% for LVI+ patients and 1.6% for LVI- patients. After a median follow up of 8.1 years the relapse rate was 2.3%, 3.4% and 1.3% for all, LVI+, and LVI-, respectively [147, 148]. These numbers imply that > 90% of relapses were prevented by adjuvant chemotherapy and, importantly, no relapses were observed later than 3.3 years.

It is, however, critical to remain aware of the possibility of slow-growing retroperitoneal teratomas after adjuvant chemotherapy [159].

Cost analyses comparing surveillance, RPLND and primary chemotherapy show different results among the reported studies, possibly because of differences in intensity and costs related to follow-up protocols [160]. With low-frequency follow-up CTs (a surveillance strategy which has been proven to be effective in non-seminoma CS1), the costs of follow up can be considerably reduced [161].

7.1.3.5 Teratoma with somatic-type malignancy

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

7.1.3.6 Guidelines for the treatment of clinical stage I non-seminomatous germ cell tumour

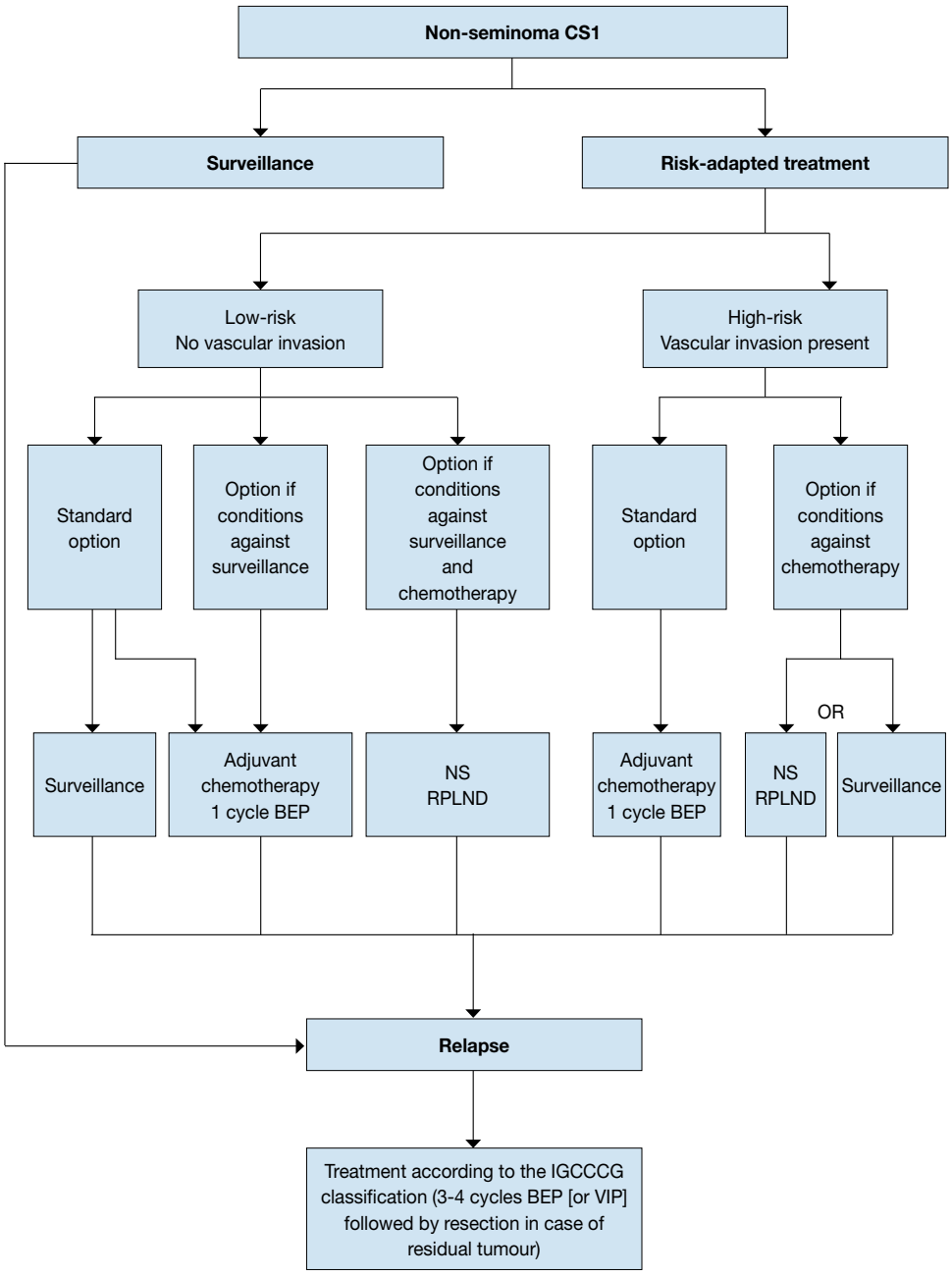
Recommendations	**Strength rating**
Inform patients with stage 1 non-seminomatous germ cell tumour (NSGCT) about all management options after orchiectomy (surveillance, adjuvant chemotherapy, and retroperitoneal lymph node dissection [RPLND]) including treatment-specific recurrence rates as well as acute and long-term side effects.	Strong
In patients with stage 1 NSGCT, offer surveillance or risk-adapted treatment based on lymphovascular invasion (see below).	Strong
If patients are not willing to undergo or comply with surveillance, offer one course of cisplatin, etoposide, bleomycin as an adjuvant treatment alternative since it has proven to be superior to RPLND in terms of recurrence rates.	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
In low-risk patients not willing (or unsuitable) to undergo surveillance, offer adjuvant chemotherapy with one course of cisplatin, etoposide, bleomycin (BEP).	Strong
Stage IB (pT2-pT4): high risk	
Offer primary chemotherapy with one course of BEP, or surveillance and discuss the advantages and disadvantages.	Strong
Offer surveillance to patients not willing to undergo adjuvant chemotherapy.	Strong

Offer nerve-sparing retroperitoneal lymph node dissection (RPLND) to highly selected patients only; those with contraindication to adjuvant chemotherapy and unwilling to accept surveillance.	Strong
Primary RPLND should be advised in men with teratoma with somatic-type malignancy.	Strong

Figure 1: Risk-adapted treatment in patients with clinical stage I non-seminoma NSGCT [163]*



**Discuss all treatment options with individual patients, to allow them to make an informed decision as to their further care.*

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) [28];
- 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 [164].

*7.2.1 **CS1S with (persistently) elevated serum tumour markers***

Serum tumour markers should be followed closely until levels fall into the reference ranges based on the expected half-lives for AFP and hCG. The clinical significance of persistently elevated LDH after orchidectomy in clinical stage I disease is unclear. If AFP or hCG increase or fail to return to normal levels after orchidectomy, US examination of the contralateral testicle must be performed.

Although some patients may have a persistent, slightly elevated but stable AFP or HCG, those with rising markers only after orchidectomy, require repeated imaging including extra-abdominal sites in order to detect and define sites of metastasis and to individually tailor treatment [163].

The treatment of true CS1S-NSGT should be the same as other good-prognosis metastatic non-seminoma (stage IIA/B). With this five and ten years disease-free survival of 87% and 85% have been recently reported [165].

*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 represent a clinical dilemma. These nodes may be benign or indicate true metastatic disease. In this situation observation for six to eight weeks with repeat staging imaging is recommended. Treatment should not be initiated unless metastatic disease is unequivocal based on biopsy, increasing nodal size/number, or subsequent marker rise [163, 166].

Standard treatment option for stage IIA/B seminoma has been radiotherapy, with reported relapse rates of 9-24% [167, 168]. Accumulating data on long-term morbidity, such as an increased risk of cardiovascular events and second malignancies following radiotherapy has raised concerns. One study with a follow up of 19 years reported a 7-fold higher all-cause mortality rate than mortality due to seminoma [169].

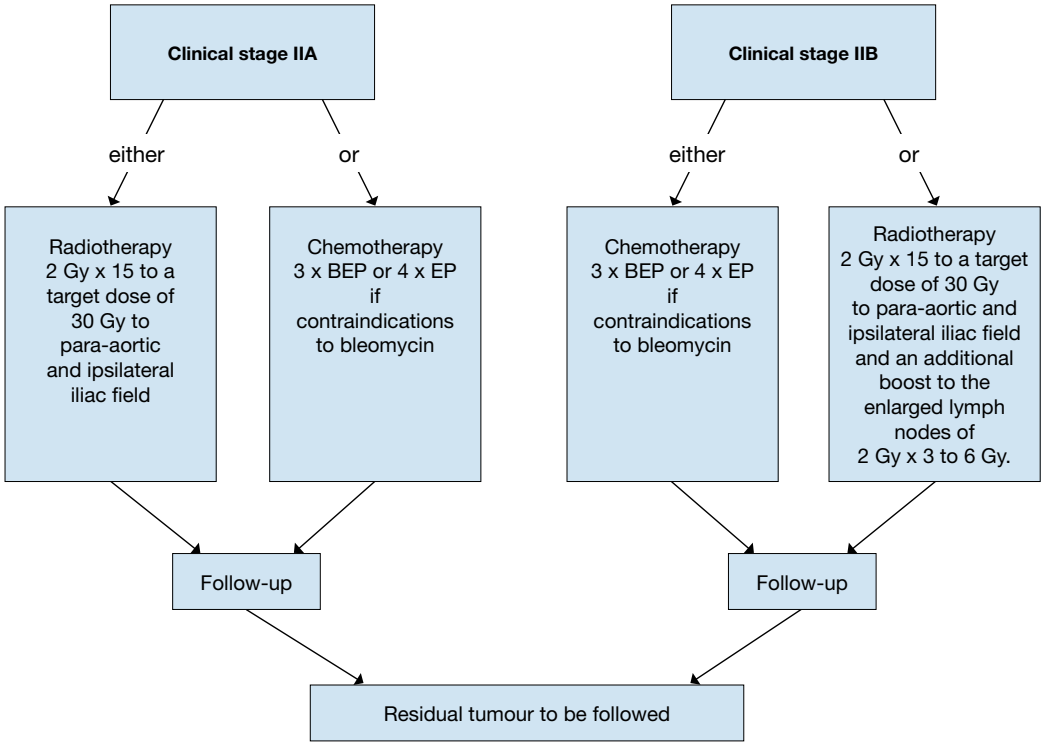
Most reports encompass patients irradiated with larger target volumes and higher doses, although recent studies with more limited radiotherapy fields report similar rates of relapse [170]. The radiation dose recommended in stage IIA and IIB is 30 Gy and 36 Gy, respectively, with the standard field encompassing the PA and ipsilateral iliac nodes. In stage IIB, the lateral borders should include the metastatic lymph nodes with a surrounding margin of 1.0-1.5 cm. This technique yields relapse-free survival rates in stage IIA and IIB of 92% and 90%, respectively [167, 168]. Dose reduction in stage IIA to 27 Gy has been associated with relapse rates of 11% [124, 170].

Currently, chemotherapy is the preferred alternative to radiotherapy for stage IIA/B. This entails three cycles BEP or four cycles of etoposide and cisplatin (EP) as an alternative in case of contraindications to bleomycin or for older patients. 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 [171], shows that radiotherapy and chemotherapy appeared to be similarly effective in both stages, with a non-significant trend towards greater efficacy for chemotherapy (HR: 2.17) in stage IIB seminoma [171]. 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 [171].

Single-agent carboplatin is not an alternative to standard EP or BEP chemotherapy for metastatic disease, with the risk of failure or relapse at the site of initial nodal disease [172].

Specific trials (e.g. including RPLND or involved field radiation combined with a single course of carboplatin chemotherapy) are addressing the role of treatment options with potentially lower toxicity compared to standard options of either radiotherapy or chemotherapy with three cycles of BEP.

Figure 2: Treatment options in patients with seminoma clinical stage IIA and B



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

7.2.2.2 Stage IIA/B non-seminoma

There is a general consensus that initial treatment should be chemotherapy in all advanced cases of NSGCT with the exception of stage IIA/B NSGCT disease consisting of post-pubertal teratoma without elevated tumour markers, which can be managed by primary RPLND [159, 173]. A recent large retrospective series reported 73% of long-lasting remissions following RPLND alone in selected patients who relapsed as stage II following surveillance for stage I non-seminoma [139].

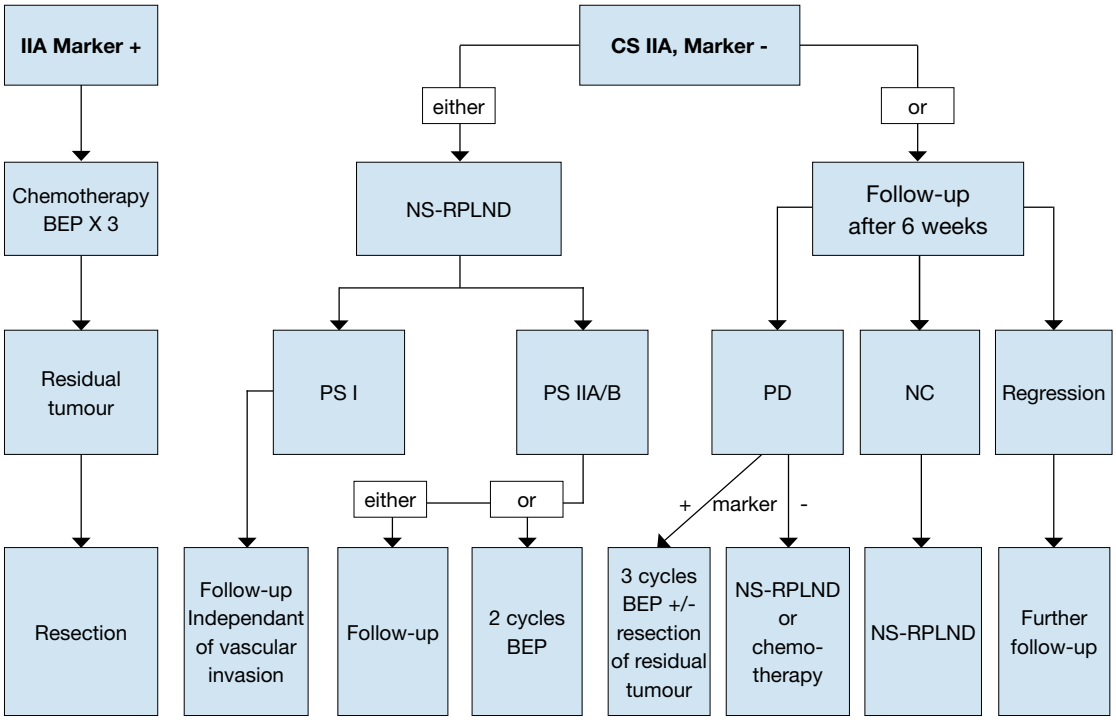
Initial surveillance may be considered in patients with “equivocal” (i.e. less than 2 cm, non-nodular shape) nodal disease and normal markers with early re-evaluation at six weeks. A shrinking lesion may be observed further. If the lesion is growing without a corresponding increase in the tumour markers AFP or β-hCG, teratoma should be considered. In this case nerve-sparing RPLND represents the first treatment option which should be performed by an experienced surgeon [173].

Patients with a growing lesion and a concomitant increase in the tumour markers 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).

When a marker negative stage IIA/B relapse is diagnosed two or more years following initial diagnosis, a CT- or US-guided biopsy should be advised to confirm the diagnosis of GCT relapse. A RPLND may be an alternative option. There is insufficient published data on PET scans in this situation to provide recommendations.

Primary chemotherapy and primary ‘nerve-sparing’ RPLND are comparable options in terms of oncological outcome, but early and long-term side-effects and toxicity are different, allowing for involvement of the patient in selecting the treatment of choice [174]. Following RPLND, PS-IIA or B, patients can be followed or receive two cycles of BEP. The cure rate with either approach will be close to 98% [175-177].

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



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 IIC and III)***

7.2.3.1 Primary chemotherapy

7.2.3.1.1 Good prognosis risk group - seminomatous germ cell tumour

For metastatic seminoma, only very limited data is available from RCTs, although studies suggest that a cisplatin-based regimen should be preferred to carboplatin chemotherapy [178]. As data from the French Groupe d'Etude des Tumeurs Genito-Urinaires (GETUG) S99 trial indicates that EP x 4 results in cure in almost all cases of good-prognosis SGCTs [179], this regimen 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 [180].

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

7.2.3.1.2 Intermediate prognosis risk group - seminomatous germ cell tumour

For patients with intermediate-risk seminoma, BEP x 4 or etoposide, cisplatin, ifosfamide (VIP) when contraindications to bleomycin, are recommended options, although no RCT has focused specifically on this group of rare patients. A risk-adapted approach with EP x 4 for patients with good prognosis and VIP x 4 for patients with intermediate-prognosis metastatic seminoma yielded an OS of 99% and 87% for good- and intermediate-prognosis patients, respectively [179].

7.2.3.1.3 Good prognosis risk group - non-seminomatous germ cell tumour

For non-seminoma, the primary treatment of choice for metastatic disease in patients with good-prognosis disease, according to the IGCCCG risk classification, is BEP x 3 (Table 7.1) [28]. This regimen is superior to cisplatin, vinblastine and bleomycin (PVB) in patients with advanced disease [181, 182]. The available randomised controlled data support the equivalence of three and four cycles of BEP x 4 and of three-day and five-day for projected two-years PFS. However, the three-days regimes experienced increased GI toxicity at three months and increased two-years risk of tinnitus (see section 8.3.9. The difference in toxicity between the three and five days regimes reached clinical relevance when BEP x 4 was given [183, 184]. Based on these data the BEP x 3 and 5-day regimen is 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 [183]. In all other cases omission of bleomycin is not recommended. Two RCTs support the superiority of 3 x BEP over other regimes or schedules/ intensities [185, 186]. Additionally, the GETUG T93BP RCT suggested that when EP is used the mortality rate is twice that of BEP, although the difference did not reach statistical significance [186]. Furthermore, the incidence of residual active cancer in the post-chemotherapy RPLND was significantly higher in patients who received EP x 4 as compared to BEP x 3 (31.9% versus 7.8%, p. < 0.0.01) [187]. The risk of requiring post-RPLND adjuvant chemotherapy could be higher after EP x 4 which could thereby offset the anticipated advantage of reduced toxicity.

A randomised study using 72 hour infusion versus bolus bleomycin in order to reduce pulmonary toxicity did not show any significant difference in efficacy or in pulmonary side effects [188].

Therapy should be given without reduction of the doses at 21-day intervals. Delaying a chemotherapy cycle is justified only in cases of fever with granulocytopenia < 1,000/mm^3 or thrombocytopenia < 100,000/ IU. Neutropenia without fever alone is not a reason to delay the next cycle. As Granulocyte colony-stimulating factor (GCS-F) lowers the risk of neutropenic sepsis, one may consider up-front administration. Granulocyte colony-stimulating factor must be given if infectious complications have occurred during or after chemotherapy, or when a treatment interval is delayed due to myelotoxicity [189].

7.2.3.1.4 Intermediate prognosis risk group - non-seminomatous germ cell tumour

The 'intermediate-prognosis' group in the IGCCCG is defined as patients with a five-year survival rate of the order of 80%. With this group the available data support BEP x 4 as standard treatment [190]. A RCT showed no significant improvement in OS with BEP x 4 plus paclitaxel (T-BEP) compared to BEP x 4 alone [191]. The overall toxicity with T-BEP was higher than with BEP; therefore, it cannot be recommended as a standard approach.

Patients with intermediate prognosis treated in recent years (after 1997) are more likely to have a five year survival of near 90% [192, 193].

7.2.3.1.5 Poor prognosis risk group - non-seminomatous germ cell tumour

For patients with a 'poor-prognosis' non-seminoma as defined by the IGCCCG, standard treatment consists of BEP x 4 with five-year PFS of 45%-50%. Four cycles of cisplatin, etoposide and ifosfamide (PEI) has similar efficacy, but is more myelotoxic [194]. Several RCTs have shown no advantage in OS for high-dose chemotherapy (HDCT) in the overall 'poor-prognosis' patients group [186, 195, 196]. Patients with a slow tumour marker decline after the first or second cycle represent a prognostically inferior subgroup [196, 197]. There are several ways to calculate slow tumour marker decline with an example available at https://www.gustaveroussy.fr/calculation-tumor/NSGCT.html.

Recently, an international randomised phase III trial (GETUG 13) conducted in 263 patients with IGCCCG poor-risk NSGCT demonstrated that intensifying treatment with dose-dense chemotherapy improves PFS, but not OS in patients with an early unfavourable tumour marker decline [198]. Based on the results from this trial, patients with an unfavourable tumour marker decline after BEP x 1 can be switched to a more intensive chemotherapy regimen [198]. Further prospective trials/registries are planned to validate this approach.

Additional patient groups that may benefit from up-front dose intensification are those with mediastinal primary non-seminoma and patients with brain metastases at initial diagnosis [199, 200].

As a matched-pair analysis comparing high-dose to conventional treatment resulted in a better survival rate [201], 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 a high volume centre [114, 202]. There are no general recommendations for treatment modifications for patients with poor performance status (Karnofsky < 50%) or extended liver infiltration (> 50%), although two small reports indicate that a first cycle of dose-reduced therapy may reduce acute mortality without compromising long-term outcome. The number of subsequent cycles of full-dose therapy should, however, not be reduced after an initial low-dose induction cycle [203, 204].

Patients with extended pulmonary infiltration are at risk for acute respiratory distress syndrome. Omitting bleomycin with the first-cycle of chemotherapy (with inclusion for subsequent cycles) has been suggested to reduce the risk of early death in this setting [204]. Management of patients with advanced disease in high-volume centres is associated with improved survival and is consequently recommended [205].

7.3 Treatment evaluation and further treatment

*7.3.1 **Treatment evaluation***

Response to treatment is assessed after the initial induction cycle by repeat imagining and re-evaluation of tumour markers. With marker decline and stable or regressive tumour features, radiologically chemotherapy should be completed (three or four cycles, depending on the initial prognostic category) [206, 207]. If markers decline, but metastases progress on imaging, these should be immediately resected where feasible after completion of induction therapy. [208].

Patients with initial disease progression following induction (primary cisplatin refractory) should be switched to experimental new drug trials [209]. Patients with slow marker decline with the first one to two cycles of chemotherapy are candidates for dose intensification (see Section 7.2.3.1.5). Patients with a low-level β-hCG marker plateau post-treatment should be observed to determine whether complete normalisation occurs. In patients with a low plateau serum AFP level after chemotherapy, surgery of residual masses should be performed, with post-surgery AFP monitoring. Salvage chemotherapy is indicated for documented marker rise only [210, 211].

*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 [212-215].

Fluorodeoxyglucose-positron emission tomography has a high NPV in patients with residual masses after treatment of seminoma. False positive results are less frequent when scans are scheduled > two months after chemotherapy. In patients with residual masses > 3 cm, FDG-PET should be performed in order to provide more information on disease viability. In patients with residual masses < 3 cm, the use of FDG-PET is optional [52, 53].

When a post-chemotherapy mass remains positive at reclassification 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 subgroup). Therefore, caution is recommended with FDG-PET and single parameters driving clinical decisions in a persistent mass [54]. 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) [216-218].

Patients with persistent and progressing β-hCG elevation after first-line chemotherapy should immediately proceed to salvage chemotherapy. Progressing patients without 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 [217]. Ejaculation may be preserved in some of these cases [219].

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 [220]. Fluorodeoxyglucose-positron emission tomography is not indicated to re-stage patients after chemotherapy [48-50]. With complete remission after first-line chemotherapy (no visible tumour), tumour resection is not indicated [221, 222].

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 at cross-sectional CECT imaging until novel predictive models are externally validated [223-226].

The role of surgery is uncertain in patients with retroperitoneal residual lesions < 1 cm. There is still a risk of cancer or teratoma, although in the vast majority of patients (> 70%) these contain only fibro-necrotic tissue [227]. Proponents of post-chemotherapy RPLND for all patients refer to the fact that both teratoma and malignant GCTs may still be present despite remission in lesions < 10 mm [228]. The alternative for patients with a residual mass < 1 cm is an observation protocol with recurrence risk of 6-9% depending on the follow-up duration [221, 222]. 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 [222]. Eight of the twelve relapsing patients were cured with subsequent treatment. Patients after salvage chemotherapy or HDCT in first or subsequent salvage situations harbour vital tumour at a much higher rate [229]. Surgery is therefore indicated in salvage patients even with residual masses < 1 cm [221, 222].

When surgery is indicated, all areas of primary metastatic sites should be completely resected within six weeks of completion of chemotherapy, when feasible. Bilateral nerve-sparing RPLND has been the standard option. Ipsilateral template resection with contralateral preservation of nerves in selected patients has been reported to yield equivalent long-term results compared to bilateral systematic resections. The mere resection of the residual tumour (so called lumpectomy) should not be performed [222, 226, 227, 229-232].

Laparoscopic RPLND may yield comparable outcomes to the open procedure in selected cases with low residual disease and when undertaken by very-experienced hands, but it is not recommended outside a specialised laparoscopic centre with specific expertise in TC. In that setting, up to 30% of post-chemotherapy RPLND may be performed via a laparoscopic approach [233-235]. Experience with robot-assisted laparoscopic RPLND in this setting is still limited [236] and atypical recurrences have been reported, and occur more often, after the robotic approach [237].

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

In general, residual surgery should start at the location with the highest volume of residual disease. The histology may diverge in different organ sites [223]. In cases of retroperitoneal and lung residual 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 [238].

Resection of contralateral pulmonary lesions is not mandatory in cases where pathologic examination of the lesions from the first lung show complete necrosis. However, discordant histology between both lungs may occur in up to 20% of patients [239, 240].

7.3.3.1 Quality and intensity of surgery

Post-chemotherapy surgery is always demanding. Whilst most post-chemotherapy RPLNDs do not require resection of major vessels or organs, a proportion of patients may require an intervention in which organs affected by the disease are removed (e.g. kidney, psoas muscle or gross vessels), and may potentially also require *ad hoc* reconstructive surgery (e.g. vascular interventions such as vena cava or aortic prostheses). Patients undergoing adjunctive complex surgery benefit from disease control but have a greater risk of complications [241, 242]. In patients with intermediate- or poor-risk and residual disease > 5 cm, the probability of vascular procedures is as high as 20% [243]. This surgery must therefore be referred to specialised centres capable of interdisciplinary surgery (hepatic resections, vessel replacement, spinal neurosurgery, thoracic surgery). Even with centralisation of treatment, the median number of RPLNDs performed per surgeon/year in the U.K. is six [244]. Nevertheless, patients treated within such centres benefit from a significant reduction in peri-operative mortality from 6% to 0.8% [245]. In addition, specialised urologic surgeons are capable of reducing the local recurrence rate from 16% to 3% with a higher rate of complete resections [246].

7.3.3.2 Salvage and desperation surgery

Surgery of resectable disease after salvage treatment remains a potentially curative option in all patients with any residual mass following salvage chemotherapy. Survival after surgery and first salvage chemotherapy improved by 70% at ten years, following taxane-containing regimens [247]. Also, even with extensive salvage chemotherapy, surgery remains a fundamental tool to achieve durable complete remissions in up to 20% of patients [248, 249].

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 [250].

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) [230]. However, caution is required with cumulative doses of bleomycin. After complete resection of 'vital' tumour < 10% of the total volume, particularly in patients who were initially good-prognosis based on IGCCCG criteria, the relapse rate is very low and adjuvant chemotherapy is not beneficial in preventing further relapse [251]. 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 [252].

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 [253]. The regimens of choice are four cycles of a three agent regimen including cisplatin and ifosfamide plus a third drug: etoposide (PEI/VIP), paclitaxel (TIP), or potentially gemcitabine (GIP) (Table 7.2) [254, 255]. 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 [256]. For methodological reasons this trial design can no longer be considered state of the art.

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

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 [255].

There is clear evidence from retrospective analyses that there are different prognostic groups at risk in the case of relapse after first-line chemotherapy. The International Prognostic Factors Study Group (IPFSG) score for patients with metastatic germ cell tumours who experienced treatment failure with first-line cisplatin-based chemotherapy is based on seven variables: histology, primary tumour location, response, progression-free interval after first-line and level of α-feto protein, hCG and the presence of liver, bone or brain metastasis at salvage treatment [164]. Using these factors, five risk-groups: *very low risk* = -1 points; *low risk* = 0 points; *intermediate-risk* = 1-2 points, *high risk* = 3-4 points; and *very high risk* > 5 points were identified with significant differences in PFS and OS. Table 7.3 illustrates these five risk groups and the corresponding two-year PFS and three-year OS rates [164].

Several recent trials have validated this scoring system [257-260]. As in first-line therapy, the prognostic impact of tumour marker decline applies in the salvage setting [261]. While progression to induction chemotherapy was negative for OS, prior use of paclitaxel was not significantly associated with a negative outcome [262].

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 international RCT of high-dose versus conventional-dose chemotherapy in patients with first-line relapse has commenced (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 [263]. 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 [264]. It is clearly of the utmost importance that these rare patients with relapse are treated within clinical trials and at specialised centres.

Table 7.3: The International Prognostic Factors Study Group Score for Seminoma and Non-seminoma that relapse after Cisplatin-based First line chemotherapy [164]

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 7.4: PFS and OS estimates for all patients according to IGCCCG prognostic score for Seminoma and Non-seminoma that relapse after Cisplatin-based First line chemotherapy [165]

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 conventional therapy does not appear to be very effective. For patients who have received two series of conventionally-dosed therapy (first-line and first-salvage), high-dose (HD) chemotherapy with autologous stem cell support should be used [258]. Even with HD-therapy the prospect of cure is only 20-25%.

Refractory disease: 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 HD- chemotherapy, are considered cisplatin refractory. For these patients, combinations of gemcitabine and oxaliplatin or the triple combination of gemcitabine, oxaliplatin and paclitaxel have resulted in response rates of 25-45%. Cisplatin re-challenge in association with gemcitabine and paclitaxel may be considered in patients with adequate renal function [265]. 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 [248, 266].

Various targeted agents have generally failed in refractory disease [267-270]. Limited responses with rapid development of resistance have been observed for Brentuximab Vedotin in CD30-expressing germ cell tumours [271, 272]. Most GCT series report a substantial expression of PDL-1 in approximately 50% of tumour cells or tumour infiltrating cells [273, 274]. Despite this, single-agent treatments with immune checkpoint inhibitors did not yield any meaningful responses [275, 276]. Trials combining PD1/PDL-1 and CTLA4 inhibitors are ongoing.

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

Late relapse is defined as recurrence more than two years following cure after chemotherapy for metastatic TC, with, or without, residual tumour surgery [51]. According to a pooled analysis, this occurs in 1.4% and 3.2% of seminoma and non-seminoma patients, respectively [277]. When feasible, all lesions of late-relapsing non-seminoma patients should be removed by radical surgery.

Patients with rapidly rising β-hCG may benefit from induction salvage chemotherapy before complete resection is attempted. In general, however, surgery 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 TSTM [159, 278].

Survival strongly relates to the histology of the removed lesions rather than the initial presenting tumour. Interestingly, in a population-based study all late-relapsing seminoma patients had viable GCT, whereas teratoma or necrosis was found in half of the patients with initial non-seminoma [279].

If the lesions are not completely resectable, biopsies should be obtained for histological assessment, and salvage chemotherapy should be initiated based on the histological phenotype. In these cases, consultation of an experienced pathologist is critical to avoid misinterpretation of the therapeutic morphological changes that occur with the treatment of germ cell malignancy [280]. If the patient responds to salvage chemotherapy, secondary surgery should be conducted, whenever possible. In the case of unresectable, but localised, refractory disease, stereotactic or conventional radiotherapy may be considered. To avoid excess mortality, late relapses should be treated only at centres experienced in managing such patients [281].

*7.3.6 **Treatment of brain metastases***

Brain metastases occur in the context of initial metastatic disease, systemic relapse and rarely as an isolated site of relapse. Long-term survival of patients presenting with brain metastases at diagnosis is poor (30-50%) and even poorer when a site of recurrent disease (the five-year survival-rate is 2-5%) [282, 283]. A large international database comprising 523 patients reported 48% three-year OS rates in patients with brain metastases at initial diagnosis and 27% three-year OS rates for patients with brain metastases at relapse [41]. Chemotherapy as initial treatment proved effective in a first-line setting (potentially even as dose-intensified therapy upfront) with data also supporting the use of multimodal treatment particularly in relapsed disease [41]. Consolidation RT, even with total response after chemotherapy, should thus be used in patients with brain metastases at relapse, but must be carefully discussed in a first-line setting [284]. Surgery can be considered in the case of 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 germ cell tumours

Recommendations	**Strength rating**
Treat low-volume non-seminomatous germ cell tumour (NSGCT) stage IIA/B with elevated markers like ‘good- or intermediate-prognosis’ advanced NSGCT, with three or four cycles of cisplatin, etoposide, bleomycin (BEP).	Strong
In stage IIA/B NSGCT without marker elevation, exclude marker negative embryonal carcinoma by obtaining histology by either retroperitoneal lymph node dissection or biopsy. If not possible, repeat staging after six weeks before making a final decision on further treatment.	Strong
In metastatic NSGCT with an intermediate prognosis, treat 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 case of poor lung function), followed by tumour marker assessment after three weeks. In case of favourable marker decline, continue BEP (or PEI) up to a total of four cycles. In case of an unfavourable decline, initiate chemotherapy intensification.	Weak
Perform surgical resection of visible residual masses after chemotherapy for NSGCT when serum levels of tumour markers are normal or normalising.	Strong
In clinical stage IIA seminoma, offer radiotherapy or chemotherapy and inform the patient of potential long-term side effects of both treatment options.	Strong
Offer initial chemotherapy in seminoma stage IIB (BEP x 3 or EP x 4, in good prognosis) as an alternative to radiotherapy.	Strong
Treat seminoma stage IIC and higher, with primary chemotherapy based on the same principles used for NSGCT.	Strong

8. FOLLOW UP AFTER CURATIVE THERAPY

8.1 Rationale for follow-up

The primary aim of follow-up in the first five years is the timely diagnosis of recurrent disease in order to enable treatment with curative intent using the least aggressive therapy [51]. An adequate follow-up relies on profound knowledge about TC with regards to histology, stage, primary treatment and treatment success. Follow-up must be tailored to the individual patient with a schedule acceptable to the patient, the clinician, and the healthcare system. The interval of follow-up visits and the clinical investigations to be performed at each visit should depend on the risk of relapse, in general, as well as the likely sites of relapse in an individual patient [285]. Only one RCT addresses the implication of different follow-up schedules and the use of imaging and tumour markers [161]. Several recent publications have provided valuable information and recommendations [105, 107, 121, 127, 129, 148, 286-289] contributing to the development of consensus recommendations by the European Society for Medical Oncology Testicular Cancer Consensus Committee [290].

To minimise ionising radiation exposure risks associated with repeated CT scanning [291] a reduction in the number of follow up CT scans advised has occurred in the past few years [1, 292].

8.2 Minimal recommendations for Follow up

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

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

It is important to note that patients not achieving a complete remission or presenting with poor-prognosis disease should be followed up individually by specialised centres. Tables 8.1-8.3 show the minimal recommendations for follow up of the three different groups based on recommendations developed at an ESMO consensus conference [290].

Generally, MRI of the abdomen can be used as an alternative to CECT in experienced centres. Regarding the use of US of the contralateral testis, the majority of the consensus meeting participants did not support repeat US investigation, either with negative biopsy or if no contralateral biopsy has been performed [290].

Follow-up for relapse beyond five years is generally not recommended. 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 [279]. The aim of follow-up beyond five years therefore shifts to detection of late side effects of treatment.

Most patients with VLR are diagnosed due to symptoms, although in up to 50% elevated tumour markers are present in both seminoma and NSGCTs [279, 293]. 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/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/magnetic resonance imaging	2 times	At 24 months****	Once at 36 months**	Once at 60 months**	

* *LVI+: Lymphovascular invasion present*

** *Recommended by 50% of the consensus group members.*

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

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

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

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	1-2 times	At 24 months	Once at 36 months	Once at 60 months	
Thorax CT	*	*	*	*	

* *Same time points as 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.*

8.3 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 [294]. 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 [142], whereas others highlight the importance of patient autonomy and consider the prospect of avoiding salvage treatment with long-term toxicities appealing [295]. 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 [144, 150, 296].

During follow-up, patients should be screened and treated for known risk factors such as hypertension, hyperlipidaemia and testosterone deficiency. When follow-up by the TC clinician is terminated, a written cancer survivorship plan addressing late toxic effects, lifestyle recommendations, recurrence risk, and cancer-specific follow-up may be helpful [51, 297]. Whilst the following overview is not complete those interested may consider review articles on this topic [294, 297, 298].

*8.3.1 **Second malignant neoplasms (SMN)***

Treatment-induced SMN usually occurs after the first ten years [297]. Testicular cancer belongs to the group of cancers commonly diagnosed in adolescents and young adults (AYA), which have a higher absolute risk of developing a subsequent primary neoplasm than survivors of childhood or adult cancer [299]. 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 20.2% (95% CI: 18·9–21·5) [299].

The risk for solid SMN increases with younger age at radio- or chemotherapy [297]. Radiotherapy-related SMN are primarily localised within, or close to, the radiotherapy field (colon, stomach, pancreas, bladder and the

urinary tract) [297]. A remarkably clear radiation-dose relationship to gastric- and pancreatic cancer has been demonstrated [300].

Modern cisplatin-based chemotherapy has been found to be associated with a 40% increased risk of a solid SMN [301]. A relationship between cumulative dose of Cisplatin and 2nd SMN, especially in the GI tract has been noted [302]. 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 20.2% after 35 years has been reported [299]. Second malignant neoplasms were identified in 9.4% of Swedish TC survivors, with half these cancers considered uncommon in men in their 40s [303]. Survival was 40% in TC survivors with a SMN as opposed to 80% in those without [303].

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 versus solid SMN (8.6 versus 34.4. months). Age ≥ 40 years at the time of HDCT was significantly associated with hematologic, but not with solid SMNs [304].

*8.3.2 **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 [305]. 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 [306]. The majority of TC patients receive much lower doses of etoposide than this so that the absolute risk of AML after three to four courses of BEP is very low. In patients requiring HDCT with cumulative etoposide doses exceeding this threshold, less than 1.5% have been reported to develop AML. There is a cumulative dose-disease risk relationship with cisplatin and AML. Chemotherapy-induced leukaemia is usually diagnosed within the first ten years after treatment for TC and has a poor prognosis [307].

*8.3.3 **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) [308]. 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.

*8.3.4 **Pulmonary complications***

Chemotherapy exposed TCSs have a nearly three-fold increased risk of dying of pulmonary diseases than the normal population [308]. Bleomycin-induced lung toxicity may affect 7-21% of patients in the long term, resulting in death in 1-3% [309]. Chemotherapy-treated TC survivors treated with high cumulative cisplatin doses and/or pulmonary surgery, have a poorer pulmonary function than those cured with surgery alone [299]. Intriguingly, long-term pulmonary complications were associated with the cumulative cisplatin doses but not the dose of bleomycin [310]. 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 [311]. 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 [312]. 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 [312]. 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 [313].

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 [314]. 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 [314].

*8.3.5 **Cardiovascular toxicity***

Thromboembolic events (mostly venous) occur more frequently in patients with GCT receiving chemotherapy than in other young male adults treated with chemotherapy for other cancers [315]. Low-dose heparins used during the course of chemotherapy may prevent the onset of thromboembolic events [316], though

level 1 evidence is lacking. Mortality from cardiovascular disease (CVD) is higher in TCSs than in the general population (OR 5) [308, 317, 318]. Furthermore, CVD is more common in chemotherapy-treated TCSs than in those who underwent surgery only [149, 319]. Feldman *et al.* applied the Framingham Risk Score (FRS) on 787 TC survivors and compared the results with controls [320]: FRS did not differ by chemotherapy regimen (BEP 3 versus 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 [320].

Metabolic syndrome, a strong risk factor for CVD and its components, hypertension, obesity and hypercholesterolaemia, increases with treatment intensity (OR 9.8) [318, 321, 322]. 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 [323]. Circulating residual serum platinum might exert endothelial stress and thereby possibly lead to hypertension [324]. Furthermore, exposure to circulating platinum is associated with paraesthesia, hypogonadism, and hypercholesterolaemia as well as major vascular events [316].

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 [325]. However, HIIT during cisplatin-based chemotherapy might be harmful as a planned study on 94 patients closed early after recruiting nineteen patients and the finding of severe CVD complications among three out of nine patients undergoing HIIT [326]. 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.

8.3.6 ***Raynaud-like phenomena***

Chemotherapy-related Raynaud-like phenomena were reported before the introduction of cisplatin and are usually attributed to bleomycin [327, 328]. 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% versus 21%, respectively [329].

8.3.7 ***Neurotoxicity***

Cisplatin induces a symmetric dose-dependent sensory, distal, length-dependent glove and stocking paraesthesias, affects 29% of TCSs who received cisplatin-based chemotherapy as opposed to 10% after orchiectomy alone [318, 330]. 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 paraesthesias more strongly associated with platinum serum level than with the cumulative dose of applied cisplatin [324]. 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 [331].

8.3.8 ***Cognitive function***

There are concerns that chemotherapy may reduce the cognitive function leading to "chemo-brain". Amidi *et al.* could show an alteration of brain structural networks after cisplatin-based chemotherapy for TC [332]. Impaired brain networks may underlie poorer performance over time on both specific and nonspecific cognitive functions in TC survivors following chemotherapy.

8.3.9 ***Ototoxicity***

Cisplatin-induced ototoxicity comprises tinnitus and hearing impairment, particularly frequencies of 4,000 Hz and higher, and is caused by damage to the outer hair cells in the inner ear [318, 333-335]. 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 (odds ratio 5.1 and 7.3, respectively), indicating a higher impact of serum peak concentrations than cumulative doses [330]. A significant association between Glutathione S-transferases (GST) genotypes and the risk of cisplatin-induced ototoxicity has been demonstrated [336, 337]. Understanding the pathogenesis of, and susceptibility to, this complication will lead to more individualised treatment in the future.

8.3.10 ***Nephrotoxicity***

Cisplatin-based chemotherapy may lead to long-term renal dysfunction in 20-30% of TCSs [316, 319, 321]. In TC patients, reduced renal excretion of cisplatin and bleomycin might increase the risk of other toxicities, e.g. bleomycin-related pneumonitis [338, 339]. A comprehensive assessment of 1,206 Danish TCSs, however, did not reveal a significant association between chemotherapy-induced impaired renal function and other toxicities [317]. Renal recovery was poor after five or more cycles of BEP as compared to after BEP x 3 [322]. 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 [340].

8.3.11 ***Hypogonadism***

Testicular endocrine dysfunction comprises insufficient testosterone production and/or compensatory increased LH levels. Subnormal testosterone levels have been reported in TCSs treated with chemotherapy, when compared to those treated with surgery only or the general population [296, 318, 338, 341]. 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 [342].

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 [323]. Wiechno *et al*. could show a decline in testosterone and an increase in LH and FSH within one year after treatment for unilateral TC [343]. 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 [344]. Furthermore, the clinical benefits of testosterone substitution are not well established. An ongoing Danish RCT might yield level 1 evidence [345].

Erectile dysfunction (OR 4.2) has been significantly associated with chemotherapy in a recent multicentre study [318].

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) [346]. Hypogonadism was associated with the number of adverse health outcomes and its risk increased with age and obesity [347].

8.3.12 ***Fatigue***

Chronic fatigue (CF) is described as a subjective feeling of emotional, physical and/or cognitive tiredness that is not relieved by rest, and persists for more than six months. Significantly higher levels of C-reactive protein and interleukin-1 receptor antagonist are measured in TCSs with CF [346]. 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%) [184]. Of note, the prevalence of CF increased from 15% to 27% during a ten year period in long-term TCSs [348].

8.3.13 ***Quality of life***

Quality of life is transiently reduced by chemotherapy, during which patients experience a loss of appetite, increased fatigue, increased dyspnoea and reduced social- and physical function [184]. When comparing three or four cycles of BEP in good-risk patients, all outcomes favour treatment with three courses [183]. 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 [152]. 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 [349]. Clinically significant anxiety is reported in approximately 1 out of 5 TCSs and distress in 1 out of 7, and is therefore more frequent among TCS than in the general population. Depression was not uniformly found to be more frequent, whereas every third TCSs reported fearing 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. These findings are mostly in line with an earlier reported survivorship study on HRQoL among 486 TCSs revealing a greater prevalence of moderate- to extremely severe anxiety (19%) and depression (20%); and significant deficits to mostly mental aspects of HRQoL. The authors found that again, helpless/hopeless coping style was correlated with psychological distress and impaired generic HRQoL [350].

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 having children being related to higher levels of anxiety and depression [351].

Among 2,479 Danish long-term TCSs higher anxiety was reported by those who experienced bilateral TC as compared to unilateral TC [352] .

For a subset of approximately 11% of TSCs, the diagnosis of TC was traumatic. This subset was found to suffer from post-traumatic stress disorder in the long term, which resulted in significant QoL reduction [353]. The authors recommend that healthcare professionals explore stress symptoms at follow-up visits in order to timely identify TSCs requiring support.

Sexual function and satisfaction was assessed in 2,260 Danish TCSs. Erectile dysfunction was found in men who underwent radiotherapy, BEP chemotherapy with subsequent surgical resection of residual masses, or more than one line of treatment. The latter group also reported orgasmic dysfunction. After radiotherapy, significantly more men reported overall decreased sexual satisfaction, whereas all other groups reported no difference in overall satisfaction, intercourse satisfaction, and sexual desire [354].

9. TESTICULAR STROMAL TUMOURS

9.1 Classification

Non-germ-cell tumours of the testicle include sex cord/gonadal stromal tumours and miscellaneous nonspecific stromal tumours. The different histological subtypes of testicular tumours are defined according to the 2016 WHO classification [23].

*9.1.1 **Epidemiology and prognosis***

Sex cord stromal tumours comprise less than 5% of testicular neoplasms. Recent population-based US registries (National Cancer Data Base and Surveillance Epidemiology and End Results) show that 0.39 to 0.59% of all testis neoplasm patients are diagnosed with a primary malignant Leydig or Sertoli cell tumour. Of these, 71-79% are malignant Leydig cell tumours and 21-29% malignant Sertoli tumours [355, 356].

Median ages at diagnosis are 39 and 47 years for malignant Sertoli and Leydig cell tumours, respectively [356]. At diagnosis approximately 96% of the malignant Leydig cell tumours are CSI, whilst 22-35% of Sertoli cell tumours are CS II-III [356].

Overall survival at one and five years for CSI Leydig cell tumours is 98% (95% CI: 96-100) and 91% (95% CI: 85-96), respectively, and for CSI Sertoli cell tumours OS is 93% (95% CI: 83-100) and 77% (95% CI: 62-95), respectively ($p = 0.015$). Overall, five-year survival estimates of stage I Leydig and Sertoli cell tumours are significantly lower compared to those of stage I GCTs, with Sertoli cell tumours significantly worse than Leydig cell tumours [355]. Presentation with metastatic disease is the only variable associated with worse CSS [357].

Only limited evidence is available for local and systemic treatment of testicular stromal tumours. After TSS, local recurrence rates up to 9.5% have been reported [358]. A systematic review [359] analysing the impact of previously identified pathologic risk factors on harbouring occult metastatic disease (OMD) in patients with CS I testicular stromal tumours showed an increased risk of occult metastatic disease for each additional risk factor ($p < .001$). Five-year OMD-free survival was 98.1% for those with < 2 risk factors versus 44.9% for those with ≥ 2 risk factors ($p < .001$). Whilst the existing literature does not support making firm recommendations, TTS instead of radical orchidectomy might be offered in patients with localised disease and risk stratification might improve clinical decision making regarding adjuvant treatment options [360].

These data support the importance of large databases to evaluate the efficacy of treatment in rare neoplasms.

9.2 Leydig cell tumours

*9.2.1 **Epidemiology***

Leydig cell tumours comprise about 1-3% of adult testicular tumours [361, 362] and 3% of testicular tumours in infants and children [362]. These tumours are most common in the third to sixth decade in adults, with a similar incidence observed in each decade. Another peak incidence is seen in children aged between three and nine years. Only 3% of Leydig cell tumours are bilateral [361]. These tumours occur in about 8% of patients with Klinefelter's syndrome [362].

*9.2.2 **Pathology of Leydig cell tumours***

Leydig cell tumours are the most common type of sex cord/gonadal stromal tumours. Histopathologically, they are well delineated and usually up to 5 cm in diameter. They are solid, yellow to tan in colour, with haemorrhage and/or necrosis in 30% of cases. Microscopically, the cells are polygonal, with eosinophilic cytoplasm and occasional Reinke crystals, regular nucleus, solid arrangement and capillary stroma. The cells express vimentin, inhibin, protein S-100, steroid hormones, calretinin and cytokeratin (focally) [81].

Approximately 10% of Leydig cell tumours are malignant and present with the following parameters [363, 364]:

- large size (> 5 cm);
- older age;
- increased mitotic activity (> 3 per 10 high-power field [HPF]);
- vascular invasion;
- cytological atypia;
- increased MIB-1 expression;
- necrosis;
- infiltrative margins;
- extension beyond the testicular parenchyma;
- DNA aneuploidy.

*9.2.3 **Diagnosis***

Patients either present with a painless enlarged testis or a tumour is found incidentally on US. In up to 80% of cases, hormonal disorders with high oestrogen and oestradiol levels, low testosterone, and increased levels of LH and FSH are reported [365, 366], while negative results are always obtained for the testicular GCT-markers AFP, hCG, LDH and PLAP. Up to 10% of adult patients present with gynaecomastia [366, 367].

Diagnostic work-up must include markers, hormones (at least testosterone, LH and FSH; if not conclusive, also oestrogen, oestradiol, progesterone and cortisol), US of both testes, and CT of chest and abdomen. On US, it may be possible to observe well-defined, small, hypoechoic lesions with hypervascularisation; however, the appearance is variable and is indistinguishable from GCTs [37]. Contrast-enhanced US [36] or contrast-enhanced MRI [44] may improve the diagnosis. The proportion of metastatic tumours in all published case reports is less than 10%. In three old series with long-term follow-up, eighteen metastatic tumours were found in a total of 83 cases (21.7%) [361, 363, 368]; while five recently published studies with long-term follow-up reported only two metastatic tumours in 156 patients (1.3%) [355, 366, 367, 369, 370].

Metastases are most frequently found in retroperitoneal lymph nodes (60%), lungs (38%) or liver (29%). A recent analysis of published case series data showed that older age, larger tumour size and the presence of any adverse factor are risk factors [371].

9.3 Sertoli cell tumours

*9.3.1 **Epidemiology***

Sertoli cell tumours account for fewer than 1% of testicular tumours, and the mean age at diagnosis is around 45 years, with sporadic cases under 20 years of age [372, 373]. On rare occasions, these occur in patients with androgen insensitivity syndrome and Peutz-Jeghers syndrome [374].

*9.3.2 **Pathology of Sertoli cell tumours***

These tumours are well circumscribed, yellow, tan or white in colour, with an average diameter of 3.5 cm [372]. Microscopically, the cells are eosinophilic to pale with a vacuolated cytoplasm. The nuclei are regular with grooves and inclusions may be present. The arrangement of the cells is tubular or solid; a cord-like or retiform pattern is possible. The stroma is fine with capillaries, but in some cases a sclerosing aspect predominates. The cells express vimentin, cytokeratins, inhibin (40%) and protein S-100 (30%) [372]. The rate of malignancy ranges between 10% and 22%. Signs of a malignant Sertoli tumour are as follows [375, 376]:

- large size (> 5 cm);
- increased mitotic activity (> 5 per 10 HPF);
- pleomorphic nuclei with nucleoli;
- necrosis;
- vascular invasion.

9.3.2.1 Classification

Three subtypes have been described [373]:

- classic Sertoli cell tumour [373];
- large cell calcifying form with characteristic calcifications [377, 378];
- sclerosing form [379, 380].

*9.3.3 **Diagnosis***

Patients present either with an enlarged testis, or the tumour is found incidentally on US. Most classic Sertoli cell tumours are unilateral and unifocal. Hormonal disorders are infrequent, although gynaecomastia may be present [381]. The testicular tumour-markers AFP, hCG, LDH and PLAP are always negative. Diagnostic work-up must include tumour markers, hormones (at least testosterone, LH and FSH; if not conclusive, also oestrogen, oestradiol, progesterone and cortisol), US of both testes and CT of chest and abdomen. Sertoli cell tumours are generally hypoechoic on US, but they can be of variant appearance and thus cannot be safely distinguished from GCTs [382]. Only the large cell calcifying form has a characteristic image with bright echogenic foci due to calcification [381]. Metastatic disease of 12% in classic Sertoli cell tumour has been reported. In general, affected patients are older, tumours are nearly always palpable, and show more than one sign of malignancy [382].

The large cell calcifying form is diagnosed in younger men and is associated with genetic dysplastic syndromes (Carney's complex [382] and Peutz-Jeghers syndrome [374]) or, in about 40% of cases, endocrine disorders. Forty-four percent of cases are bilateral, either synchronous or metachronous, and 28% show multifocality with good prognosis [378].

Up to 20% of the large cell calcifying forms are malignant. It has been suggested that discrimination between an early and late onset type may define a different risk for metastatic disease (5.5% compared to 23%) [373].

The sclerosing subtype is very rare, unilateral, with a mean age around 40 years and metastases are infrequent [380].

9.4 Treatment of Leydig- and Sertoli cell tumours

Asymptomatic, small volume testicular tumours are often misinterpreted as GCTs and inguinal orchidectomy is performed. An organ-sparing procedure for small US-detected, non-palpable intraparenchymal lesions is highly recommended in order to obtain a histological diagnosis. The incidence of benign definitive histology is high at approximately 80% [383]. When a non-GCT is suggested by frozen section immediate orchidectomy may be avoided. In cases with GCT in either frozen section or paraffin histology, orchidectomy is recommended as long as a contralateral normal testicle is present.

When diagnosed and treated early, long-term favourable outcomes are seen at follow up in Leydig cell tumours, even with its potential metastatic behaviour. In stromal tumours with histological signs of malignancy, especially in older patients, orchidectomy and early RPLND may be an option to prevent metastases [355, 384] or to achieve long-term cure in stage IIA cases [385]. Prophylactic RPLND is unjustified for patients with CS I disease without high-risk features [386].

Tumours that have metastasised to lymph nodes, lung, liver or bone respond poorly to chemotherapy or radiation and survival is poor [355, 384]. No recommendations are available for the treatment of these patients.

9.5 Granulosa cell tumour

This is a rare tumour with two variants: juvenile and adult. Less than 100 cases are reported with a predominance of the juvenile type.

- The juvenile type is benign. It is the most frequent congenital testicular tumour and represents about 1-5% of all pre-pubertal testicular neoplasms. The cystic appearance is characteristic of this tumour type [387, 388].
- The average age of the adult type at presentation is 45 years. The typical morphology is a homogeneous, yellow-grey tumour, with elongated cells with grooves in microfollicular and Call-Exner body arrangements [389].

Only 20% of granulosa tumours appear malignant. Lymphovascular invasion, necrosis, infiltrative borders and size > 4 cm may help in identifying cases with aggressive behaviour. Mitotic counts vary and do not appear to be of prognostic significance [390].

9.6 Thecoma/fibroma group of tumours

These tumours are rare with variable histology such as minimal invasion into surrounding testis, high cellularity, and increased mitotic rate. Their immunoprofile is variable and typically not diagnostic. These tumours seem to be uniformly benign [391].

9.7 Other sex cord/gonadal stromal tumours

Sex cord/gonadal stromal tumours may be incompletely differentiated or in mixed forms. There is limited

experience with incompletely differentiated sex cord/gonadal stromal tumours and no reported cases of metastasis. In mixed tumour forms, all the histological components should be reported. However, the clinical behaviour most likely reflects the predominant pattern or the most aggressive component of the tumour [392].

9.8 Tumours containing germ cell and sex cord/gonadal stroma (gonadoblastoma)

Some patients with disorders of sex development (DSDs) have abnormal gonadal development with ambiguous genitalia and an increased risk of GCTs. If the arrangement of the germ cells is in a nested pattern and the rest of the tumour is composed of sex cord/gonadal stroma, the term gonadoblastoma is used. Bilateral tumours are present in 40% of cases. The prognosis correlates with the invasive growth of the germinal component [393, 394].

In the case of a diffuse arrangement of the different components, there are some doubts about the neoplastic nature of the germinal cells and some authors consider these to be entrapped rather than neoplastic [395].

9.9 Miscellaneous tumours of the testis

*9.9.1 **Tumours of ovarian epithelial types***

These tumours resemble epithelial tumours of the ovary. A cystic appearance with occasional mucinous material can be observed. Microscopically, the aspect is identical to their ovarian counterparts, and their evolution is similar to that of the different epithelial ovarian subtypes. Some Brenner types are malignant [81].

*9.9.2 **Tumours of the collecting ducts and rete testis***

These tumours are very rare. Benign (adenoma) and malignant (adenocarcinoma) variants have been reported, with malignant tumours showing local growth with a mortality rate of 40% within one year [396].

*9.9.3 **Tumours (benign and malignant) of non-specific stroma***

These are very uncommon and have similar criteria, prognosis and treatment to soft tissue sarcomas.

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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 publically accessible through the European Association of Urology website: http://www.uroweb.org/guidelines.

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