EAU Guidelines on Testicular Cancer

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1. INTRODUCTION

1.1 Aim and objectives

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

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

1.2 Panel composition

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

1.3 Available publications

A quick reference document (Pocket guidelines) is available in print. This is an abridged version 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 TC Guidelines. All documents are accessible through the EAU website Uroweb: http://www.uroweb.org/guideline/testicularcancer/. A EAU Guidelines App for iOS and Android devices is also available containing the Pocket Guidelines, interactive algorithms and calculators, clinical decision support tools, guidelines cheat sheets and links to extended guidelines.

1.4 Publication history and summary of changes

1.4.1 Publication history

The EAU published the first guidelines on TC in 2001. Since 2008, the TC Guidelines contains a separate chapter on testicular stromal tumours. The 2024 TC guideline presents a limited update of the 2023 publication. A summary paper of the EAU TC guideline has been published in the society's scientific journal European Urology in 2023 [1].

1.4.2 Summary of changes

The 2025 edition of the Testicular Cancer Guidelines is a reprint of the 2024 version, with adaptions to the following sections:

- A restructure and rewrite of section 4.3 on Risk factors for relapse in clinical stage I testicular cancer;
- The section on Pathological examination of the testis has been moved to online Appendix 2 – Pathological examination of the testis;
- Restructure and rewrite of section 6.1.2 on Seminoma germ cell tumour clinical stage I

2. METHODS

2.1 Introduction

The 2025 edition of the TC Guidelines is a reprint of the 2024 version. For the 2024 EAU Guidelines on TC, new and relevant evidence was identified, collated and appraised through a structured assessment of the literature. A broad and comprehensive literature search, covering all sections of the TC Guidelines was performed. The search was limited to studies representing high levels of evidence, i.e., systematic reviews (SRs) with meta-analysis, randomised controlled trials (RCTs), and prospective non-randomised comparative studies, published in the English language. Databases searched included Medline, EMBASE, and the Cochrane Libraries, covering a time frame between May 1st 2021 and May 1st 2023. A total of 1,867 unique records were identified, retrieved and screened for relevance.

Detailed search strategies for the 2024 guideline are available online:
https://uroweb.org/guidelines/testicular-cancer/publications-appendices

Recommendations within the Guidelines are developed by the panels to prioritise clinically important care decisions. 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 the nature and variability of patient values and preferences. This decision process, which can be reviewed in the strength rating forms which accompany each guideline statement, addresses a number of key elements:

1. the overall quality of the evidence which exists for the recommendation [2];
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 and certainty of patient values and preferences on the intervention.

Strong recommendations typically indicate a high degree of evidence quality and/or a favourable balance of benefit to harm and patient preference. Weak recommendations typically indicate availability of lower quality evidence, and/or equivocal balance between benefit and harm, and uncertainty or variability of patient preference [3].

Additional information can be found in the general Methodology section of this print, and online at the EAU website: https://uroweb.org/guidelines.

A list of associations endorsing the EAU Guidelines can also be viewed online at the above address.

2.2 Review

The 2020 Guidelines document was subjected to peer-review following publication. The next peer-review is scheduled for 2025.

2.3 Future goals

- A collaborative SR on hypogonadism following orchidectomy with the EAU Male Sexual Health guidelines panel;
- The development of a TC survivorship plan in collaboration with patient associations;
- Care Pathways on diagnostic, treatment clinical stage (CS) 1, and treatment of metastatic disease;
- Collaboration with the patient office and patient representatives to develop a care pathway focusing on what the patient needs to know from diagnosis through to follow-up.

3. EPIDEMIOLOGY, AETIOLOGY & PATHOLOGY

3.1 Epidemiology and Aetiology

Testicular cancer represents 1% of adult neoplasms and 5% of urological tumours, with three to ten new cases per 100,000 males/per year in Western societies [4]. The incidence of TC has increased during recent decades, predominantly in industrialised countries [5-8], and it continues to rise. At diagnosis, 1-2% are bilateral and 90-95% of cases are germ cell tumours (GCT) [4]. The peak incidence is in the third decade of life for non-seminomatous germ cell tumour (NSGCT) and mixed GCT patients, and in the fourth decade for seminoma testis (ST) patients. In 5% of GCT patients, the primary site is at an extragonadal location [9].

There are two fundamental categories of GCTs based on their development and epigenetic features. Most malignant post-pubertal GCTs originate from germ cell neoplasia "*in situ*" (GCNIS). Histologically and clinically, these are subdivided into seminomas and non-seminomas, the latter encompassing somatic and extra-embryonal elements of embryonal carcinoma, yolk sac, choriocarcinoma and post-pubertal teratoma (PPT) [10].

Non GCNIS derived tumours include pre-pubertal type teratoma and yolk sac tumour, which occur in early childhood, and spermatocytic tumours which usually occurs in older men. Although there is overlapping histology between the pre-pubertal type teratoma/yolk sac and the teratoma and yolk sac tumour elements in the GCNIS-derived NSGCT, these have a separate and independent pathogenesis [10].

Risk factors for GCNIS-derived GCTs are components of the testicular dysgenesis syndrome, which encompasses cryptorchidism, hypospadias, decreased spermatogenesis and impaired fertility [11-13] or disorders of sex development [14]. Additional risk factors include a family history of TC among first-degree relatives and the presence of a contralateral testicular tumour or GCNIS [15-23] although the risk was lower if TC patients previously had received platinum-based chemotherapy [24, 25]. Genome-wide association studies revealed detectable susceptibility loci leading to an increased relative risk to develop TC [26].

3.2 Histological classification

General:
The recommended pathological classification is based on the 2022 update of the World Health Organization (WHO) pathological classification [27]. This outlined in Appendix 1- Pathological classification.

4. STAGING & PROGNOSIS

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 1) [28].

Table 1: TNM classification for testicular cancer (adapted from UICC, 2016, 8th edn.) [28]

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 (including rete testis) and epididymis without vascular/lymphatic invasion and without invasion of the epididymis*#
pT2	Tumour limited to testis with vascular/lymphatic invasion, or invading hilar soft tissue or the epididymis or tumour extending through tunica albuginea with involvement of visceral tunica vaginalis**#
pT3	Tumour invades spermatic cord with or without vascular/lymphatic invasion**
pT4	Tumour invades scrotum with or without vascular/lymphatic invasion
N - Regional Lymph Nodes – Clinical	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis with a lymph node mass 2 cm or less in greatest dimension or multiple lymph nodes, none more than 2 cm in greatest dimension
N2	Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension; or more than 5 nodes positive, none more than 5 cm; or evidence of extranodal extension of tumour
N3	Metastasis with a lymph node mass more than 5 cm in greatest dimension
Pn - Regional Lymph Nodes – Pathological	
pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis with a lymph node mass 2 cm or less in greatest dimension and 5 or fewer positive nodes, none more than 2 cm in greatest dimension
pN2	Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension; or more than 5 nodes positive, none more than 5 cm; or evidence of extranodal extension of tumour
pN3	Metastasis with a lymph node mass more than 5 cm in greatest dimension

M - Distant Metastasis			
MX	Distant metastasis cannot be assessed		
M0	No distant metastasis		
M1	Distant metastasis **		
	M1a	Non-regional lymph node(s) or lung metastasis	
	M1b	Distant metastasis other than non-regional lymph nodes and lung	
S - Serum Tumour Markers (Pre-chemotherapy)			
SX	Serum marker studies not available or not performed		
S0	Serum marker study levels within normal limits		
	LDH (U/l)	**hCG (mIU/mL)**	**AFP (ng/mL)**
S1	< 1.5 x N and	< 5,000 and	< 1,000
S2	1.5-10 x N or	5,000-50,000 or	1,000-10,000
S3	> 10 x N or	> 50,000 or	> 10,000

N indicates the upper limit of normal.
LDH = lactate dehydrogenase; hCG = human chorionic gonadotrophin; AFP = alpha-fetoprotein.
[1] Except for pTis and pT4, where radical orchidectomy is not always necessary for classification purposes, the extent of the primary tumour is assessed in the radical orchidectomy specimen; 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 [29].*
*** AJCC eighth edition considers hilar soft tissue invasion and epididymal invasion as pT2, while the discontinuous involvement of the spermatic cord is considered as pM1 [29].*
[#] As updated in the UICC 8th Edition Errata [28b].

4.2 The Union for International Cancer Control prognostic groups

According to the 2016 TNM classification, the following prognostic groups are defined:

Table 2: Prognostic groups for testicular cancer (UICC, 2016, 8th edn.) [28]

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

Stage IA: 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 Clinical Stage I (CS I) disease should be assessed until normalisation occurs on two consecutive measurements.

Stage IB: More locally invasive primary tumour, but no sign of metastatic disease.

Stage IS: Following orchiectomy tumour markers increase, remain persistently elevated or fail to decline as expected by half-lives indicating the presence of subclinical metastatic disease. The presence of a second GCT in the contralateral testis should also be excluded.

In population-based patient series from developed countries, 75-80% of seminoma germ cell tumour (SGCT) patients, and 55-64% of NSGCT patients had CS I disease at diagnosis [30, 31]. True CS I, i.e., persistently elevated or increasing serum tumour marker levels after radical orchidectomy, was found in approximately 5% of NSGCT patients [30].

4.3 Risk factors for relapse in clinical stage I testicular cancer

4.3.1 ***Seminoma***

Primary testicular tumor size and stromal invasion of the rete testis have been considered the prognostic risk factors associated with relapse in CS I (SGCT). Two SRs assessed the prognostic value of both risk factors [32, 33]. While tumour size (continuous or dichotomised) and rete testis invasion (RTI) were associated with a higher risk of relapse, both SRs highlighted the low quality of the studies included and concluded that the level of evidence was too low justify the use of both risk factors to drive adjuvant treatment decisions in routine practice.

Recently, two large series re-assessed prognostic risk factors in CS I SCGT patients under surveillance [34, 35]. A multi-institutional retrospective series including 1,016 patients and an additional validation cohort of 285 patients identified primary testicular tumour size (size < 2 cm, 2-5 cm, and > 5), RTI (pagetoid + stromal invasion) and lymphovascular invasion (LVI) to be associated with risk of relapse [34]. A three-tier risk stratification was compiled, including a small proportion of high-risk patients (2.3%) with tumour size > 5 cm and both RTI and LVI present who had a five-year cumulative probability of relapse of 44%.

A large prospective series from Denmark [35] including 924 patients with central pathology review identified invasion of the testicular hilum (rete testis and hilar soft tissue), LVI, and elevated β-HCG and LDH prior to orchiectomy as independent predictors of relapse. In contrast to previous studies, tumour size was not identified as a risk factor. A six-tier risk stratification was developed and the estimated five-year probability of relapse ranged from 6% in patients without risk factors to 62% in patients with all four risk factors, which was 22% of the patient population. Both series demonstrated that the vast majority of patients with CS I SGCT are cured by orchiectomy alone as the overall relapse rate was 14.7% and 16%, supporting “active surveillance” (AS) as the preferred adjuvant strategy for all CS I seminoma patients irrespective of risk factors.

4.3.2 ***NSGCT***

For CS I NSGCT, invasion of the primary tumour into blood or lymphatic vessels, (i.e., lymphovascular invasion [LVI]), has long been described to be strongly associated with the risk of relapse [39-41]. According to historical figures, relapse risk for patients with LVI-positive tumours was 50% vs. 15% in patients with LVI-negative tumours.

A recent Danish study of more than 400 patients with central pathology review suggested tumour size, invasion of the hilar soft tissue and presence of embryonal carcinoma as additional risk factors [36]. Depending on the combination of factors, relapse risk ranged from < 5% to > 85%.

4.4 The International Germ Cell Cancer Collaborative Group (IGCCCG) classification for the prognostic risk groups of metastatic germ cell cancer

The 1997 IGCCCG defined a prognostic risk-factor system for metastatic GCT based on identification of clinically independent adverse factors [37]. The classification has been revalidated on a contemporary cohort of metastatic TGCTs treated with cisplatin/etoposide based first-line chemotherapy [38].

Compared to the 1997 figures, the five-year progression-free survival (PFS) of NSGCT patients was unchanged for good- and intermediate-risk, but significantly improved for poor-risk patients (from 41% to 54%). The five-year overall survival (OS) was substantially better for all groups. In addition to the traditional components of the IGCCCG risk-prognostic groups previously described, older age (linear association) and lung metastases were confirmed as negative factors for PFS [38].

For SGCT, revalidation of the IGCCCG classification showed that the five-year PFS increased to 89% and 79% in good- and intermediate-risk patients with corresponding OS rates of 95% and 88%. Testicular lactate dehydrogenase (LDH) over 2.5 times the upper limit of normal (ULN) was identified as a possible adverse prognostic factor in regard to reduced three-year PFS; however, overall three-year survival was not affected [39].

Table 3: Prognostic-based staging system for metastatic germ cell cancer (IGCCCG) [37]*

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

** Pre-chemotherapy serum tumour markers should be assessed immediately prior to the administration of chemotherapy (same day).*
AFP = alpha-fetoprotein; β-hCG = human chorionic gonadotrophin; LDH = lactate dehydrogenase; PFS = progression-free survival.

5. DIAGNOSTIC EVALUATION

5.1 Physical examination

Testicular cancer usually presents as a painless testicular mass or incidental finding on ultrasound (US). Pain, either scrotal or abdominal/back, may occur and result in delayed diagnosis [40]. Gynaecomastia may be present in a small number of patients. Clinical assessment should thus include abdominal, chest and supraclavicular examination.

5.2 Imaging

5.2.1 ***Primary tumour***

The primary tumour and contralateral testis need to be assessed radiologically to:

1. confirm the presence of a mass;
2. determine whether it is intra- or extra-testicular;
3. assess its volume and anatomical location;
4. characterise the contralateral testicle – to exclude other lesions and identify risk factors for GCNIS (see section 5.4.4).

High-frequency (>10 MHz) testicular US is recommended. Scrotal US is also recommended for all men with retroperitoneal or visceral masses with/or without elevated serum β-hCG or Alpha-fetoprotein (AFP) in the absence of a palpable testicular mass [41].

Small, usually non-palpable incidental masses, may be incidental findings on scrotal US which may be benign. Of lesions with small diameter, virtually all < 3mm, 87% of those < 5mm, and 70% < 10mm are benign [42-44]. With small masses, US features may assist in discriminating between benign and malignant tumours although none are completely reliable [42].

Scrotal magnetic resonance imaging (MRI) provides higher sensitivity and specificity than US in the diagnosis of TC, but its high cost does not justify its routine use for this purpose [45]. It should only be considered when US is inconclusive as local staging for potential testis-sparing surgery (TSS), to differentiate between paratesticular and intratesticular lesions, and/or to characterise intratesticular masses (e.g., distinctive features of Leydig tumours) [45].

5.2.2 ***Staging***

Cross-sectional imaging of the chest, abdomen and pelvis is recommended in patients with elevated markers or clinical suspicion of metastases for staging before orchidectomy and remains standard practice. This may be postponed in patients with small or indeterminant masses until histopathological confirmation of malignancy. Contrast enhanced CT scan (CECT) and MRI are the imaging modalities used. Evidence does not support the use of Fluorodeoxyglucose-positron emission tomography (FDG-PET) for initial staging of TC [46, 47].

a. Abdomen and Pelvis

Contrast enhanced CT scan is the long-established imaging modality used to assess the abdomen and pelvis to identify nodal and visceral metastases. The size of metastases should be described in three dimensions, or at least by the greatest diameter. The expected patterns of nodal spread in TC should be considered when evaluating small and borderline nodes.

A SR of a number of small studies, with a total of 102 evaluable patients, has suggested that MRI appears comparable to CECT in detecting nodal metastases [48]. It is significantly more expensive and less available than CECT for routine use. It clearly has utility in patients who have contra-indications to iodine-based contrast media or likely to require numerous subsequent scans.

b. Thorax

The chest and supraclavicular fossa should also be imaged with CECT to assess for nodal and pulmonary disease. Magnetic resonance imaging appears equivalent to CT in detecting supra-diaphragmatic lymph nodes but less sensitive in detecting pulmonary nodules. Thus, it is not recommended as a routine alternative to CT [49].

c. Other Sites

Cerebral and spinal imaging is recommended in GCT patients with either multiple lung metastases or poor-prognosis IGCCCG risk group (especially with β-hCG values > 5,000 UI/L), or clinical symptoms [50]. Data from cerebral and spinal metastasis detection in other malignancies suggest that MRI is far more sensitive than CECT but requires specific expertise [51, 52]. When available, MRI should be used to evaluate for both cerebral and spinal metastases in GCTs if there are clinical concerns. Contrast enhanced computerised tomography may be used if MRI is not available or contraindicated.

5.3 Serum tumour markers

5.3.1 ***Pre-operative serum tumour markers***

Serum AFP, beta subunit of human Chorionic Gonadotropin (β-hCG) and LDH should be determined before orchidectomy as they support the diagnosis of TC and may be indicative of GCT histology.

Up to 90% of NSGCT's have elevated AFP or β-hCG at diagnosis with 39% having an increased level of both [40, 53]. Pure seminomas may also have elevated β-hCG level at diagnosis in up to 30% of cases [53]. Significant elevation of AFP in patients with seminomas should raise concerns of a NSGCT component. Modest stable marker elevations may be considered 'normal' and of no clinical significance [37].

Thus, current tumour markers have limitations due to their low sensitivity as normal levels do not exclude the presence of disease.

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

Tumour markers need to be repeated following orchidectomy providing staging and prognostic information [37]. If elevated pre-operatively, normalisation may take several weeks as the serum half-lives of AFP and β-hCG are five to seven days and one to three days, respectively. If these remain elevated or increase, metastatic disease is likely [53]. Marker normalisation after orchiectomy, however, does not exclude the possibility of metastatic disease.

In addition to staging, marker levels are used to define risk stratification and prognosis (Table 3). They are also used to monitor treatment response and detect disease relapse [53]. With follow-up, the precise frequency of testing is not well defined [54].

5.3.3 ***Other tumour markers***

Micro RNAs (miRNAs) are emerging as potential new biomarkers. Pre-operative elevation has been reported in 80-90% of both SGCT and NSGCT with higher levels in metastatic compared to localised disease [55]. A number of studies suggest higher discriminatory accuracy for miRNAs (particularly miR-371a-3p) compared to conventional GCT markers in diagnosis, clinical staging, treatment monitoring, and predicting residual or recurrent viable disease [55-57]. Furthermore, they may differentiate between GCT and other (stromal/non-germ cell originated) tumours [57]. Issues which need to be resolved for use in routine clinical practice include laboratory standardisation, availability of the test and, importantly, prognostic validation [58]. As with both AFP and β-hCG, miRNA is not expressed in teratoma which will limit its use in NSGCT.

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 for patients with a TGTC. A scrotal approach should be avoided when TC is suspected as it results in a higher local recurrence rate [59].

5.4.2 ***Testis-sparing surgery***

In men with GCTs, orchidectomy represents the standard of care as pathological studies describe multifocal and/or adjacent GCNIS in 20-30% of patients [60]. Testis sparing surgery when feasible, may be considered in synchronous bilateral tumours or in tumours in solitary testis [61]. In these settings, at least two additional testicular biopsies should be taken to exclude GCNIS [62].

Testis-sparing surgery is a valid treatment option in men with interstitial cell or benign testicular tumours and may prevent hypogonadism and infertility in young men. These tumours are often small although larger lesions may be difficult to differentiate from GCT.

Accordingly, TSS may be considered in patients with small or indeterminate testicular masses, negative tumour markers and a normal contralateral testis to avoid over-treatment of potentially benign lesions and preserve testicular function [61, 63]. Patients should be informed that cancer may be present even in small (i.e., < 1 cm) masses [61, 64, 65].

In both settings, TSS should be offered together with frozen section examination (FSE). Frozen section examination has shown to be reliable and highly concordant with final histopathology in expert hands, with a 99% and 96% of sensitivity and specificity, respectively, and 98% and 97% of PPV and NPV, respectively [63]. In cases of discordance between FSE and final pathology delayed orchiectomy may be required.

In cases of a history of GCT or indeterminate small testicular lesion, patients should be made aware of the following issues regarding TSS practice: that limited data exists regarding oncological safety of TSS; that local recurrence rates have been reported (up to 26.9%), when TC is present in the specimen [61, 66], and that TSS has implications for ongoing surveillance of the testis. Similarly, patients should be informed about the role and impact of adjuvant radiotherapy (RT) when GCNIS is present, potential infertility, the need for hormonal supplementation despite parenchyma preservation [61, 67], and any discordance between FSE and final pathology requiring a delayed orchidectomy.

5.4.3 Insertion of testicular prosthesis

Testicular prosthesis should be offered to all patients receiving unilateral or bilateral orchidectomy [68]. The prosthesis can be inserted at orchidectomy or subsequently without adverse consequences, including infection [69].

5.4.4 Contralateral biopsy

Contralateral biopsy has been advocated to exclude GCNIS [70] and is routine policy in some countries [71]. It is, however, controversial to recommend routine contralateral biopsy in all patients due to the low incidence of GCNIS and metachronous contralateral testicular tumours (up to 9% and approximately 2.5%, respectively) [72, 73], the morbidity of GCNIS treatment (see section 6.1.1), and the fact that most metachronous tumours are low stage at presentation [74, 75]. 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 > 40 years without risk factors [62, 76, 77]. Patients should be informed that a subsequent GCT may arise despite a negative biopsy [78]. When indicated, a two-site surgical testicular biopsy is the technical procedure recommended [62].

5.5 Pathological examination of the testis

The recommendations for reporting and handling the pathological examination of a testis neoplasm are based on the recommendations of the International Society of Urological Pathology (ISUP) [79-82]. This is outlined in Appendix 2 - Pathological examination of the testis.

5.6 Screening

No high-level evidence studies supporting screening programs exists [83, 84]. In contrast, young males should be informed about the importance of testicular self-examination. Testicular self-examination is recommended in high-risk groups which include a history of cryptorchidism, as well as those with a personal or family history of TC [83, 85].

5.7 Summary of evidence and recommendations for the diagnosis and staging of testicular cancer

Summary of evidence	LE
Poor sperm quality is frequently found in TC patients, before and after treatment. Semen preservation is the most cost-effective strategy for fertility preservation.	2b
Serum tumour markers (AFP, β-hCG and LDH) should be determined before and after orchidectomy and throughout follow-up. They are used for accurate staging, risk stratification, to monitor treatment and to detect relapse.	2b
For abdominal staging, CECT has a median sensitivity, specificity, PPV, NPV and accuracy of 67%, 95%, 87%, 73% and 83%, respectively. Sensitivity decreases and specificity increases with increasing lymph node size.	2a

For chest staging, CECT has a median sensitivity, specificity, PPV, NPV and accuracy of 100%, 93%, 68%, 100% and 93%, respectively.	2a
Magnetic resonance imaging and CECT are key image modalities for the detection of brain metastasis. Magnetic resonance imaging is far more sensitive than CECT, though it does require expertise.	2b
Fluorodeoxyglucose-positron emission tomography has a limited diagnostic accuracy for staging before chemotherapy.	2b
There are no high-level evidence studies supporting screening programs.	2b
In testicular sparing surgery, FSE has shown to be reliable and highly concordant with final histopathology.	1b
There is no evidence supporting any size criteria for a testicular lesion to be safely followed-up.	2b
In patients without risk factors, there is low incidence of contralateral GCNIS and of metachronous GCT.	2b

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

6. DISEASE MANAGEMENT

6.1 Stage I germ cell tumours

6.1.1 ***Germ cell neoplasia "in situ" (GCNIS)***

If GCNIS is diagnosed and the contralateral testis is normal, options include orchidectomy or close observation, as the five-year risk of developing TC is 50% [86]. In a solitary testis, local RT (18-20 Gy in fractions of 2 Gy) should be considered [87-90]. Radiotherapy to a solitary testis will result in infertility and increased long-term risk of Leydig cell insufficiency [87]. Fertile patients who wish to father children may defer radiation therapy and be monitored with regular testicular US [62].

Chemotherapy is ineffective to reliably eradicate GCNIS [91, 92].

6.1.2 ***Seminoma germ cell tumour clinical stage I***

As outlined in 4.3.1 [34, 36], approximately 15% of patients relapse after orchiectomy alone.

Individual relapse risk can range from 5 to 60%, depending on a combination of risk factors. Adjuvant treatment decisions should be based on thorough discussions with the patient, incorporating potential risks and benefits, as well as individual patient circumstances. The majority of patients are cured with orchiectomy alone and survival rates in CS I are close to 100% regardless of treatment strategy; thus, AS is the preferred option for the majority of patients. Higher risk patients may wish to consider the option of adjuvant treatment.

6.1.2.1 Active Surveillance

This requires a strict protocol of repeated cross-sectional imaging, monitoring of serum tumour markers and clinical assessment for the early identification of patients experiencing relapse who must receive salvage treatment (See Table 9).

Several prospective, non-randomised surveillance studies have been conducted over the past decade. These have shown an overall risk of relapse in unselected CS I patients of 12-20% at five years with 17% in the largest series of over 1,500 patients [93]. Most occur in the retroperitoneum during the first two years [94, 95].

According to a SR, AS offers almost identical OS as adjuvant management strategies, approaching 100% [96].

The cancer-specific survival (CSS) rate on AS for CS I seminoma is over 99% [93, 95, 97]. This is dependent on compliance with surveillance and treatment of relapse if this occurs. Whilst cost effective compared to other management strategies [98], surveillance can represent a burden to the patient due to the need for repeated imaging of the retroperitoneum and clinic visits. These may negatively impact patient compliance which is crucial to an AS strategy.

6.1.2.2 Adjuvant chemotherapy

An RCT comparing one cycle of carboplatin reaching area under curve of 7 mg/mL/min (AUC 7) to adjuvant RT showed no difference in relapse-free rates (95% and 96%), time to recurrence and survival after a median follow-up of four years [99]. Adjuvant carboplatin (AUC 7) is therefore an alternative to surveillance in CS I SGCT [99]. Time to relapse after Carboplatin may be longer than with AS, with retrospective data reporting a median time to relapse of nineteen months, with 15% of relapses occurring beyond three years. Most patients relapsing after adjuvant carboplatin can be successfully treated by standard, stage-adapted cisplatin-based chemotherapy [100]. In some selected cases, retroperitoneal lymph-node dissection (RPLND) may be adopted in specific protocols (see below).

One cycle of adjuvant carboplatin does not seem to have significant long-term toxicities. In a series of 199 CS I SGCT patients, there was no increase in overall mortality, mortality from cardiovascular events, and no excess of haematological or non-testicular solid malignancies compared to the general population in the UK [101].

6.1.2.3 Adjuvant radiotherapy

Radiotherapy should generally be reserved for a highly selective group of patients, who would be unsuitable for systemic chemotherapy in the event of relapse. This relates to the toxicity of RT, specifically the long-term risk of non-germ cell malignancies in the radiation field [102-105]. Generally, adjuvant RT should be avoided, particularly in young patients with a long, life expectancy.

6.1.2.4 *Risk-adapted treatment*

Prospective trials based on tumour size > 4 cm and stromal RTI have demonstrated the feasibility of a risk-adapted approach [106-110].

A trial of 897 patients offered surveillance to those with no or one of these two risk factors whilst patients with both risk factors were offered one dose of carboplatin, AUC 7 [106]. At a median follow-up of 5.6 years, 4% of patients under surveillance relapsed, compared to 2% of patients who received adjuvant carboplatin. With one or both risk factors 15.5% of surveillance patients relapsed vs. 9% receiving adjuvant carboplatin. Thirty-three per cent of relapses after adjuvant carboplatin occurred more than three years after orchidectomy with 3% occurring after five years [106].

6.1.2.5 *Summary of evidence and recommendations for the treatment of clinical stage I seminoma germ cell tumour of the testis*

Summary of evidence	**LE**
Patients with CS I SGCT have, in general, a low risk of recurrence after radical orchiectomy.	2a
A combination of tumour size category, RTI and lymphovascular invasion correlate with the risk of relapse at five years after orchiectomy.	2a
Evidence and ease of use are limited for a routine use in guiding adjuvant treatment decisions upon risk factors.	2a
Active surveillance is a feasible approach with conditional relapse risk in unselected series up to 20%, meaning that > 80% of patients is cured by orchiectomy alone. Disease-free survival approaches 100% independently of treatment.	2a
In non-randomised prospective series five-year relapse rates with adjuvant carboplatin are 2% in patients without conventional risk factors and 9% in patients with one or both risk factors.	2b
Adjuvant chemotherapy with one course carboplatin AUC 7 is not inferior to adjuvant radiotherapy when pathological risk factors are considered.	1b
Adjuvant radiotherapy is associated with an increased risk of developing secondary non-germ cell malignancies.	2b

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

6.1.3 ***Non-seminomatous germ cell tumours clinical stage I***

Management options for CS I NSGCTs include surveillance and adjuvant chemotherapy. Retroperitoneal lymph node dissection has a limited role.

Overall, approximately 70% of CS I NSGCTs are cured with orchiectomy alone. In those with the high-risk feature of LVI, historical figures reported relapse in 50% compared to 15% in those without LVI. A thorough discussion should be undertaken with the patient outlining the potential advantages and disadvantages of treatment options, as well as individual co-morbidities, disease features, risk factors, specific circumstances, and personal preferences, to guide their treatment decision.

6.1.3.1 Surveillance

Surveillance for CS I NSGCT entails a strict protocol of repeated cross-sectional imaging, monitoring of serum tumour markers and clinical assessment for the early identification of patients experiencing relapse who must receive salvage treatment (See Table 9).

The largest reports of surveillance indicate a cumulative relapse risk in about 30% of CS I NSGCT (five-year conditional risk of relapse 42% and 17% for high- and low-risk CS I-NSGCT, respectively) [93, 111]. Of these, 92% present within the first two years [93, 111-114].

6.1.3.2 Retroperitoneal lymph node dissection

Since the introduction of cisplatin-based chemotherapy the role of adjuvant primary RPLND in men with CS I NSGCTs has decreased. According to data from high-volume and expert centres, primary RPLND is associated with a risk of relapse < 15% [115]. More recent data report on a relapse rate of 10% in case of negative nodes (pathologic stage [PS] - I) and < 30% in case of nodal metastases (PS II) [115-117], possibly due to selection or stage migration.

The few indications in CS I disease include men with teratoma with somatic malignant component (TSMC), or patients who are not willing or suitable to undergo chemotherapy in case of recurrence, in particular in those where vascular invasion is present.

Recent publication supports the safety of surveillance alone, in PS II disease following RPLND, as 75-80% are relapse free at two and five years [116-118]. Those with relapse can be rescued with standard chemotherapy [119, 120]. With PS II, both adjuvant chemotherapy comprising two cycles of (B)EP (PPT only) and AS are standard options to be discussed with each individual.

Strategies to reduce the morbidity of primary RPLND include nerve-sparing and minimally invasive approaches. In a multi-centre setting, higher rates of in-field recurrences and complications have been reported with nerve-sparing RPLND [121, 122]. This suggests that primary RPLND, when indicated and chosen, should be performed by an experienced surgeon in a specialist centre. Minimally invasive (laparoscopic or robot-assisted) primary RPLND, appears feasible and safe (e.g., low-complication rate) in experienced hands. This must only be performed in high-volume RPLND centres with appropriate minimal-invasive surgery expertise [123-130]. There is limited recent data on mid-term follow-up.

Despite some advantages, such as good efficacy and a less demanding and costly follow-up due to reduced need for cross-sectional imaging [131], RPLND for CS I NSGCT has seen a diminished role. This is due to the high CSS rates of surveillance, the low relapse rates following adjuvant chemotherapy, and the challenges in achieving large-scale reproducibility of primary RPLND.

6.1.3.3 Adjuvant chemotherapy

Adjuvant chemotherapy has been evaluated with both one and two cycles of BEP (cisplatin, etoposide, bleomycin) in CS I NSGCT. A prospective trial from 1996, as well as subsequent studies, used two cycles of BEP in high-risk patients (LVI present) [132-134]. In these series, including 200 patients, some with a median follow-up of nearly 7.9 years [132], a relapse rate of only 2.7% was reported, with minimal long-term toxicity. Two cycles of cisplatin-based adjuvant chemotherapy do not appear to adversely affect fertility or sexual activity [135].

Other studies have shown one cycle of adjuvant BEP results in similar very low recurrence rates (2-3%) [136, 137]. Reduction from two to one cycle of BEP improves the risk-benefit ratio of adjuvant chemotherapy considerably. A randomised phase III trial has also compared two-year recurrence free survival with adjuvant BEP x 1 to RPLND. Results favoured chemotherapy with recurrence free survival of 99.5% vs. 91% [122]. No clinically relevant differences in quality of life (QoL) were detected [138].

A community based prospective study of 490 unselected patients with CS I NSGCT that received adjuvant single cycle BEP had five-year relapse rates of 3% and 2% for LVI+ and LV- patients, respectively. After a median follow-up of eight years these rates were sustained, no relapses were observed beyond 3.3 years [136, 137]. These numbers imply that > 90% of relapses are prevented by single cycle BEP which is now the recommended strategy if adjuvant chemotherapy is considered [136, 137]. The very-long term (> 20 years) side effects of adjuvant chemotherapy, particularly cardiovascular, are yet to be fully defined and this should be considered during shared decision-making [139, 140].

Limited data are available on outcomes with relapse after adjuvant BEP. A retrospective analysis indicated that about one third of these relapses were late and that the outcome may be slightly worse compared to those presenting with *de novo* metastatic disease [141].

6.1.3.4 Risk-adapted treatment

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

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

Some patients may wish to consider primary RPLND although they need to be aware of the potential additional requirement of adjuvant chemotherapy if nodes contain active disease (pN1), as well as the 10% risk of systemic relapse, even if pN0, requiring subsequent chemotherapy treatment (BEP x 3).

6.1.3.5 Post-Pubertal Teratoma with somatic-type malignancy

A multi-institutional study analysing retrospective datasets of CS I patients with PPT with TSMC suggested these patients had inferior five-year OS of approximately 10% compared to other CS I GCT patients. Furthermore, CS I TSMC cases undergoing primary RPPLND had a much higher proportion of nodal metastases (PS II) than expected (37.5%). Despite its limitations, this study provides the only evidence on this issue and supports primary RPLND in CS I NSGCT with TSMC [142].

For patients presenting with CS I pure PPT surveillance provides comparable survival outcomes to primary RPLND [143]. A mixed population based study on 237 CS I with pure teratoma in the testis, showed an increasing trend favouring surveillance over RPLND as well as a not significant difference in OS at a median follow-up of 54 months [143].

However, subtype discrepancies in the primary diagnosis of PPT are not infrequent and involve secondary somatic malignancies in 83% of cases. As such, central review by an expert genitourinary pathologist is recommended when teratoma is diagnosed in the orchidectomy specimen [144].

6.1.3.6 Summary of evidence and recommendations for the treatment of clinical stage I non-seminoma germ cell tumour of the testis

Summary of evidence	**LE**
Lymphovascular invasion increases the risk of relapse.	2a
The relapse rate with AS is up to 50%, when LVI is present.	2a
The relapse rate in patients who receive adjuvant chemotherapy with BEP (x 1 cycle) is up to 3%.	2a
Adjuvant chemotherapy with BEP x 1 is superior to adjuvant RPLND in terms of the risk of relapse when the two strategies are not centralised in expert centres.	1b
A risk-adapted approach, based on LVI invasion is feasible.	2b
The acute toxicity of one cycle adjuvant BEP is low.	1b

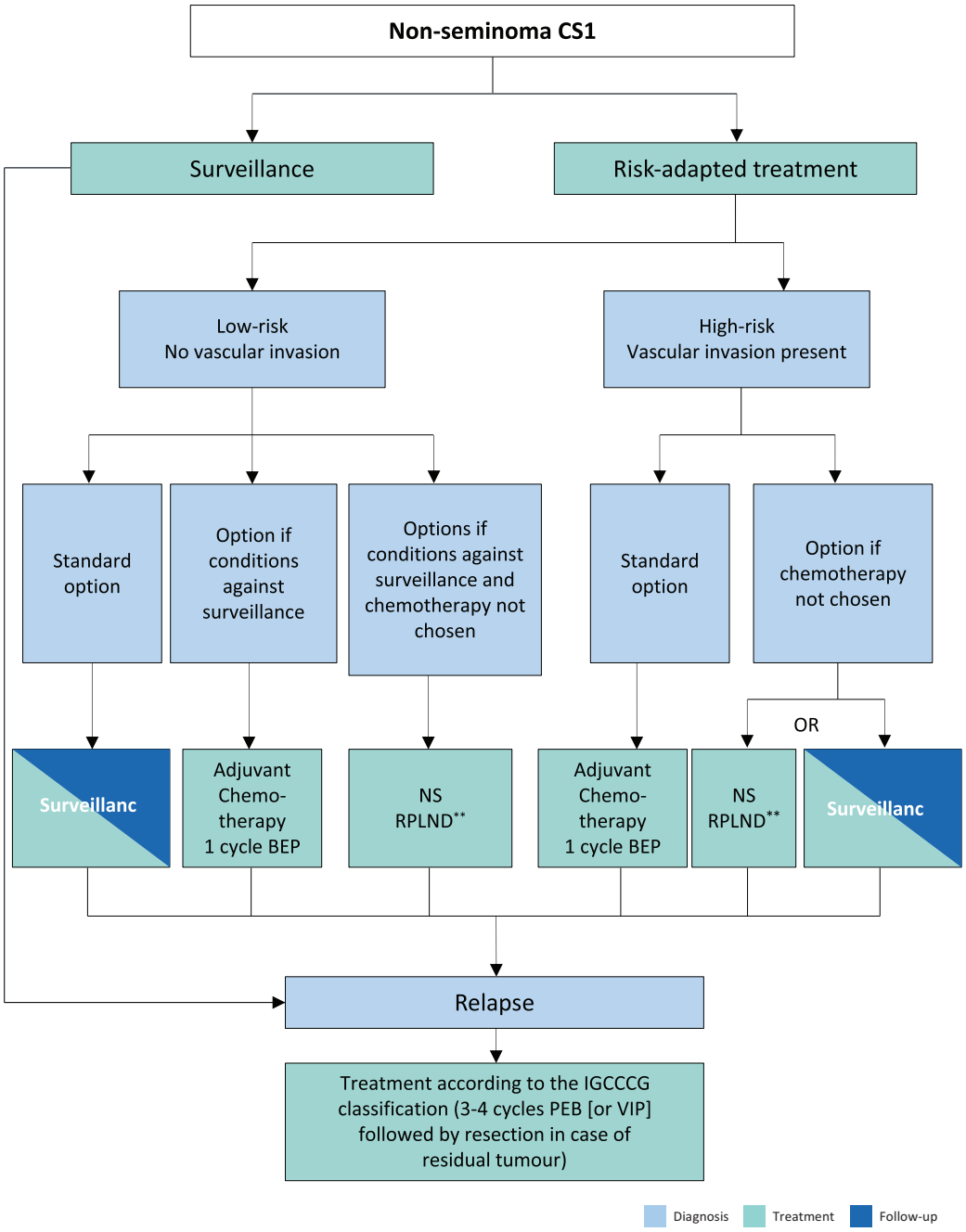
Recommendations	**Strength rating**
Inform patients about all management options after orchidectomy: surveillance, adjuvant chemotherapy, and retroperitoneal lymph node dissection, including treatment-specific recurrence rates as well as acute and long-term side effects.	Strong
Offer surveillance or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

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

invasion

Recommendations	Strength rating
Stage IA (pT1, no vascular invasion): low risk	
Offer surveillance if the patient is willing and able to comply.	Strong
Offer adjuvant chemotherapy with one course of cisplatin, etoposide, bleomycin (BEP) in low-risk patients not willing (or unsuitable) to undergo surveillance.	Strong
Stage IB (pT2-pT4): high risk	
Offer adjuvant chemotherapy with one course of BEP, or surveillance and discuss the advantages and disadvantages.	Strong
Offer surveillance to patients not willing to undergo adjuvant chemotherapy.	Strong
Offer nerve-sparing retroperitoneal lymph node dissection to highly selected patients only; those with contraindication to adjuvant chemotherapy and unwilling to accept surveillance.	Strong

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



** Discuss all treatment options with individual patients, to allow them to make an informed decision as to their further care.*
*** In case of PS II, the rate of recurrence is higher, and chemotherapy can be discussed (max. 2 cycles).*
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.

6.2 Metastatic germ cell tumours

The first-line treatment of metastatic GCTs depends on:

I. the histology of the primary tumour;
II. prognostic groups as defined by the IGCCCG (Table 3) [37];
III. serum tumour marker decline at the end of 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 [145].

6.2.1 ***Clinical stage I with (persistently) elevated serum tumour markers***

With elevated markers and CS I, weekly measurement of markers are recommended. If AFP or β-hCG increase or fail to normalise following orchidectomy, US examination of the contralateral testicle must be performed. If a contralateral tumour is excluded, unequivocal rising tumour markers indicates CS I, and treatment for good prognosis metastatic GCT should be given. With stable markers, a new staging procedure, 4-6 weeks after orchidectomy, is recommended.

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

The treatment of true CS I SGCT should be the same as other metastatic GCT. With this, ten-year OS of 95%, have been reported [146, 147].

6.2.2 ***Metastatic disease (stage IIA/B)***

6.2.2.1 Stage IIA/B seminoma

Patients with enlarged retroperitoneal lymph nodes < 2 cm in greatest diameter and normal markers may be observed for six to eight weeks with repeat-staging imaging as these may be non-metastatic on average in 10% of cases. Treatment should only be initiated if metastatic disease is unequivocal, based on biopsy, increasing nodal size/number, or subsequent marker rise [38, 146]. A special case are those patients who can undergo primary RPLND within a trial or institutional study (see below for further details).

Historically, radiotherapy has been the primary treatment for stage II A/B seminoma, showing relapse rates between 9-24% [148, 149]. Recommended radiation doses for stage IIA and IIB are 30 Gy and 36 Gy, respectively. With these doses, five-year relapse-free survival rates stand at 92% for stage IIA and 90% for IIB [148, 149]. A reduced dose of 27 Gy for stage IIA has been associated with a higher relapse rate [95].

Chemotherapy is a standard option for stage IIA/B seminoma, with relapse rates of 0-8% for stage IIA disease and 8-14% for stage IIB disease, and an excellent OS of 99% [150, 151]. The standard regimen in stage II seminoma is BEP x 3 (see Appendix 3.1.2) or EPx4 if there are concerns with the use of bleomycin [152]. There are no randomised studies comparing radiotherapy and chemotherapy. A meta-analysis of thirteen high-quality studies, comparing efficacy and toxicity of radiotherapy and chemotherapy showed that these appeared similarly effective in both stage IIA/IIB patients although with a non-significant trend towards greater efficacy for chemotherapy (HR: 2.17) in stage IIB seminoma [150]. 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 [150]. Several series have shown an increased risk of developing a second solid cancer of 1.8-2.0-fold with radiotherapy [153]. Long term toxicities of chemotherapy including second cancers are also a concern [153].

6.2.2.1.1 Retroperitoneal lymph node dissection

Several institutional series and a few single-arm phase II studies have explored primary RPLND with or without adjuvant chemotherapy as an alternative to chemotherapy in men with low volume CS II A/B [154-158]. Differences in surgical technique/template, extent of use of adjuvant chemotherapy, patient selection, and length of follow-up make direct comparisons of these surgical series to chemotherapy difficult. In these reports, patients with low-volume CS II A/B seminoma had two-year recurrence rates of 5-30%, with immature OS outcomes owing to short follow-up. Relapse will almost always be cured by standard chemotherapy. Longer follow-up and ideally, comparative prospective studies are required to ensure this can be recommended as a safe stand-alone treatment option equivalent to chemotherapy alone.

Primary RPLND for men with low volume CS II seminoma should only be performed by surgeons with extensive experience in specialised TC centres. Ideally, the procedure should take place within a prospective cohort or clinical trial in order to maintain surgical quality and monitor long-term oncological outcomes.

6.2.2.1.2 De-escalating approaches

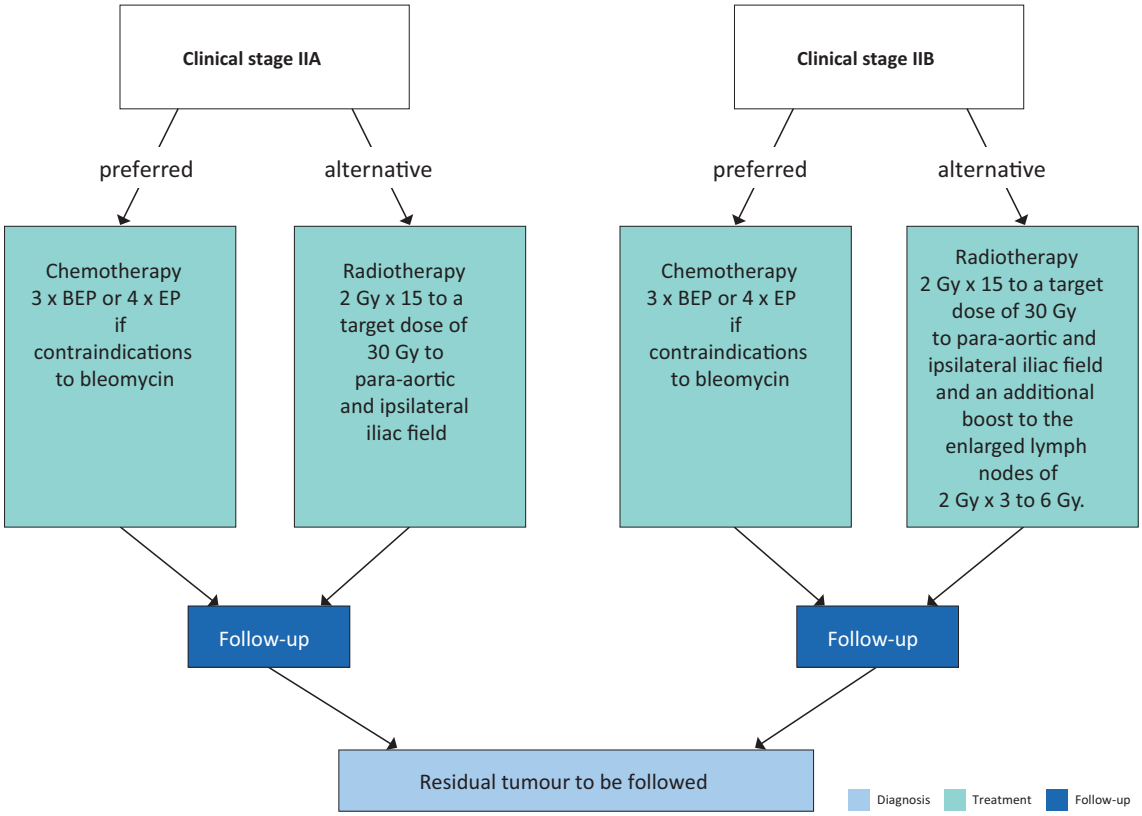
Several trials attempted to de-escalate chemotherapy and RT, aiming at maintaining the traditional excellent oncologic result, while minimising treatment burden and toxicity.

Such an approach was evaluated in a phase II randomised trial, assessing chemotherapy de-escalation in patients guided by metabolic response on FDG-PET/CT after two initial cycles of etoposide, cisplatin (EP) chemotherapy [159]. Patients with complete metabolic response after EP x 2 received de-escalated treatment with one subsequent cycle of carboplatin AUC7, whilst patients with residual metabolic activity completed the initial schedule of EP x 4. The study showed comparable three-year PFS rate of 90% and 91% for the EP and carboplatin groups respectively, and a two-year OS of 100% for both groups. Despite the apparently maintained oncological efficacy, larger studies and longer follow-up is needed. For these reasons and owing to the absence of consensus criteria for FDG-PETC/CT interpretation, making treatment decisions based solely on FDG-PET/CT responses is not currently recommended for routine use [159].

Another de-escalation option emerged, involving one cycle of carboplatin followed by involved-node (small-volume) radiotherapy (30 Gy in 15 sessions for stage IIA and 36 Gy in 18 sessions for stage IIB). This approach has shown a three-year PFS rate of 93.7% in a single-arm phase II trial, narrowly missing its target primary endpoint of 95% three-year PFS [160]. Currently such approaches lack the level of evidence needed for routine use recommendation.

Summary of evidence	**LE**
At this stage all de-escalation strategies, including RPLND remain under evaluation and should only be considered in high volume specialised centres within a prospective cohort or clinical trial.	3

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



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

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

6.2.2.2.1 Serum tumour marker negative

Patients with normal markers and equivocal lymph nodes (< 2 cm) may be considered for initial surveillance with early re-evaluation at six weeks. If the lesion progresses or fails to resolve it should be regarded and treated as CS II.

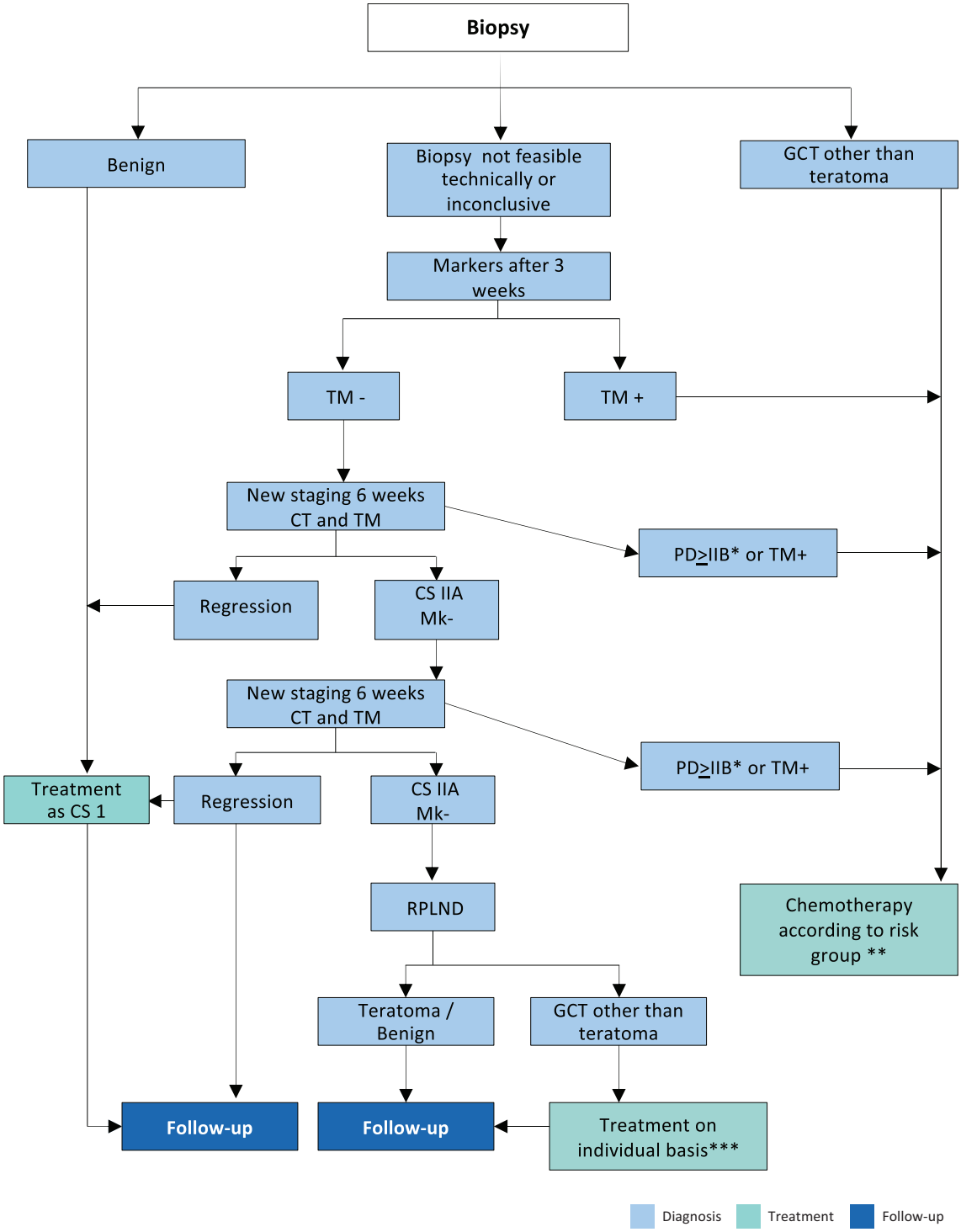
With CS IIA NSGCT disease and normal or normalised tumour markers, nerve-sparing RPLND performed by an experienced surgeon in a specialised centre is the recommended initial treatment. Patients may be down-staged to PS I in up to 20% of cases and require no further treatment. Patients with PPT alone will avoid unnecessary chemotherapy as surgery alone is curative. The oncological outcomes after RPLND in CS II NSGCT have been evaluated in a SR [161]. Of the included studies the majority were retrospective with included patients differing substantially in histopathology, size and number of retroperitoneal lymph nodes resected, surgical templates, and the use of adjuvant chemotherapy. In men with marker negative CS II NSGCT, PS II is confirmed in 80%. Without adjuvant chemotherapy 12-40% recurred compared to 0-4% in those who received adjuvant chemotherapy.

These findings align with large single centre reports of outcomes following RPLND alone for PS II NSGCT with active disease [112, 119, 120, 162]. These studies reported five-year relapse of less than 30%, with the majority occurring outside the retroperitoneum requiring systemic chemotherapy according to risk group.

Adjuvant chemotherapy may be discussed with the patient to reduce the risk of relapse in this setting. Key issues include risk factors for relapse (as positive lymph node-ratio), the risk of overtreatment in up to 70% of cases and the need for rigorous follow-up. When adjuvant chemotherapy is chosen, standard treatment is BEP or EP for a maximum of two cycles [161, 163].

A recent single institution real world study including 61 CS IIA/B < 3cm NSGCT (out of 66 GCT) with active disease, showed a 77% two-year PFS without adjuvant chemotherapy in stage IIA/B < 3 cm, with the greatest benefit achieved in stage IIA marker negative cases [162].

Figure 3: Flowchart Nonseminoma CS IIA Mk- at Diagnosis/Staging



CS = clinical stage; CT = computed tomography; GCT = germ cell tumour; GCC =Germ Cell Cancer; RPLND = retroperitoneal lymph node dissection; PD = progressive disease; TM = tumour markers.

* *With marker negative PD > IIB RPLND may be considered if radiological features of teratoma*

** *Most will be good prognostic group (BEP x3 or EP x4) - see Appendix 3 https://uroweb.org/guidelines/testicular-cancer/publications-appendices.*

*** *In case of PS II A/B patient can be followed-up or receive adjuvant chemotherapy (maximum of 2 cycles).*

6.2.2.2.2 Serum tumour marker positive

Patients with elevated tumor markers and radiological stage IIA/B at diagnosis or relapse should be treated with chemotherapy as outlined in tables 4 and 5 and section 6.2.3.1 based on IGCCCG risk group. Most patients will have a good prognosis for whom BEP x 3 is most appropriate or EP x 4 if there are concerns with the use of bleomycin.

Primary RPLND for CS IIA/B disease with elevated markers is not recommended outside a specific study in a referral centre [162, 164].

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

6.2.3.1 Primary chemotherapy

6.2.3.1.1 Good-prognosis risk group - seminomatous germ cell tumour

For metastatic seminoma, a cisplatin-based regimen should be used. A cisplatin-based combination chemotherapy has shown superior efficacy over carboplatin-based regimens [165]. The standard regimen in good-risk seminoma is three, twenty-one days cycles of BEP (Table 4). Alternatively, EP x 4 may be considered especially when bleomycin is contraindicated [166]. This achieves similar response rates but may have a slightly higher risk of relapse.

Post-chemotherapy masses should be managed as described in Section 6.3.2.

6.2.3.1.2 Intermediate-prognosis risk group - seminomatous germ cell tumour

For patients with intermediate-risk seminoma, BEP x 4 is the standard regimen. If bleomycin is contraindicated the combination of etoposide, cisplatin, ifosfamide (VIP) should be given. No RCT has focused specifically on this rare group of patients (see Table 3).

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

The standard regimen in good-risk non-seminoma is BEP x 3 (Table 4) [166].

An RCT supports the equivalence of three or five-day regimes with three or four cycles of BEP for projected two-years PFS. Three-day regimes are associated with increased toxicity [167, 168]. Based on these data BEP x 3 as a five-day regimen is strongly recommended in the good-prognosis risk group.

Two RCTs support the superiority of BEP x 3 over other regimes or schedule intensities [152, 169]. A further RCT has suggested that when EP is used, the mortality rate is twice that of with BEP, although the difference did not reach statistical significance [152].

Patients with a clear contraindication to bleomycin may receive EP x 4 [167]. In all other cases omission of bleomycin is not recommended.

For more information regarding Chemotherapy protocols, please visit the EAU guidelines website: https://uroweb.org/guidelines/testicular-cancer/publications-appendices

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

The standard regimen is BEP x 4 [170]. Four cycles of VIP has similar efficacy but is more myelotoxic [171]. Four cycles of VIP including primary granulocyte colony stimulating factor (G-CSF) prophylaxis should be applied in patients with contraindications to bleomycin.

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

The standard regimen is BEP x 4. Four cycles of VIP have similar efficacy, but is more myelotoxic [171]. Four cycles of VIP including primary G-CSF prophylaxis should be applied in patients with contraindications to bleomycin [172, 173].

Serum tumour marker decline is the only prospectively confirmed predictor for response to cisplatin chemotherapy in metastatic germ cell tumour patients. Patients with inadequate tumour marker decline after the first or second cycle of BEP represent a prognostically inferior subgroup [173, 174]. There are several ways to calculate tumour marker decline kinetics with an example available at: https://www.gustaveroussy.fr/calculation-tumor/.

An RCT demonstrated improved PFS when intensifying treatment with dose-dense chemotherapy in patients with an early unfavourable tumour marker decline [175]. The trial was not powered to estimate OS differences. Based on the results from this trial, patients with an unfavourable tumour marker decline after BEP x 1 can be switched to a more intensive (dose-dense) chemotherapy regimen [175]. Additional patient groups with an unfavourable prognosis on standard treatment are primary mediastinal non-seminoma and patients with brain metastases at initial diagnosis [176, 177]. These may also be candidates for upfront intensified treatment, preferably in a prospective study.

In RCTs, primary high-dose chemotherapy (HDCT) with subsequent autologous stem cell transplantation has not shown an OS benefit in the overall poor-prognosis patient population in RCTs [172, 173]. Selected patients, such as primary mediastinal nonseminoma, do have poor survival following standard dose chemotherapy [178]. They may derive a benefit from primary HDCT [179], preferably within a prospective protocol.

Better outcomes are reported for intermediate and poor prognosis patients treated at high-volume centres [180-182]. Due to their unfavourable survival, poor-prognosis patients should be managed at centres with interdisciplinary germ cell tumour expertise and treated in ongoing prospective trials or registries, whenever possible.

There are no general recommendations for treatment modifications for patients with poor performance status (Karnofsky < 50%) or extended liver infiltration (> 50%), although two small patient series indicate that an initial cycle of dose-reduced therapy may reduce acute mortality without compromising long-term outcomes. The number of subsequent cycles of full-dose therapy should, however, not be reduced after an initial low-dose induction cycle [181, 183].

Patients with widespread pulmonary metastases are at risk for pulmonary haemorrhage and subsequent acute respiratory distress syndrome (ARDS) with induction chemotherapy. To reduce this risk, primary cytoreductive induction chemotherapy with EP over two to three days should be administered, followed by the first cycle of standard chemotherapy when the risk of ARDS has passed (typically after ten days) [181].

Table 4: Level of evidence for prognostic group and treatment

Prognostic group IGCCCG	Treatment	LE
Good (SGCT and NSGCT)	BEP x 3 or EP x 4	1b
Intermediate (SGCT and NSGCT)	BEP x 4 or VIP x 4	1b
Poor (NSGCT)	BEP x 4 or VIP x 4 if favourable marker decline	1b
	Dose escalation in selected cases with inadequate serum tumour marker decline	1b

6.2.3.1.6 Prevention of thromboembolism events during chemotherapy

Some RCTs have assessed the risks and benefits of thromboprophylaxis in ambulatory cancer patients receiving chemotherapy and report a relative risk reduction of 30-60% in venous thromboembolic events (VTE) at the cost of a doubling in bleeding risk [184-187]. Based on these results, the most recent American Society of Clinical Oncology (ASCO) Clinical Practice Guideline Update recommends thromboprophylaxis with apixaban, rivaroxaban, or low molecular weight heparin (LMWH) to cancer patients with a high risk of VTE and low risk of bleeding [188]. Metastatic germ cell tumour (mGCT) patients were under-represented in all trials and thus, it is not clear whether this recommendation applies to this group although retrospective data suggests a similar efficacy of VTE prophylaxis [189].

The EAU Guideline panel has discussed a recommendation regarding thromboprophylaxis. All members agreed that men with mGCTs undergoing cisplatin-based chemotherapy are at high-risk for VTE, and with the exception of those with choriocarcinoma and high volume extra-peritoneal disease, are at low risk of bleeding. Given the apparent high VTE incidence* and only non-validated VTE risk factors, the panel preferences were divided between those panel members that favoured thromboprophylaxis in all men and those panel members that restricted thromboprophylaxis to men with certain risk factors. Additionally, the majority of the panel agreed that a central venous-access device should be avoided whenever possible as this represents the only modifiable risk factor, which remained significantly associated with VTE in a multivariable risk-prediction model [190, 191].

* For more information regarding the prevention of thromboembolism events during chemotherapy, please see appendix 4, available online: https://uroweb.org/guidelines/testicular-cancer/publications-appendices

6.2.3.1.7 Summary of evidence and recommendations for the prevention of thromboembolism events during chemotherapy

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

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

6.3 Treatment evaluation and further treatment

6.3.1 Treatment evaluation

Response to treatment should be assessed after the initial induction cycle by repeat imagining and/or re-evaluation of tumour markers. With marker decline and/or radiologically regressing or stable tumour features, the planned chemotherapy should be completed [189, 191]. If markers decline, but metastases progress on imaging, induction therapy must be completed [192]. If markers have normalised and masses with features of PPT progress early surgical resection should be considered.

Slow marker-decline with the initial one to two cycles of chemotherapy warrants consideration for dose intensification (see section 7.2.3.1.5 re https://www.gustaveroussy.fr/calculation-tumor/.

Following completion of treatment, cases with a low-level β-hCG plateau should be observed to determine whether complete normalisation subsequently occurs. In patients with a low plateau serum AFP level after chemotherapy, removal of residual masses should be undertaken, with subsequent AFP monitoring. Preoperative AFP levels of > 30 µg/l and viable cancer found in the histological examination of the resected specimen have been described as predictors of relapse after first line chemotherapy [193]. Salvage chemotherapy is thus only indicated for documented marker progression [192, 194].

6.3.2 Residual tumour resection

6.3.2.1 Seminoma

A residual mass of seminoma should initially be monitored with imaging and tumour markers [195-197].

As FDG-PET has a high NPV, in patients with residual masses > 3 cm in largest diameter, this should be considered in order to provide more information on disease viability [198-200]. It should not be performed until at least two months after completion of chemotherapy, as inflammation and the desmoplastic reaction induced by chemotherapy may result in a false positive result [201]. The NPV for active disease is > 90% which can be reassuring [198, 199]. In contrast, PPV ranges from 23-69% and thus caution is advised on initiating active therapy driven only by positive findings on FDG-PET-CT [202].

When a post-chemotherapy mass remains positive at reclassification with FDG-PET with no volume increase, repeat FDG-PET should be performed six weeks later. A recent publication shows a low PPV for vital tumours in residual lesions (generally > 3 cm) after chemotherapy in metastatic seminoma (11-38% depending on sub-group). Therefore, caution is recommended with FDG-PET as a single parameter to drive clinical decisions in a persistent mass [202]. 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 [203-205].

Patients with persistently high and/or progressing β-hCG elevation after first-line chemotherapy should proceed to salvage chemotherapy. Progressing patients without β-hCG progression should undergo histological verification (e.g., by percutaneous or surgical biopsy) before salvage chemotherapy is given. When RPLND is indicated, this should be performed in referral centres, as residual seminoma masses may be extremely difficult to remove due to intense fibrosis [204].

6.3.2.2 Non-seminoma

Following first-line BEP it has be reported that about 7% of residual masses contain active cancer, 33% PPT, and 40% necrotic-fibrotic tissue only [206]. The remainder comprise rarer entities including teratoma with somatic-type malignancy. Restaging patients following chemotherapy with FDG-PET is not indicated [46, 47, 201]. With complete radiological remission, RPLND is not indicated [207, 208].

Usual timing for restaging is three to four weeks after the beginning of the last cycle. No diagnostic or risk calculator can accurately predict histology of the residual masses. Thus, resection is mandatory in all patients with a residual mass > 1 cm measured in transaxial long axis at cross-sectional CECT imaging until novel predictive models are externally validated [209-212]. Surgery when indicated should be performed within six to eight weeks after the last chemotherapy cycle.

The role of surgery with residual retroperitoneal lesions < 1 cm is uncertain. It is difficult to distinguish between a true residual node below 10 mm and a complete remission, and many authors consider these situations as equivalent. Residuals containing cancer or teratoma are possible, but the vast majority of patients have fibro-necrotic tissue only [213]. Whilst post-chemotherapy RPLND with residuals < 10 mm in transaxial long axis or complete remission is an option [214], the alternative option is close surveillance with recurrence risk of 6-9% depending on the follow-up duration [206-208, 215]. 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 [208, 215]. Eight of the twelve relapsing patients were cured with subsequent treatment. These cases should be discussed on an individual basis considering the orientation and expectations of the patient.

Residual masses after salvage chemotherapy or HDCT in first or subsequent salvage situations have a greater risk of active disease [216]. Surgery is therefore indicated even with residual masses < 1 cm [207, 208].

When resection is indicated, bilateral nerve-sparing RPLND is the standard option. Ipsilateral template resection avoids contralateral nerve dissection and may be considered for residuals with a diameter < 5 cm [217], as well as unilateral lymph node metastases on pre- and post-chemotherapy CT scans, left-sided tumours only require para-aortic resection whereas right-side tumours need paracaval and inter-aortocaval resection down to the iliac arteries [218, 219]. Mapping studies indicate the potential risk of contralateral disease with this approach is low at around 1-3% [218, 220]. The mere resection of the residual tumour (so called lumpectomy) should not be performed [208, 212, 213, 216, 217, 219, 221].

Laparoscopic or robotic RPLND may yield comparable outcomes to open procedures in selected cases, with low-volume residual disease and when undertaken by very-experienced surgeons. This should only be considered in specialist TC centres with expertise in open RPLND and minimally invasive surgery to ensure appropriate case selection. In this setting, up to 30% of post-chemotherapy RPLND have been reported via a laparoscopic approach [222-224]. Experience with robot assisted laparoscopic RPLND, and specifically long-term outcomes remains limited [225]. Atypical recurrences have been reported and occur more often with this approach [124].

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

In general, surgery should commence at the site with the highest volume of residual disease. The histology of the mass diverges in different organ sites [209]. In cases of residual retroperitoneal and lung masses, the presence of fibro-necrotic tissue in the retroperitoneum is associated with a probability as high as 90%, that lung masses contain the same histology [226]. When pathologic examination of the lesions from the initial side show complete necrosis, observation may be considered when there are multiple contralateral tumours for which resection may be challenging. Discordant histology between lung sites, however, may occur in up to 20% of cases and thus, patients in this situation should be closely monitored with reconsideration of surgery or biopsy if radiological features change [227, 228].

6.3.3.1 Quality and intensity of surgery

Resection of visceral structures and/or major vessels, requiring vascular reconstruction/replacement may be required to achieve radical resection and patients undergoing adjunctive complex surgery have a greater risk of complications [229, 230]. In patients with intermediate- or poor-risk and residual disease > 5 cm, the probability of vascular procedures is as high as 20% [231]. These cases must therefore be referred to specialised centres capable of interdisciplinary surgery (gastro-enteric and vascular surgery, spinal neurosurgery, thoracic surgery). Even with centralisation of treatment, the median number of RPLNDs performed per surgeon/year in the U.K. is six [232]. Nevertheless, patients treated within such centres benefit from a significant reduction in peri-operative mortality from 6% to 0.8% [233]. In addition, specialised urologic surgeons are capable of reducing the local recurrence rate from 16% to 3% with a higher rate of complete resections [234].

6.3.3.2 Salvage and desperation surgery

Surgery of resectable disease after salvage treatment remains a potentially curative option in patients with any residual mass following salvage chemotherapy. Survival after surgery and first salvage chemotherapy improved by 70% at ten years, following taxane-containing regimens [235]. Even with extensive salvage chemotherapy, surgery remains a fundamental tool to achieve durable complete remissions in up to 20% of patients [236, 237].

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 [238].

6.3.3.3 Consolidation chemotherapy after secondary surgery

After resection of necrosis or PPT, no further treatment is required. With 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) [221]. Caution is required with cumulative doses of bleomycin which should not exceed twelve in total. With complete resection of active disease, comprising < 10% of the total volume of the mass, particularly in patients who initially had a good-prognosis based on IGCCCG criteria, the relapse rate is very low and adjuvant chemotherapy is not beneficial in preventing further relapse [239]. The prognosis is worse if malignant disease is present in masses resected after second- and third-line chemotherapy, although further chemotherapy is not indicated [240].

6.3.4 ***Systemic salvage treatment for relapse or refractory disease***

Cisplatin 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 [241]. The regimens of choice are four cycles of a three-agent regimen including cisplatin and ifosfamide plus a third drug: etoposide (VIP), paclitaxel (TIP), or potentially gemcitabine (GIP) (Table 5) [242, 243]. 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.

Table 5: Standard VIP, TIP and GIP salvage chemotherapy (interval 21 days)

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

[xx] An MRC schedule uses paclitaxel at 175 mg/m^2 in a 3 hour infusion infusion [243].

Please refer to appendix 3 – Chemotherapeutic protocols https://uroweb.org/guidelines/testicular-cancer/publications-appendices for more detailed information.

A retrospective analysis by the International Prognostic Factors Study Group (IPFSG) evaluated the risk of relapse in patients in whom this occurred after at least three cisplatin cycles and subsequent cisplatin conventional-dose or carboplatin-based high-dose salvage chemotherapy [145]. Seven variables: histology, primary tumour location, response, progression-free interval after first-line treatment and level of AFP, β-hCG and the presence of liver, bone or brain metastasis at salvage treatment, were identified as independent prognostic variables of relapse after initial cisplatin chemotherapy [145]. 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 illustrates these five risk groups and the corresponding two-year PFS and three-year OS rates [145]. Several recent trials have validated this scoring system [244-247]. As in first-line therapy, the prognostic impact of tumour marker decline applies in the salvage setting [248]. While progression to induction chemotherapy was negative for OS, prior use of paclitaxel was not significantly associated with a negative outcome [249].

A secondary analysis of the IPFSG cohort (n = 1,600 patients) showed a 10-15% improvement in OS in all prognostic subgroups when treated with high-dose salvage therapy compared to standard dose therapy. This is being evaluated in an RCT of HDCT vs. conventional dose chemotherapy in patients with first-line relapse is underway (Tiger trial). When HDCT is used as a salvage treatment, sequential treatment cycles of high-dose carboplatin and etoposide (HD-CE) should be preferred to a single high-dose regimen as the former is associated with less toxicity-related deaths [244]. A recent SR confirmed the superiority of using at least two high-dose cycles in the salvage setting over a single high-dose cycle [250]. It is clearly of the utmost importance that these rare patients with relapse are treated within clinical trials and at specialised centres.

Table 6: The International Prognostic Factors Study Group Score for seminoma and non-seminoma that relapse after cisplatin-based first-line chemotherapy [189]

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

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

Table 7: PFS and OS estimates for all patients according to IGCCCG prognostic score for seminoma and non-seminoma that relapse after cisplatin-based first-line chemotherapy [190]

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

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

6.3.5 Second relapse

No RCTs have been reported for patients with second and subsequent relapse and conventional therapy appears to have limited effect. For patients who have received two series of conventionally dosed therapy (first line and first-salvage), HDCT with autologous stem cell support should be used although the prospect of cure is < 25% [245]. Retrospective data from Indiana University suggest that patients who completed HDCT may derive additional benefit from daily maintenance therapy with oral etoposide for three months post-HDCT [251]. Prospective evaluation of this in a randomised phase II trial is ongoing.

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 HDCT, are considered as cisplatin refractory. Combinations of gemcitabine and oxaliplatin or the triple combination of gemcitabine, oxaliplatin and paclitaxel have resulted in response rates of 25-45% in this setting. Cisplatin re-challenge in association with gemcitabine and paclitaxel may be considered in patients with adequate renal function [252]. 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 [236, 253].

Various targeted agents have generally failed in refractory disease, including immune checkpoint inhibitors [244-250, 254]. Trials combining PD1/PDL-1 and CTLA4 inhibitors are ongoing; however, even for those combinations early results are not encouraging.

6.3.5.1 Late relapse (more than two years after end of first-line treatment)

Late relapse is defined as recurrence more than two years after completion of successful primary treatment of metastatic TC [200, 255]. According to a pooled analysis, this occurs in 1.4% and 3.2% of seminoma and non-seminoma patients, respectively [256].

Based on a population-based study all late-relapsing seminoma patients have viable GCT [257]. These can be treated with chemotherapy and radiotherapy [258].

In contrast, patients with late-relapsing NSGCT should undergo surgical resection when feasible, alone or in combination with chemotherapy. Some patients, including those with rapidly rising β-hCG, may benefit from induction salvage chemotherapy with subsequent reconsideration of surgery for resection of persisting residual masses [259]. In general, however, surgery represents the mainstay of treatment and it should be performed in most patients when feasible irrespective of the level of their tumour markers, in order to completely resect all viable GCT PPT [258-262].

Survival strongly relates to the histology of the recurrent lesions rather than that of the initial disease. If not completely resectable, biopsies should be obtained for histological evaluation to direct salvage chemotherapy based on the tumour phenotype. Review by an experienced pathologist is critical to avoid misinterpretation of the therapeutic morphological changes that occur with the treatment of GCT [263]. If the patient responds to salvage chemotherapy, secondary surgery should then be undertaken if feasible. With unresectable, but localised refractory disease, stereotactic or conventional radiotherapy may be considered. To avoid excess mortality, late relapses should be treated only at centres experienced in managing such patients [264].

6.3.6 Treatment of brain metastases

Brain metastases occur in the context of initial metastatic disease, systemic relapse and rarely as an isolated site of relapse. Long-term survival of patients presenting with brain metastases at diagnosis is poor (30-50%) and even poorer when a site of recurrent disease (five-year survival-rate is 2-5%) [265, 266]. 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 [50].

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 [50]. Consolidation RT, even with total response after chemotherapy, should therefore be used in patients with brain metastases at relapse, but must be carefully discussed in a first-line setting [267]. Surgery may be considered in cases with a persistent solitary metastasis, depending on the systemic disease status, histology of the primary tumour and the location of the metastasis.

6.3.6.1 *Summary of evidence and recommendations for the treatment of metastatic testicular germ cell tumours*

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

Recommendations	Strength rating
Treat low-volume non-seminomatous germ cell tumour (NSGCT) stage IIA/B with elevated markers like metastatic good- or intermediate-prognosis risk group IGCCCG with three or four cycles of cisplatin, etoposide, bleomycin (BEP).	Strong
Nerve-sparing retroperitoneal lymph node dissection when performed by an experienced surgeon in a specialised centre is the recommended initial treatment in clinical stage (CS) IIA NSGCT disease without elevated tumour markers.	Weak
Repeat staging after six weeks before making a final decision on further management should be considered in patients with small volume (CS IIA < 2 cm) marker-negative NSGCT.	Weak
Treat metastatic NSGCT (stage > IIC) with an intermediate prognosis with four cycles of standard BEP.	Strong
Treat metastatic NSGCT with a poor prognosis and favourable marker decline with four cycles of BEP.	Strong
Assess tumour marker decline after one cycle of standard chemotherapy in metastatic NSGCT with a poor-prognosis. With unfavourable decline, consider chemotherapy intensification.	Weak
Perform surgical resection of visible (> 1 cm in longest diameter) residual masses after chemotherapy for NSGCT when serum levels of tumour markers are normal or normalising.	Strong
Offer cisplatin chemotherapy according to IGCCCG prognosis groups, or alternatively radiotherapy to seminoma patients with stage II A/B and, inform the patient of potential long-term side effects of both treatment options.	Weak
Treat seminoma stage IIC and higher, with primary chemotherapy according to IGCCCG classification (BEP x 3 in good-prognosis and BEP x 4 in intermediate prognosis).	Strong

7. FOLLOW-UP AFTER CURATIVE THERAPY

7.1 Minimal recommendations for follow-up

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

1. patients with seminoma stage I;
2. patients with non-seminoma stage I on AS;
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 FDG-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 8-10 show the minimal recommendations for follow-up of the three different groups based on recommendations developed at a European Society for Medical Oncology (ESMO) consensus conference [268].

Both MRI and CT can be used to evaluate the retroperitoneum, pelvis and inguinal regions for sites of metastatic disease from GCT [269, 270]. Magnetic resonance imaging benefits from an absence of ionising radiation but is more time consuming and less readily available than CT [271]. Given the frequency of follow-up, over a number of years some studies have estimated a risk of up to 1 in 300 of second malignancy related to CT imaging follow-up alone [272], although more recent dose saving protocols and limitations on field of view will have mitigated this somewhat. Nevertheless, this risk could be excluded by the use of MRI for follow-up.

Both MRI and CT rely predominantly on size cut-offs for evaluation given the excellent spatial resolution of both modalities, with morphological assessment for features such as necrosis and irregular shape an adjunct. Sensitivity and specificity vary according to the size cut-off used [269]. However, studies have shown comparable excellent results between MRI and CT with up to 98% sensitivity on MRI for the detection of retroperitoneal nodal metastases in GCT [273]. It has, however, been demonstrated that reader experience is important when interpreting images [274]. In the setting of GCT, one study demonstrated decreased sensitivity for detection of retroperitoneal nodal disease on MRI when reported by a trainee radiologist with sensitivity of detection of 80% [272]. However, experienced radiologists in the same study achieved sensitivity for detection of nodal disease of 97% with good interobserver agreement. It was therefore suggested that if MRI is to be used instead of CT for follow-up this be done in centres/units with oncological radiologists who routinely report MRI and CT in patients with GCT, rather than general radiologists who may only occasionally see such imaging. Consequently, MRI of the abdomen can be used as an alternative to CECT in experienced centres [275].

The diagnostic accuracy of FDG-PET-CT is best described and therefore recommended in seminoma patients with post-chemotherapy residual masses > 3 cm in largest diameter as outlined in section 6.3.2.1. This should be performed at least two months after completion of chemotherapy as earlier scans may be misleading due to inflammation. The changes are related to tumour necrosis. The use of FDG-PET-CT is not currently recommended during surveillance. Retrospective analyses have indicated a high diagnostic accuracy for staging and follow-up in patients with CS 1 during surveillance or for determining the stage in more advanced disease [276]. However, to minimise radiation exposure and considering the supporting data for the use of MRI [270], the panel currently do not recommend the use of FDG-PET-CT during surveillance.

Serum tumour markers are the least invasive and most accessible follow-up investigations. The established serum tumour markers, such as AFP, β-hCG, and LDH, may yield false positive results, so their levels should be correlated with imaging findings or repeated in serial measurements [277]. Serum tumour markers can detect microscopic disease that is not yet visible on cross-sectional imaging in a small proportion of patients, and therefore, they should be measured at the recommended prescribed intervals [278].

MiR-371a-3p has a high diagnostic accuracy for detecting all histologies of GCT except teratoma and has potential to detect disease recurrence earlier than AFP, β-hCG, LDH, or cross-sectional imaging [279]. However, before this promising test can be recommended in routine practice, a validated assay and cut-off definitions in prospective cohorts are required to mitigate the risk of false positive findings, unnecessary restaging, anxiety, or over-treatment.

Regarding the use of US examination of the contralateral testis, the majority of the consensus meeting participants did not support repeat US investigation, either with negative biopsy or if no contralateral biopsy has been performed [268].

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 [257]. The aim of follow-up beyond five years therefore shifts to detection of late side effects of treatment and imaging tests are not routinely recommended.

Most patients with VLR are diagnosed due to symptoms, although in up to 50% elevated tumour markers are present in NSGCTs [257, 280]. 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: 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 magnetic resonance imaging (MRI)/ computed tomography (CT)	2 times	2 times	Once at 36 months	Once at 60 months	

Table 9: 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 magnetic resonance imaging (MRI)/ computed tomography (CT)	2 times	At 24 months**	Once at 36 months***	Once at 60 months***	

* *In case of high-risk (LVI+) a minority of the consensus group members recommended six times.*
** *In case of high-risk (LVI+) a majority of the consensus group members recommended an additional CT at eighteen months.*
*** *Recommended by 50% of the consensus group members.*
LVI+ = Lymphovascular invasion present.

Table 10: 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 magnetic resonance imaging (MRI)/ computed tomography (CT)	1-2 times	At 24 months	Once at 36 months	Once at 60 months	
Thorax CT	1-2 times*	At 24 months*	Once at 60 months*	Once at 60 months*	

* *In conjunction with abdominopelvic MRI/CT in case of pulmonary metastases at diagnosis.*
** *In case of teratoma in resected residual disease: the patient should remain with the uro-oncologist.*

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

The vast majority of patients will be cured with five-year relative survival rates of approximately 95% in Western Europe. Testicular cancer patients are usually between 18-40 years of age at diagnosis and life expectancy after cure extends over several decades [281]. Patients should be informed before treatment of common long-term toxicities, which are avoided or minimised by adherence to international guidelines.

During follow-up, patients should be screened and treated for known risk factors such as hypertension, hyperlipidaemia, and testosterone deficiency. Adverse health outcomes (AHOs) are more commonly found in TC patients who received chemotherapy than those cured by surgery alone. Further, modifiable risk factors do contribute to AHOs like hypertension and noise exposure to hearing impairment or smoking to Raynaud phenomenon [282]. Therefore, a healthy lifestyle should be promoted during the follow-up consultations. Adverse health outcomes are associated with unemployment, which is found clearly increased in TC survivors (TCSs) as compared to a male normative population [283]. 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 [200, 284].

*For more information regarding long term toxicities and QoL issues, please see appendix 5, available online https://uroweb.org/guidelines/testicular-cancer/publications-appendices

8. RARE ADULT PARA- AND TESTICULAR TUMOURS

Less than 5% of TCs are unrelated to GCNIS and lack 12p alterations [285, 286]. These tumours are rare with available literature based on case reports and small retrospective series. Given the rarity of non-germ cell para-/testicular cancers, referral of these cases to specialist units for multidisciplinary discussion including central image and pathology review is highly recommended. As a result of publication bias related to these types of study, the risk of metastatic disease may be less than that reported in the literature.

8.1 Classification

These testicular tumours have a similar presentation as TC and are only identified after histopathologic examination. They are classified according to the WHO Classification of Tumours of the Urinary System and Male Genital Organs [287].

8.2 Spermatocytic Tumours

Spermatocytic tumours are GCTs unrelated to GCNIS. They may show a unique amplification of chromosome 9 corresponding to the DMRT1 gene and are never associated with other forms of GCTs [287].

Spermatocytic tumours are rare, occur exclusively in the testis and do not normally show elevated tumour markers [287]. Previously named “spermatocytic seminomas” they have been recently reclassified as spermatocytic tumours [287]. As those tumours cannot be differentiated from seminoma GCT by FSE, radical orchiectomy is the standard treatment option. Outcomes after TSS or adjuvant treatment is unknown and therefore not recommended [288]. Metastatic disease is very rare, usually associated with ‘sarcomatoid change’ and typically presents at or soon after initial diagnosis with limited survival [288].

8.3 Sex cord-stromal tumours

Sex cord–stromal tumours are relatively uncommon but represent the second largest group of primary testicular tumours after GCT’s [289]. As a small subset of these tumours are clinically malignant, a thorough evaluation of those morphological features associated with malignancy should be performed to guide management. Two or more of the following features are associated with malignant potential: size > 5 cm, infiltrative borders, cytological atypia, three or more mitotic figures per ten high-power fields, vascular invasion and necrosis [289].

8.3.1 ***Leydig cell tumours***

Leydig cell tumours comprise about 4% of adult testicular tumours [290]. These mainly present as localised tumours with metastases occurring in only 2.5% [291]. They may present with hormonal manifestations, including gynaecomastia and more rarely are accompanied by Cushing's Syndrome [389]. With TSS a local recurrence rate of 7% has been reported although no adjuvant treatment options can be recommended [292]. Several risk factors for metastatic disease have been proposed which may guide image-guided follow-up intensity [292]. Survival of men with metastatic disease is poor but occasional responses to surgical resection, if feasible, and to a lesser extent systemic treatment have been reported [292].

8.3.2 ***Sertoli cell tumours***

Sertoli cell tumours account for approximately 1% of testicular neoplasms [289]. The risk of metastases is unclear. With TSS a local recurrence rate of < 1% has been reported although no adjuvant treatment options can be recommended [293]. Several risk factors for metastatic disease have been proposed which may guide image guided follow-up intensity [293]. Survival of men with metastatic disease is poor although response to surgery has been occasionally reported [293].

8.3.3 ***Granulosa cell tumour***

Granulosa cell tumours, which include adult and juvenile variants, are extremely rare and metastatic potential is unclear [289]. With TSS a local recurrence rate of 5% has been reported although no adjuvant treatment options can be recommended [294]. Whereas metastatic disease has never been reported in juvenile granulosa cell tumours, men with adult type may occasionally present with metastatic disease [294]. Survival of men with metastatic disease is poor although rare instances of response to surgical or systemic treatment has been reported [294].

8.3.4 ***Thecoma/fibroma group of tumours***

These tumours derive from the testicular parenchymal stroma or from the tunica albuginea. They seem to be uniformly benign [289, 295].

8.3.5 ***Paratesticular tumours of the epididymis or spermatic cord***

The majority of epididymal masses are benign cystic or inflammatory conditions. Solid epididymal tumours are rare and comprise numerous benign and neoplastic lesions. In the only population-based analyses [296], the majority of neoplastic lesions of the epididymis or spermatic cord were sarcomas, metastases from other organs or primary adenocarcinomas similar to proportions reported in institutional studies [297, 298]. Benign lesions, which may comprise the majority in clinical practice include lipomas, adenomatoid tumours leiomyomas and papillary cystadenomas.

Robust criteria to differentiate between neoplastic benign lesions have not been defined although ultrasonography with or without fine needle aspiration [299] MRI [45, 300] or surgical exploration with FSE or histopathological confirmation can be considered. No clear recommendation can be provided regarding surgical approach, extent of resection and neo- or adjuvant treatment can be given.

8.4 Mesothelioma of the tunica vaginalis testis

Mesothelioma of the tunica vaginalis testis is a rare but aggressive disease [301]. Beside older age, larger tumour size, presence of necrosis, angiolymphatic invasion or a high mitotic index the only modifiable risk factors represents local recurrence. Therefore, aggressive local treatment with hemiscrotectomy is recommended. No clear recommendation can be given regarding adjuvant treatment. In case of metastatic disease, the median OS is a few months only and multimodal treatment could be considered.

8.5 Follow-up of rare adult para- and testicular cancers

After local surgical treatment is completed, attention turns to follow-up strategies with the aims of detecting recurrence or secondary cancers at a stage when further curative procedures are possible whilst minimising the burden of follow-up and the potential for over-treatment and concomitant treatment toxicity. Data for rare para- and testicular cancers are limited but recommended follow-up schedules based on published case series have been suggested [302].

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10. CONFLICT OF INTEREST

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

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