ESMO Consensus Conference on testicular germ cell cancer: diagnosis, treatment and follow-up


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The European Society for Medical Oncology (ESMO) consensus conference on testicular cancer was held on 3–5 November 2016 in Paris, France. The conference included a multidisciplinary panel of 36 leading experts in the diagnosis and treatment of testicular cancer (34 panel members attended the conference; an additional two panel members [CB and K-PD] participated in all preparatory work and subsequent manuscript development). The aim of the conference was to develop detailed recommendations on topics relating to testicular cancer that are not covered in detail in the current ESMO Clinical Practice Guidelines (CPGs) and where the available level of evidence is insufficient. The main topics identified for discussion related to: (1) diagnostic work-up and patient assessment; (2) stage I disease; (3) stage II-III disease; (4) post-chemotherapy surgery, salvage chemotherapy, salvage and desperation surgery and special topics; and (5) survivorship and follow-up schemes. The experts addressed questions relating to one of the five topics within five working groups. Relevant scientific literature was reviewed in advance. Recommendations were developed by the working groups and then presented to the entire panel. A consensus vote was obtained following whole-panel discussions, and the consensus recommendations were then further developed in post-meeting discussions in written form. This manuscript presents the results of the expert panel discussions, including the consensus recommendations and a summary of evidence supporting each recommendation. All participants approved the final manuscript.

Key words: testicular germ cell cancer, consensus, diagnosis, treatment, quality of life, follow-up
Introduction

See Section 1 of supplementary data, available at Annals of Oncology online.

Methods

On 3–5 November 2016, the European Society for Medical Oncology (ESMO) held a consensus conference in Paris, France, to discuss controversial issues relating to the diagnosis, treatment and follow-up of patients with testicular cancer that have not been addressed in the current Clinical Practice Guideline (CPG). The conference included a multidisciplinary panel of 36 leading experts in the diagnosis and treatment of testicular germ cell cancer (TGCC) [34 panel members attended the conference; an additional 2 panel members (CB and K-PD) participated in all preparatory work and subsequent manuscript development] and was chaired and co-chaired by F. Honecker and A. Horwich, respectively. All experts were allocated to one of the five working groups.

Each working group covered a specific subject area and was appointed a chair as follows:

1. Diagnostic work-up and patient assessment (Chair: G. Cohn-Cedermark)
2. Stage I disease (Chair: J. Aparicio)
3. Stage II–III disease (Chair: K. Fizazi)
4. Post-chemotherapy surgery, salvage chemotherapy, salvage and desperation surgery and special topics (Chair: J. Beyer)
5. Survivorship and follow-up schemes (Chair: J. Oldenburg)

The level of evidence and grade of each recommendation proposed by the group was defined based on information shown in Table 1. Further details of methods can be found in Section 2 of the supplementary data, available at Annals of Oncology online.

Table 1. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System [1])

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By permission of the Infectious Diseases Society of America [1].

Results

Diagnostic work-up and patient assessment

1. Is there a role for targeted screening?

Incidence of testicular cancer by ethnic origin. The incidence of testicular cancer varies by ethnic origin, with the highest rates reported in developed countries and lowest in developing countries. The highest incidence rates of testicular cancer are in Norway (11.8 per 100 000) and the lowest are in India (0.5 per 100 000) and Thailand (0.4 per 100 000) [2]. The increase in incidence rates of testicular cancer in both developed and developing countries is due to a birth cohort effect [3]. In high-incidence Scandinavian countries, the increase has levelled off. The risk of testicular cancer in Swedish-born sons of low-risk Finnish immigrant parents is no longer different from that in native Swedes, which implies a strong environmental influence [4].

Risk factors of testicular cancer. Individual risk factors (RFs) for testicular cancer include cryptorchidism [relative risk (RR) ≥3.18], hypospadias (RR 2.41), inguinal hernia (RR 1.37) and other birth-related factors of a lower risk [5, 6]. Among endocrine disruption chemicals, organochlorine compounds have been associated with a risk of developing testicular cancer [6]. Cryptorchidism is associated with a higher risk for ipsilateral testicular cancer (RR 6.33) than contralateral testicular cancer (RR 1.74) [7]; however, men with a family history of cryptorchidism or hypospadias have no increased risk of testicular cancer [8].

Approximately 5% of men with testicular cancer develop contralateral testicular cancer, of which one-third are synchronous tumours and two-thirds are metachronous tumours [9]. Compared with the incidence rates of a first testicular cancer, the RR for developing a second testicular cancer is 29 after seminoma and 13 after non-seminoma [10].
Familial risk is more relevant for testicular cancer than in the majority of other cancers. The risk is significantly higher if the affected family member is a brother (RR 6.94) rather than the father (RR 3.90), which is likely due to a recessive genetic or birth cohort-related effect [11]. About 1.8% of patients have a parent or a sibling also diagnosed with testicular cancer [11].

According to a Nordic study on testicular cancer, the standardised incidence risk ratios for seminoma in brothers (4.2) had no major difference from the risk of all testicular cancer subtypes in brothers (4.1). However, fraternal risk for non-seminomatous germ cell tumours (NSGCTs) (10) and mixed germ cell tumours (17) were higher compared with all testicular cancer subtypes (11). In the same study, high familial risks were observed for men who had two or more affected relatives (17) or if a twin brother was diagnosed with testicular cancer (20). The absolute population risk of testicular cancer in the Nordic countries was 0.6% by the age of 79 years. This increased to 1.2%, 2.3%, 10.3% and 56.2% if a father, brother, >2 relatives or a twin brother was diagnosed, respectively [12].

**Genetic predisposition for testicular cancer.** Over 20 single nucleotide polymorphisms (SNPs) have been associated with the risk of testicular cancer [13, 14]. Polygenic risk scores have been used to show that men in the top 1% of this genetic risk score have a ninefold increased risk of testicular cancer compared with the population median [15]. Collectively, the SNPs identified to-date explain ~19% of the empirical fraternal familial risk [15]. Based on the Swedish Family-Cancer Database [16], population-based heritability of testicular cancer is estimated at 49%.

**Targeted screening for testicular cancer.** Due to the shortage of randomised, controlled trials on the benefits of screening for testicular cancer, no screening recommendations can be given [17]. However, the above data show that it is possible to define men who have a substantially increased risk for the development of a testicular cancer based on family history, genetic predisposition (polygenic risk score), individual history of testicular cancer or cryptorchidism, or a combination of these factors. Screening after testicular cancer diagnosis is discussed later in this article.

**Recommendation 1.1:** Targeted screening should be advised for either a twin brother or those with two close family members with a history of germ cell tumours.

- Level of evidence: III–V
- Strength of recommendation: A–C
- Level of consensus: 97% (32) yes, 3% (1) no (33 voters)

**Recommendation 1.2:** Since elevated testicular cancer risk exists for brothers and fathers, the patient should be encouraged to inform them of the need for self-examination.

- Level of evidence: III
- Strength of recommendation: B
- Level of consensus: 100% yes (33 voters)

2. **Pathology assessments**

**Misdiagnosis and overtreatment of testicular tumours.** Despite their relative rarity, testicular tumours are regarded as one of the most diverse areas of human pathology. They are further complicated by post-chemotherapy changes that can be seen after treatment. Even pathologists with an interest in uro-pathology may see relatively few tumours in a year, and so subtypes are prone to misdiagnosis and potential overtreatment.

The potential for misdiagnosis of stage and type of testicular tumour has been demonstrated in multiple articles and the dangers of subsequent mistreatment are substantial [18–22]. Based on these findings, The National Institute for Health and Clinical Excellence (NICE) guidance [Improving Outcomes in Urological Cancer (www.nice.org.uk)] recommended the establishment of a supra-network of specialised testicular cancer uro-pathologists, serving a population base of 2–4 million and managing 50–100 new patients per year. Central review of tumours by a specialist testicular pathologist is mandatory [23]. Recently, a survey of expert and non-expert uro-pathologists in Europe was conducted [24], which showed variability in reporting stage, rete testis invasion and other potentially prognostic parameters. If pathology is not centralised but pooled from reports, this could impact studies of testicular RFs for recurrence.

**Typing of testicular tumours for oncology assessment.** Testicular tumours should be typed in line with the World Health Organization (WHO) 2016 classification [25]. This allows for a modified nomenclature and a more patho-genetic approach to TGCCs, the final aim being to avoid overtreatment of patients with negligible risk of spread. The new name for pre-neoplastic lesions of TGCCs has been agreed upon as germ cell neoplasia in situ (GCNIS). GCNIS were formerly named carcinoma in situ or testicular intraepithelial neoplasia [26]. Prepubertal-type teratomas are known to exist in adults, and may require less surveillance [27]. For optimal management of testicular tumours, whenever possible, oncologists should request a review of each case by an expert testicular pathologist who sees a minimum of 30 cases per year.

**Recommendation 2.1:** The pathology of testicular tumours should be assessed, or at least reviewed, by a specialist testicular pathologist who sees a minimum of 30 cases per year.

- Level of evidence: III
- Strength of recommendation: A
- Level of consensus: 87.1% (27) yes, 12.9% (4) abstain (31 voters)

**Recommendation 2.2:** The WHO 2016 classification should be routinely adopted for testicular pathology assessment.

- Level of evidence: III
- Strength of recommendation: A
- Level of consensus: 74.2% (23) yes, 25.8% (8) abstain (31 voters)

**Staging in testicular cancer tumours.** The Seventh Tumour Node and Metastases (TNM) classification does not adequately supply all information required by many oncologists for patient treatment [28], as rete testis invasion and tumour size are not included in its assessments. Recently, both the American Joint Committee on Cancer (AJCC) Eighth TNM version [29] and the Union for International Cancer Control (UICC) Eighth edition [30] have been published, and the AJCC version has addressed some of these issues. For seminoma, T1 has been subdivided into pT1a and 1b for tumours < versus ≥3 cm. Soft tissue and epididymal invasion have been redefined as pT2. Rete testis invasion remains as T1 disease. Unfortunately, these changes have not been adopted by the UICC, which may lead to some confusion in
Contralateral GCNIS in patients with unilateral TGCC include testing according to the ICCR minimum dataset. These guidelines have been combined to form an international dataset on minimum standards, which has been published by the International Collaboration on Cancer Reporting (ICCR) [32]. It is recommended that testicular pathologists should use one of these datasets for guidance in reporting.

**Recommendation 2.3:** National or international minimum dataset guidelines should be used by testicular pathologists. The dataset for pathology reporting to minimum standards should be according to the ICCR minimum dataset.

- Level of evidence: III
- Strength of recommendation: A
- Level of consensus: 100% yes (31 voters)

### 3. Should contralateral biopsy be carried out?

**Contralateral biopsies in testicular cancer.** Early detection of TGCC is possible by diagnosing GCNIS, the pre-invasive stage of TGCC [33, 34]. The current theory of TGCC pathogenesis asserts that GCNIS cells arise from embryonic germ cells that are present in a dormant state in the juvenile testicle; after adolescence, it is possible for GCNIS to progress to invasive TGCC at any time [6]. The current understanding of the pathogenesis of TGCC provides clinically useful knowledge because it suggests: (i) all TGCCs develop from GCNIS (i.e. without previous GCNIS, there can be no invasive TGCC); (ii) there is no de novo development of GCNIS in adulthood; (iii) GCNIS is present many years before the clinical manifestation of TGCC; (iv) GCNIS can be detected patho-histologically; (v) as it is usually distributed over wide areas, GCNIS can be detected by surgical biopsy [35, 36].

**Surgical technique.** Evidence suggests that performing two-site testicular biopsies provides an increased sensitivity of 18% compared with single-site biopsy [35, 37]. Surgical complications have been reported to occur in 2%–3% of patients, most of which can be managed conservatively [38]. Currently available data suggest that screening for GCNIS by needle biopsy or semen examination yields inferior results to two-site surgical testicular biopsy [39, 40].

**Histological technique.** Histological detection of GCNIS cells can usually be achieved using conventional haematoyxlin and eosin staining. In unresolved cases, supplementary immunohistochemical staining can be carried out with immunohistochemistry for placental alkaline phosphatase, D2–40 or OCT3/4 [41, 42]. Spermatogenesis should also be assessed morphologically.

**Clinical data.** In central and northern European countries, GCNIS was found to be present in the contralateral testis of 4.4%–8.1% of patients with TGCC [35, 37, 43–45]. Major RFs associated with contralateral GCNIS in patients with unilateral TGCC include testicular atrophy, younger age (<40 years), testicular microlithiasis and infertility [46]; the GCNIS rate was 18% in patients aged <40 years with testicular atrophy (≤12 mL). The prevalence of contralateral GCNIS appears to correspond to the reported 2%–4% frequency of bilateral testicular tumours [9, 47, 48]. In patients with extragonadal TGCCs, testicular biopsies have revealed the presence of GCNIS in ~31% of these patients, with the risk being higher in retroperitoneal primaries [49].

The rate of false-negative biopsies (i.e. patients who developed TGCC after having negative biopsy results) has been reported as 0.5%–2% [43, 47]. However, diagnostic failure is likely related to methodological inadequacies, such as use of single-site rather than two-site biopsies and lack of immunohistological examination, or the timing of biopsy (e.g. after chemotherapy). Nevertheless, the possibility of a false-negative biopsy must be taken into consideration as, contrary to former opinion, GCNIS cells are not homogeneously distributed over the testis [43, 50].

**General considerations of the usefulness of contralateral biopsies.** There is currently no consensus amongst experts of TGCC treatment as to whether a contralateral biopsy should be carried out [51]. There are no data to show that it can provide an additional survival advantage [52]. However, performing a contralateral biopsy may confer additional benefits to the patient. Firstly, in those with a ‘positive’ biopsy result, the potential early diagnosis of a second testicular cancer allows for prospective testis-preserving treatment; importantly, this not only minimises the aggressiveness of treatment required, including reduced exposure to treatment-related toxicity, but also reduces the extent of follow-up clinical and radiological examinations required compared with treatment and follow-up for a more advanced second tumour. Secondly, patients with a ‘negative’ biopsy result benefit from the knowledge that their risk of developing a contralateral tumour is very low, which also translates into a reduced scrotal follow-up schedule. Thirdly, the biopsy can provide valuable information regarding the fertility potential of the patient. The risk of damage to the contralateral testis because of the surgical biopsy procedure has been shown to be minimal [38]. Furthermore, concerns that GCNIS treatment may potentially harm fertility may be irrelevant for many patients, as a large proportion of testes with GCNIS are primarily associated with poor spermatogenesis [53].

Overall, it seems reasonable to discuss the value of performing contralateral biopsies with patients who have high-RFs for a second TGCC (i.e. those aged <40 years with a small atrophic testis and those with testicular microlithiasis upon scrotal sonography).

**Recommendation 3.1:** Biopsies of the contralateral testis at the time of orchietomy should be discussed with, and recommended to, high-risk patients (i.e. those aged <40 years with a small atrophic testis and or microlithiasis).

- Level of evidence: III
- Strength of recommendation: A
- Level of consensus: 93.8% (30) yes, 3.1% (1) no, 3.1% (1) abstain (32 voters)

### 4. Imaging techniques

**Diagnosis of testicular cancer.** Testicular ultrasound (US) should be carried out using a high frequency (>10 MHz) probe with...
colour Doppler assessment to confirm the presence of a testicular mass [54], before orchiectomy and exploration of the contralateral testis. In addition to confirming the presence of an intra-testicular mass, US can be used to evaluate the contralateral testis for the presence of synchronous tumours and microcalcifications, and to measure the testicular volume. US can also be used to detect an occult testicular mass in patients presenting with metastatic disease. Contrast-enhanced US of the testis is a technique that is particularly helpful in identifying and characterising small intra-testicular masses of < 1 cm [55–59].

Although scrotal magnetic resonance imaging (MRI) is good at identifying and characterising testicular tumours [60], currently its role is to help distinguish between an intra- and extra-testicular mass when this cannot be confirmed clinically or with US [61].

**Recommendation 4.1:** Testicular US using high frequency (>10 MHz) probe with colour Doppler assessment should be carried out to confirm the presence of a testicular mass before orchiectomy or possible exploration of the contralateral testis.

- Level of evidence: V
- Strength of recommendation: A
- Level of consensus: No vote obtained

**Staging of testicular cancer.** Computed tomography (CT) of the thorax, abdomen and pelvis is the imaging modality of choice in the staging of testicular tumours. In order to optimise the assessment of the retroperitoneum and to identify metastases, CT should be carried out with intravenous contrast media and oral opacification of the bowel with water or positive contrast media. The size of any metastases should preferably be described in three dimensions, and at least by the maximum axial diameter.

**Is there a role for PET-CT or MRI versus CT in testicular cancer?** Brain MRI (or contrast-enhanced CT if MRI is contraindicated) is required in patients with central nervous system symptoms or those presenting with widespread metastatic disease and/or high levels of beta-human chorionic gonadotropin (β-hCG) [62].

Fluorodeoxyglucose-positron emission tomography (FDG-PET) demonstrates no advantage over CT as an imaging modality in patients with clinical stage I disease, due to its inability to reliably identify disease activity in sub-centimetre lymph nodes [63]. However, FDG-PET may have a role in resolving equivocal CT findings, as the slightly higher sensitivity with FDG-PET may be useful in evaluating borderline lymph nodes [64]. Alternatively, targeted interval CT provides an option to assess growth of the borderline nodes using a lower dose of radiation. Importantly, clinicians must be aware of the limitations of FDG-PET if it is used as a problem-solving tool to resolve CT findings, for example, inflammatory lesions can also be FDG-avid on PET.

Currently, MRI is used when CT is inconclusive or contraindicated because of an allergy to the contrast media. MRI is the modality of choice for suspected bone marrow or central nervous system involvement and may be a useful problem-solving tool in difficult cases.

**Recommendation 4.2:** Contrast-enhanced CT is recommended in all patients for staging before orchiectomy.

- Level of evidence: III
- Strength of recommendation: A
- Level of consensus: No vote obtained

**Recommendation 4.3:** MRI may be helpful for characterisation of equivocal CT findings (e.g. in liver, bone, brain).

- Level of evidence: IV
- Strength of recommendation: A
- Level of consensus: No vote obtained

**Recommendation 4.4:** Brain MRI (or contrast-enhanced CT if MRI is contraindicated) is recommended in patients with symptoms or those with widespread metastatic disease and high levels of β-hCG.

- Level of evidence: IV
- Strength of recommendation: A
- Level of consensus: No vote obtained

**Recommendation 4.5:** MRI is not routinely recommended in all patients for staging of the retroperitoneum.

- Level of evidence: III
- Strength of recommendation: B
- Level of consensus: 94.1% (32) yes, 5.9% (2) abstain (34 voters)

**Recommendation 4.6:** PET-CT is not routinely recommended in all patients for staging.

- Level of evidence: I
- Strength of recommendation: B
- Level of consensus: 94.1% (32) yes, 5.9% (2) abstain (34 voters)

**Recommendation 4.7:** PET-CT is not considered to be useful for staging in the case of negative contrast-enhanced CT and marker-positive disease.

- Level of evidence: V
- Strength of recommendation: C
- Level of consensus: 88.2% (30) yes, 5.9% (2) no, 5.9% (2) abstain (34 voters)

**Recommendation 4.8:** In marker-negative disease, if contrast-enhanced CT shows equivocal lymph nodes, repeated staging with contrast-enhanced CT after 6–8 weeks is recommended.

- Level of evidence: V
- Strength of recommendation: B
- Level of consensus: 97.1% (33) yes, 2.9% (1) abstain (34 voters)

**Recommendation 4.9:** In marker-negative disease, if contrast-enhanced CT shows equivocal lymph nodes, repeated staging with PET-CT is not recommended.

- Level of evidence: V
- Strength of evidence: C
- Level of consensus: 88.2% (30) yes, 5.9% (2) no, 5.9% (2) abstain (34 voters)

**Post-treatment assessment of testicular cancer.** In the post-treatment assessment and follow-up of patients, CT is the primary imaging technique used. However, due to the radiation risk associated with CT, MRI may be used as an alternative in assessing the abdomen and pelvis. MRI is comparable to CT in the detection of retroperitoneal nodal metastases when interpreted by an experienced radiologist [65]. The detection of lymph nodes is enhanced by the addition of diffusion-weighted imaging to conventional MRI sequences (i.e. T1- and T2-weighted images) [66]. The Swedish-Norwegian Testicular Cancer Project (SWENOTECA) has used MRI extensively.
during follow-up instead of CT and has recorded excellent data for survival and tumour stage at disease recurrence [67]. Results are awaited from a multicentre, randomised, prospective study (TRISST) in the UK, which is using MRI and CT to evaluate the abdomen in patients with stage I seminoma managed by surveillance [68].

**Recommendation 4.10:** An MRI can be recommended for follow-up of the retroperitoneum, if standard protocols are used and the results are reported by an experienced radiologist.

- Level of evidence: III
- Strength of recommendation: A
- Level of consensus: 85.3% (29) yes, 2.9% (1) no, 11.8% (4) abstain (34 voters)

**Residual mass evaluation:** Imaging is used to assess residual disease and may allow for selection of patients who could potentially benefit from further treatment. In patients with large volume residual disease, CT, MRI and FDG-PET may be useful in surgical planning. Multipplanar reformat and identification of critical structures with CT or MRI could direct the surgical approach required. In addition, the use of FDG-PET may facilitate tailoring of surgery to metabolically active sites of disease. The chosen imaging modality carried out and any subsequent interpretation depends on whether the lesion is a seminoma or NSGCT.

FDG-PET is a valuable tool for clinical decision-making in post-chemotherapy seminoma residual masses [69–74]. In residual masses >3 cm, an appropriately timed PET is more reliable than CT in predicting necrosis/fibrosis or viable tumour, and thus able to spare patients unnecessary additional treatment such as surgery or radiation (sensitivity in lesions >3 cm is 88% and negative predictive value is 96%) [72]. The limitations of FDG-PET include false-positive scans due to inflammatory and granulomatous tissue and performing the PET too soon after chemotherapy. In such circumstances, a subsequent follow-up PET may show a negative PET result or decreasing FDG uptake. False-negative PET results may be caused by limited resolution as a result of tiny (5 mm) residual disease or by inadequate timing.

In NSGCT, CT can facilitate assessment of post-treatment residual masses by depicting changes in morphology [75]. As teratoma has variable, low or no FDG uptake, FDG-PET cannot be used to distinguish this from fibrosis or necrosis [76–78]; thus FDG-PET is unable to assist in the decision as to whether the response requires surgery or not.

**Recommendation 4.11:** FDG-PET-CT may be helpful to assess residual masses >3 cm in patients with seminoma if carried out at least 8 weeks after the end of chemotherapy. If the results are negative, FDG-PET-CT has a very high negative predictive value.

- Level of evidence: III
- Strength of recommendation: B
- Level of consensus: No vote obtained

**Recurrence post chemotheraphy:** FDG-PET may also have a role in the detection of recurrent disease. In patients with raised tumour markers and negative imaging findings (including negative FDG-PET), follow-up with a repeat FDG-PET is the most sensitive imaging modality to identify the site of relapse [64,77].

**Recommendation 4.12:** Repeat FDG-PET-CT may be useful in patients with marker-positive relapse and a negative contrast-enhanced CT result.

- Level of evidence: IV
- Strength of recommendation: B
- Level of consensus: No vote obtained

**Recommendation 4.13:** The follow-up contrast-enhanced CT should be of the abdomen only.

- Level of evidence: IV
- Strength of recommendation: C
- Level of consensus: 78.8% (26) yes, 9.1% (3) no, 12.1% (4) abstain (33 voters)

## 5. Diagnostic tools

See Section 3 of the supplementary data, available at *Annals of Oncology* online.

## 6. Are there RFs validated and/or accepted for seminoma?

In the absence of adjuvant treatment, ~15%–20% of patients with stage I testicular seminoma will develop recurrence. Most of these recurrences arise in retroperitoneal lymph nodes [79–81]. In contrast to non-seminoma, RFs to guide adjuvant treatment in patients with stage I seminoma are not well established. The two main RFs that have been studied are primary tumour size and stromal (but not pagetoid) invasion of the rete testis by seminoma. A nomogram produced by Warde et al. [82] suggested a 12% risk of recurrence in the absence of both RFs, a 16% risk of recurrence in the presence of either of the two RFs and a 32% risk of recurrence in the presence of both RFs. However, subsequent studies have shown more heterogeneous results. In a prognostic model based on data from 685 stage I seminoma patients, Chung et al. [83] failed to validate the nomogram and simply identified tumour size as an RF for recurrence without any clear, size-related cut-off. In contrast, a Japanese study of 425 patients undergoing orchiectomy for stage I testicular seminoma concluded that rete testis involvement is an RF for recurrence with or without adjuvant treatment [84]. A large retrospective Danish analysis concluded that tumour size was a significant factor for relapse, together with either invasion of epididymis or vascular invasion [79]. SWENOTECAs describes both primary tumour size and rete testis involvement as RFs for recurrence [80]. The Spanish Germ Cell Cancer Group (SGCCG) has published three consecutive studies on the management of stage I seminoma with different risk-adapted treatment strategies [85–87]. The nomogram developed by the SGCCG takes into account both primary tumour size (as a continuous variable) and stromal involvement of the rete testis [88]. For objective evaluation of the individual risk of recurrence, the SGCCG nomogram may be the most useful.

**Recommendation 6.1:** Both rete testis stromal invasion and primary tumour size should be considered as RFs for relapse in stage I seminoma.
Level of evidence: III  
Strength of recommendation: B  
Level of consensus: 91% (29) yes, 9% (3) abstain (32 voters)

**Recommendation 6.2:** In patients with seminoma, in the case of primary tumour size, there is no definitive cut-off value; however, larger tumours appear to confer higher risk of recurrence as a continuous variable.  
Level of evidence: III  
Strength of recommendation: B  
Level of consensus: 94% (30) yes, 6% (2) abstain (32 voters)

**Recommendation 6.3:** Patients with seminoma without any identified RF (e.g. no rete testis involvement and small tumour size) have a very low risk of recurrence.  
Level of evidence: III  
Strength of recommendation: B  
Level of consensus: 75% (24) yes, 25% (8) abstain (32 voters)

7. Are there RFs validated and/or accepted for non-seminoma?

Active surveillance studies have identified the presence of vascular invasion, the presence of undifferentiated cells and the absence of yolk sac elements as RFs for relapse in patients with non-seminoma [89]. In a cohort of 373 patients, the presence of no, one, two or three RFs was associated with 2-year relapse rates of 0%, 16%, 21% and 47%, respectively. In the case of isolated lymphatic or venous invasion with no other RFs, the 2-year relapse rate was 41% and 35%, respectively [89]. In recent studies, the prognostic significance of the presence of lymphovascular invasion (LVI) has been validated. Evaluating 1139 clinical stage I patients under active surveillance, Kollmannsberger et al. [81] described relapse rates of 44% and 14% in patients with and without LVI. Additionally, the median time to relapse was different between patients with and without LVI (4.0 versus 8.0 months). In a large Danish study, the relapse rate after orchiectomy alone was 30.6% at 5 years. Presence of vascular invasion together with embryonal carcinoma (EC) and rete testis invasion in the testicular primary identified a group with a relapse risk of 50%. Without RFs, the relapse risk was 12% [90].

Retrospective studies based on the patho-histology of resected lymph nodes following retroperitoneal lymph node dissection (RPLND) in clinical stage I non-seminoma have identified the presence of vascular invasion, the percentage of EC and the presence of infiltration of the tunica albuginea as prognostic RFs associated with pathological stage II disease [91]. Combining the percentage of EC with the presence or absence of vascular invasion enabled correct prediction of final pathological stage for 88% of clinical stage I patients. For patients with <45% EC and no vascular invasion, pathological stage I disease was correctly identified in 91.5% of patients; in the case of >80% EC and the presence of vascular invasion, pathological stage II was correctly predicted in 88% of patients [91].

A recent retrospective study on 226 clinical stage I non-seminoma patients has validated the clinical RFs mentioned above [92]. NSGCT patients were stratified according to predominance of EC and LVI, using an RF scoring system with the scale RF0, RF1 and RF2. Relapse rates and median time-to-relapse were 25% and 8.5 months, 41% and 6.8 months, and 78% and 3.8 months for RF0, RF1 and RF2, respectively. NSGCT patients grouped by a risk score system based on EC and LVI provided three groups of patients with distinct patterns of relapse [92].

**Recommendation 7.1:** In patients with non-seminoma, LVI is the key RF indicating disease relapse.  
Level of evidence: III  
Strength of recommendation: B  
Level of consensus: 100% (32) yes (32 voters)

**Recommendation 7.2:** In patients with non-seminoma, a combination of LVI and predominance of EC appears to be associated with an even higher rate of stage II progression or relapse versus LVI alone.  
Level of evidence: III  
Strength of recommendation: B  
Level of consensus: 94% (30) yes, 6% (2) abstain (32 voters)

**Recommendation 7.3:** Prospective collection of data on both markers (LVI and EC) is warranted.  
Level of evidence: III  
Strength of recommendation: B  
Level of consensus: 100% (32) yes (32 voters)

8. Who should be offered adjuvant chemotherapy?

**Seminoma.** In clinical stage I seminoma, several studies have found a low risk of relapse (~5%) in patients without RFs [87, 88, 93]. In these patients, adjuvant chemotherapy will therefore result in over-treatment in ~95% of cases. In patients with a higher risk of relapse, adjuvant chemotherapy remains an option. Adjuvant carboplatin reduces the risk of relapse by ~60% [93], which provides a number-needed-to-treat (NNT) value in the range of 15–20 to prevent one relapse.

**Recommendation 8.1:** Patients with seminoma and a low risk of relapse should **not** be offered adjuvant chemotherapy.  
Level of evidence: III  
Strength of recommendation: C  
Level of consensus: 91% (30) yes, 6% (2) no, 3% (1) abstain (33 voters)

**Recommendation 8.2:** In patients with seminoma and a higher risk of relapse, surveillance or adjuvant carboplatin are options.  
Level of evidence: III  
Strength of recommendation: C  
Level of consensus: 91% (30) yes, 6% (2) no, 3% (1) abstain (33 voters)

**Recommendation 8.3:** In patients with seminoma, patient autonomy should be taken into account following thorough provision of information regarding the pros and cons of the alternative treatment strategies.  
Level of evidence: III  
Strength of recommendation: C  
Level of consensus: 91% (30) yes, 6% (2) no, 3% (1) abstain (33 voters)

**Non-seminoma.** LVI is the major validated RF in stage I non-seminoma. In patients with LVI, the risk of relapse without
adjuvant therapy is ~50% [94–97]. Salvage treatment generally consists of three to four courses of chemotherapy and possibly RPLND, which results in established patterns of side-effects and late toxicity [98]. Adjuvant chemotherapy in the form of a single cycle of bleomycin/etoposide/cisplatin (BEP) will reduce the risk of relapse by over 90% [99]. As a consequence, adjuvant chemotherapy will spare ~50% of patients from salvage chemotherapy at the cost of 50% of patients unnecessarily receiving one course of BEP. This provides an NNT of 2.0–2.5 to avoid one relapse. In low-risk patients (LV1-negative), the relapse risk of 15% is reduced by 90%-95% following a single cycle of adjuvant BEP [99].

**Recommendation 8.4:** In patients with high-risk non-seminoma, adjuvant chemotherapy with one cycle of BEP is recommended if the patient is considered eligible for such treatment. Surveillance may be an alternative to adjuvant chemotherapy.

- Level of evidence: III
- Strength of recommendation: B
- Level of consensus: 72% (23) yes, 25% (8) no, 3% (1) abstain (32 voters)

**Recommendation 8.5:** In patients with high-risk non-seminoma, patient autonomy should be taken into account following the provision of thorough information regarding the pros and cons of alternative management strategies.

- Level of evidence: III
- Strength of recommendation: B
- Level of consensus: 72% (23) yes, 25% (8) no, 3% (1) abstain (32 voters)

**Recommendation 8.6:** In patients with low-risk non-seminoma who are eligible for adjuvant chemotherapy, surveillance is recommended. Adjuvant chemotherapy may be an alternative to surveillance.

- Level of evidence: III
- Strength of recommendation: B
- Level of consensus: 97% (32) yes, 3% (1) abstain (33 voters)

**Recommendation 8.7:** In patients with low-risk non-seminoma, patient autonomy should be taken into account following the provision of thorough information regarding the pros and cons of the alternative management strategies.

- Level of evidence: III
- Strength of recommendation: B
- Level of consensus: 97% (32) yes, 3% (1) abstain (33 voters)

9. Should adjuvant chemotherapy be limited to one course of chemotherapy?

**Seminoma.** In stage I seminoma, one course of adjuvant carboplatin has been compared with adjuvant radiotherapy in the large randomised Medical Research Council (MRC) TE19/European Organisation for Research and Treatment of Cancer (EORTC) 30982 trial [100]. In an unselected population, the relapse rate of 5.1% after one course of adjuvant carboplatin was comparable to that for adjuvant radiotherapy (4.1%). Some studies have used two courses of adjuvant carboplatin either dosed at area under the curve (AUC) 6–7 or at a fixed dose of 400 mg/m², with a reported relapse rate of 3%–4%, even in patients with RFs [85–87, 101]. Two courses of adjuvant carboplatin are likely to be more effective than one course, but this has never been tested in a head-to-head study. Adjuvant carboplatin has only a modest effect in reducing the risk of relapse, and even with two courses of carboplatin, the risk of relapse is reduced from 15%–20% to 3%–4% [98]. Thus, there is a need to explore more efficient adjuvant therapies in patients with RFs.

**Recommendation 9.1:** One course of carboplatin AUC 7 is the standard adjuvant chemotherapy in stage I seminoma.

- Level of evidence: I
- Strength of recommendation: B
- Level of consensus: 97% (30) yes, 3% (1) abstain (31 voters)

**Non-seminoma.** The first large series on the use of adjuvant chemotherapy in clinical stage I non-seminoma was published in 1996 and used two courses of BEP chemotherapy [102]. Since then, two courses of BEP have been the standard adjuvant treatment in clinical stage I non-seminoma. The first large studies using one course of BEP for non-seminoma patients were published in 2008 and 2009 [95, 103]. In 2015, a large study with mature follow-up on 517 patients treated with 1 course of adjuvant BEP was published. With a median follow-up of 7.9 years, no relapses beyond 3.3 years were detected, and a reduction in relapses of over 90% was reported [80].

**Recommendation 9.2:** One course of adjuvant BEP is the standard adjuvant chemotherapy in stage I non-seminoma.

- Level of evidence: III
- Strength of recommendation: B
- Level of consensus: 97% (30) yes, 3% (1) abstain (31 voters)

10. What is the optimal treatment of relapse after adjuvant chemotherapy?

**Seminoma.** Treatment of relapse after adjuvant chemotherapy should be standard treatment according to the prognostic classification for metastatic disease [93, 104].

**Recommendation 10.1:** In patients with seminoma, treatment of relapse after adjuvant chemotherapy should be standard treatment according to the prognostic classification for metastatic disease.

- Level of evidence: III
- Strength of recommendation: B
- Level of consensus: 93% (28) yes, 7% (2) abstain (30 voters)

**Non-seminoma.** Treatment of relapse after adjuvant chemotherapy should be standard treatment of metastatic disease, as defined by the international prognostic classification. Patients with localised abdominal and marker-negative relapse often show teratoma upon resection, and RPLND should be chosen as primary salvage treatment. This strategy has proven efficient and yields a 100% cause-specific survival rate [99].

**Recommendation 10.2:** In patients with non-seminoma, treatment of relapse after adjuvant chemotherapy should be standard chemotherapy for metastatic disease.

- Level of evidence: III
11. Other treatment alternatives for stage I disease: is there a role for RPLND?

RPLND is neither recommended nor carried out as standard treatment of stage I testicular cancer [62]. However, it represents an alternative to active surveillance or adjuvant chemotherapy in clinical stage I non-seminoma patients who are not eligible for or not willing to accept one of the above mentioned therapeutic options. If conducted, RPLND needs to be done at tertiary referral centers with high levels of experience (i.e. ≥20 cases per year) [62, 105]. Furthermore, RPLND should preferably be carried out as an open, nerve-sparing procedure. RPLND might be conducted laparoscopically; however, a higher level of experience is needed for this procedure than for open RPLND [106].

Primary NS-RPLND should be discussed in patients with pure teratoma and with RFs associated with occult retroperitoneal lymph node metastases [107]. The chance of detecting lymph node metastases by NS-RPLND is in the range 16.7%–20% [107]. The presence of scars and/or calcifications in the non-tumour bearing testicular parenchyma or the presence of microscopic non-teratomatous germ cell tumour elements have been shown to be associated with higher risk [108]. The majority of metastases harbour chemorefractory teratoma cells [109]; therefore, RPLND seems to be the treatment of choice in these cases. We recommend performing serial sections of the orchietomy specimen in men with pure teratoma.

Primary NS-RPLND may also be discussed among patients with clinical stage I teratoma with malignant somatic transformation. In a recent report, Giannatempo et al. [110] demonstrated that, of 28 stage I patients who underwent primary RPLND, 35.7% harboured viable tumour cells in the resected lymph node samples.

Recommendation 11.1: RPLND is an alternative treatment option to active surveillance or adjuvant chemotherapy in patients with stage I non-seminoma who are not eligible for or not willing to accept one of the above mentioned therapeutic options.

- Level of evidence: III
- Strength of recommendation: B
- Level of consensus: 90% (28) yes, 6% (2) no, 3% (1) abstain (31 voters)

Recommendation 11.2: RPLND is the standard treatment in patients with clinical stage I pure teratoma and RFs for occult retroperitoneal disease.

- Level of evidence: III
- Strength of recommendation: B
- Level of consensus: 62% (20) yes, 16% (5) no, 22% (7) abstain (32 voters)

Recommendation 11.3: RPLND is the standard treatment in patients with clinical stage I teratoma with malignant somatic transformation.

- Level of evidence: III
- Strength of recommendation: B
- Level of consensus: 90% (28) yes, 3% (1) no, 6% (2) abstain (31 voters)

12. Is there still a role for radiotherapy in clinical stage I testicular seminoma?

Adjuvant radiotherapy was the standard adjuvant treatment in clinical stage I seminoma patients for several decades [111]. The recurrence rate after modern radiation therapy is below 5%, and therefore equivalent to adjuvant carboplatin chemotherapy [100]. Patients treated with radiotherapy for testicular tumours are at an increased risk for secondary malignancies [112]. Treatment-related secondary tumours occur mostly in organs within the fields used for radiation treatment and the excessive risk appears ≥15 years after treatment [113]. On the other hand, the previously reported excessive risk of cardiovascular disease after radiation therapy [112] does not seem to materialise in patients treated with radiotherapy for stage I testicular seminoma [114], although this is controversial [115, 116].

Modern adjuvant radiotherapy for stage I testicular seminoma is delivered with a lower dose [117] and on a smaller treatment volume [118–121] compared with historical practice patterns. The irradiation of the para-aortic region (superior border at T11/12, inferior border at L4/L5) with a dose of 20 Gy at 10 fractions of 2 Gy each is the current standard for adjuvant radiotherapy. Currently, the secondary malignancy risk after modern radiotherapy is probably a lot lower than that seen with the doses, volumes and techniques used in the past [122]. This risk may further decrease in the future with advances in radiotherapy [123].

In terms of costs, adjuvant radiotherapy and carboplatin chemotherapy are equal [124]. Nevertheless, carboplatin chemotherapy should be the preferred option for patients scheduled to undergo adjuvant treatment due to the possibility of increased late morbidity associated with radiotherapy [125] (especially increased risk for secondary malignancies).

Radiotherapy can be used in exceptional cases where carboplatin chemotherapy is not an option due to other medical conditions (e.g. impaired bone marrow function or severe cardiovascular morbidity) in patients at increased risk of recurrence.

Recommendation 12.1: Adjuvant radiation therapy is not recommended for clinical stage I seminoma except in exceptional cases.

- Level of evidence: I
- Strength of recommendation: B
- Level of consensus: 100% (25) yes (25 voters)

Stage II–III testicular cancer

13. How should patients with stage IIA or IIB seminoma be treated?

Radiotherapy has long been the standard treatment of patients with stage IIA and IIB seminoma [126–128]. Currently, the
standard radiation field involves the para-aortic region and ipsilateral iliac nodes, with doses of 30 Gy in 2 Gy fractions for stage IIA, and 36 Gy in 2 Gy fractions for stage IIB [126].

As an alternative to radiotherapy, cisplatin-based combination chemotherapy with three cycles of BEP or four cycles of etoposide/cisplatin (EP) have been evaluated in stage II seminoma, with good results [129, 130]. Carboplatin monotherapy has been evaluated but has shown significantly inferior results [131]. Combination therapy with carboplatin and radiotherapy has shown interesting results but remains investigational [127, 132].

There are no randomised prospective data comparing treatment with radiotherapy to cisplatin-based combination chemotherapy in stage II seminoma, and both options are used interchangeably in clinical practice. A recent systematic review concluded that radiotherapy and cisplatin-based combination chemotherapy are equally effective in clinical stage IIA and IIB seminoma, with a trend in favour of chemotherapy in stage IIB because of fewer side-effects and lower relapse rates [133]. In a recent retrospective data analysis from the United States national cancer database, with data from 2437 patients with stage II seminoma, including 960 stage IIA and 812 stage IIB, radiotherapy was associated with improved survival compared with cisplatin-based combination chemotherapy for stage IIA patients, but no significant survival difference for stage IIB patients [134].

**Recommendation 13.1:** Evidence of metastatic disease has to be unequivocal in order to make a diagnosis of clinical stage IIA seminoma.

- **Level of evidence:** V
- **Strength of recommendation:** A
- **Level of consensus:** 91% (29) yes, 3% (1) no, 6% (2) abstain (32 voters)

**Recommendation 13.2:** Patients with clinical stage IIA seminoma can be treated with radiotherapy (30 Gy in 2 Gy fractions) or chemotherapy (three cycles of BEP or four cycles of EP).

- **Level of evidence:** IV
- **Strength of recommendation:** B
- **Level of consensus:** 43% (12) chemotherapy, 32% (9) radiotherapy, 18% (5) no preference, 7% (2) abstain (28 voters)

**Recommendation 13.3:** Patients with clinical stage IIB seminoma should be treated with three cycles of BEP or four cycles of EP. Radiotherapy (36 Gy in 2 Gy fractions) should only be given in selected cases.

- **Level of evidence:** IV
- **Strength of recommendation:** B
- **Level of consensus:** 91% (31) yes, 3% (1) no, 6% (2) abstain (34 voters)

14. Should different chemotherapy regimens be used in different clinical scenarios of metastatic seminoma?

Metastatic seminoma is less common than metastatic non-seminoma [105], and is associated with a comparatively good prognosis. Combination chemotherapy based on etoposide and cisplatin has been most commonly used either as a doublet (EP), or with the addition of bleomycin (BEP) or ifosfamide (VIP). Few trials have specifically investigated patients with seminoma; these patients were usually included alongside patients with NSGCT in trials of patients with a good prognosis. This makes specific recommendations for chemotherapy in seminoma difficult. The largest reported series, from Groupe d’Étude des Tumeurs Uro-génitales (GETUG), Memorial Sloan Kettering Cancer Center (MSKCC), the UK MRC and the Swedish Norwegian Testicular Cancer Study Group, included prospective studies, and used four cycles of EP [135–138]. These studies showed more favourable outcomes in good prognosis metastatic seminoma, defining four cycles of EP as a standard of care in this setting. Additionally, in an EORTC/MRC study, which included 20% of good prognosis metastatic seminoma patients, three cycles of BEP showed a good level of efficacy [projected 2-year progression-free survival (PFS) of 90.4%] [139] and is therefore also regarded as a standard of care.

As evidence supporting the value of bleomycin in metastatic seminoma is weak, four cycles of EP are a reasonable option in cases where bleomycin should be avoided (e.g. due to age, impaired renal function, significant lung disease or active smoking history).

Four cycles of BEP or four cycles of VIP are options for patients with seminoma and intermediate prognosis [135].

A single-centre UK study has shown that conventional-dose single-agent carboplatin (400 mg/m²) results in high rates of PFS in advanced seminoma [140]; however, a pooled analysis [141] that combined the UK data with those of a German study [142] reported significantly inferior 5-year PFS rates (72% versus 92%; \( P < 0.0001 \)) and a trend towards poorer 5-year overall survival (OS) rates (89% versus 94%; \( P = 0.09 \)) for single-agent carboplatin versus cisplatin combination therapy [141]. Single-agent carboplatin use is therefore not routinely recommended and is only an option in cases where cisplatin is contraindicated (e.g. impaired renal function). Recent work has suggested better results can be obtained by the use of high-dose carboplatin (AUC 10) [143], but this should be regarded as investigational and requires confirmation in prospective studies.

**Recommendation 14.1:** Three cycles of BEP is the recommended first-line chemotherapy for most good prognosis patients with metastatic seminoma. Four cycles of EP may be considered as an alternative.

- **Level of evidence:** II
- **Strength of recommendation:** A
- **Level of consensus:** 80% (24) yes, 10% (3) no, 10% (3) abstain (30 voters)

**Recommendation 14.2:** Four cycles of EP should be considered as the alternative first-line chemotherapy for good prognosis patients with metastatic seminoma who are not suitable for bleomycin.

- **Level of evidence:** II
- **Strength of recommendation:** A
- **Level of consensus:** 100% (30) yes (30 voters)

**Recommendation 14.3:** Four cycles of BEP (or four cycles of VIP) should be considered in patients with intermediate prognosis seminoma. VIP is favoured in patients with contraindications to bleomycin.

- **Level of evidence:** III
- **Strength of recommendation:** A
- **Level of consensus:** 94% (29) yes, 6% (2) abstain (31 voters)
15. What is the optimal treatment of patients with clinical stage IIA and IIB non-seminoma with normal or normalised serum tumour markers after orchiectomy?

The optimal management of patients with clinical stage IIA and IIB non-seminoma is a matter of debate. Firstly, not all patients with a small-volume disease on CT scan ultimately demonstrate metastatic disease. For this reason, metastatic disease should be confirmed by US-guided biopsy or a confirmatory CT scan after \( \sim 8 \) weeks in patients presenting with retroperitoneal lymph nodes of \( \leq 2 \) cm in the absence of other disease parameters (i.e. elevated serum tumour markers (STMs)).

In patients with confirmed clinical stage II NSGCT, it is usual to initiate chemotherapy according to the prognostic risk category, with the possible exception of patients with stage IIA disease or those who have special rare histologies in the orchiectomy specimen (i.e. patients with teratoma and/or somatic-type malignant transformation) [62].

The published literature indicates that the presence of elevated pre-RPLND STMs is associated with a 5.6-fold increased risk of systemic relapse and is the most significant predictor of relapse after primary RPLND [144, 145]. Hence, patients with elevated STMs should not be considered candidates for primary surgery.

For patients with clinical stage IIA and IIB NSGCT and normal or normalised STMs, the overall cure rate is \( \sim 98\% \), regardless of the therapeutic option; therefore, maintaining efficacy while minimising toxicity is the chief driver of treatment decisions. Only two studies have compared primary RPLND (with or without adjuvant chemotherapy) with primary chemotherapy [146, 147]. The largest of these was a retrospective study of 252 patients, in which primary chemotherapy was associated with improved 5-year relapse-free survival (RFS) compared with RPLND (98% versus 79%; \( P < 0.001 \)) [146]. In the other study, which had a prospective design and included 187 assessable patients, relapse rates were similar between groups. Loss of ejaculation occurred in 32% of patients treated with primary RPLND and in 16% of those treated with primary chemotherapy. Acute chemotherapy toxicity was higher in the primary chemotherapy group [147].

In patients managed with primary RPLND, post-RPLND adjuvant chemotherapy with two cycles of EP has been associated with an RFS rate of 99% at a median follow-up of 8 years [148]. However, the indication for this treatment is not clearly defined, and it is mostly considered for patients with pN2 tumours. The alternative is surveillance, with chemotherapy in case of relapse [148, 149].

Patient counselling should focus on aspects such as: the need for post-chemotherapy RPLND in some patients treated with primary chemotherapy, relapse rates after RPLND only, the role of adjuvant chemotherapy after primary RPLND, and morbidity following each therapeutic choice.

Treatment options for stage IIA and IIB non-seminoma are shown in supplementary Table S2, available at Annals of Oncology online.

**Recommendation 15.1:** All patients with clinical stage IIA NSGCT (evidence of enlarged retroperitoneal lymph nodes of \( \leq 2 \) cm) and normal STMs should have metastatic disease confirmed (e.g. by biopsy or repeated imaging \( \sim 8 \) weeks after surgery).

- Level of evidence: III
- Strength of recommendation: A
- Level of consensus: No vote obtained

**Recommendation 15.2:** The recommended treatment of confirmed clinical stage IIA non-seminoma with normal/normalised STMs is either BEP/EP \( \pm \) NS-RPLND, or primary NS-RPLND \( \pm \) adjuvant chemotherapy. Discussion regarding the pros and cons of these options with the patient is recommended.

- Level of evidence: III
- Strength of recommendation: A
- Level of consensus: 45% (13) BEP/EP \( \pm \) NS-RPLND; 34% (10) NS-RPLND \( \pm \) adjuvant chemotherapy; 7% (2) no preference, 14% (4) abstain (29 voters)

**Recommendation 15.3:** The recommended treatment of clinical stage IIB non-seminoma with normal/normalised STMs is primary BEP/EP \( \pm \) NS-RPLND.

- Level of evidence: III
- Strength of recommendation: B
- Level of consensus: 88% (29) BEP/EP \( \pm \) NS-RPLND, 3% (1) NS-RPLND \( \pm \) adjuvant chemotherapy, 6% (2) no preference, 3% (1) abstain (33 voters)

16. How should intermediate prognosis metastatic non-seminoma be treated?

According to the International Germ Cell Consensus Classification Group (IGCCCG), intermediate prognosis metastatic non-seminoma is defined as a metastatic primary testicular (or retroperitoneal) NSGCT with at least one elevated tumour marker at an S2 level [hCG, \( \alpha \)-foetoprotein (AFP) or lactate dehydrogenase] and no extra-pulmonary visceral metastases (see supplementary Table S3, available at Annals of Oncology online) [150]. Until the mid-1990s, patients were usually included in trials of poor-prognosis NSGCT, and by default, standard treatment became four cycles of BEP plus surgery of the residual mass, since this approach became the standard of care in 1987 [151]. Replacement of bleomycin by ifosfamide does not improve outcome and increases haematotoxicity. However, four cycles of VIP can be delivered in specific situations when bleomycin needs to be avoided due to pulmonary contraindications and is associated with similar efficacy to four cycles of BEP [152, 153]. If VIP is being used, primary prophylactic granulocyte colony-stimulating factor (G-CSF) is recommended due to the high risk of severe neutropaenia.

Only one phase III trial has specifically focused on the IGCCCG-defined intermediate prognosis group of NSGCT. This trial compared four cycles of BEP with four cycles of paclitaxel plus BEP (T-BEP). In the intent-to-treat analysis, no significant difference was detected in PFS or OS, and more toxicity was reported with T-BEP than BEP [152]. Unfortunately, this trial was hampered by the fact that the planned accrual was not reached and by the erroneous randomisation of some patients with good or poor prognosis NSGCT.

**Recommendation 16.1:** The recommended treatment of intermediate prognosis metastatic NSGCT is four cycles of BEP or four cycles of VIP with G-CSF support in cases where bleomycin is contraindicated. Chemotherapy should be followed by resection of residual masses when present.

- Level of evidence: II
- Strength of recommendation: A
- Level of consensus: 89% (25) yes, 11% (3) abstain (28 voters)
17. In patients with poor-prognosis NSGCT, should chemotherapy be intensified upfront, be adjusted based on tumour marker decline, or be administered using standard dosing schedules?

Historically, the outcomes of IGCCCG-defined poor prognosis patients were disappointing, with 5-year PFS and OS rates of 41% and 48%, respectively [150]. A more recent retrospective analysis of 223 poor prognosis patients treated centrally with the standard treatment of four cycles of BEP reported 5-year PFS and OS rates of 55% and 64%, respectively [154]. Two randomised, controlled trials comparing four cycles of BEP to four cycles of VIP reported similar outcomes for both regimens in IGCCCG-defined poor prognosis patients [155]. Consequently, VIP is a recognised alternative to BEP if bleomycin needs to be replaced.

Randomised trials directly comparing either dose-dense alternating regimens or primary high-dose chemotherapy (HDCT) with subsequent autologous stem cell support to BEP alone in unselected poor prognosis patients have generally failed to demonstrate substantial improvements in treatment outcomes [156, 157]. The Intergroup US phase III trial that used two cycles of BEP followed by two cycles of HDCT, and compared this with four cycles of BEP, showed no improvement in PFS or OS in 174 patients with poor prognosis NSGCT [158]. A randomised, phase II UK MRC trial (TE23), which included 89 patients with poor prognosis NSGCT, reported a 1-year PFS rate of 65% for patients undergoing intensified treatment with carboplatin/bleomycin/vincristine/cisplatin/BEP. Although the trial was not powered for comparison, results suggested that patients randomised to BEP achieved a 1-year PFS rate of only 43% [159]. A phase III EORTC trial evaluating primary sequential high-dose VIP (HD-VIP) in 137 patients closed accrual early and reported a 2-year PFS rate of 58% with HD-VIP versus 45% with four cycles of BEP (P = 0.057) [160]. In all trials, OS did not differ significantly between treatment groups, which may be related to the limited numbers of enrolled patients.

The outcome of poor prognosis TGCC patients differs markedly depending on the presence of key prognostic features. The worst prognostic has been reported for patients with either a primary mediastinal NSGCT or non-pulmonary visceral metastases [161–164]. The only prospectively assessed predictor for treatment outcome and survival in poor prognosis NSGCT is the kinetics of decline in the STMs, hCG and AFP [158, 165–167]. Marker decline can be assessed by several methods, including marker half-life [166] and time-to-normalisation (TTN) calculation, which also takes into account the extent of marker elevation above normal [167]. Notably, patients with very highly elevated markers (e.g. hCG 500 000 mIU/mL) are more often identified as not achieving adequate marker decline when assessed by TTN. One major advantage of the TTN methodology relates to the fact that it provides early information for treatment decision-making, given that tumour marker decline is calculated just 3 weeks after the initiation of chemotherapy, before the second cycle is given [167]. The methodology was established using a retrospective cohort of 139 patients and showed that early tumour marker decline has a prognostic impact on both PFS (4-year PFS rates: 64% versus 38%, respectively, for patients with and without favourable tumour marker decline) and OS (83% versus 58%, respectively) [167]. Subsequently, it was prospectively validated in the GETUG-13 phase III trial [165], where an impact on PFS (corresponding 3-year rates: 70% versus 48%) and OS (84% versus 65%) was confirmed.

In the international GETUG-13 phase III trial, tumour marker decline was assessed after the first cycle of BEP. Patients with favourable decline (20%) were assigned to receive three more cycles of BEP, while patients with an unfavourable decline (80%) were randomised to undergo either three more cycles of BEP or a dose-dense alternating chemotherapy regimen adding paclitaxel, oxaliplatin and ifosfamide to the BEP drugs (bleomycin dose was also individualised according to pulmonary assessment). Early application of dose-dense chemotherapy significantly improved PFS (the primary end point of the study) in patients with an unfavourable decline (3-year PFS rate: 59% versus 48%; hazard ratio (HR) 0.66 [95% confidence interval (CI) 0.44–1.00], P = 0.05) [165]. The updated analysis (median follow-up of 5.6 years) reported at ASCO 2016 confirmed the PFS benefit of early intensification [5-year PFS: 60% versus 47%; HR 0.65 (95% CI 0.43–0.97); P = 0.037], and suggested a favourable, but non-significant long-term impact on survival [5-year OS: 70.4% versus 60.8%; HR 0.69 (95% CI 0.43–1.11), P = 0.12], with reversible toxicity (long-term side-effects were similar after 5–6 years for patients who received BEP or dose-dense chemotherapy) [168].

**Recommendation 17.1:** Tumour marker decline (i.e. using the GETUG risk calculator: https://www.gustaveroussy.fr/calculatortumor/NSGCT.html) after one to two cycles of first-line cisplatin-based chemotherapy should be assessed to predict outcomes in poor prognosis patients.

Level of evidence: II
Strength of recommendation: B
Level of consensus: 68% (17) yes, 8% (2) no, 24% (6) abstain (25 voters)

**Recommendation 17.2:** Tumour marker decline after one to two cycles of first-line cisplatin-based chemotherapy should be used to guide treatment in poor prognosis patients with inadequate decline.

Level of evidence: II
Strength of recommendation: B
Level of consensus: 71% (17) yes, 17% (4) no, 12% (3) abstain (24 voters)

**Recommendation 17.3:** Early treatment intensification (dose-intensified chemotherapy) should be considered in the event of inadequate tumour decline after one to two cycles of first-line cisplatin-based chemotherapy. However, four cycles of BEP remains standard in patients with a favourable tumour decline.

Level of evidence: II
Strength of recommendation: C
Level of consensus: 65% (17) dose intensification in selected patients, 23% (6) four cycles of BEP, 12% (3) dose intensification in all patients (26 voters)

18. How should we treat primary mediastinal NSGCT (localised and metastatic)?

Primary mediastinal NSGCT is a rare clinical and biological entity [169] characterised by a higher incidence in men with...
Klinefelter’s syndrome than in those without, and a higher frequency of the yolk sac tumour subtype, AFP secretion and TP53 alterations than in primary TGCCs [170]. Primary mediastinal NSGCT has a unique capacity to evolve to various haematological malignancies that contain the 12p isochromosome, which is both a distinct feature of TGCCs [171] and an indicator of poor outcome [172, 173]. These characteristics have led to the classification of primary mediastinal NSGCT as belonging to the IGCCCG-defined poor prognosis subgroup, regardless of metastatic extent or tumour marker levels [150].

Treatment of poor prognosis NSGCT is typically based on cisplatin-based chemotherapy and surgery (with an unclear sequence); however, due to the rarity of this disease, no level 1 evidence is available from randomised trials. Post-chemotherapy, there is a high rate of residual and often refractory cancer in patients with primary mediastinal nonseminoma [174, 175]. Although not adequately assessed, the lower chemosensitivity of primary mediastinal NSGCT compared with other TGCCs means that primary surgery or early surgery after one to two cycles of chemotherapy in patients with localised disease may be advantageous to the classical sequence used in metastatic NSGCT (i.e. completion of chemotherapy followed by resection of residual masses). No data are available on the role of radiotherapy in primary mediastinal NSGCT. In contrast to other types of poor prognosis NSGCT, the benefit of early chemotherapy intensification for patients with an unfavourable decline in tumour markers is less clear for primary mediastinal NSGCT than for other tumour types [165]. Caution should be exercised with the use of bleomycin (conduct repeated lung function assessment and/or replace with ifosfamide) to limit the risk of pulmonary complications during thoracic surgery.

All attempts should be made to achieve cure after first-line therapy because primary mediastinal NSGCT is generally incurable in the salvage setting, even with HDCT and autologous transplant [169, 176, 177].

**Recommendation 18.1:** For patients with primary mediastinal NSGCT, treatment with chemotherapy regimens used for poor prognosis NSGCT are recommended. Post-chemotherapy surgery is recommended for all patients irrespective of marker status. Bleomycin should either be closely monitored to prevent clinical lung toxicity or replaced by ifosfamide.

- Level of evidence: III
- Strength of recommendation: B
- Level of consensus: 46% (12) chemotherapy, with intensification in case of unsatisfactory tumour marker decline, followed by surgery (if technically feasible), 23% (6) four cycles of BEP followed by surgery (if technically feasible), 19% (5) upfront intensified chemotherapy irrespective of tumour marker decline followed by surgery, 8% (2) four cycles of VIP followed by surgery (if technically feasible), 4% (1) primary surgery followed by chemotherapy (26 voters)

19. What is the appropriate management for patients with upfront brain or bone metastases?

Patients with upfront brain and/or bone metastases are rare and are classified as having a poor prognosis [150]. Optimal treatment remains unclear and is open for debate. There are no adequately powered prospective clinical trials to answer questions concerning reasonable imaging techniques, use of radiotherapy and/or the incorporation of additional surgery [164, 178, 179]. All reports are based on retrospective data derived from small patient numbers or from single-centre experiences.

Upfront brain metastases occur in ~19%–2% of patients with advanced TGCC [180]. Routine brain imaging is not recommended other than in patients with neurological symptoms, those with highly elevated hCG levels and multiple lung metastases or those with widespread disease [181]. A recently published analysis including 228 patients with upfront brain metastases identified several adverse prognostic features such as histology, NSGCT mediastinal primary tumour and multiple (versus single) brain lesions [182]. Currently, patients with upfront brain metastases are treated with chemotherapy regimens recommended for poor prognosis NSGCT according to the IGCCCG classification. The role of brain radiotherapy remains poorly defined, with several reports (including the recent pooled analysis) indicating no clear survival benefit and a risk of severe late neurotoxicity, including progressive leukoencephalopathy [182–184]. The role of brain surgery for post-chemotherapy residual masses is a relatively uncommon scenario as these patients often have widespread, multi focal disease. However, patients with accessible, solitary or limited residual masses who showed a good response in other secondary sites and whose STMs have normalised, may be considered for post-chemotherapy resections. Long-term survival is reported in up to 60% of such patients if complete resections can be achieved [179]. In contrast, a large retrospective analysis did not show any additional benefit of post-chemotherapy resections of residual brain lesions after first-line chemotherapy [182]. For patients with unresectable isolated residual brain metastases, stereotactic radiosurgery is considered as an option, though with a similarly low level of evidence.

Upfront bone metastases are rare and are reported in ~3%–9% of patients, and are an adverse feature with poor treatment outcome, particularly in patients with non-seminoma. Bone metastases are mainly localised within the spine, pelvis and ribs. In a recent retrospective analysis of 123 patients with metastatic bone disease from TGCC, concomitant non-pulmonary visceral metastases and a mediastinal primary tumour were predictors of inferior outcome according to univariate analysis [185]. At present, no optimal treatment approach has been defined; however, patients with upfront bone metastases should be treated with chemotherapy regimens used for IGCCCG-defined poor prognosis NSGCT. The role of dose-intensified primary treatment and/or multimodal approaches, including additional local treatment by secondary resection and/or additional radiotherapy of residual bone lesions, could not be defined by the aforementioned retrospective analysis due to low patient numbers in the different subgroups [185]. Post-chemotherapy resections may be considered in localised, accessible lesions, but decisions regarding post-chemotherapy surgery should be taken on an individual basis and by an experienced, multidisciplinary team. Post-chemotherapy radiation might be an alternative to surgery [186–188].

**Recommendation 19.1:** Chemotherapy according to the IGCCCG classification for poor prognosis TGCC is recommended as standard of care for patients with upfront brain and/
or bone metastases. Patients with upfront symptomatic or asymptomatic multiple brain metastases should commence systemic treatment before using other (local) treatment modalities.

Recommendation 19.2: There are no high-quality data governing routine use of post-chemotherapy local treatment (surgery or radiation) for the brain or bone. Primary whole-brain radiotherapy is not recommended.

Recommendation 19.3: Patients with upfront brain metastases, single residual lesions after chemotherapy and normal or normalised tumour markers should be considered for additional surgery or stereotactic radiation.

Recommendation 20.1: In patients with advanced metastatic TGCC and/or those with impeding organ failure, orchietomy can be postponed until the completion of chemotherapy. However, removal of the tumour-bearing testicle is mandatory after termination of chemotherapy or in-between cycles (without postponing the next cycle).

Recommendation 20.2: In patients with widespread lung metastases, pure choriocarcinoma and high hCG, there is a high risk of fatal lung bleeding that often develops during the first days of chemotherapy. This complication can probably be reduced by avoiding full-dose chemotherapy during initial treatment. However, there are few data available on how to optimally administer such early induction chemotherapy.

Recommendation 20.3: Patients with chronic kidney disease (stage II–III or GFR 50–90 mL/min/1.73 m²) before treatment should have any hydronephrosis relieved to enable delivery of full-dose cisplatin-based chemotherapy with little risk of clinically relevant changes in GFR.

Recommendation 20.4: In patients with a GFR of 30–50 mL/min/1.73 m², after relief of mechanical obstruction (hydrenephrosis), carboplatin-based chemotherapy (or cisplatin-based chemotherapy in patients undergoing haemodialysis) are options. Adapted doses of carboplatin are recommended in patients when it is believed that the impaired renal function is related to the cancer and may eventually recover. On the other hand, cisplatin can be used safely in patients with chronically impaired renal function who are undergoing haemodialysis.

Recommendation 20.5: Regardless of the degree of renal function, patients with hydronephrosis (unilateral or bilateral) should be relieved with either stent or nephrostomy before chemotherapy.
21. What is the optimal treatment of older patients with metastatic TGCCs?

Data from 2482 patients treated at two institutions in Germany suggest that there is a significant shift towards older age at diagnosis of TGCC (mean age at diagnosis increased from 28 to 36 years) [193], and this is paralleled by the increasing number of cases of seminomatous TGCC. Furthermore, poorer survival is observed for patients with metastatic TGCC aged >40 years [194–196], and this is partly attributable to the non-seminomatous histology in that age group.

The optimal treatment of older patients with metastatic TGCC, as well as the optimal cut-off age to define older patients (e.g. 40, 50 or 60 years old), if any, is unknown. Many authors have reported data from retrospective analyses which suggest that increased age has a detrimental effect on OS [154, 197–199]. In a large Danish series [195], as well as in another double-institution dataset [199], age emerged as a statistically significant poor prognostic factor in multivariate analyses. It is unknown whether this adverse outcome related to age is due to treatment deviating from standard recommendations, poor treatment tolerance or the underlying biology of the disease. In general, for patients aged >50 years, there are some concerns regarding the feasibility of administering standard chemotherapy and preserving the full dose and schedule of all drugs at each cycle. In the MSKCC experience, among 236 patients aged ≥50 years, a high rate of neutropaenic fever and haematological severe toxicities were recorded, and dose reductions, delays or treatment changes were needed in 30 patients [200]. However, in an English study, no substantial toxicities were reported with the use of chemotherapy in patients >60 years old [201].

Although the use of primary prophylaxis with G-CSF in young patients with TGCC receiving BEP is an area of debate [202, 203], G-CSF use may be indicated in selected high-risk cases among older patients.

In the setting of second-line chemotherapy, where cure is still a realistic treatment goal, substantial uncertainties remain regarding the superiority of HDCT versus conventional-dose chemotherapy (CDCT) in both young adults and older patients with metastatic TGCC. Even in the context of salvage CDCT, the toxicity profiles of the most frequently utilised regimens (including ifosfamide and cisplatin combinations) in older patients is largely unknown. In the series of the European Society of Blood and Marrow Transplantation (EBMT) [204], 1169 patients aged >40 years received at least one cycle of HDCT from 1981 to 2015. In this study, age did not emerge as a significant prognostic factor for transplant-related mortality in multivariable analyses. Consequently, the administration of HD-carboplatin and etoposide appears feasible in older patients with advanced and relapsed TGCC. However, in the salvage setting, limited data are available regarding acute and long-term toxicities of dose-intensified regimens.

22. Should care of patients with metastatic TGCC be centralised?

In the last 20 years, many studies have emphasised a key role for centralisation of care for patients with rare cancers, especially those with TGCC, in order to achieve the best chance of cure and also to lower the likelihood of undue side-effects related to overtreatment. Perhaps the clearest demonstration for this was shown in an analysis of an EORTC/MRC phase III trial in patients with poor prognosis TGCC which looked at patient outcomes according to the experience of the treating centre, as assessed by the number of patients accrued in the trial (more or fewer than five patients). A reduction of ~20% in the chance of cure was observed in less experienced centres compared with more experienced centres [205]. Detailed analyses suggested that cumulative chemotherapy doses were lower, toxicity and treatment-related mortality were higher, and the use of post-chemotherapy resection of residual masses were lower in low volume centres, which may help to explain the poorer outcomes. These data, obtained from a large multinational prospective trial, confirmed previous evidence from retrospective analyses of various databases from Europe and the United States [206, 207]. In 1999, an editorial was subsequently written in the Journal of the National Cancer Institute where the authors called for treatment of patients with testicular cancer by experts at high volume centres [208].

Since then, some countries, such as Denmark and England, have embraced a centralisation policy for all patients with TGCC. The Scandinavian SWENOTECA group has also been able to centralise chemotherapy delivery and surgery to several high-volume centres, with excellent outcomes at a national level [209]. In contrast, most other countries leave the decision and delivery of treatment to the local physician or medical team who first sees the patient. National surveys, when available, have repeatedly demonstrated that treatments administered differ from guidelines in several countries, possibly leading to higher relapse rates [210, 211].
Besides inadequate chemotherapy delivery (with a risk of overtreatment and excessive toxicity or insufficient treatment and poorer outcome), inadequate post-chemotherapy RPLND or other resections of residual masses carried out at community centres can also lead to a higher risk of in-field relapses compared with centralised care, as demonstrated in a German trial [103].

The benefits of centralised care include a pathological review of orchiectomy or other tissue material when needed, specialist radiological evaluation at diagnosis, post-chemotherapy, and during follow-up, guideline-based indication and delivery of chemotherapy and surgery by expert teams, all of which might be crucial for success. Models exist for the identification and development of high-volume specialist centres [212].

**Recommendation 22.1:** Besides orchiectomy, treatment of patients with TGCC should be conducted in high-volume centres.

- **Level of evidence:** IV
- **Strength of recommendation:** A
- **Level of consensus:** 77% (20) agree for all patients; 23% (6) agree only for patients with metastases (26 voters)

### Post-chemotherapy surgery, salvage chemotherapy, salvage and desperation surgery, and special topics

**23. When is post-chemotherapy retroperitoneal lymph-node dissection (PC-RPLND) indicated?**

See Section 3 of the supplementary data, available at Annals of Oncology online.

**Seminoma.** Patients should be assessed for residual lesions by CT or MRI and tumour markers ~8 weeks after day 21 of last course of chemotherapy. Patients with a complete response should be scheduled for routine follow-up. For patients who do not achieve a complete response with remaining lesions >3 cm, an FDG-PET scan should be carried out no earlier than 2 months after completion of chemotherapy. The negative predictive value of FDG-PET is >90%, and a negative scan with a non-growing or regressing lesion warrants routine follow-up only [69]. With a positive FDG-PET scan, the possibility of residual seminoma is in the range of 20%, and so false-positive results are common [69, 213]. FDG-PET-positive lesions can show an unpredictable behaviour; some lesions might decrease in size and activity over time. Thus, monitoring using repeat FDG-PET scans until resolution or progression is advised. PC-RPLND can be an alternative in resectable lesions, when a persistent FDG-PET positive residual mass is nodular in shape. However, the procedure is technically demanding, and often requires adjunctive procedures [69, 72, 214, 215]. In the majority of patients with seminoma, necrosis or fibrosis will be found at PC-RPLND. These patients require no further treatment [216].

**Non-seminoma.** Patients should be assessed for residual masses by CT or MRI and tumour markers ~4–6 weeks after the start of the last chemotherapy cycle.

PC-RPLND is indicated in patients with non-seminoma who have residual retroperitoneal lesions ≥1 cm in size, as determined by the largest axial dimension on CT scan in the presence of normal markers [216–223]. However, small residual lesions at or just above the 1 cm cut-off may continue to decrease. Retrospective studies suggest that these patients can be treated individually using immediate post-chemotherapy surgery or short-term active monitoring in case of good prognosis disease. If these lesions do not continue to shrink on follow-up scans and remain ≥1 cm in largest axial diameter, they should be resected. Patients with residual lesions <1 cm (including those with complete clinical remission) have a <10% relapse risk, presumably due to residual teratoma or viable cancer. Treatment of these patients includes either active monitoring or PC-RPLND, which should be discussed individually [224–227].

Patients with post-chemotherapy residual lesions and positive STMs should be followed with STM determinations at brief intervals and should not undergo surgery immediately. Patients with declining STMs or low-level STM stabilisation are candidates for surgery, whereas patients with increasing STMs, especially a rising β-hCG, should undergo full salvage chemotherapy before residual tumour resection is considered.

Treatment decisions in patients with post-chemotherapy positive STMs and potentially resectable lesions are complex and must take into account the location of the primary tumour (primary mediastinal non-seminoma versus others), the type of elevated STM (e.g. β-hCG is of more concern than AFP), the degree of post-chemotherapy STM elevation, STM kinetics and the location, number and resectability of the lesions.

**Recommendation 23.1:** PC-RPLND is indicated in patients with non-seminoma and residual retroperitoneal lesions ≥1 cm in size.

- **Level of evidence:** IV
- **Strength of recommendation:** A
- **Level of consensus:** 89.3% (25) yes, 10.7% (3) no (28 voters)

**Recommendation 23.2:** Indication for PC-RPLND should be determined based on the largest axial dimension of residual retroperitoneal lesions on CT scan in the presence of normal markers.

- **Level of evidence:** IV
- **Strength of recommendation:** A
- **Level of consensus:** 100% (28) yes (28 voters)

**24. Salvage therapy**

**Salvage surgery.** Salvage surgery refers to surgery in patients with relapsing or progressing disease following salvage chemotherapy, as an alternative to palliative chemotherapy. A proportion of these patients may benefit from complete removal of disease, with long-term survival reported in selected patients [228–230]. Ideal candidates include patients with resectable radiological lesions in the retroperitoneum and potentially one additional site, those with declining STMs or a STM plateau after chemotherapy, and patients with a slowly rising AFP. Viable cancer or teratoma with somatic-type malignant transformation is more frequent after salvage or desperation surgery [110].

**Salvage chemotherapy.** Patients who relapse or progress after three or more cycles of cisplatin-based first-line chemotherapy for metastatic disease can be cured by salvage chemotherapy. Treatment decisions about salvage chemotherapy are complex,
taking into account multiple factors, including primary tumour location, histology, response to first-line chemotherapy, location of metastases and tumour marker levels at the time of relapse or progression. These patients should therefore be referred to high-volume centres with individual decisions made by a multidisciplinary team experienced in treating such patients [231].

First-salvage chemotherapy. The prognosis of patients who progress or relapse after first-line chemotherapy for metastatic disease, comprising at least three cisplatin-based cycles, should be assessed and classified using the international prognostic factor classification (supplementary Table S4, available at Annals of Oncology online) [176]. There is insufficient evidence to determine whether CDCT or HDCT produces superior outcomes as first-salvage chemotherapy. Therefore, either CDCT or HDCT are acceptable options for first-salvage chemotherapy. Salvage CDCT should be delivered as four cycles of cisplatin/ifosfamide-based triple-drug combinations. The two most widely used CDCT regimens are cisplatin/ifosfamide/paclitaxel (TIP) using different schedules [232, 233] and VIP (Table 2) [234, 235]. Salvage HDCT is delivered as two or three sequential cycles of high-dose carboplatin and etoposide without additional agents such as ifosfamide, cyclophosphamide or thiotepa [236–238].

Second-salvage chemotherapy. HDCT should be considered as second-salvage treatment in patients with a good performance status and adequate organ function who relapse or progress with systemic disease and/or increasing tumour markers after first-salvage CDCT [197, 240]. Selected ‘third-line’ regimens are suitable for patients relapsing after HDCT, or in cases where HDCT cannot be carried out. In individual patients, cures may still be achievable using these regimens (see Table 3) followed by surgical resection of residual masses or using desperation surgery alone.

### Table 2. First-salvage regimens for CDCT and HDCT [104, 234, 235]

<table>
<thead>
<tr>
<th>CDCT regimens</th>
<th>VIP/PEI</th>
<th>Four cycles, repeat every 3 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>20 mg/m²</td>
<td>Days 1–5</td>
</tr>
<tr>
<td>Etoposide</td>
<td>100 mg/m²</td>
<td>Days 1–5</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>1.2 g/m²</td>
<td>Days 1–5</td>
</tr>
<tr>
<td>TIP</td>
<td></td>
<td>Four cycles, repeat cycle every 3 weeks</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>250 mg/m²</td>
<td>Day 1</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>25 mg/m²</td>
<td>Days 2–5</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>1.5 g/m²</td>
<td>Days 2–5</td>
</tr>
<tr>
<td>HDCT regimens</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TI-CE</td>
<td>Two TI cycles to be repeated after 2 weeks</td>
<td></td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>200 mg/m²</td>
<td>Day 1</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>2 g/m²</td>
<td>Days 2–4</td>
</tr>
<tr>
<td>Followed by:</td>
<td></td>
<td>Three CE cycles to be repeated after 3 weeks</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>AUC 8</td>
<td>Days 1–3</td>
</tr>
<tr>
<td>Etoposide</td>
<td>400 mg/m²</td>
<td>Days 1–3</td>
</tr>
<tr>
<td>VIP-CE</td>
<td>One VIP cycle</td>
<td></td>
</tr>
<tr>
<td>Cisplatin</td>
<td>20 mg/m²</td>
<td>Days 1–5</td>
</tr>
<tr>
<td>Etoposide</td>
<td>100 mg/m²</td>
<td>Days 1–5</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>1.2 g/m²</td>
<td>Days 1–5</td>
</tr>
<tr>
<td>Followed by:</td>
<td></td>
<td>Three CE cycles to be repeated after 3 weeks</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>500 mg/m²</td>
<td>Days 1–3</td>
</tr>
<tr>
<td>Etoposide</td>
<td>500 mg/m²</td>
<td>Days 1–3</td>
</tr>
<tr>
<td>Indiana-CE</td>
<td>Two cycles to be repeated after haematopoietic recovery</td>
<td></td>
</tr>
<tr>
<td>Carboplatin</td>
<td>700 mg/m²</td>
<td>Days 1–3</td>
</tr>
<tr>
<td>Etoposide</td>
<td>750 mg/m²</td>
<td>Days 1–3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HDCT regimens</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>TI-CE</td>
<td>Two TI cycles to be repeated after 2 weeks</td>
<td></td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>200 mg/m²</td>
<td>Day 1</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>2 g/m²</td>
<td>Days 2–4</td>
</tr>
<tr>
<td>Followed by:</td>
<td></td>
<td>Three CE cycles to be repeated after 3 weeks</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>AUC 8</td>
<td>Days 1–3</td>
</tr>
<tr>
<td>Etoposide</td>
<td>400 mg/m²</td>
<td>Days 1–3</td>
</tr>
<tr>
<td>VIP-CE</td>
<td>One VIP cycle</td>
<td></td>
</tr>
<tr>
<td>Cisplatin</td>
<td>20 mg/m²</td>
<td>Days 1–5</td>
</tr>
<tr>
<td>Etoposide</td>
<td>100 mg/m²</td>
<td>Days 1–5</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>1.2 g/m²</td>
<td>Days 1–5</td>
</tr>
<tr>
<td>Followed by:</td>
<td></td>
<td>Three CE cycles to be repeated after 3 weeks</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>500 mg/m²</td>
<td>Days 1–3</td>
</tr>
<tr>
<td>Etoposide</td>
<td>500 mg/m²</td>
<td>Days 1–3</td>
</tr>
<tr>
<td>Indiana-CE</td>
<td>Two cycles to be repeated after haematopoietic recovery</td>
<td></td>
</tr>
<tr>
<td>Carboplatin</td>
<td>700 mg/m²</td>
<td>Days 1–3</td>
</tr>
<tr>
<td>Etoposide</td>
<td>750 mg/m²</td>
<td>Days 1–3</td>
</tr>
</tbody>
</table>

AUC, area under the curve; CDCT, conventional-dose chemotherapy; CE, carboplatin/etoposide; HDCT, high-dose chemotherapy; TI, paclitaxel/ifosfamide; TIP, paclitaxel/ifosfamide/cisplatin; VIP/PEI, etoposide/ifosfamide/cisplatin.

Paclitaxel and ifosfamide are used before HDCT (carboplatin/etoposide) for two cycles in the TI-CE regimen [236]. One study used a single cycle of VIP before HDCT [237]. As neither CDCT nor HDCT has unequivocal superiority as first-salvage treatment, patients should, where possible, be treated in the prospective randomised phase III TIGER trial (NCT02375204) comparing CDCT, TIP, HDCT and TI-CE [239].

### Table 3. ‘Third-line’ regimens used for second or subsequent salvage treatment

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Dose</th>
<th>Schedule</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemcitabine</td>
<td>1000 mg/m²</td>
<td>d1, 8, 15 q3w</td>
<td>[241]</td>
</tr>
<tr>
<td></td>
<td>1200 mg/m²</td>
<td>d1, 8, 15 q3w</td>
<td>[242]</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>60 mg/m² or 85 mg/m²</td>
<td>d1, 15 q4w</td>
<td>[243]</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>170 mg/m²</td>
<td>d1, q3w</td>
<td>[244]</td>
</tr>
<tr>
<td></td>
<td>225 mg/m²</td>
<td>d1, q3w</td>
<td>[245]</td>
</tr>
<tr>
<td></td>
<td>250 mg/m²</td>
<td>d1, q3w</td>
<td>[246]</td>
</tr>
<tr>
<td></td>
<td>250 mg/m²</td>
<td>d1, q3w</td>
<td>[247]</td>
</tr>
<tr>
<td>Oral etoposide</td>
<td>50 mg/m²/day</td>
<td>Continuously</td>
<td>[248]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Dose</th>
<th>Schedule</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemcitabine</td>
<td>1000 mg/m² or 1250 mg/m²</td>
<td>d1, 8 q3w</td>
<td>[249–251]</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>130 mg/m²</td>
<td>d1, q3w</td>
<td>[249, 251]</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>1000 mg/m²</td>
<td>d1, 8, 15 q4w</td>
<td>[252, 253]</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>100 mg/m²</td>
<td>d1, 8, 15 q4w</td>
<td>[252, 253]</td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>Regimen</th>
<th>Dose</th>
<th>Schedule</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemcitabine</td>
<td>800 mg/m²</td>
<td>d1, 8 q3w</td>
<td>[254]</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>130 mg/m²</td>
<td>d1, q3w</td>
<td>[254]</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>80 mg/m²</td>
<td>d1, 8 q3w</td>
<td>[255]</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>800 mg/m²</td>
<td>d1, 8 q3w</td>
<td>[255]</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>50 mg/m²</td>
<td>d1, 8 q3w</td>
<td>[255]</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>80 mg/m²</td>
<td>d1, 8 q3w</td>
<td>[255]</td>
</tr>
</tbody>
</table>

d, day; q3w, every 3 weeks; q4w, every 4 weeks.
Recommendation 24.1: In patients with disease relapse, immediate surgery without prior biopsy should only be considered for:

- non-seminoma patients relapsing with localised resectable lesions and negative STMs, as lesions may be due to enlarging teratoma without malignant components;
- late relapses in both seminoma and non-seminoma with localised resectable lesions due to the high incidence of chemotherapy-refractory disease.

Level of evidence: V
Strength of recommendation: A
Level of consensus: 76.5% (26) yes, 5.9% (2) no, 17.6% (6) abstain (34 voters)

Recommendation 24.2: In all other patients, particularly those with increasing STMs, surgery should be postponed until completion of salvage chemotherapy, even in the presence of resectable lesions.

Level of evidence: III
Strength of recommendation: A
Level of consensus: 87.5% (28) yes, 12.5% (4) abstain (32 voters)

25. Salvage treatment of patients with brain metastases

Patients who relapse or progress with brain metastases after first-line cisplatin-based chemotherapy have a poor prognosis, but cure can be achieved in individual cases by multimodality treatment, preferably including HDCT plus radiation and/or surgery [179, 182]. With current optimised treatments in men with poor-risk NSGCT, for those who experience a relapse, it was not uncommon that brain was the only relapse site, and this raises the question of systematic early detection and optimal treatment of brain metastases [256].

In the rare case of an isolated brain relapse without evidence of systemic disease, prognosis appears to be better only in patients with a single brain metastasis. Surgery as well as stereotactic radiation, with or without chemotherapy, are valid options. When radiotherapy is considered, stereotactic radiation should be used rather than whole brain radiation whenever technically feasible.

Recommendation 25.1: Surgery as well as stereotactic radiation with or without chemotherapy may be considered for patients with isolated brain relapse without evidence of systemic disease. When radiotherapy is considered, stereotactic radiation should be used rather than whole brain radiation whenever technically feasible.

Level of evidence: V
Strength of recommendation: B
Level of consensus: 53.3% (16) yes, 26.7% (8) no, 20.0% (6) abstain (30 voters)

Survivorship and follow-up schemes

Most of the recommendations given in this chapter are based on cross-sectional studies, typically covering the first decade after treatment. Further, age-matched control groups are often missing such that the effect of ageing is not easy to disentangle. As such, uncertainty remains regarding the longer-term survivorship outcomes and causal relationships. This uncertainty is reflected by low levels of evidence (IV–V) and lower grades of recommendation (usually B).

26. How can post-therapeutic psychosocial issues be minimised, and health-related quality of life (HRQoL) protected?

HRQoL: emotional and psychosocial issues. See Section 3 of the supplementary data, available at Annals of Oncology online.

Quality of life and post-therapeutic psychosocial issues. See Section 3 of the supplementary data, available at Annals of Oncology online.

Recommendation 26.1: Patients should be informed of the potential long-term toxicities of treatment (i.e. ototoxicity and neurotoxicity, second cancers and cardiovascular disease [CVD], as well as sexual difficulties, fatigue and cognitive dysfunction).

Level of evidence: III/IV
Strength of recommendation: B
Level of consensus: 97% (32) yes, 3% (1) abstain (33 voters)

Recommendation 26.2: Patients should be reassured that in most cases, long-term overall HRQoL is similar to that in men who have not undergone treatment of testicular cancer.

Level of evidence: IV
Strength of recommendation: B
Level of consensus: 97% (32) yes, 3% (1) abstain (33 voters)

Recommendation 26.3: Vulnerable patients (e.g. those with psychological distress and poor social support) should be identified early to assess the need for support by social workers and psychological assistance.

Level of evidence: IV
Strength of recommendation: B
Level of consensus: 97% (32) yes, 3% (1) abstain (33 voters)

Recommendation 26.4: Physical activity and a healthy lifestyle should be recommended to all patients.

Level of evidence: IV
Strength of recommendation: B
Level of consensus: 97% (32) yes, 3% (1) abstain (33 voters)

27. How should fatigue be identified, prevented and treated?

Chronic fatigue. See Section 3 of the supplementary data, available at Annals of Oncology online.

Recommendation 27.1: In order to prevent fatigue, overtreatment should be avoided (i.e. by adherence to treatment guidelines).

Level of evidence: V
Strength of recommendation: B
Level of consensus: 100% (33) yes (33 voters)

Recommendation 27.2: Fatigue should be addressed and documented during follow-up.

Level of evidence: V
Strength of recommendation: B
Level of consensus: 100% (33) yes (33 voters)
**Recommendation 27.3:** Contributing conditions should be identified and treated.
- Level of evidence: V
- Strength of recommendation: B
- Level of consensus: 100% (33) yes (33 voters)

**Recommendation 27.4:** Personalised physical training should be recommended.
- Level of evidence: IV
- Strength of recommendation: B
- Level of consensus: 100% (33) yes (33 voters)

**Recommendation 27.5:** Referral for cognitive behavioural therapy should be considered.
- Level of evidence: IV
- Strength of recommendation: B
- Level of consensus: 100% (33) yes (33 voters)

**28. How can the risk of ototoxicity and neurotoxicity be minimised?**

**Ototoxicity.** See Section 3 of the supplementary data, available at Annals of Oncology online.

**Neurotoxicity.** See Section 3 of the supplementary data, available at Annals of Oncology online.

**Recommendation 28.1:** Symptomatic ototoxicity and neurotoxicity are unpreventable complications of cisplatin-based chemotherapy and should generally not influence treatment intensity.
- Level of evidence: III
- Strength of recommendation: B
- Level of consensus: 100% (33) yes (33 voters)

**Recommendation 28.2:** Patients should be informed about the risk of ototoxicity and neurotoxicity before receiving cisplatin-based chemotherapy.
- Level of evidence: IV
- Strength of recommendation: B
- Level of consensus: 100% (33) yes (33 voters)

**Recommendation 28.3:** Further RFs for ototoxicity and neurotoxicity should be avoided (e.g. aminoglycosides within weeks of chemotherapy, exposure to loud noises, smoking and poorly regulated diabetes).
- Level of evidence: IV
- Strength of recommendation: B
- Level of consensus: 100% (33) yes (33 voters)

**29. Which testicular germ cell cancer survivors (TGCCSs) should be offered testosterone replacement therapy?**

**Leydig cell dysfunction and testosterone.** See Section 3 of the supplementary data, available at Annals of Oncology online.

**Recommendation 29.1:** Asymptomatic TGCCSs with testosterone levels below the normal range should not routinely be offered testosterone replacement therapy.
- Level of evidence: V
- Strength of recommendation: C
- Level of consensus: 74% (20) yes, 19% (5) no, 7% (2) abstain (27 voters)

**Recommendation 29.2:** TGCCSs with testosterone levels below the normal range and clinical symptoms* should be offered testosterone replacement therapy.
- Level of evidence: V
- Strength of recommendation: B
- Level of consensus: 100% (33) yes (33 voters)

**Recommendation 29.3:** TGCCSs with low testosterone levels and clinical symptoms* which resolve after short-term (3–6 months) testosterone substitution should continue testosterone replacement therapy.
- Level of evidence: V
- Strength of recommendation: B
- Level of consensus: 100% (33) yes (33 voters)

**Recommendation 29.4:** TGCCSs with normal testosterone levels and clinical symptoms* which resolve after short-term (3–6 months) testosterone substitution should not continue testosterone replacement therapy.
- Level of evidence: V
- Strength of recommendation: C
- Level of consensus: 94% (30) yes, 12% (3) no, 4% (1) abstain (32 voters)

*Clinical symptoms: decreased sexual function (often including loss of morning- and spontaneous erection), less active and more sedate lifestyle.

**Semen cryopreservation.** Semen quality is reduced before orchietomy due to testicular cancer, and sperm count and concentration decrease further after orchietomy [257, 258]. Thus, all patients should be offered semen preservation before initiation of treatment, preferably before orchietomy. Patients who subsequently receive chemotherapy or radiotherapy in particular should be encouraged to undertake semen preservation, as their fertility is further decreased compared with those who undergo orchietomy alone [259–264]. If cryopreservation is not possible before the start of treatment, fatherhood may still be possible in the majority of patients via natural conception or in vitro fertilisation. Obviously, patients whose treatment involves bilateral orchietomy or contralateral testicular radiotherapy due to GCNIS should, in particular, be informed about a pre-treatment sperm preservation programme.

**30. How can the risk of CVD be reduced in TGCCSs?**

See Section 3 of the supplementary data, available at Annals of Oncology online.

**Recommendation 30.1:** In order to reduce the risk of CVD, overtreatment should be avoided, especially the combination of chemotherapy and radiotherapy.
- Level of evidence: IV
- Strength of recommendation: B
- Level of consensus: 100% (33) yes (33 voters)
32. How should follow-up schedules be planned?

Follow-up of TGCCSs on active surveillance or in remission after treatment of the first five years. The primary aim of follow-up in the first 5 years is the timely diagnosis of recurrent disease in order to treat the patient with curative intent using the least aggressive therapy [51]. An adequate follow-up relies on profound knowledge about testicular cancer with regards to histology, stage, primary treatment and treatment success. Follow-up may require tailoring of individual schedules to ensure they are acceptable for the patient, physician and the healthcare system. The interval of follow-up visits and the tests to be carried out at each visit should depend on the risk of relapse in general and on the likely site of relapse in particular [265]. Only one randomised trial is available regarding the implications of different follow-up schedules and the respective use of imaging and tumour markers [266]. All published guidelines regarding follow-up therefore rely on information from case series reports or therapeutic trials. However, several recent publications have added valuable information, enhancing the basis for the formulation of evidence-based recommendations [79, 81, 90, 93, 99, 100, 198, 267, 268].

For a long time, most recommendations included tight schedules with extensive imaging using CT scans. However, with the recognition of the risk of carcinogenesis due to ionising radiation from CT scanning [269], most guidelines have reduced the recommended number of CT scans [62, 270].

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

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

It is important to note that patients not achieving complete remission or presenting with poor prognosis disease should receive individualised follow-up, ideally in specialised centres.

<p>| Table 4. Recommended minimal follow-up for seminoma stage I on active surveillance or after adjuvant treatment (carboplatin or radiotherapy) |</p>
<table>
<thead>
<tr>
<th>Modality</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Years 4 + 5</th>
<th>After 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumour markers ± doctor visit</td>
<td>2 times</td>
<td>2 times</td>
<td>2 times</td>
<td>1 time</td>
<td>Further management according to survivorship care plan</td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>Abdominal CT/MRI</td>
<td>2 times</td>
<td>2 times</td>
<td>1 at 36 months</td>
<td>1 at 60 months</td>
<td>—</td>
</tr>
</tbody>
</table>

*a Level of evidence: V; strength of recommendation: B; level of consensus: 97% (33) yes, 3% (1) abstain (34 voters) (in general, patients are seen by a doctor during follow-up, but some routine control visits may be carried out by specially trained nurses).*

*b Level of evidence: V; strength of recommendation: B; level of consensus: 97% (33) yes, 3% (1) abstain (34 voters).*

*c Level of evidence: V; strength of recommendation: B; level of consensus: 97% (33) yes, 3% (1) abstain (34 voters).*
**Recommendation 32.1:** When considering the risks of relapse depending on diagnosis and initial treatment, all seminoma stage I patients should be grouped together.

- **Level of evidence:** IV
- **Strength of recommendation:** B
- **Level of consensus:** 88% (29) yes, 6% (2) no, 6% (2) abstain (33 voters)

Tables 4–6 show the recommended schedules for minimal follow-up of the above three groups based on the discussions and voting by the group of experts at the consensus conference.

Generally, MRI of the abdomen can be used instead of CT in experienced centers. Regarding the use of US of the contralateral testis, the majority of the consensus panel members recommend no regular US both in the case of a negative biopsy [68% (21 of 31 panel members)] and also if no contralateral biopsy had been carried out [53% (17 of 32 panel members)].

**Follow-up of TGCCs beyond 5 years.** Follow-up for relapse beyond 5 years is generally not recommended. According to a population-based analysis, very late relapse (VLR) after 5 years is a rare event occurring in ~0.5% of patients [272]. Thus, the aim of follow-up beyond 5 years shifts to the detection of the late side-effects of treatment. As patients with TGCC who receive >1 line of treatment for disseminated disease have a highly increased risk of late toxicity and death as a result of causes other than TGCC, life-long follow-up has been suggested for those cases [273]. Survivorship care plans (see below) are recommended for all

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### Table 5. Recommended minimal follow-up for non-seminoma stage I on active surveillance

<table>
<thead>
<tr>
<th>Modality</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4 + 5</th>
<th>After 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumour markers ± doctor visit</td>
<td>4 times</td>
<td>4 times</td>
<td>2 times</td>
<td>1–2 times</td>
<td>Further management according to survivorship care plan</td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>At 60 months if LVI+</td>
<td></td>
</tr>
<tr>
<td>Abdominal CT/MRI</td>
<td>2 times</td>
<td>At 24 months</td>
<td>At 36 months (optional)</td>
<td>At 60 months (optional)</td>
<td></td>
</tr>
<tr>
<td>Abdominal CT/MRI</td>
<td>2 times</td>
<td>At 24 months</td>
<td>1 if LVI+</td>
<td>At 36 months (optional)</td>
<td></td>
</tr>
</tbody>
</table>

*Level of evidence: V; strength of recommendation: B; level of consensus: 97% (33) yes, 3% (1) abstain (34 voters). (In general patients are seen by a doctor during follow-up, but some routine control visits may be carried out by specially trained nurses).*

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### Table 6. Recommended minimal follow-up after adjuvant treatment or complete remission for advanced disease (excludes patients with a poor prognosis or no remission)

<table>
<thead>
<tr>
<th>Modality</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4 + 5</th>
<th>After 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumour markers ± doctor visit</td>
<td>4 times</td>
<td>4 times</td>
<td>2 times</td>
<td>2 times</td>
<td></td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>1–2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Abdominal CT/MRI</td>
<td>1–2 times</td>
<td>At 24 months</td>
<td>1 at 36 months (optional)</td>
<td>1 at 60 months (optional)</td>
<td></td>
</tr>
<tr>
<td>Thorax CT</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
</tbody>
</table>

*Level of evidence: V; strength of recommendation: B; level of consensus: 97% (33) yes, 3% (1) abstain (34 voters). (In general patients are seen by a doctor during follow-up, but some routine control visits may be carried out by specially trained nurses).*

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CT, computed tomography; ESMO, European Society for Medical Oncology; LVI, lymphovascular invasion; MRI, magnetic resonance imaging.

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patients. Most patients with VLR are diagnosed due to symptoms; however, elevated tumour markers can be detected in both seminomatous and NSGCTs in up to 50% of patients [272, 274]. Patient education and physician awareness of relapse symptoms are therefore very important in survivorship management. The early use of imaging and tumour markers is encouraged if relapse is suspected.

Survivorship care plan

An example of a patient care plan to be provided to the patient and their general practitioner at termination of uro-oncological follow-up is provided in supplementary Table S5, available at Annals of Oncology online.

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DB (provided lecturing and advice to AstraZeneca, Roche, Merck, Sanofi and Menarini Diagnostics), CB (research funding from Sanofi), SG [attended advisory boards and/or independent data monitoring committee meetings (compensated) for AIA International, Active Biotech, Astellas Pharma, Bayer, Bristol-Myers Squibb, Clovis, Curevac, Dendreon Corporation, Ferring, Innocrin Pharmaceuticals, Janssen Cilag, MaxiVAX SA, Millennium Pharmaceuticals, Novartis, Pfizer, Orion, Roche, Sanofi Aventis Group; attended advisory boards (uncompensated) for Astellas Pharma, Bayer, ESSA Pharmaceuticals Corporation, Nectar, ProteoMediX, Sanofi; participated in speakers bureau (compensated) for Janssen and Novartis; participated in speakers bureau (uncompensated) for Amgen, Astellas Pharma, Bayer, Janssen, Sanofi Aventis Group; has a pending patent application for a method for biomarker WO 2009138392 A1], K-PD (holds stocks in miRDetect GmbH, Bremen; currently conducting research sponsored by miRDetect GmbH, Bremen). All remaining authors have declared no conflicts of interest.

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