

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

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ABSTRACT

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 [C.B. and K.-P.D.] 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 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.

Word count: 228 (limit: 300 words)

KEY WORDS: testicular germ cell cancer, consensus, diagnosis, treatment, quality of life, follow-up

KEY MESSAGES

- This ESMO consensus conference manuscript on testicular germ cell cancer was compiled by a multidisciplinary panel of experts
- It provides guidance on controversial issues surrounding the diagnosis, treatment and follow-up of early- and late-stage testicular cancer, and for rare clinical problems and survivorship issues
- Recommendations are accompanied by relevant/available supporting evidence

Character count: 398 (limit: 400, including spaces)

INTRODUCTION

See Section 1 of supplementary text, 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 [C.B. and K.-P.D.] 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 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**)

Further details of methods can be found in Section 2 of the supplementary text, available at *Annals of Oncology* online.

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) [1]. The increase in incidence rates of testicular cancer in both developed and developing countries is due to a birth cohort effect [2]. 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 [3].

Risk factors of testicular cancer.

Individual risk factors 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 [4, 5]. Among endocrine disruption chemicals, organochlorine compounds have been associated with a risk of developing testicular cancer [5]. Cryptorchidism is associated with a higher risk for ipsilateral testicular cancer (RR 6.33) than contralateral testicular cancer (RR 1.74) [6]; however, men with a family history of cryptorchidism or hypospadias have no increased risk of testicular cancer [7].

Approximately 5% of men with testicular cancer develop contralateral testicular cancer, of which one-third are synchronous tumours and two-thirds are metachronous tumours [8].

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 [9].

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 [10]. About 1.8% of patients have a parent or a sibling also diagnosed with testicular cancer [10].

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 [11].

Genetic predisposition for testicular cancer.

Over 20 single nucleotide polymorphisms (SNPs) have been associated with the risk of testicular cancer [12, 13]. Polygenic risk scores have been used to show that men in the top 1% of this genetic risk score have a 9-fold increased risk of testicular cancer compared with the population median [14]. Collectively, the SNPs identified to-date explain around 19% of the empirical fraternal familial risk [14]. Based on the Swedish Family-Cancer Database [15], 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 [16]. 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 [17-21]. 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 [22]. Recently, a survey of expert and non-expert uro-pathologists in Europe was conducted [23], 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 risk factors for recurrence.

Typing of testicular tumours for oncology assessment.

Testicular tumours should be typed in line with the World Health Organization (WHO) 2016 classification [24]. 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 [25]. Prepubertal type teratomas are known to exist in adults, and may require less surveillance [26]. 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 7th Tumour Node and Metastases (TNM) classification does not adequately supply all information required by many oncologists for patient treatment [27], as rete testis invasion and tumour size are not included in its assessments. Recently, both the American Joint Committee on Cancer (AJCC) 8th TNM version [28] and the Union for International Cancer Control (UICC) 8th edition [29] 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 prospective staging. At present, the AJCC provides a better staging method and has been endorsed by the International Society of Urological Pathology [30]. *[Note to Ann Oncol: We have used UK spelling when defining the abbreviation TNM (tumour instead of tumor) to align with journal style. Please confirm you agree]*

Minimum pathological datasets for oncological assessment of relapse risk in testicular cancer.

Guidelines on pathological datasets are available from The College of American Pathologists, The Royal College of Pathologists [22] and The Royal College of Pathologists of Australia. 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) [31]. 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 performed?

Contralateral biopsies in testicular cancer.

Early detection of TGCC is possible by diagnosing GCNIS, the pre-invasive stage of TGCC [32, 33]. 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 [5]. The current understanding of the pathogenesis of TGCC provides clinically useful knowledge because it suggests: (1) all TGCCs develop from GCNIS (i.e. without previous GCNIS, there can be no invasive TGCC); (2) there is no *de novo* development of GCNIS in adulthood; (3) GCNIS is present many years before the clinical manifestation of TGCC; (4) GCNIS can be

detected patho-histologically; (5) as it is usually distributed over wide areas, GCNIS can be detected by surgical biopsy [34, 35].

Surgical technique.

Evidence suggests that performing two-site testicular biopsies provides an increased sensitivity of 18% compared with single-site biopsy [34, 36]. Surgical complications have been reported to occur in 2%–3% of patients, most of which can be managed conservatively [37]. Currently available data suggest that screening for GCNIS by needle biopsy or semen examination yields inferior results to two-site surgical testicular biopsy [38, 39].

Histological technique.

Histological detection of GCNIS cells can usually be achieved using conventional haematoxylin and eosin staining. In unresolved cases, supplementary immunohistochemical staining can be performed with immunohistochemistry for placental alkaline phosphatase, D2–40 or OCT3/4 [40, 41]. 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 [34, 36, 42–44]. Major risk factors associated with contralateral GCNIS in patients with unilateral TGCC include testicular atrophy, younger age (<40 years), testicular microlithiasis and infertility [45]; 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 [8, 46, 47]. In patients with extragonadal TGCCs, testicular biopsies have revealed the presence of GCNIS in approximately 31% of these patients, with the risk being higher in retroperitoneal primaries [48].

The rate of false-negative biopsies (i.e. patients who developed TGCC subsequent to having negative biopsy results) has been reported as 0.5%–2% [42, 46]. 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 [42, 49].

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 performed [50]. There are no data to show that it can provide an additional survival advantage [51]. 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 [37]. 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 [52].

Overall, it seems reasonable to discuss the value of performing contralateral biopsies with patients who have high-risk factors 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 orchiectomy 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 performed using a high frequency (>10MHz) probe with colour Doppler assessment to confirm the presence of a testicular mass [53], prior to 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 [54-58].

Although scrotal magnetic resonance imaging (MRI) is good at identifying and characterising testicular tumours [59], currently its role is to help distinguish between an intra- and extra-testicular mass when this cannot be confirmed clinically or with US [60].

Recommendation 4.1: Testicular US using high frequency (>10MHz) probe with colour Doppler assessment should be performed to confirm the presence of a testicular mass prior to 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 performed 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) [61].

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 [62]. 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 [63]. 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 prior to 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)

[Note to Ann Oncol: We bolded the term 'not' in the above recommendations to highlight recommendations against a particular practice - please can we retain this bolding in final publication]

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)

[*Note to Ann Oncol: We bolded the term 'not' above to highlight that this is a recommendation against a particular practice - please can we retain this bolding in final publication*]

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 [64]. 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) [65]. 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 [66]. 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 [67].

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. Multiplanar 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 performed 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 [68-73]. 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%) [71]. 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 [74]. As teratoma has variable, low or no FDG uptake, FDG-PET cannot be used to distinguish this from fibrosis or necrosis [75-77]; 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 performed 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

Recurrent testicular cancer: 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 [63, 76].

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 text, available at *Annals of Oncology* online.

Stage I testicular cancer

6. Are there risk factors validated and/or accepted for seminoma?

In the absence of adjuvant treatment, approximately 15%–20% of patients with stage I testicular seminoma will develop recurrence. Most of these recurrences arise in retroperitoneal lymph nodes [78-80]. In contrast to non-seminoma, risk factors to guide adjuvant treatment in patients with stage I seminoma are not well established. The two main risk factors 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. suggested a 12% risk of recurrence in the absence of both risk factors, a 16% risk of recurrence in the presence of either of the two risk factors and a 32% risk of recurrence in the presence of both risk factors [81]. However, subsequent studies have shown more heterogeneous results. In a prognostic model based on data from 685 stage I seminoma patients, Chung et al. failed to validate the nomogram and simply identified tumour size as a risk factor for recurrence without any clear, size-related cut-off [82]. In contrast, a Japanese study of 425 patients undergoing orchiectomy for stage I testicular seminoma concluded that rete testis involvement is a risk factor for recurrence with or without adjuvant treatment [83]. A large retrospective Danish analysis concluded that tumour size was a significant factor for relapse, together with either invasion of epididymis or vascular invasion [78]. SWENOTECA describes both primary tumour size and rete testis involvement as risk factors for recurrence [79]. 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 [84-86]. The nomogram developed by the SGCCG takes into account both primary tumour size (as a continuous variable) and stromal involvement of the rete testis [87]. 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 risk factors 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 risk factor (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 risk factors 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 risk factors for relapse in

patients with non-seminoma [88]. In a cohort of 373 patients, the presence of no, one, two or three risk factors 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 risk factors, the 2-year relapse rate was 41% and 35%, respectively [88]. 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. described relapse rates of 44% and 14% in patients with and without LVI [80]. 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 and rete testis invasion in the testicular primary identified a group with a relapse risk of 50%. Without risk factors, the relapse risk was 12% [89].

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 embryonal carcinoma (EC) and the presence of infiltration of the tunica albuginea as prognostic risk factors associated with pathological stage II disease [90]. 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 less than 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 [90].

A recent retrospective study on 226 clinical stage I non-seminoma patients has validated the clinical risk factors mentioned above [91]. NSGCT patients were stratified according to predominance of EC and LVI, using a risk factor (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 [91].

Recommendation 7.1: In patients with non-seminoma, LVI is the key risk factor 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 risk factors [86, 87, 92]. In these patients, adjuvant chemotherapy will therefore result in over-treatment in approximately 95% of cases. In patients with a higher risk of relapse, adjuvant chemotherapy remains an option. Adjuvant carboplatin reduces the risk of relapse by about 60% [92], 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 risk factor in stage I non-seminoma. In patients with LVI, the risk of relapse without adjuvant therapy is approximately 50% [93-96]. 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 [97]. Adjuvant chemotherapy in the form of a single cycle of bleomycin/etoposide/cisplatin (BEP) will reduce the risk of relapse by over 90% [98]. As a consequence, adjuvant chemotherapy will spare approximately 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 (LVI-negative), the relapse risk of 15% is reduced by 90%–95% following a single cycle of adjuvant BEP [98].

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 [99]. 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 risk factors [84-86,

100]. 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% [97]. Thus, there is a need to explore more efficient adjuvant therapies in patients with risk factors.

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 [101]. 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 [94, 102]. In 2015, a large study with mature follow-up on 517 patients treated with one 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 [79].

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 [92, 103].

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 [98].

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

Strength of recommendation: B

Level of consensus: 90% (28) yes, 10% (3) abstain (31 voters)

Recommendation 10.3: In patients with non-seminoma with localised abdominal and marker-negative relapse, nerve-sparing (NS)-RPLND is the preferred option for primary salvage treatment.

Level of evidence: III

Strength of recommendation: B

Level of consensus: 90% (28) yes, 10% (3) abstain (31 voters)

11. Other treatment alternatives for stage I disease: is there a role for RPLND?

RPLND is neither recommended nor performed as standard treatment for stage I testicular cancer [61]. 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 centres with high levels of experience (i.e. ≥ 20 cases per year) [61, 104]. Furthermore, RPLND should preferably be performed 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 [105].

Primary nerve-sparing RPLND should be discussed in patients with pure teratoma and with risk factors associated with occult retroperitoneal lymph node metastases [106]. The chance of detecting lymph node metastases by nerve-sparing RPLND is in the range 16.7%–20% [106]. 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 [107]. The majority of metastases harbour chemorefractory teratoma cells [108]; therefore, RPLND seems to be the treatment of choice

in these cases. We recommend performing serial sections of the orchiectomy specimen in men with pure teratoma.

Primary nerve-sparing RPLND may also be discussed among patients with clinical stage I teratoma with malignant somatic transformation. In a recent report, Giannatempo et al. demonstrated that, of 28 stage I patients who underwent primary RPLND, 35.7% harboured viable tumour cells in the resected lymph node samples [109].

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 risk factors 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 [110]. The recurrence rate after modern radiation therapy is below 5%, and therefore equivalent to adjuvant carboplatin chemotherapy [99]. Patients treated with radiotherapy for testicular tumours are at an increased risk for secondary malignancies [111]. Treatment-related secondary tumours occur mostly in organs within the fields used for radiation treatment and the excessive risk appears ≥ 15 years after treatment [112]. On the other hand, the previously reported excessive risk of cardiovascular disease after radiation therapy [111] does not seem to materialise in patients treated with radiotherapy for stage I testicular seminoma [113], although this is controversial [114, 115].

Modern adjuvant radiotherapy for stage I testicular seminoma is delivered with a lower dose [116] and on a smaller treatment volume [117-120] 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 [121]. This risk may further decrease in the future with advances in radiotherapy [122].

In terms of costs, adjuvant radiotherapy and carboplatin chemotherapy are equal [123].

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 [124] (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 (for example 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)

[Note to Ann Oncol: We bolded the term ‘not’ above to highlight that this is a recommendation against a particular practice - please can we retain this bolding in final publication]

Stage II–III testicular cancer

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

Radiotherapy has long been the standard treatment for patients with stage IIA and IIB seminoma [125-127]. 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 [125].

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 [128, 129]. Carboplatin monotherapy has been evaluated but has shown significantly inferior results [130]. Combination therapy with carboplatin and radiotherapy has shown interesting results but remains investigational [126, 131].

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 relapses rates [132]. In a recent retrospective data analysis from the United States national cancer database, with data from 2,437 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 [133].

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 [104], 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 Urogénitales (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 [134-137]. These studies showed very 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%) [138] 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 [134].

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 [139]; however, a pooled analysis [140] that combined the UK data with those of a German study [141] 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 [140]. 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) [142], 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 for 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 approximately 8 weeks in patients presenting with retroperitoneal lymph nodes of <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) [61].

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 [143, 144]. 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 approximately 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 [145, 146]. 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%; $P < 0.001$) [145]. In the other study, which had a prospective design and included 187 evaluable 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 [146].

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 [147]. 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 [147, 148].

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 2**, available at *Annals of Oncology* online.

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

Level of evidence: III

Strength of recommendation: A

Level of consensus: No vote obtained

Recommendation 15.2: The recommended treatment for confirmed clinical stage IIA non-seminoma with normal/normalised STMs is either BEP/EP ± NS-RPLND, or primary NS-RPLND ± 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 ± NS-RPLND; 34% (10) NS-RPLND ± adjuvant chemotherapy; 7% (2) no preference, 14% (4) abstain (29 voters)

Recommendation 15.3: The recommended treatment for clinical stage IIB non-seminoma with normal/normalised STMs is primary BEP/EP ± NS-RPLND.

Level of evidence: III

Strength of recommendation: B

Level of consensus: 88% (29) BEP/EP ± NS-RPLND, 3% (1) NS-RPLND ± 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, α -fetoprotein [AFP] or lactate dehydrogenase) and no extra-pulmonary visceral metastases (see **supplementary Table 3**, available at *Annals of Oncology* online) [149]. 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 [150]. 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 [151, 152]. If VIP is being used, primary prophylactic granulocyte colony-stimulating factor (G-CSF) is recommended due 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 [151].

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 for 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 [149]. 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 [153]. 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 [154]. 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 [155, 156]. 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 [157]. 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% [158]. 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 ($P = 0.057$) [159]. 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 prognosis has been reported for patients with either a primary mediastinal NSGCT or non-pulmonary visceral metastases [160-163]. 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 [157, 164-166]. Marker decline can be assessed by several methods, including marker half-life [165] and time-to-normalisation (TTN) calculation, which also takes into account the extent of marker elevation above normal [166]. 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 [166]. 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) [166]. Subsequently, it was

prospectively validated in the GETUG-13 phase III trial [164], 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 endpoint 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], $P = 0.05$) [164]. 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) [167].

Recommendation 17.1: Tumour marker decline (i.e. using the GETUG risk calculator: <https://www.gustaveroussy.fr/calculatation-tumor/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 [168] 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 [169]. 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 [170] and an indicator of poor outcome [171, 172]. 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 [149].

Treatment for 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 chemorefractory cancer in patients with primary mediastinal non-seminoma [173, 174]. 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 [164]. 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 non-curable in the salvage setting, even with HDCT and autologous transplant [168, 175, 176].

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 [149]. 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 [163, 177, 178]. All reports are based on retrospective data derived from small patient numbers or from single-centre experiences.

Upfront brain metastases occur in approximately 1%–2% of patients with advanced TGCC [179]. 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 [180]. 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 [181]. 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 [181-183]. 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 [178]. In contrast, a large retrospective analysis did not show any additional benefit of post-chemotherapy resections of residual brain lesions after first-line chemotherapy [181]. 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 about 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 [184]. 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 [184]. 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 [185-187].

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.

Level of evidence: III

Strength of recommendation: A

Level of consensus: 100% (24) yes (24 voters)

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.

Level of evidence: IV

Strength of recommendation: C

Level of consensus: 100% (24) yes (24 voters)

[Note to Ann Oncol: We bolded the term ‘not’ above to highlight that this is a recommendation against a particular practice - please can we retain this bolding in final publication]

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.

Level of evidence: V

Strength of recommendation: A

Level of consensus: 75% (18) additional surgery or stereotactic radiation, 25% (6) no further local treatment (24 voters)

20. Poor prognosis NSGCT: when can orchiectomy be postponed and when should initial chemotherapy be reduced?

Initial orchiectomy should not be performed in patients with TGCC and extended visceral metastases, in those with very elevated hCG or AFP (thus establishing the diagnosis of TGCC with no need for histological confirmation), and when patient conditions related to metastatic dissemination require immediate chemotherapy. In those cases, orchiectomy should be postponed until completion of chemotherapy, or at least until several weeks after chemotherapy has started when the general condition of the patient will allow it [188-191].

There appears to be a partial blood-testicular barrier, which makes the testis a potential sanctuary for chemo-protected cancer cells. Studies have suggested that histological findings may vary if orchiectomy is postponed too long after completion of chemotherapy. In a series of 21 patients with delayed orchiectomy, necrosis, teratoma and viable cancer were found in 13, 3 and 0 patients, respectively, among the 16 patients who had an orchiectomy immediately after completion of chemotherapy, whereas viable seminoma was found in three of the five patients where orchiectomy was delayed further (19–68 months; mean 45.1 months) [190]. Moreover, discrepancies are found between the histology of the residual mass and that of the post-chemotherapy orchiectomy specimen: in a series of 352 patients, viable cancer and teratoma was found in 15% and 42% in the RPLND specimens compared with 21% and 30% of post-chemotherapy orchiectomy specimens, respectively [191]. In

another report of 42 patients, post-chemotherapy teratoma and viable cancer were reported in 14 (33%) and 3 (7%) of the RPLND specimens, and in 15 (36%) and 12 (29%) of the orchiectomy specimens, respectively [188].

Recommendation 20.1: In patients with advanced metastatic TGCC and/or those with impending organ failure, orchiectomy 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).

Level of evidence: V

Strength of recommendation: B

Level of consensus: 88% (28) yes, 12% (4) abstain (32 voters)

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 20.2: In patients with widespread lung metastases, pure choriocarcinoma and high hCG, 2–3 days of full dose cisplatin and etoposide are suggested, with continuation of chemotherapy when the patient has recovered (e.g. day 14).

Level of evidence: V

Strength of recommendation: B

Level of consensus: No vote obtained

In the majority of patients, pre-chemotherapy renal impairment is presumably due to mechanical obstruction from the malignant disease. In patients with a glomerular filtration

rate (GFR) of 30–50 mL/min/1.73 m², after relief of mechanical obstruction (hydronephrosis), 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 20.3: 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.

Level of evidence: IV

Strength of recommendation: B

Level of consensus: 91% (30) yes, 9% (3) abstain (33 voters)

Recommendation 20.4: In patients with a GFR of 30–50 mL/min/1.73 m², carboplatin-based chemotherapy (or cisplatin-based chemotherapy in patients undergoing haemodialysis) are options. Bleomycin should be omitted.

Level of evidence: V

Strength of recommendation: C

Level of consensus: No vote obtained

Recommendation 20.5: Regardless of the degree of renal function, patients with hydronephrosis (unilateral or bilateral) should be relieved with either stent or nephrostomy prior to chemotherapy

Level of evidence: V

Strength of recommendation: B

Level of consensus: 100% (33) yes (33 voters)

Recommendation 20.6: Patients with poor renal function should **not** be routinely treated with carboplatin but should be referred to high-volume centres for evaluation.

Level of evidence: V

Strength of recommendation: A

Level of consensus: 100% (32) yes (32 voters)

[*Note to Ann Oncol: We bolded the term 'not' above to highlight that this is a recommendation against a particular practice - please can we retain this bolding in final publication*]

21. What is the optimal treatment of older patients with metastatic TGCCs?

Data from 2,482 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) [192], 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 [193-195], 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 [153, 196-198]. In a large Danish series [194], as well as in another double-institution dataset [198], 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 [199]. However, in an English study, no substantial toxicities were reported with the use of chemotherapy in patients >60 years old [200].

Although the use of primary prophylaxis with G-CSF in young patients with TGCC receiving BEP is an area of debate [201, 202], 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) [203], 1,169 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.

Recommendation 21.1: Comprehensive risk-benefit evaluation of older patients with TGCC should include assessment of co-morbidities and patient disease risk category.

Level of evidence: IV

Strength of recommendation: B

Level of consensus: No vote obtained

Recommendation 21.2: In the first-line setting, there is generally no reason not to administer standard chemotherapy according to the risk category. Primary G-CSF prophylaxis is recommended in these patients as the risk of neutropaenic sepsis is higher in older patients.

Level of evidence: IV

Strength of recommendation: B

Level of consensus: No vote obtained

Recommendation 21.3: Standard-dose chemotherapy may be the preferred choice in most elderly patients, although limited safety data are available. Referral to an experienced centre is strongly recommended to help make treatment decisions.

Level of evidence: IV

Strength of recommendation: B

Level of consensus: No vote obtained

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 over-treatment. 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 approximately 20% in the chance of cure was observed in less experienced centres compared with more experienced centres [204]. 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 multi-national prospective trial, confirmed previous evidence from retrospective analyses of various databases from Europe and the US [205, 206]. 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 [207].

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 [208]. 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 [209, 210]. Besides inadequate chemotherapy delivery (with a risk of over-treatment and excessive toxicity or insufficient treatment and poorer outcome), inadequate post-chemotherapy RPLND or other resections of residual masses performed at community centres can also lead to a higher risk of in-field relapses compared with centralised care, as demonstrated in a German trial [102].

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 [211].

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 text, available at *Annals of Oncology* online.

Seminoma.

Patients should be assessed for residual lesions by CT or MRI and tumour markers approximately 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 performed 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 [68]. With a positive FDG-PET scan, the possibility of residual seminoma is in the range of 20%, and so false-positive results are common [68, 212]. 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 [68, 71, 213, 214]. In the majority of patients with seminoma, necrosis or fibrosis will be found at PC-RPLND. These patients require no further treatment [215].

Non-seminoma.

Patients should be assessed for residual masses by CT or MRI and tumour markers approximately 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 [215-222]. 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 for these patients includes either active monitoring or PC-RPLND, which should be discussed individually [223-226].

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, 0% (0) abstain (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 [227-229]. 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 [109].

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 [230].

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 4**, available at *Annals of Oncology* online) [231]. 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]. Paclitaxel and ifosfamide are used prior to HDCT (carboplatin/etoposide) for two cycles in the TI-CE regimen [236]. One study used a single cycle of VIP prior to 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].

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 [196, 240].

Selected ‘third-line’ regimens are suitable for patients relapsing after HDCT, or in cases where HDCT cannot be performed. 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.

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 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 for 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 [178, 181]. 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 [241].

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 (32 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 text, available at *Annals of Oncology* online.

Quality of life and post-therapeutic psychosocial issues.

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

Neurotoxicity.

See Section 3 of the supplementary text, 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)

[*Note to Ann Oncol: We bolded the term 'not' above to highlight that this is a recommendation against a particular practice - please can we retain this bolding in final publication*]

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 risk factors 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 text, 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: 94% (30) yes, 6% (2) abstain (32 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: 44% (11) yes, 12% (3) no, 44% (11) abstain (25 voters)

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

[*Note to Ann Oncol: We bolded the term 'not' above to highlight that this is a recommendation against a particular practice - please can we retain this bolding in final publication*]

Semen cryopreservation.

Semen quality is reduced prior to orchiectomy due to testicular cancer, and sperm count and concentration decrease further after orchiectomy [242, 243]. Thus, all patients should be offered semen preservation before initiation of treatment, preferably prior to orchiectomy. 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 orchiectomy alone [244-249]. 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 orchiectomy 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 text, 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)

Recommendation 30.2: Patients should receive repeated counselling about the importance of a healthy lifestyle in preventing CVD.

Level of evidence: IV

Strength of recommendation: B

Level of consensus: 100% (33) yes (33 voters)

Recommendation 30.3: Patients should receive regular check-ups to prevent CVD, including measurements of blood pressure, weight, sex hormones, lipids and glucose.

Level of evidence: IV

Strength of recommendation: B

Level of consensus: 100% (33) yes (33 voters)

Recommendation 30.4: Patients should receive treatment for hypertension, hypercholesterolaemia and diabetes to prevent CVD.

Level of evidence: IV

Strength of recommendation: B

Level of consensus: 100% (33) yes (33 voters)

31. How can the risk of a second cancer and its consequences be reduced in TGCCSs?

Second non-germ cell cancer.

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

Second germ cell testicular cancer.

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

Recommendation 31.1: TGCCSs who receive treatment in addition to orchiectomy should be informed about the risk of second cancers and the importance of contacting their healthcare provider if suspicious symptoms arise.

Level of evidence: V

Strength of recommendation: B

Level of consensus: 94% (31) yes, 6% (2) no (33 voters)

Recommendation 31.2: TGCCSs should receive lifestyle counselling and be encouraged not to smoke.

Level of evidence: V

Strength of recommendation: B

Level of consensus: 94% (31) yes, 6% (2) no (33 voters)

32. How should follow-up schedules be planned?

Follow-up of TGCCSs on active surveillance or in remission after treatment for 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 [50]. 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 performed at each visit should depend on the risk of relapse in general and on the likely site of relapse in particular [250]. Only one randomised trial is available regarding the implications of different follow-up schedules and the respective use of imaging and tumour markers [251]. 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 [78, 80, 89, 92, 98, 99, 197, 252, 253].

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 [254], most guidelines have reduced the recommended number of CT scans [61, 255].

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 \geq 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.

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 centres. Regarding the use of ultrasound of the contralateral testis, the majority of the consensus panel members recommend no regular ultrasound both in the case of a negative biopsy (68% [21 of 31 panel

members]) and also if no contralateral biopsy had been performed (53% [17 of 32 panel members]).

Follow-up of TGCCs beyond 5 years.

Follow-up for relapse beyond five years is generally not recommended. According to a population-based analysis, very late relapse (VLR) after 5 years is a rare event occurring in approximately 0.5% of patients [256]. 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 [257]. Survivorship care plans (see below) are recommended for all 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 [256, 258]. 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.

33. 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 5**, available at *Annals of Oncology* online.

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Bayer, Janssen, Sanofi Aventis Group; has a pending patent application for a method for biomarker WO 2009138392 A1; K.-P.D.: holds stocks in miRDetect GmbH, Bremen; currently conducting research sponsored by miRDetect GmbH, Bremen. All remaining authors have declared no conflicts of interest.

TABLES

Table 1. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System [259])

| Levels of evidence | |
|---------------------------------|--|
| I | Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity |
| II | Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity |
| III | Prospective cohort studies |
| IV | Retrospective cohort studies or case-control studies |
| V | Studies without control group, case reports, experts' opinions |
| Grades of recommendation | |
| A | Strong evidence for efficacy with a substantial clinical benefit, strongly recommended |
| B | Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended |
| C | Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, ...), optional |
| D | Moderate evidence against efficacy or for adverse outcome, generally not recommended |
| E | Strong evidence against efficacy or for adverse outcome, never recommended |

By permission of the Infectious Diseases Society of America [259].

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

| CDCT regimens | | |
|----------------------|-----------------------|--|
| VIP/PEI | | Four cycles, repeat every 3 weeks |
| Cisplatin | 20 mg/m ² | Day 1–5 |
| Etoposide | 100 mg/m ² | Day 1–5 |
| Ifosfamide | 1.2 g/m ² | Day 1–5 |
| TIP | | Four cycles, repeat cycle every 3 weeks |
| Paclitaxel | 250 mg/m ² | Day 1 |
| Cisplatin | 25 mg/m ² | Day 2–5 |
| Ifosfamide | 1.5 g/m ² | Day 2–5 |
| HDCT regimens | | |
| TI-CE | | Two TI cycles to be repeated after 2 weeks |
| Paclitaxel | 200 mg/m ² | Day 1 |
| Ifosfamide | 2 g/m ² | Days 2–4 |
| Followed by: | | Three CE cycles to be repeated after 3 weeks |
| Carboplatin | AUC 8 | Days 1–3 |
| Etoposide | 400 mg/m ² | Days 1–3 |
| VIP-CE | | One VIP cycle |
| Cisplatin | 20 mg/m ² | Days 1–5 |
| Etoposide | 100 mg/m ² | Days 1–5 |
| Ifosfamide | 1.2 g/m ² | Days 1–5 |
| Followed by: | | Three CE cycles to be repeated after 3 weeks |
| Carboplatin | 500 mg/m ² | Days 1–3 |
| Etoposide | 500 mg/m ² | Days 1–3 |

| | | |
|-------------|-----------------------|---|
| Indiana-CE | | Two cycles to be repeated after haematopoietic recovery |
| Carboplatin | 700 mg/m ² | Days 1–3 |
| Etoposide | 750 mg/m ² | Days 1–3 |

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.

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

| Single agent | | | |
|--------------------------------|----------------------------------|-----------------|------------------|
| Regimen | Dose | Schedule | Reference |
| Gemcitabine | 1000 mg/m ² | d1, 8,15 q3w | [260] |
| | 1200 mg/m ² | d1, 8,15 q3w | [261] |
| Oxaliplatin | 60 mg/m ² <i>or</i> | d1, 15 q4w | [262] |
| | 85 mg/m ² | | |
| Paclitaxel | 170 mg/m ² | d1, q3w | [263] |
| | 225 mg/m ² | d1, q3w | [264] |
| | 250 mg/m ² | d1, q3w | [265] |
| | 250 mg/m ² | d1, q3w | [266] |
| Oral Etoposide | 50 mg/m ² /day | Continuously | [267] |
| Two drug combinations | | | |
| Regimen | Dose | Schedule | Reference |
| Gemcitabine | 1000 mg/m ² <i>or</i> | d1, 8 q3w | [268-270] |
| | 1250 mg/m ² | | |
| Oxaliplatin | 130 mg/m ² | d1, q3w | |
| Gemcitabine | 1000 mg/m ² | d1, 8, 15 q4w | [271, 272] |
| Paclitaxel | 100 mg/m ² | | |
| Three drug combinations | | | |
| Regimen | Dose | Schedule | Reference |

| | | | |
|-------------|-----------------------|-----------|-------|
| Gemcitabine | 800 mg/m ² | d1, 8 q3w | [273] |
| Oxaliplatin | 130 mg/m ² | d1, q3w | |
| Paclitaxel | 80 mg/m ² | d1, 8 q3w | |
| Gemcitabine | 800 mg/m ² | d1, 8 q3w | [274] |
| Cisplatin | 50 mg/m ² | d1, 8 q3w | |
| Paclitaxel | 80 mg/m ² | d1, 8 q3w | |

d, day; q3w, every 3 weeks; q4w, every 4 weeks.

Table 4. Recommended minimal follow-up for seminoma stage I on active surveillance or after adjuvant treatment (carboplatin or radiotherapy)

| Modality | Year 1 | Year 2 | Year 3 | Years 4+5 | After 5 years |
|---|---------------|---------------|----------------|------------------|--|
| Tumour markers +/- doctor visit* | 2 times | 2 times | 2 times | 1 time | Further management according to survivorship care plan |
| Chest X-ray** | 0 | 0 | 0 | - | |
| Abdominal CT/MRI*** | 2 times | 2 times | 1 at 36 months | 1 at 60 months | |

* 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 performed by specially trained nurses)

** Level of evidence: V; strength of recommendation: B; level of consensus: 88% (28) yes, 3% (1) no, 9% (3) abstain (32 voters)

*** Level of evidence: V; strength of recommendation: B. Schedule based on previous follow-up recommendations provided by international groups, including ESMO. Pelvic imaging should also be included for patients with an increased risk of pelvic recurrence (i.e. bulky abdominal disease [>5 cm], prior history of maldescent testis or orchidopexy, history of previous scrotal surgery, invasion of the carcinoma into the tunica vaginalis of the testis) (Level of evidence: III; strength of recommendation: B) [275].

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

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

| Modality | Year 1 | Year 2 | Year 3 | Year 4+5 | After 5 years |
|---|----------------------|---------------------------|--------------------------------------|--------------------------------------|--|
| Tumour markers +/- doctor visit* | 4 times ^a | 4 times | 2 times | 1-2 times | Further management according to survivorship care plan |
| Chest X-ray** | 2 | 2 | 1 if LVI+ | At 60 months if LVI+ | |
| Abdominal CT/MRI*** | 2 times | At 24 months ^b | At 36 months ^c (optional) | At 60 months ^c (optional) | |

* 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 performed by specially trained nurses)

** Level of evidence: V; strength of recommendation: B; level of consensus to abandon chest X-ray: 3% (1) yes, 88% (30) no, 9% (3) abstain (34 voters)

*** Level of evidence: V; strength of recommendation: B. Schedule based on previous follow-up recommendations provided by international groups, including ESMO. Pelvic imaging should also be included for patients with an increased risk of pelvic recurrence (i.e. bulky abdominal disease [>5 cm], prior history of maldescent testis or orchidopexy, history of previous scrotal surgery, invasion of the carcinoma into the tunica vaginalis of the testis) (Level of evidence: III; strength of recommendation: B) [275].

^aIn high-risk patients (LVI+), a minority of consensus panel members recommended six assessments in Year 1 instead of four. Level of consensus: 39% (12) yes, 55% (17) no, 6% (2) abstain (31 voters)

^bIn high-risk patients (LVI+), the majority of consensus panel members recommended an additional CT scan at 18 months. Level of consensus: 62% (21) yes, 32% (11) no, 6% (2) abstain (34 voters)

^cAlmost half of consensus panel members recommended additional scans at 36 and 60 months. Level of consensus: 47% (16) yes, 44% (15) no, 9% (3) abstain (34 voters).

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

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

| Modality | Year 1 | Year 2 | Year 3 | Year 4+5 | After 5 years |
|---|---------------|---------------|---------------------------|---------------------------|---|
| Tumour markers +/- doctor visit* | 4 times | 4 times | 2 times | 2 times | Further management according to survivorship care plan ^a |
| Chest X-ray** | 1-2 | 1 | 1 | 1 | |
| Abdominal CT/MRI*** | 1-2 times | At 24 months | 1 at 36 months (optional) | 1 at 60 months (optional) | |
| Thorax CT**** | - | - | - | - | |

* 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 performed by specially trained nurses)

** Level of evidence: V; strength of recommendation: B; level of consensus to abandon chest X-ray: 3% (1) yes, 94% (32) no, 3% (1) abstain (34 voters)

*** Level of evidence: V; strength of recommendation: B. Schedule based on previous follow-up recommendations provided by international groups, including ESMO. Pelvic imaging should also be included for patients with an increased risk of pelvic recurrence (i.e. bulky abdominal disease [>5 cm], prior history of maldescent testis or orchidopexy, history of previous scrotal surgery, invasion of the carcinoma into the tunica vaginalis of the testis) (Level of evidence: III; strength of recommendation: B) [275]

**** Same time points as abdomino-pelvic CT/MRI in case of pulmonary metastases at diagnosis. Level of evidence: V; strength of recommendation: B. Schedule based on previous follow-up recommendations provided by international groups, including ESMO.

^aIn case of teratoma in resected residual disease, patient follow-up should remain with uro-oncologist.

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

[Note to Annals: Refs Ilic, Misso. Cochrane Rev 2011 and Albers et al Cochrane Rev 2014 do not have a volume number and are therefore correct as written below]

[Note to Authors: endnote output style errors - need to be manually corrected following manuscript approval and prior to typesetting:

Necchi 2015 - e81 should be e1 at end of page numbers

Necchi 2014 - e61 should be e1 at end of page numbers

Ruf 2014 - 33.e31-33.e36 should be 33.e1-33.e6

Necchi 2017 312.e303 should be 312.e3

Seidel 2016 - 167.e121-e128 should be 167.e21-e28]

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SUPPLEMENTARY TEXT

SECTION 1: INTRODUCTION

Testicular germ cell cancer (TGCC) accounts for only 1%–2% of tumours in men overall, but is the most commonly diagnosed malignancy in young men [1]. The incidence of TGCC varies by ethnic origin, with the highest rates reported in developed countries and the lowest in developing countries [2]. The European Society for Medical Oncology (ESMO) Clinical Practice Guideline (CPG) provides high-level guidance on optimal strategies for the diagnosis, treatment and follow-up of patients with TGCC [3, 4]. However, some issues relating to the optimal management of patients with TGCC remain controversial and warrant further discussion and clarification. Accurate diagnosis of stage and type of testicular cancer is also a concern since testicular cancers are one of the most diverse areas of human pathology and pathologists may see few tumours in a year [5-8].

Regarding the treatment of TGCC, the optimal use of adjuvant chemotherapy in stage I disease remains an area of controversy. Defined strategies to accurately identify those patients who require adjuvant chemotherapy could therefore protect low-risk patients from the toxicities associated with over-treatment. The optimal treatment approach for stage IIA and IIB seminoma and non-seminoma is also a matter of debate and is discussed in this manuscript. Other areas which are currently only supported by marginally higher levels of evidence, but nonetheless often require treatment decisions in clinical practice, are issues of post-chemotherapy surgery, salvage chemotherapy and salvage and/or desperation surgery.

Finally, given the excellent prognosis of most patients with TGCC, high quality follow-up care and survivorship care plan recommendations are crucial. Indeed, the long-term global health-related quality of life (HRQoL) of testicular germ cell cancer survivors (TGCCSs) is

similar to that of the general population [9], although chronic side effects can adversely affect HRQoL, particularly after chemotherapy [10, 11]. However, the optimal follow-up of TGCCSs has not yet been defined and is an unmet need.

Collectively, these and other topics represent points in the care pathway where a consistent approach between physicians is lacking. Given these unresolved and complex issues, the aim of this consensus conference was to produce multidisciplinary evidence-based guidelines on selected clinically relevant questions that complement the existing ESMO CPG where possible and facilitate an optimal and consistent approach to the diagnosis, treatment and follow-up of patients with testicular cancer.

SECTION 2: METHODS

Leading up to the consensus conference, all five working group chairs developed clinically relevant questions surrounding their given subject area, which were subsequently discussed with their group members and modified as needed. Key literature relevant to the subject areas and questions were then reviewed by each working group prior to the consensus conference in order to draft preliminary recommendations. No systematic literature search was undertaken. During the conference, preliminary recommendations were discussed and prepared for voting by the five working groups in parallel breakout sessions. The level of evidence and strength of each recommendation proposed by the group was defined based on the 'Infectious Diseases Society of America-United States Public Health Service Grading System', as shown in **Table 1** [12]. Recommendations from all working groups were then presented to the full expert panel for deliberation and amendment, as needed. Finally, a vote was carried out to establish the level of agreement among the expert panel. Members of the panel were given the opportunity to abstain from the voting process, to allow for cases where

they felt they did not have enough expertise in the area to agree or disagree, or if they had any conflict of interest which could influence their vote.

Results from this consensus conference, including all agreed recommendations and a summary of evidence supporting each recommendation, are described in this article. A summary of all recommendations is included in supplementary **Table S1**, available at *Annals of Oncology* online.

The draft manuscript was reviewed by two representatives of patient advocacy groups from France (Olivier Jerome, President of CERHOM, Villejuif, France) and Norway (Hans Sverre Hansen-Gaard, TGCCS, Oslo, Norway). The final manuscript was reviewed and approved by all ESMO consensus panel members.

SECTION 3: RESULTS

Diagnostic work-up and patient assessment

5. Old and new biomarkers

Assessment of the serum biomarkers α -fetoprotein (AFP), beta-human chorionic gonadotropin (β -hCG) and lactate dehydrogenase is a prerequisite for the staging of TGCC, monitoring of treatment outcomes and early detection of TGCC relapse [13, 14]. Drawbacks of these classical biomarkers include having a diagnostic sensitivity of only 60%–80% and a wide variation in marker expression levels in different histologic subgroups and clinical stages [15, 16]. Potential new biomarkers include the microRNAs miR-371-3 and miR-302/367 cluster, which are present in TGCC tissue [17, 18] and are also known to circulate in serum [19, 20]. These microRNAs can be measured using the quantitative polymerase chain reaction method. Currently, results from four pilot studies have suggested that serum levels of

miR-302/367 and miR-371-3 are promising biomarkers of TGCC [19, 21-23]. More recently, a prospective study in Germany in 166 patients with TGCC and 106 healthy controls has indicated that mi-R371a-3p may be a highly useful marker, featuring a sensitivity of 86.3% (95% confidence interval [CI]: 79.7-90.4) and a specificity of 92.5% (95% CI: 89.0 -95.9) [24]. Serum levels of miR-371a-3p were significantly higher in patients with metastatic disease than in those with localised disease. In addition, serum levels of miR-371a-3p correlated with tumour size in stage I disease and decreased to normal after completion of treatment. Increasing serum levels of miR-371-3p were associated with treatment failure, and high levels were observed in patients with disease relapse. Importantly, teratoma and germ cell neoplasia *in situ* (GCNIS) do not appear to express these particular microRNAs, as shown in two recent studies [24, 25]. Thus, miR-371a-3p outperforms the classical biomarkers and represents a highly sensitive and specific new biomarker for TGCC. While this marker deserves attention by clinicians managing patients with TGCC, particularly given that a serum diagnostic test for miR-371a-3p is expected to be introduced soon into clinical practice [26], issues around laboratory standardisation and availability of the test must be resolved before this new biomarker can be recommended for routine clinical use.

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

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

The most important consideration for post-chemotherapy surgery is whether a complete resection of residual radiological lesions is possible. Patients do not usually benefit from debulking or incomplete resections. Removal of the residual mass only (lumpectomy) is

associated with a risk of incomplete resections and should not be performed. Post-chemotherapy surgery should therefore only be performed at high-volume centres with multidisciplinary teams who perform this procedure regularly. Patients with residual lesions after chemotherapy should be referred to these centres [27, 28].

A bilateral open PC-RPLND remains the standard of care, based on mapping studies of nodal deposits and retrospective studies [29-33]. The field and extent of surgery should be based on the pre-chemotherapy pattern of metastases, and a nerve-sparing technique is recommended whenever possible. In patients presenting with infra-hilar nodal metastatic disease, the bilateral resection template, when indicated, should include infra-hilar, pre-caval and para-caval nodes medial to the right ureter, and retro-caval, inter-aorto-caval, pre-aortic, retro-aortic and para-aortic nodes medial to the left ureter, as well as the ipsilateral iliac nodes. In patients presenting with nodal metastatic disease outside the classical template, all sites outside the template should be included in the resection. This particularly applies to patients with supra-hilar and pelvic disease.

A more limited dissection, defined as a 'unilateral' template, may be an alternative to a full bilateral resection. Eligible patients include those with resectable residual lesions <5 cm in the maximum axial diameter within the planned template, and those with residual retroperitoneal nodal disease within the pre-chemotherapy primary landing site of the tumour-bearing testis. [34-37]. Minimally-invasive laparoscopic RPLND should only be performed in high-volume, multidisciplinary testicular cancer centres with additional laparoscopic expertise.

Adjunctive resections in addition to PC-RPLND are required in up to 20% of patients, and may include nephrectomy, vascular resection and/or other intra-abdominal visceral resections [38-40]. The aim of these procedures is complete resection of all residual disease. Where this does not appear feasible due to multi-focality or anatomical difficulty, incomplete resections

may not be beneficial. The combination of thoracic and retroperitoneal resections is relatively common. The timing and sequence of combined resections should be based on the location of the highest volume of residual disease [41]; usually, the first site of resection is in the retroperitoneum. The histology of residual disease in different organs may be discordant [42-44]. Therefore, in the presence of resectable disease in the retroperitoneum and thorax, lesions in the thorax should also be resected.

In patients with bilateral thoracic disease, the initial resection should be unilateral. A discordance rate of up to 20% has been reported [45]. Decisions for contralateral pulmonary resections are complex and should be based on the number of lesions, their size and location.

Surgery for liver lesions may involve wedge resection or full lobectomy and may be performed at the time of RPLND or as a separate procedure [46, 47].

Patients with necrosis or complete resection of differentiated teratoma require no further treatment. The benefit of adjuvant treatment with two cycles of cisplatin-based chemotherapy in patients with an International Germ Cell Consensus Classification Group classification of ‘intermediate risk’ or ‘poor risk’ at initial presentation, those with >10% viable tumour in the resection specimen, and/or in patients with incomplete resection, has recently been questioned as the value of complete resection of residual masses is more relevant for improving outcome than any adjuvant chemotherapy [48, 49].

A small number of patients will experience radiological progression during chemotherapy despite tumour marker decline or normalisation (so called ‘growing teratoma’). If possible, chemotherapy should be completed as planned followed by resection of all radiological lesions [50]. Salvage chemotherapy is not indicated in patients with ‘growing teratoma’.

Late relapses are defined as evidence of new lesions, or sequentially increasing serum tumour markers (AFP or HCG), more than 2 years after ≥ 3 cycles of cisplatin-based chemotherapy.

Viable cancer and/or somatic-type malignant transformation that do not respond well to chemotherapy are more frequent in late relapse than in early relapses [51-53]. Available evidence emphasises the central role of surgery in these patients [54, 55]. There is currently no evidence to show that chemotherapy, either before or after complete resection, improves the overall outcome. However, conventional-dose chemotherapy and high-dose chemotherapy have both been associated with long-term remissions in a small proportion of patients with unresectable late relapses [56, 57].

Survivorship and follow-up schemes

26. How can post-therapeutic psychosocial issues be minimised, and HRQoL protected?

HRQoL: emotional and psychosocial issues.

Long term global HRQoL is similar between TGCCSs and the general population, regardless of the applied treatment [9]. However, chronic side effects, particularly after chemotherapy (including peripheral neuropathy, Raynaud's syndrome, hearing loss and chronic fatigue [CF]), impact negatively on global, physical and mental HRQoL [10, 11].

Patients with a 'helpless-hopeless' coping style and limited social support experience poorer mental HRQoL, anxiety and depression [58]. In comparison with the general population, long-term TGCCSs express higher levels of anxiety; young age and certain socio-economic factors (including unemployment, low educational level and alcohol problems) can increase anxiety and stress, which in turn reduce HRQoL [59]. Some patients experience fear of recurrence in the long term, especially those with a medium educational level, traumatic cancer-related stress symptoms and neurotic personality [60]. Although there is currently no evidence of testicular cancer leading to subsequent unemployment or reduced work

engagement, poorer health and reduced work ability related to physical and psychological symptoms after cancer treatment is reported for a subgroup of patients [61, 62].

Quality of life and post-therapeutic psychosocial issues.

TGCCSs are more likely to have impaired sexuality (ejaculation and erectile disorders, reduced sexual interest and enjoyment) compared with healthy men of the same age [63-65]. Ejaculation impairment is usually caused by damage to sympathetic nerves after RPLND and may reduce sexual satisfaction [65]. Overall sexual problems are associated with older age, lack of a partner, high anxiety and change in body image [64, 65].

Self-reported cognitive complaints are common among TGCCSs and are linked with CF (i.e. fatigue above a certain level after a median observation time, as defined by the fatigue scale used) and emotional distress [66]. Recent studies have also identified objective cognitive impairments (mainly in verbal learning, memory and processing speed) after treatment, with younger age and a higher number of chemotherapy cycles associated with a greater incidence of overall decline in cognitive function [67, 68].

Most patients with testicular cancer have at least one supportive care need, including physical care, lifestyle programme support, attitude towards self-management (including psychological support) and eHealth [69, 70]. Recent survivorship care plans among cancer survivors have generally not demonstrated improvements in HRQoL, satisfaction or distress [71]. Nevertheless, healthcare professionals should inform patients about the potential late negative effects of treatment, and endeavour to identify psychological distress early. A healthy lifestyle should always be promoted. Future research will examine the potential benefit of TGCCS-specific patient care plans.

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

Chronic fatigue

CF has been described as one of the most common and distressing adverse effects of cancer and its treatment [72]. CF should be regularly assessed using validated questionnaires [73].

Commonly used fatigue questionnaires include the Fatigue Questionnaire (FQ) [74], Functional Assessment of Cancer Therapy - Anaemia and Fatigue (FACT-An) [75] and the EORTC Quality of Life Questionnaire (QLQ C30) (fatigue subscale) [76]. *[Note to Annals:*

The above abbreviations have been retained, despite only appearing once, since these are the known terms for these questionnaires and will likely be more recognisable to the reader than the terms written in full. Also, the term Anaemia is in UK spelling to align with journal style]

CF (i.e. fatigue above a certain level after a median observation time as defined by the fatigue scale used) is more common in TGCCSs (16%) than in the general male population (10%) [77-79]. The prevalence of CF increases with age in the general male population, from 9.6% to 12.2% in the age cohorts 40–49 and 50–59 years, respectively [79], with a substantial increase in CF from 12 to 19 years after treatment combined with biochemical hypogonadism [80]. Moderate or high physical activity appears to have a preventive and therapeutic effect [80]. CF has been mitigated by cognitive behavioural therapy and mindfulness-based cancer recovery [81]. Healthcare professionals should strive to prevent CF through early detection of fatigue and lifestyle interventions throughout treatment and follow-up of co-morbid conditions. Testosterone substitution may be considered. CF may dramatically impair HRQoL and work ability, and the disturbing increase in CF among TGCCSs and its association with partly treatable side effects underlines the importance of continued long-term assessments of TGCCSs.

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

Ototoxicity.

Ototoxicity and neurotoxicity are both important toxicities related to cisplatin treatment as well as ageing, and may substantially impair HRQoL [82]. After treatment of metastatic disease with standard-dose bleomycin/etoposide/cisplatin (BEP) regimens, 20%–25% of patients report long-term hearing impairment and tinnitus [83, 84]. When objectively measured by audiograms covering frequencies up to 12 kHz, and without any comparison with age-matched controls, only 20% of patients have normal audiograms [85]. However, daily life hearing ability is associated with findings on audiograms up to only 6–8 kHz [86]. The cumulative dose of cisplatin has consistently been shown to be a risk factor for ototoxicity, and scheduled administration with cisplatin 100 mg/m² as 20 mg/m²/day over 5 days, as opposed to 50 mg/m²/day over just 2 days, reduces the risk of hearing impairment and tinnitus [85, 87, 88]. Cisplatin-induced ototoxicity may become an increasing problem with increasing age-related hearing loss (premature presbycusis). Various genetic polymorphisms have been associated with an increased risk of ototoxicity [89-93], but these findings have not influenced clinical practice. Other possible risk factors include severe noise exposure prior to treatment, co-treatment with other ototoxic agents (such as aminoglycosides) and abnormal renal function [94, 95]. Drugs to prevent ototoxicity, or therapy to relieve symptoms, have not yet been identified.

Neurotoxicity.

Self-reported chemotherapy-induced peripheral sensory neuropathy (CIPN) has been reported in 5% of patients after one cycle of BEP [96], and in 25%–35% of patients with germ cell cancer treated with three to four cycles of BEP [87]. The risk of neuropathy increases with cumulative cisplatin doses exceeding 300 mg/m², and almost every patient receiving doses

higher than 500–600 mg/m² will experience neurotoxicity [97]. Although patient-reported symptoms are often partly reversible, not least due to patients' adjustment to the problem ('response shift'), they persist in 20%–25% of patients after 2 years of follow-up [83]. The risk of CIPN has been associated with polymorphisms in *glutathione S-transferases* and *excision repair cross-complementation group 1 protein* (ERCC1) [98-100], and long-term neurotoxicity has been associated with residual serum platinum levels [101]. However, these findings have not led to new management strategies. *[Note to Annals/ESMO: ERCC1 retained, despite only being mentioned once, as it is more commonly used than the description as written in full]*

Various neuroprotective therapies have been tested [102]. Vitamin E has shown some effect [103, 104] but results could not be replicated in larger studies [105]. Promising results were achieved with amifostine, but as this drug has acute side effects and may also reduce the anticancer potency of chemotherapy, it is not routinely used [106]. In one study, treatment with duloxetine was associated with positive effects on long-term CIPN; however, the majority of patients in this study were experiencing oxaliplatin-induced CIPN [107]. Other potentially therapeutic agents include tricyclic antidepressants and anticonvulsants [108].

Thus, although symptomatic ototoxicity and neurotoxicity are currently unpreventable complications of cisplatin-based chemotherapy, they should generally not influence curative treatment. Nevertheless, patients should be informed about the risk of long-term ototoxicity and neurotoxicity prior to treatment.

29. Which TGCCSs should be offered testosterone replacement therapy?

Leydig cell dysfunction and testosterone.

Primary biochemical hypogonadism (low testosterone and high luteinising hormone [LH] levels) is prevalent in 5%–13% of patients after orchiectomy, increasing to 11%–27% after subsequent chemotherapy [109-112]. Furthermore, mean levels of LH are higher in chemotherapy-treated patients than in stage I patients after orchiectomy only, while mean testosterone levels are either comparable or decreased, suggesting compensated (high LH, normal testosterone) or uncompensated (high LH, low testosterone) chemotherapy-induced damage to Leydig cells [109-112].

Sprauten *et al.* demonstrated that TGCCSs had lower testosterone and higher LH and follicle-stimulating hormone levels than healthy controls of a similar age at a median of 11 and 18 years after orchiectomy [113]. Importantly, the proportion of biochemically hypogonadal TGCCSs seemed to increase between the 11-year follow-up and the 18-year follow-up [113]. Symptoms of hypogonadism include decreased sexual function (often including loss of morning and spontaneous erections), a more sedate lifestyle and decreased bone health [114]. High body weight and the metabolic syndrome also seem to be related to testosterone levels in TGCCSs, but it is unclear whether obesity and the metabolic syndrome develop as a result of hypogonadism or *vice versa* [114].

Potential benefits of testosterone replacement therapy in young men with subclinical biochemical hypogonadism, or only mildly decreased testosterone levels, are uncertain. Howell *et al.* evaluated testosterone replacement in a randomised placebo-controlled trial among survivors of haematological malignancies with testosterone levels of <20 nmol/L (i.e. in the lower half of the normal range) [115]. They demonstrated a significant reduction in fatigue and low-density lipoprotein cholesterol, but no change in bone mineral density or

other lipids, in the testosterone replacement group compared with the placebo group. Studies of testosterone supplementation in TGCCSs are ongoing.

In conclusion, the effect size of testosterone replacement in TGCCSs with low or low-to-normal testosterone levels remains unclear. Whether the effects of testosterone replacement therapy are sustained during long-term use, and whether the beneficial effects outweigh any negative effects, are also unknown and warrant further investigation. It is also unclear if testosterone replacement therapy is a valuable treatment strategy in the management of obesity and the metabolic syndrome in TGCCSs. The current recommendation is that TGCCSs with repeatedly low testosterone levels and clinical symptoms of hypogonadism should be offered testosterone replacement therapy for a trial period of 3–6 months.

30. How can the risk of cardiovascular disease (CVD) be reduced in TGCCSs?

CVD, in particular coronary artery disease, is one of the most serious late effects after treatment for testicular cancer. Most studies have shown a 2–3-fold increase in risk for CVD in men previously treated with cisplatin-based chemotherapy or radiotherapy, compared with men treated with surgery only or the general population [116-118]. The risk is increased beyond ten years of follow-up, and risk prediction tools such as Framingham or SCORE, applied among all TGCCSs, have failed to identify high-risk individuals, likely due to their limited follow-up period (only 5 or 10 years) [119].

The absolute CVD risk 20 years after treatment is 6%–10%, with a particularly high risk (20%) after combined chemotherapy and radiotherapy [118]. The elevated risk of CVD in TGCCSs is thought to be primarily mediated by increases in CVD risk factors such as hypertension, obesity, hypercholesterolaemia, diabetes, smoking and physical inactivity [120]. The clustering of CVD risk factors into the metabolic syndrome [121] is a possible link

between cytotoxic treatment and later development of CVD [122]. Low testosterone levels, which are relatively common in TGCCSs, are related to increased risks for the metabolic syndrome and CVD [120]. In addition, platinum is detectable in serum up to 20 years after treatment [123], and circulating platinum may continuously damage the endothelium, resulting in an accelerated atherosclerotic process [124].

Healthcare providers should focus on the prevention of CVD from the start of cytotoxic treatment and throughout follow-up. Early and repeated counselling about the importance of a healthy lifestyle including smoking cessation, keeping a healthy diet and being physically active, play an important role in reducing the potential CVD risk among TGCCSs. Lifelong check-ups for CVD risk factors should be performed every 2 years, including measurements of blood pressure, weight, sex hormones, lipids and glucose [125]. Hypertension, hypercholesterolaemia, diabetes and hypogonadism should be treated. All patients with testicular cancer should have a survivorship care plan in place, including tools for acquiring and maintaining a healthy lifestyle.

31. How can the risk of a second cancer and its consequences be reduced in TGCCSs?

Second non-germ cell cancer.

A significantly increased risk of a second cancer (relative risk ~1.5–2.1) represents one of the most feared long-term adverse effects after treatment for testicular cancer [126]. Before the introduction of cisplatin-based chemotherapy, most second cancers were localised below the diaphragm (pancreas, ventricle, bladder), within or close to the radiation fields [127, 128]. A significant dose-relationship has been demonstrated between the target radiation dose and incidence of a second cancer [129, 130]. The combination of radiotherapy and older chemotherapy regimens also increase the risk of a second cancer [131]. The increased risk of

a second solid malignancy becomes measurable 10–15 years after diagnosis and remains elevated for at least 35 years after initial treatment [131].

Following the gradual decline of radiotherapy as a treatment modality for testicular cancer since the mid-1970s, the pattern of second cancer development has changed. Leukaemia (mainly acute myeloid leukaemia) is most often diagnosed within the first 10 years after cisplatin-based chemotherapy and is associated with the cumulative dose of etoposide administered [132, 133]. The few published studies that have looked at the long-term incidence of solid tumours in patients treated with cisplatin-based chemotherapy indicate an increased risk of urological cancer and probably thyroid and lung cancer [128, 134].

However, larger studies are needed to clarify the risk of a second cancer in relation to treatment received for the primary testicular cancer. The prognosis of patients with post-testicular cancer second non-germ cell cancers is similar to that of patients with the same non-germ cell cancers as their first lifetime malignancy [135].

Second germ cell testicular cancer.

Between 2% and 5% of patients with testicular cancer develop a germ cell tumour in the contralateral testicle, most frequently on the basis of GCNIS [136-138]. It is not clear whether early histological demonstration and treatment (most often radiotherapy) of this pre-invasive stage is of overall clinical benefit for the individual patient [139].

Four or more cycles of cisplatin-based chemotherapy delayed or prevented the development of an invasive testicular germ cell cancer, halving the rate at 5 years [140, 141].

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Table S1. Summary of recommendations

| Guidelines statement | LoE | GoR | Level of consensus |
|--|------------|------------|--|
| 1. Is there a role for targeted screening? | | | |
| 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 | III-V | A-C | 97% (32) yes, 3% (1) no (33 voters) |
| 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 | III | B | 100% (33) yes (33 voters) |
| 2. Pathology assessments | | | |
| 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 | III | A | 87.1% (27) yes, 12.9% (4) abstain (31 voters) |
| 2.2 The WHO 2016 classification should be routinely adopted for testicular pathology assessment | III | A | 74.2% (23) yes, 25.8% (8) abstain (31 voters) |
| 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 | III | A | 100% (31) yes (31 voters) |

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| <p>3. Should contralateral biopsy be performed?</p> <p>3.1 Biopsies of the contralateral testis at the time of orchiectomy should be discussed with, and recommended to, high-risk patients (i.e. those aged <40 years with a small atrophic testis and/or microlithiasis)</p> | III | A | 93.8% (30) yes, 3.1% (1) no, 3.1% (1) abstain (32 voters) |
| <p>4. Imaging techniques</p> <p>4.1 Testicular US using high frequency (>10 MHz) probe with colour Doppler assessment should be performed to confirm the presence of a testicular mass prior to orchiectomy or possible exploration of the contralateral testis</p> <p>4.2 Contrast-enhanced CT is recommended in all patients for staging prior to orchiectomy</p> <p>4.3 MRI may be helpful for characterisation of equivocal CT findings (e.g. in liver, bone, brain)</p> <p>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</p> | V | A | No vote obtained |
| | III | A | No vote obtained |
| | IV | A | No vote obtained |
| | IV | A | No vote obtained |

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| 4.5 | MRI is not routinely recommended in all patients for staging of the retroperitoneum | III | B | 94.1% (32) yes, 5.9% (2) abstain (34 voters) |
| 4.6 | PET-CT is not routinely recommended in all patients for staging | I | B | 94.1% (32) yes, 5.9% (2) abstain (34 voters) |
| 4.7 | PET-CT is not considered to be useful for staging in the case of negative contrast-enhanced CT and marker-positive disease | V | C | 88.2% (30) yes, 5.9% (2) no, 5.9% (2) abstain (34 voters) |
| 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 | V | B | 97.1% (33) yes, 2.9% (1) abstain (34 voters) |
| 4.9 | In marker-negative disease, if contrast-enhanced CT shows equivocal lymph nodes, repeated staging with PET-CT is not recommended | V | C | 88.2% (30) yes, 5.9% (2) no, 5.9% (2) abstain (34 voters) |
| 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 | III | A | 85.3% (29) yes, 2.9% (1) no, 11.8% (4) abstain (34 voters) |
| 4.11 | FDG-PET-CT may be helpful to assess residual masses >3 cm in patients with | III | B | No vote obtained |

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| seminoma if performed at least 8 weeks after the end of chemotherapy. If the results are negative, FDG-PET-CT has a very high negative predictive value | | | |
| 4.12 Repeat FDG-PET-CT may be useful in patients with marker-positive relapse and a negative contrast-enhanced CT result | IV | B | No vote obtained |
| 4.13 The follow-up contrast-enhanced CT should be of the abdomen only | IV | C | 78.8% (26) yes, 9.1% (3) no, 12.1% (4) abstain (33 voters) |
| 5. Old and new biomarkers | | | |
| See Section 3 of supplementary text for recommendations | | | |
| 6. Are there risk factors validated and/or accepted for seminoma? | | | |
| 6.1 Both rete testis stromal invasion and primary tumour size should be considered as risk factors for relapse in stage I seminoma | III | B | 91% (29) yes, 9% (3) abstain (32 voters) |
| 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 | III | B | 94% (30) yes, 6% (2) abstain (32 voters) |

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| 6.3 | Patients with seminoma without any identified risk factor (e.g. no rete testis involvement and small tumour size) have a very low risk of recurrence | III | B | 75% (24) yes, 25% (8) abstain (32 voters) |
| 7. Are there risk factors validated and/or accepted for non-seminoma? | | | | |
| 7.1 | In patients with non-seminoma, LVI is the key risk factor indicating disease relapse | III | B | 100% (32) yes (32 voters) |
| 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 | III | B | 94% (30) yes, 6% (2) abstain (32 voters) |
| 7.3 | Prospective collection of data on both markers (LVI and EC) is warranted | III | B | 100% (32) yes (32 voters) |
| 8. Who should be offered adjuvant chemotherapy? | | | | |
| 8.1 | Patients with seminoma and a low risk of relapse should not be offered adjuvant chemotherapy | III | C | 91% (30) yes, 6% (2) no, 3% (1) abstain (33 voters) |
| 8.2 | In patients with seminoma and a higher risk of relapse, surveillance or adjuvant carboplatin are options | III | C | 91% (30) yes, 6% (2) no, 3% (1) abstain (33 voters) |

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| 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 | III | C | 91% (30) yes, 6% (2) no, 3% (1) abstain (33 voters) |
| 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 | III | B | 72% (23) yes, 25% (8) no, 3% (1) abstain (32 voters) |
| 8.5 In patients with non-seminoma, patient autonomy should be taken into account following the provision of thorough information regarding the pros and cons of alternative management strategies | III | B | 72% (23) yes, 25% (8) no, 3% (1) abstain (32 voters) |
| 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 | III | B | 97% (32) yes, 3% (1) abstain (33 voters) |
| 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 | III | B | 97% (32) yes, 3% (1) abstain (33 voters) |

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| <p>9. Should adjuvant chemotherapy be limited to one course of chemotherapy?</p> <p>9.1 One course of carboplatin AUC 7 is the standard adjuvant chemotherapy in stage I seminoma</p> <p>9.2 One course of adjuvant BEP is the standard adjuvant chemotherapy in stage I non-seminoma</p> | <p>I</p> <p>III</p> | <p>B</p> <p>B</p> | <p>97% (30) yes, 3% (1) abstain (31 voters)</p> <p>97% (30) yes, 3% (1) abstain (31 voters)</p> |
| <p>10. What is the optimal treatment of relapse after adjuvant chemotherapy?</p> <p>10.1 In patients with seminoma, treatment of relapse after adjuvant chemotherapy should be standard treatment according to the prognostic classification for metastatic disease</p> <p>10.2 In patients with non-seminoma, treatment of relapse after adjuvant chemotherapy should be standard chemotherapy for metastatic disease</p> <p>10.3 In patients with non-seminoma with localised abdominal and marker-negative relapse, NS-RPLND is the preferred option for primary salvage treatment</p> | <p>III</p> <p>III</p> <p>III</p> | <p>B</p> <p>B</p> <p>B</p> | <p>93% (28) yes, 7% (2) abstain (30 voters)</p> <p>90% (28) yes, 10% (3) abstain (31 voters)</p> <p>90% (28) yes, 10% (3) abstain (31 voters)</p> |
| <p>11. Other treatment alternatives for stage I disease: is there a role for RPLND?</p> | | | |

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| 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 | III | B | 90% (28) yes, 6% (2) no, 3% (1) abstain (31 voters) |
| 11.2 RPLND is the standard treatment in patients with clinical stage I pure teratoma and risk factors for occult retroperitoneal disease | III | B | 62% (20) yes, 16% (5) no, 22% (7) abstain (32 voters) |
| 11.3 RPLND is the standard treatment in patients with clinical stage I teratoma with malignant somatic transformation | III | B | 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? | | | |
| 12.1 Adjuvant radiation therapy is not recommended for clinical stage I seminoma except in exceptional cases | I | B | 100% (25) yes (25 voters) |
| 13. How should patients with stage IIA or IIB seminoma be treated? | | | |
| 13.1 Evidence of metastatic disease has to be unequivocal in order to make a diagnosis of clinical stage IIA seminoma | V | A | 91% (29) yes, 3% (1) no, 6% (2) abstain (32 voters) |

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| <p>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)</p> | <p>IV</p> | <p>B</p> | <p>43% (12) chemotherapy, 32% (9) radiotherapy, 18% (5) no preference, 7% (2) abstain (28 voters)</p> |
| <p>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</p> | <p>IV</p> | <p>B</p> | <p>91% (31) yes, 3% (1) no, 6% (2) abstain (34 voters)</p> |
| <p>14. Should different chemotherapy regimens be used in different clinical scenarios of metastatic seminoma?</p> | | | |
| <p>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</p> | <p>II</p> | <p>A</p> | <p>80% (24) yes, 10% (3) no, 10% (3) abstain (30 voters)</p> |
| <p>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</p> | <p>II</p> | <p>A</p> | <p>100% (30) yes (30 voters)</p> |

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| <p>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</p> | <p>III</p> | <p>A</p> | <p>94% (29) yes, 6% (2) abstain (31 voters)</p> |
| <p>15. What is the optimal treatment for patients with clinical stage IIA and IIB non-seminoma with normal or normalised serum tumour markers after orchiectomy?</p> | | | |
| <p>15.1 All patients with clinical stage IIA NSGCT (evidence of enlarged retroperitoneal lymph nodes of <2 cm) and normal STMs should have metastatic disease confirmed (e.g. by biopsy or repeated imaging 8 weeks after surgery)</p> | <p>III</p> | <p>A</p> | <p>No vote obtained</p> |
| <p>15.2 The recommended treatment for confirmed clinical stage IIA non-seminoma with normal/normalised STMs is either BEP/EP ± NS-RPLND, or primary NS-RPLND ± adjuvant chemotherapy. Discussion regarding the pros and cons of these options with the patient is recommended</p> | <p>III</p> | <p>A</p> | <p>45% (13) BEP/EP ± NS-RPLND; 34% (10) NS-RPLND ± adjuvant chemotherapy; 7% (2) no preference, 14% (4) abstain (29 voters)</p> |

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| <p>15.3 The recommended treatment for clinical stage IIB non-seminoma with normal/normalised STMs is primary BEP/EP ± NS-RPLND</p> | <p>III</p> | <p>B</p> | <p>88% (29) BEP/EP ± NS-RPLND, 3% (1) NS-RPLND ± adjuvant chemotherapy, 6% (2) no preference, 3% (1) abstain (33 voters)</p> |
| <p>16. How should intermediate prognosis metastatic non-seminoma be treated?</p> | | | |
| <p>16.1 The recommended treatment for 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</p> | <p>II</p> | <p>A</p> | <p>89% (25) yes, 11% (3) abstain (28 voters)</p> |
| <p>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?</p> | | | |
| <p>17.1 Tumour marker decline (i.e. using the GETUG risk calculator: https://www.gustaveroussy.fr/calculacion-tumor/NSGCT.html) after one to two cycles of first-line cisplatin-based chemotherapy should be assessed to predict</p> | <p>II</p> | <p>B</p> | <p>68% (17) yes, 8% (2) no, 24% (6) abstain (25 voters)</p> |

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| <p>outcomes in poor prognosis patients</p> <p>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</p> <p>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</p> | <p>II</p> <p>II</p> | <p>B</p> <p>C</p> | <p>71% (17) yes, 17% (4) no, 12% (3) abstain (24 voters)</p> <p>65% (17) dose intensification in selected patients, 23% (6) four cycles of BEP, 12% (3) dose intensification in all patients (26 voters)</p> |
| <p>18. How should we treat primary mediastinal NSGCT (localised and metastatic)?</p> <p>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</p> | <p>III</p> | <p>B</p> | <p>46% (12) chemotherapy, with intensification in case of unsatisfactory tumour marker decline, followed by surgery (if</p> |

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| <p>toxicity or replaced by ifosfamide</p> | | | <p>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)</p> |
| <p>19. What is the appropriate management for patients with upfront brain or bone metastases?</p> <p>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</p> | <p>III</p> | <p>A</p> | <p>100% (24) yes (24 voters)</p> |

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| <p>other (local) treatment modalities</p> <p>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</p> <p>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</p> | <p>IV</p> <p>V</p> | <p>C</p> <p>A</p> | <p>100% (24) yes (24 voters)</p> <p>75% (18) additional surgery or stereotactic radiation, 25% (6) no further local treatment (24 voters)</p> |
| <p>20. Poor prognosis NSGCT: when can orchiectomy be postponed and when can initial chemotherapy be reduced?</p> <p>20.1 In patients with advanced metastatic TGCC and/or those with impending organ failure, orchiectomy 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)</p> | <p>V</p> | <p>B</p> | <p>88% (28) yes, 12% (4) abstain (32 voters)</p> |

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| <p>20.2 In patients with widespread lung metastases, pure choriocarcinoma and high hCG, 2–3 days of full dose cisplatin and etoposide are suggested, with continuation of chemotherapy when the patient has recovered (e.g. day 14)</p> | V | B | No vote obtained |
| <p>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</p> | IV | B | 91% (30) yes, 9% (3) abstain (33 voters) |
| <p>20.4 In patients with a GFR of 30–50 mL/min/1.73 m², carboplatin-based chemotherapy (or cisplatin-based chemotherapy in patients undergoing haemodialysis) are options. Bleomycin should be omitted</p> | V | C | No vote obtained |

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| <p>20.5 Regardless of the degree of renal function, patients with hydronephrosis (unilateral or bilateral) should be relieved with either stent or nephrostomy prior to chemotherapy</p> | <p>V</p> | <p>B</p> | <p>100% (33) yes (33 voters)</p> |
| <p>20.6 Patients with poor renal function should not be routinely treated with carboplatin but should be referred to high-volume centres for evaluation</p> | <p>V</p> | <p>A</p> | <p>100% (32) yes (32 voters)</p> |
| <p>21. What is the optimal treatment of older patients with metastatic TGCCs?</p> | | | |
| <p>21.1 Comprehensive risk-benefit evaluation of older patients with TGCC should include assessment of co-morbidities and patient disease risk category</p> | <p>IV</p> | <p>B</p> | <p>No vote obtained</p> |
| <p>21.2 In the first-line setting, there is generally no reason not to administer standard chemotherapy according to the risk category. Primary G-CSF prophylaxis is recommended in these patients as the risk of neutropaenic sepsis is higher in older patients</p> | <p>IV</p> | <p>B</p> | <p>No vote obtained</p> |
| <p>21.3 Standard-dose chemotherapy may be the preferred choice in most elderly patients, although limited safety data are available. Referral to an experienced</p> | <p>IV</p> | <p>B</p> | <p>No vote obtained</p> |

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| centre is strongly recommended to help make treatment decisions | | | |
| 22. Should care of patients with metastatic TGCC be centralised? | | | |
| 22.1 Besides orchiectomy, treatment of patients with TGCC should be conducted in high-volume centres | IV | A | 77% (20) agree for all patients; 23% (6) agree only for patients with metastases (26 voters) |
| 23. When is PC-RPLND indicated? | | | |
| 23.1 PC-RPLND is indicated in patients with non-seminoma and residual retroperitoneal lesions ≥ 1 cm in size | IV | A | 89.3% (25) yes, 10.7% (3) no, 0% (0) abstain (28 voters) |
| 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 | IV | A | 100% (28) yes (28 voters) |
| 24. Salvage therapy | | | |

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| <p>26. How can post-therapeutic psychosocial issues be minimised, and HRQoL protected?</p> <p>26.1 Patients should be informed of the potential long-term toxicities of treatment (i.e. ototoxicity and neurotoxicity, second cancers and CVD, as well as sexual difficulties, fatigue and cognitive dysfunction)</p> <p>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 for testicular cancer</p> <p>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</p> <p>26.4 Physical activity and a healthy lifestyle should be recommended to all patients</p> | <p>III/IV</p> <p>IV</p> <p>IV</p> <p>IV</p> | <p>B</p> <p>B</p> <p>B</p> <p>B</p> | <p>97% (32) yes, 3% (1) abstain (33 voters)</p> |
| <p>27. How should fatigue be identified, prevented and treated?</p> | | | |

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| 27.1 In order to prevent fatigue, overtreatment should be avoided (i.e. by adherence to treatment guidelines) | V | B | 100% (33) yes (33 voters) |
| 27.2 Fatigue should be addressed and documented during follow-up | V | B | 100% (33) yes (33 voters) |
| 27.3 Contributing conditions should be identified and treated | V | B | 100% (33) yes (33 voters) |
| 27.4 Personalised physical training should be recommended | IV | B | 100% (33) yes (33 voters) |
| 27.5 Referral for CBT should be considered | IV | B | 100% (33) yes (33 voters) |
| 28. How can the risk of ototoxicity and neurotoxicity be minimised? | | | |
| 28.1 Symptomatic ototoxicity and neurotoxicity are unpreventable complications of cisplatin-based chemotherapy and should generally not influence treatment intensity | III | B | 100% (33) yes (33 voters) |
| 28.2 Patients should be informed about the risk of ototoxicity and neurotoxicity before receiving cisplatin-based chemotherapy | IV | B | 100% (33) yes (33 voters) |

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| <p>28.3 Further risk factors for ototoxicity and neurotoxicity should be avoided (e.g. aminoglycosides within weeks of chemotherapy, exposure to loud noises, smoking and poorly regulated diabetes)</p> | <p>IV</p> | <p>B</p> | <p>100% (33) yes (33 voters)</p> |
| <p>29. Which TGCCSs should be offered testosterone replacement therapy?</p> | | | |
| <p>29.1 Asymptomatic TGCCSs with testosterone levels below the normal range should not routinely be offered testosterone replacement therapy</p> | <p>V</p> | <p>C</p> | <p>74% (20) yes, 19% (5) no, 7% (2) abstain (27 voters)</p> |
| <p>29.2 TGCCSs with testosterone levels below the normal range and clinical symptoms* should be offered testosterone replacement therapy</p> | <p>V</p> | <p>B</p> | <p>100% (33) yes (33 voters)</p> |
| <p>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</p> | <p>V</p> | <p>B</p> | <p>94% (30) yes, 6% (2) abstain (32 voters)</p> |
| <p>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</p> | <p>V</p> | <p>C</p> | <p>44% (11) yes, 12% (3) no, 44% (11) abstain (25 voters)</p> |

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| <p>30. How can the risk of CVD be reduced in TGCCSs?</p> <p>30.1 In order to reduce the risk of CVD, overtreatment should be avoided, especially the combination of chemotherapy and radiotherapy</p> <p>30.2 Patients should receive repeated counselling about the importance of a healthy lifestyle in preventing CVD</p> <p>30.3 Patients should receive regular check-ups to prevent CVD, including measurements of blood pressure, weight, sex hormones, lipids and glucose</p> <p>30.4 Patients should receive treatment for hypertension, hypercholesterolaemia and diabetes to prevent CVD</p> | <p>IV</p> <p>IV</p> <p>IV</p> <p>IV</p> | <p>B</p> <p>B</p> <p>B</p> <p>B</p> | <p>100% (33) yes (33 voters)</p> |
| <p>31. How can the risk of second non-germ cell cancer and its consequences be reduced in TGCCSs?</p> <p>31.1 TGCCSs who receive treatment in addition to orchiectomy should be informed about the risk of second cancers and the importance of contacting their healthcare provider if suspicious symptoms arise</p> | <p>V</p> | <p>B</p> | <p>94% (31) yes, 6% (2) no (33 voters)</p> |

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| 31.2 TGCCSs should receive lifestyle counselling and be encouraged not to smoke | V | B | 94% (31) yes, 6% (2) no (33 voters) |
| 32. How should follow-up schedules be planned? | | | |
| 32.1 When considering the risks of relapse depending on diagnosis and initial treatment, all seminoma stage I patients should be grouped together Recommendations for minimal follow-up for seminoma stage I on active surveillance, non-seminoma stage I on active surveillance and after adjuvant treatment or complete remission for advanced disease are summarised in Tables 4–6 | IV | B | 88% (29) yes, 6% (2) no, 6% (2) abstain (33 voters) |
| 33. Suggested patient care plan to be provided to the patient and general practitioner at termination of uro-oncological follow-up | | | |
| A suggested survivorship care plan is provided in Table S5 | | | |

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

AUC, area under the curve; BEP, bleomycin/etoposide/cisplatin; CBT, cognitive behavioural therapy; CT, computed tomography; CVD, cardiovascular disease; EC, embryonal carcinoma; EP, etoposide/cisplatin; FDG, fludeoxyglucose; G-CSF, granulocyte colony-stimulating factor; GFR, glomerular filtration rate; GoR, grade of recommendation; hCG, human chorionic gonadotropin; HRQoL, health-related quality of life; ICCR, International Collaboration on Cancer Reporting; IGCCCG, International Germ Cell Cancer Collaborative Group; LoE, level of

evidence; LVI, lymphovascular invasion; MRI, magnetic resonance imaging; NS, nerve-sparing; NSGCT, non-seminomatous germ cell tumour; PC, post-chemotherapy; RPLND, retroperitoneal lymph node dissection; PET, positron emission tomography; STM, serum tumour marker; TGCC, testicular germ cell cancer; TGCCS, testicular germ cell cancer survivor; US, ultrasound; VIP, vinblastine/ifosfamide/cisplatin; WHO, World Health Organization.

Table S2. Treatment options for stage IIA and IIB non-seminoma

| Treatment | Characteristic | |
|--|---|---|
| | Pros | Cons |
| BEP x 3 ± RPLND | <ul style="list-style-type: none"> • No peri-operative morbidity in 75% of patients with a CR | <ul style="list-style-type: none"> • Two therapies needed in 25% of patients • Side effects of chemotherapy seen in 100% of patients • Risk of relapse 5%–10% if no RPLND (including growing teratoma and GTS) |
| RPLND without adjuvant chemotherapy | <ul style="list-style-type: none"> • Histological confirmation • Immediate chemotherapy avoided | <ul style="list-style-type: none"> • Serious side effects of RPLND (Clavien-Dindo grade IIIB-V) in up to 5% of patients • 25% relapse rate in pathologic stage IIA • Up to 50% relapses in pathological stage IIB patients • Close follow-up needed |

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| RPLND + adjuvant EP or BEP x 2 | <ul style="list-style-type: none"> • Histological confirmation of stage (25% pathological stage I with no need for adjuvant chemotherapy) • Low risk of relapse (1%–4%) | <ul style="list-style-type: none"> • Serious side effects of RPLND (Clavien-Dindo grade IIIB-V) in up to 5% of patients • Side effects of chemotherapy in 100% of confirmed pathological stage II patients |
|---|---|--|

BEP, bleomycin/etoposide/cisplatin; CR, complete response; EP, etoposide/cisplatin; GTS, growing teratoma syndrome; RPLND, retroperitoneal lymph node dissection.

Table S3. Criteria and projected outcomes for patients with intermediate prognosis testicular cancer

| | |
|------------------------------------|---------------------------------------|
| <i>Non-seminoma (28% of cases)</i> | <i>Criteria:</i> |
| 5-year PFS 75% | Testis/retroperitoneal primary |
| 5-year survival 80% | No non-pulmonary visceral metastases |
| | AFP 1000–10 000 ng/mL or |
| | hCG 5000–50 000 IU/L or |
| | LDH 1.5–10 x ULN |
| <i>Seminoma (10% of cases)</i> | <i>All of the following criteria:</i> |
| 5-year PFS 67% | Any primary site |
| 5-year survival 72% | Non-pulmonary visceral metastases |
| | Normal AFP |
| | Any hCG |
| | Any LDH |

AFP, α -fetoprotein; hCG, human chorionic gonadotropin; LDH, lactate dehydrogenase;

PFS, progression-free survival; ULN, upper limit of normal.

Table 4. Relapsed GCC: International Prognostic Factors Study Group classification [1]

| Parameter | Score points | | | |
|--|--------------|--------------|-------|-----------------------------|
| | 0 | 1 | 2 | 3 |
| Primary site | Gonadal | Extragonadal | - | Mediastinal non-seminoma |
| Prior response | CR/PRm- | PRm+/SD | PD | - |
| PFI, months | >3 | ≤3 | - | - |
| AFP salvage | Normal | ≤1000 | >1000 | - |
| hCG salvage | ≤1000 | >1000 | - | - |
| Score sum (values from 0 to 10) | | | | |
| Regroup score sum into categories: (0) = 0; (1 or 2) = 1; (3 or 4) = 2; (5 or more) = 3 | | | | |
| Add histology score points: pure seminoma = -1; non-seminoma or mixed tumours = 0 | | | | |
| Final prognosis score (-1 = very low risk; 0 = low risk; 1 = intermediate risk; 2 = high risk; 3 = very high risk) | | | | |

AFP, α -fetoprotein; CR, complete remission; GCC, germ cell cancer; hCG, human chorionic gonadotrophin; PD, progressive disease; PFI, progression-free interval; PRm-, partial remission, negative markers; PRm+, partial remission, positive markers; SD, stable disease.

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REFERENCE

1. Lorch A, Beyer J, Bascoul-Mollevis C et al. Prognostic factors in patients with metastatic germ cell tumors who experienced treatment failure with cisplatin-based first-line chemotherapy. *J Clin Oncol* 2010; 28 (33): 4906-4911.

Table S5. Suggested survivorship care plan

| |
|---|
| <p>You were operated in the year _____ for testicular cancer, subtype:</p> <p><input type="checkbox"/> Seminoma <input type="checkbox"/> Non-seminoma</p> |
| <p><input type="checkbox"/> No dissemination of disease was confirmed</p> <p><input type="checkbox"/> Dissemination of disease was confirmed to _____</p> |
| <p>Additional treatment</p> <p><input type="checkbox"/> No</p> <p><input type="checkbox"/> Chemotherapy (number of cycles: _____)</p> <p><input type="checkbox"/> Radiotherapy</p> <p><input type="checkbox"/> Surgery in addition to removal of the testicle: _____</p> |
| <p>Date for last follow-up: _____ Hospital: _____</p> <p>Responsible doctor: _____ Telephone: _____</p> |
| <p>You have completed the last oncological follow-up after previous treatment for testicular cancer. The risk for relapse of the disease is very low, and you will be taken care of by your general practitioner in the future. This patient care plan should be shown in case of future contact with the health services.</p> <p>You are at risk of a new tumour in the remaining testicle and regular self-examinations are important. Furthermore, another cancer type may develop after treatment with chemotherapy and/or radiotherapy. Some side effects from testicular cancer treatment may emerge several years after treatment (e.g. sub-normal values of the male sex hormone[testosterone]). In addition, men previously treated with chemotherapy and/or radiotherapy have an increased risk of hypertension, being overweight, elevated cholesterol levels and cardiovascular</p> |

disease. Thus, it is advisable to exercise regularly, refrain from smoking and avoid becoming overweight.

We recommend that the following are monitored by the general practitioner:

- 1) Blood pressure, height, weight, waist circumference
- 2) Blood samples including fasting lipids (total cholesterol, HDL-cholesterol and LDL-cholesterol, triglycerides), fasting glucose and hormones (testosterone, FSH and LH)
- 3) Clinical examination if symptoms arise

The purpose of these tests is to prevent, identify and possibly treat risk factors which might lead to complications (e.g. cardiovascular disease). We recommend tests every 2-3 years. If abnormal values are detected, further follow-up will be initiated by the general practitioner.

FSH, follicle-stimulating hormone; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LH, luteinising hormone.