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SPECIAL ARTICLE

Testicular seminoma and non-seminoma: ESMO-EURACAN Clinical Practice Guideline for diagnosis, treatment and follow-up☆

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INCIDENCE AND EPIDEMIOLOGY

Germ-cell tumours (GCTs) affect predominantly younger males aged between 15 and 40 years, with nearly 74 500 new cases estimated globally in 2020.[1] About one-third of all GCT cases worldwide are diagnosed in Europe. Testicular GCT (TGCT) is the most common malignant GCT, with noted geographic variations.[2] The highest incidence rates in 2010 (per 100 000) were observed in Denmark with 10.2 and Norway with 11.5 and are currently declining in these two countries. TGCT incidence rates (per 100 000) will probably increase particularly in areas with low incidences, e.g. Eastern Europe exemplified by Belarus and Ukraine with 2010 rates of 2.3 and 2.2, respectively.[2] Although exposure to endocrine-disrupting chemicals has been hypothesised, the aetiology of GCTs remains elusive.[2] Also, in ageing European populations with relatively fewer younger men aged 15-40 years, unconfirmed factors are believed to increase the number of future GCT patients.

TGCT is associated with cryptorchidism, hypospadias and decreased fertility, often referred to as the testicular dysgenesis syndrome.[3] *In utero* exposure to endocrine disruption chemicals might increase the likelihood of this syndrome. Among these chemicals, organochlorine insecticides have been demonstrated to increase the risk of GCT.[4] Furthermore, GCT seems to be more frequent in certain families,[5] with higher risks among brothers [relative risk (RR) 6.3] than for sons or fathers (RR 4.4-4.7) of affected family members.

So far, no highly penetrant GCT genes have been identified. Genome-wide association studies have identified several low-risk and moderate-risk single nucleotide polymorphisms associated with the risk of GCT, estimated to account for ∼37% of the familial GCT risk.[6,7] A recent study found pathogenic germline DNA repair gene variants among 10% of TGCT cases, of which *CHEK2* was suggested to be a potential novel moderate-penetrance susceptibility gene for GCT.[8] About 5% of men with GCT are diagnosed with contralateral TGCT, further suggesting a genetic disposition.[9] Regardless of whether GCT has genetic and/or environmental causes, the interindividual risk is remarkable as patients diagnosed with seminoma and non-seminoma have standardised incidence ratios of 13 and 29, respectively, of developing a contralateral TGCT as compared with the incidence of first GCT in the general population.[10]

Approximately 55%-60% of the GCTs are pure seminomas and 40%-45% are non-seminomas.[4] Probably due to a slower progression, ∼85% of seminomas are diagnosed as clinical stage I disease as compared with 60% among non-seminomas. Approximately 95% of GCTs arise in the

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testicles, with 5% developing outside the gonads, i.e. extragonadal GCT (EGGCT). EGGCTs are usually found in the body's midline, e.g. retroperitoneum, mediastinum or cerebrum, sometimes posing diagnostic difficulties.

DIAGNOSIS, PATHOLOGY AND MOLECULAR BIOLOGY

Diagnosis

Testicular cancer is usually diagnosed as a unilateral testicular mass detected by the patient or identified incidentally during an ultrasound (US). Together with an incidental or palpable mass, patients may have scrotal pain (27%) or back or flank pain (11%), and 1% might present with gynaecomastia (germ-cell or sex cord/gonadal tumour of the testes).[11-13]

Diagnosis of a GCT is based on histology of the testicular mass [II, A]. In patients with a testicular lesion (even when palpable), however, testicular US should be carried out with a high-frequency (>10 MHz) probe with colour Doppler assessment.[14] In addition to confirming the presence of an intratesticular mass, US permits evaluation of the contralateral testicular volume, presence of synchronous tumours and microcalcifications. US may also reveal an impalpable testicular lesion in patients assessed for fertility problems, metastatic disease or elevated serum tumour markers.[15-18] The broadening use of testicular US is detecting increasing numbers of impalpable tumours of which many turn out to be of no significance, such as small Leydig-cell tumours.[19] The role of scrotal magnetic resonance imaging (MRI) is limited and it may be used to distinguish between an intra- and extra-testicular mass when this cannot be confirmed clinically or with US.[20]

Serum tumour markers are part of the initial work-up and diagnosis for patients with suspected testicular cancer, see Table 1.[11,16] α-Fetoprotein (AFP), beta subunit of human chorionic gonadotropin (β-hCG) and lactate dehydrogenase (LDH) levels should be determined before carrying out orchiectomy, as they are associated with germ-cell cancer histology and support the diagnosis of testicular cancer.[16,21] Overall, serum tumour markers have a low sensitivity (especially in seminoma) such that normal marker levels do not exclude GCTs. LDH has a low specificity since it may be elevated due to a number of reasons.[21,22] Post-orchiectomy levels of serum tumour markers are nevertheless important for prognostic stratification and should be followed in patients with initially elevated markers (AFP half-life is 5-7 days and β-hCG half-life is 1-3 days) until normalisation.[21] Persistent or increasing tumour markers after orchiectomy usually indicate metastatic disease. Circulating serum microRNAs (miRNAs) are reported to have a high sensitivity and specificity and are discussed in the section on personalised medicine.

Table 1. Serum tumour markers for non-seminoma testicular cancer

	LDH (U/l)	β-hCG (IU/l)	AFP (ng/ml)
SX	Marker studies not available or not carried out	Marker studies not available or not carried out	Marker studies not available or not carried out
S0	Normal	Normal	Normal
S1	<1.5 × ULN	<5000	<1000
S2	1.5-10 × ULN	5000-50 000	1000-10 000
S3	>10 × ULN	>50 000	>10 000

AFP, α-fetoprotein; β-hCG, beta subunit of human chorionic gonadotropin; LDH, lactate dehydrogenase; ULN, upper limit of normal.

Pathology

Testicular neoplasia is a complex and challenging area of pathology due to the large range of entities and relative rarity of diagnosis. More than 95% of malignant testicular tumours arise from germ cells. While immediate treatment may be based on classic clinical presentation of life-threatening GCT and elevated serum markers only, the vast majority of tumours are diagnosed on primary orchiectomy specimen. The rarity of these tumours, combined with their complex morphology, means that, in non-expert hands, there is a significant risk of misdiagnosis of both type and staging of these neoplasms.[23-25] It has been recommended by ESMO that expert pathologists should see a minimum of 30 cases a year.[13] Testicular tumours should be typed in line with the World Health Organization (WHO) 2016 classification.[26] This is a modified nomenclature from previous iterations to align morphology with molecular and outcome data. The major pre-neoplastic lesion of GCTs is germ-cell neoplasia *in situ* (GCNIS).[27] GCTs may be simply divided into those derived from GCNIS (most adult GCTs) and those not derived from GCNIS. The latter is a heterogeneous group including spermatocytic tumour and most prepubertal GCTs. A new classification was published by the WHO during the writing of this guideline; modifications are minor.[28] Histopathologically, seminomas are characterised by cells analogous to the primordial germ cells/gonocytes present during early embryonic development, while non-seminomas show a variety of differentiation patterns from embryonic and extra-embryonic tissues.

Biopsy for diagnosis of GCNIS in the contralateral testis and subsequent management. Around 5% of testicular cancer patients have GCNIS in the contralateral testis with the highest risk (~30%) in men with testicular atrophy (volume <12 ml) and age <40 years. Approximately 30%-40% of patients with retroperitoneal EGGCT harbour testicular GCNIS.[29-31]

In 2%-5% of TGCT patients a GCT is diagnosed in the contralateral testicle, either metachronously or synchronously. A recent population-based study reported a 20-year crude cumulative incidence rate of a metachronous contralateral GCT of 5.4% [95% confidence interval (CI) 4.2-6.8] after surgery only. Treatment with three or more cycles of cisplatin-based chemotherapy (ChT) was associated with significantly reduced risks of 3.2% (95% CI 2.5-4.0) for a second GCT.[32] Radiotherapy (RT) is the standard treatment of GCNIS with 9-10 fractions of 2 Gy corresponding to a total dose of 18-20 Gy. As this treatment renders the patient infertile and also weakens testosterone production, the indication for, and timing of this treatment has to be discussed carefully with the patient.[29]

The majority of European testicular cancer consensus experts do not consider a routine biopsy of the contralateral testis as indicated [V, C].[13]

Recommendations

- Diagnosis of GCT should generally be based on histology [II, A] except when urgent ChT is required.
- Symptomatic patients with high tumour burden and elevated tumour markers should receive ChT without delay caused by attempts to achieve a biopsy when the clinical picture is clear [III, A].
- Serum tumour markers (AFP, β-hCG and LDH) should be determined before and after orchiectomy and throughout follow-up. They are used for accurate staging and risk stratification to monitor treatment and to detect relapse [II, A].
- Approximately 5% of GCT patients harbour GCNIS in the contralateral testis, requiring physical and/or US examinations during follow-up [III, A].
- As RT for GCNIS prevents fatherhood by natural means, upfront versus delayed RT should be carefully discussed with patients [III, A].

STAGING AND RISK ASSESSMENT

Post-orchiectomy management should be the responsibility of clinicians with experience in the classification and treatment of TGCT [III, A].

Staging and risk group categorisation are carried out according to the Union for International Cancer Control (UICC) and the International Germ Cell Cancer Collaborative Group (IGCCCG), comprising the original publication from 1997 as well as updates with contemporary outcomes and refined risk categorisations for metastatic seminoma and non-seminoma, respectively, reflecting the extent of the disease based on clinical and radiological examinations and the results of serum tumour markers after orchiectomy, including LDH.[33-35] Risk factors for recurrence in clinical stage I GCTs include tumour (T) stage comprising vascular invasion by the primary tumour as well as size, rete testis invasion and the amount of embryonal carcinoma in non-seminomas. Unfortunately, at present there is disparity between American Joint Committee on Cancer (AJCC) and UICC versions of the TGCT TNM (tumour—node—metastasis) staging such that the applied staging system should always be specified.[36]

Tumour markers (AFP, β-hCG, LDH) are determined preferably before and after orchiectomy and followed until normalisation or lack of further decrease. The half-life for β-hCG is 1-3 days and 5-7 days for AFP.

For stage I disease, different risk factors have been identified for seminoma and non-seminoma based on histological features in the primary tumour and the 5-year survival rate of adequately managed patients approaches 100%.[37]

In non-seminoma stage I tumours, vascular invasion of blood or lymphatic vessels is most often caused by embryonal carcinoma. Although the presence of embryonal carcinoma might represent an individual risk factor, most experts recommend considering the presence of vascular invasion as the single and most important predictor of micrometastases and subsequent recurrence.

In seminoma clinical stage I, tumour size and possibly rete testis infiltration represent weaker risk factors identifying 'higher-risk' patients.[38-41] The ESMO consensus conference voting resulted in >90% majority voting in favour of applying both rete testis infiltration and tumour size as continuous variables for risk categorisation.[13] In the following text, this definition of 'higher-risk' seminoma, which is in line with the view of the European Association of Urology (EAU) testis panel as well, will be used when discussing the indication of adjuvant treatment.[16]

In patients without visible radiological metastatic lesions, a slower than expected decline of increased pre-orchiectomy β-hCG and AFP might indicate systemic disease. In some rare patients, β-hCG or AFP are elevated without GCT activity, e.g. liver disease, hypogonadism, hereditary AFP elevation. These patients should be referred to and at least discussed with GCT experts, before considering initiation of systemic treatment. Increasing serum markers without identification of metastases indicate the need of systemic treatment of (stage IS) testicular cancer (i.e. serum marker-positive without radiological evidence of metastases).

In patients with metastatic disease, serum marker values are integrated into the IGCCCG risk classification.[33-35] To rule out the presence of nodal or distant metastases, contrast-enhanced computed tomography (CT) of the chest, abdomen and pelvis should be carried out [III, A]. MRI has been established as a substitute for CT in the follow-up, but its role in staging is less clear. Accuracy of abdominal—pelvic staging should be similar between MRI and CT, but for the chest and lungs, CT is superior. Therefore, and due to the lack of evidence for MRI-based staging, contrast-enhanced CT of chest, abdomen and pelvis is recommended as the standardised, robust, reproducible, widely available technique. An MRI of the central nervous system (CNS) is advisable in non-seminoma patients with high β-hCG values or multiple lung metastases belonging to the poor-prognostic group. There is no evidence to support the routine use of [^{18}F]2-fluoro-2-deoxy-D-glucose-positron emission tomography (FDG-PET) in the staging of GCT [III, D]. Serum levels of total testosterone, sex hormone-binding globulin, luteinizing hormone and follicle-stimulating hormone should be determined.

IGCCCG identified three prognostic groups for patients with metastatic GCTs (MGCTs) with a disease-specific survival rate of 95%, 85% and 64% for good, intermediate and poor prognosis, respectively (Table 2).[42] A more recent update has shown that both progression-free survival (PFS) and overall survival (OS) have improved since the original IGCCCG publication. In the updated IGCCCG analysis, age, presence of lung metastases and an LDH value higher than 2.5 × the upper limit of normal (ULN) have been identified as additional prognostic factors.[34] More precise risk categorisation should yield more homogenous groups of patients, thus facilitating more specific hypotheses and trials. For non-seminoma, use of the online calculator allowing incorporation of age,

Table 2. The IGCCCG prognostic classification for metastatic germ cell cancers

Prognostic group and survival	Prognostic factors
Good	
Non-seminoma	All of the following criteria:
5-Year PFS 92% 5-Year OS 96%	Testicular/retroperitoneal primary No non-pulmonary visceral metastases AFP <1000 ng/ml hCG <5000 IU/l (1000 ng/ml) LDH <1.5 × ULN
Seminoma with LDH <2.5 × ULN	All of the following criteria:
3-Year PFS 92% and 93%, in training and validation set, respectively 3-Year OS 97% and 99%, in training and validation set, respectively	Any primary site No non-pulmonary visceral metastases Normal AFP Any hCG LDH within 2.5 × ULN
Seminoma with LDH >2.5 × ULN	All of the following criteria:
3-Year PFS 80% and 75%, in training and validation set, respectively 3-Year OS 92% and 96%, in training and validation set, respectively	Any primary site No non-pulmonary visceral metastases Normal AFP Any hCG LDH >2.5 × ULN
Intermediate	
Non-seminoma	Criteria for patients not belonging to good/poor prognosis
5-Year PFS 78% 5-Year OS 89%	Testicular/retroperitoneal primary No non-pulmonary visceral metastases And any of the following criteria: AFP 1000-10 000 ng/ml, hCG 5000-50 000 IU/l or LDH 1.5-10 × ULN
Seminoma	All of the following criteria:
3-Year PFS 78% and 61%, in training and validation set, respectively 3-Year OS 93% and 80%, in training and validation set, respectively	Any primary site Non-pulmonary visceral metastases Normal AFP Any hCG Any LDH
Poor	
Non-seminoma	Any of the following criteria:
5-Year PFS 54% 5-Year OS 67%	Mediastinal primary Non-pulmonary visceral metastases AFP >10 000 ng/ml or hCG >50 000 IU/l (10 000 ng/ml) or LDH >10 × ULN
Seminoma	No patients classified as poor prognosis

Adapted with permission from Beyer et al.[35] and Gillessen et al.[34] Published by Walters Kluwer Health, Inc. on behalf of the American Society of Clinical Oncology.
Pre-ChT serum tumour markers should be assessed after orchiectomy and immediately before the administration of ChT (same day).
AFP, α-fetoprotein; ChT, chemotherapy; hCG, human chorionic gonadotropin; IGCCCG, International Germ Cell Cancer Collaborative Group; LDH, lactate dehydrogenase; OS, overall survival; PFS, progression-free survival; ULN, upper limit of normal.

presence of lung metastases as well as ULN of LDH may be helpful: https://www.eortc.org/IGCCCG-Update.

Recommendations

- Post-orchiectomy management should only be carried out by highly experienced clinicians [III, A].
- CT scan with contrast enhancement of the thorax, abdomen and pelvis is mandatory for all patients [III, A].
- MRI of the CNS is indicated in poor-prognosis patients, particularly in case of choriocarcinoma/high β-hCG, multiple lung metastases or in those with cerebral symptoms [III, A].
- Routine positron emission tomography (PET) scanning is not recommended [V, D].
- IGCCCG is recommended for stratification of metastatic patients [III, A].

MANAGEMENT OF LOCOREGIONAL DISEASE

Before treatment, patients should be well informed about the potential treatment modalities, their acute and late toxicities and the overall outcome. The majority of patients with locoregional disease have stage I TCGT. A few patients, however, present with only small retroperitoneal lymph nodes, which require careful assessment regarding their potential likelihood of representing metastases. Locoregional management might cure patients with early stage II MGCT without systemic ChT for metastatic disease.

Management of the primary tumour

Semen analysis and sperm cryopreservation should be offered to all patients, preferably before orchiectomy [II, B].[43,44] Semen preservation is the most cost-effective strategy for fertility preservation [II, A]. Radical orchiectomy provides the histological diagnosis and should be carried out before any further treatment, unless the clinical situation requires immediate ChT in patients with elevated tumour markers and a clinical presentation of a typical germ-cell malignancy. Any testicular mass of uncertain ranking must be explored by the inguinal approach to verify or exclude malignancy. Tumour markers should be assessed before and after surgery until normalisation, progression or plateau development, since this information is used for final staging.

Radical orchiectomy is carried out through an inguinal incision [III, A]. Any scrotal violation for biopsy or open surgery should be avoided. The tumour-bearing testis is resected with the spermatic cord at the level of the internal inguinal ring.

In experienced centres, testis-sparing surgery may be feasible in case of a small tumour, particularly in patients with synchronous bilateral testicular tumours, tumour in a solitary testis or contralateral atrophic testis. Testis-sparing surgery should only be offered together with frozen section examination (FSE), which in the hands of expert pathologists is reported to be reliable and highly concordant with final histopathology. Nevertheless, patients should be informed about the risk of completion orchiectomy in case of discordance between FSE and final pathology. If a GCT is diagnosed, post-resection testicular RT or completion orchiectomy is mandatory due to a high risk of GCNIS in the remaining testis [III, A]. This renders the residual testicular tissue azoospermic but may retain some testosterone production.[45]

Seminoma

Stage I. Approximately 80% of patients with seminoma present with stage I disease, with a survival rate of ~99% that is independent of the chosen strategy. In light of this very high cure rate, minimising toxicities is the priority. Surveillance is

considered the preferred strategy.[46] Adjuvant RT should not be given as the risk of second malignancies is considered too high [II, A].[13] Adjuvant ChT with one course of carboplatin with an area under the curve (AUC) of 7 should be discussed with patients not willing or not able to undergo surveillance or higher-risk patients, defined by the presence of one or both risk factors, i.e. tumour size and rete testis invasion [III, B].[40] Two cycles of carboplatin AUC 7 yield similar good or even better results than one cycle. Based on the modest benefit of the second course of carboplatin and the limited data available, one course of carboplatin AUC 7 is recommended. Approximately 15%-30% of higher-risk patients develop a relapse under surveillance.[46]

In the absence of high evidence and due to dissensus among the panellists, the authors refer to the ESMO consensus meeting, which yielded >90% majority for:

- not offering carboplatin to low-risk patients [III, D];
- considering carboplatin and surveillance as options for higher-risk patients;
- taking patient autonomy into the decision-making process.[13]

Adjuvant carboplatin reduces but does not eliminate the risk of recurrence and even late relapses after carboplatin can occur.[47,48] Relapse occurs usually in the retroperitoneal or iliac lymph nodes. Rarely, late-occurring relapses may contain non-seminoma components [IV, B].[49]

Stage IIA lymph nodes 1-2 cm. Lymph nodes might be enlarged for a number of reasons and the risk of overtreatment might be reduced by either histological/cytological verification of metastasis or at minimum, an observed radiological progression over time. Treatment consists of either ChT according to IGCCCG recommendations or RT to para-aortic and ipsilateral iliac lymph nodes (30 Gy in 2 Gy fractions for stage IIA) [II, A] (Figure 1), without randomised trials comparing the outcomes.

A meta-analysis of stage IIA-IIB studies found that in clinical stage IIA with lymph nodes of <2 cm in axial diameter, RT and ChT seem to be equally effective at reducing recurrence, while in clinical stage IIB, ChT was more effective.[50] ChT is associated with higher acute toxicity and late cardiovascular disease, while extended-field RT seems to be associated with a higher incidence of secondary malignancies.[50,51]

A number of studies aim to spare patients with seminoma stage IIA-IIB for the toxicities induced by RT or three cycles of bleomycin, etoposide and cisplatin (BEP) or four cycles of etoposide and cisplatin (EP). Patients should be encouraged and supported to participate in ongoing clinical trials.

Non-seminoma

Stage I. Stage I non-seminoma infers excellent survival rates of 98%-100% and is categorised by the absence or presence of vascular invasion into 'low-risk' (12% relapse rate) or 'high-risk' (40%-50% relapse rate), respectively.[37]

Low-risk non-seminoma stage I. Surveillance is recommended. For the rare patients not suited for surveillance due to difficulties with repeated imaging or low compliance, adjuvant ChT with one cycle of BEP (see below) or open nerve-sparing retroperitoneal lymph node dissection (RPLND) in highly experienced centres are the alternative options. Some experts consider nerve-sparing RPLND the preferred treatment of patients with somatic

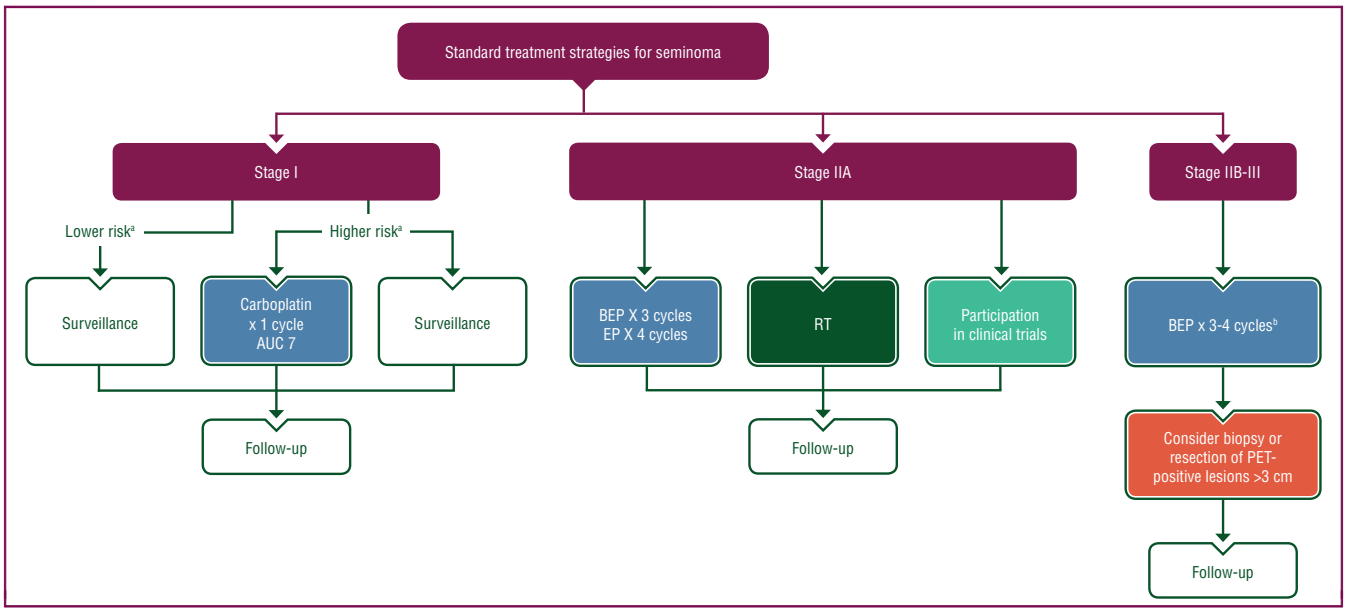

Figure 1. Standard treatment strategies for seminoma. Purple: general categories or stratification; dark green: radiotherapy; blue: systemic anticancer therapy; turquoise: combination of treatments or other systemic treatments; red: surgery; white: other aspects of management. AUC 7, area under the curve of 7; BEP, bleomycin—etoposide—cisplatin; EP, etoposide—cisplatin; PET, positron emission tomography; RT, radiotherapy.
[a]Lower and higher risk based on size of primary tumour and infiltration of rete testis with lower risk defined as absence of both risk factors and higher risk as presence of one or both risk factors.
[b]In case of contradiction against bleomycin, refer to text.

transformation in the primary tumour.[52] Patients with pure teratoma in the primary tumour may not benefit from adjuvant ChT either, as an assumed benefit of primary RPLND was not identified.[53] Patients with low-risk non-seminoma stage I considering adjuvant therapy should be informed about the risk of overtreatment [IV, B].

High-risk non-seminoma stage I. Patients with vascular invasion together with the presence of embryonal carcinoma in the primary tumour have a relapse rate of ∼40%-50% if followed in a surveillance program.[37] Ninety-five percent of the relapses belong to the good prognosis group and 5% to the intermediate or poor prognosis groups. Patients with vascular invasion are candidates for adjuvant ChT with one cycle of BEP. The relapse rate after one cycle of BEP is <5%.[54,55] In case of relapse, outcome seems to be better after adjuvant BEP compared with patients relapsing after metastatic disease, but worse compared with *de novo* metastatic patients.[56] The cancer-specific survival is the same whichever option is used, but long-term toxicities of one adjuvant BEP cycle versus three to four cycles of BEP in case of relapse have to be discussed with the patient (Figure 2).[54,55]

Nerve-sparing RPLND should only be considered in case of contraindications against the strategies recommended above. Some experts consider nerve-sparing RPLND the preferred treatment of patients with somatic transformation in the primary tumour.[52]

Stage IIA, marker-negative. In ∼15%-35% of patients with clinical stage IIA, the enlarged lymph nodes do not harbour metastases. The risk of overtreatment may be reduced by the following strategies:

- Close follow-up with abdominal imaging every 6 weeks until regression or progression, resulting in observation only or treatment, respectively. Treatment may consist of primary nerve-sparing RPLND in case of a single progressing lymph node, suggestive of teratoma. These potentially curative RPLNDs should only be carried out by high-volume surgeons in expert centres. Patients with multiple progressive lymph nodes and/or rising tumour markers are to be treated for MGCT according to the IGCCCG risk classification (Figure 2);
- Lymph node biopsy or primary nerve-sparing RPLND. The latter approach comprising both diagnostic and therapeutic potential. In case of vital GCT in the specimen, adjuvant ChT post-RPLND should be considered.[57] This is a rare situation in a rare cancer and studies yielding a high level of evidence are lacking. In stage I non-seminoma, adjuvant ChT was reduced from two cycles of BEP to the current standard of one cycle of BEP. Thus, the ESMO consensus panellists consider one cycle of BEP as appropriate adjuvant ChT after RPLND revealing vital GCT[13];
- Completely removed pure teratoma should not trigger ChT. For treatment of biopsy-proven vital GCT, see treatment of MGCT according to the IGCCCG categorisation.

Stage IIA-IIB, marker-positive. Treatment according to IGCCCG recommendations, see section on Management of metastatic disease.

Recommendations

Management of the primary tumour

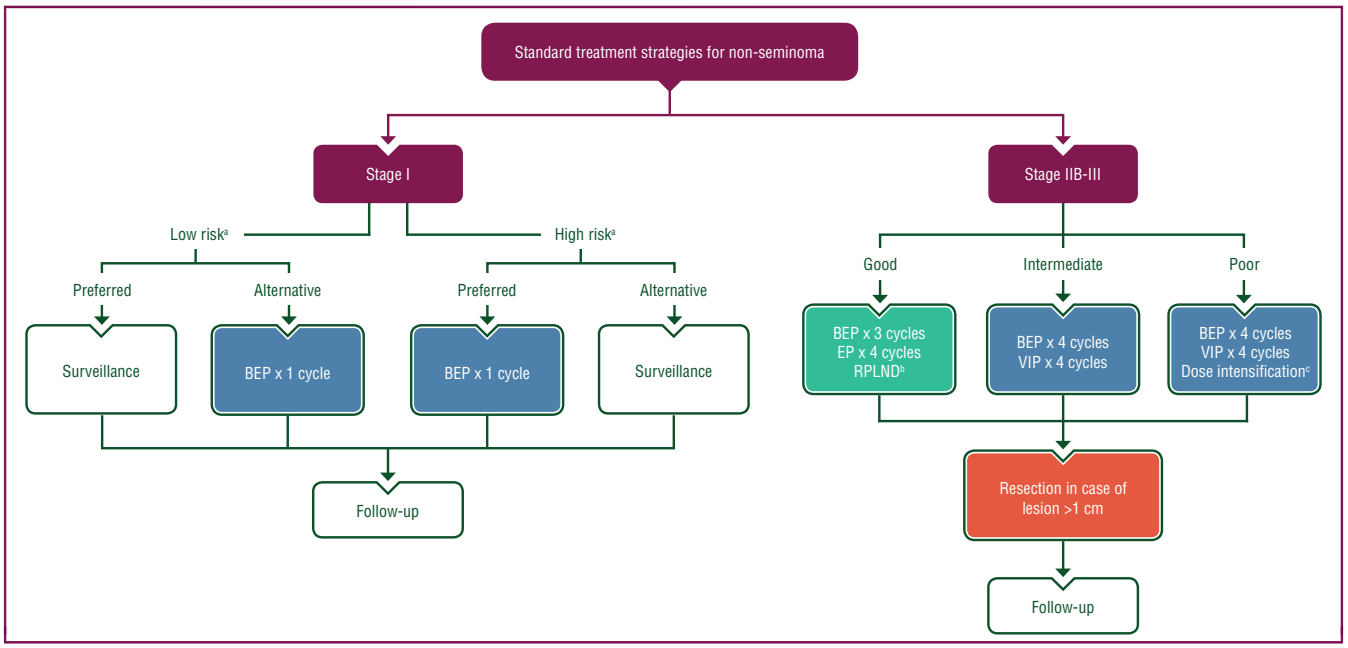

Figure 2. Standard treatment strategies for non-seminoma. Purple: general categories or stratification; blue: systemic anticancer therapy; turquoise: combination of treatments or other systemic treatments; red: surgery; white: other aspects of management. BEP, bleomycin—etoposide—cisplatin; EP, etoposide—cisplatin; RPLND, retroperitoneal lymph node dissection; VIP, etoposide—ifosfamide—cisplatin.
[a] low risk and high risk based on absence and presence of vascular invasion, respectively.
[b] (RPLND) marker-negative stage IIA/IIB.
[c] (Dose intensification): In selected cases, e.g. poor marker decline.

- Semen analysis and sperm cryopreservation should be offered to all patients, preferably before orchiectomy [II, B].
- Semen preservation is the most cost-effective strategy for fertility preservation [II, A].
- Radical orchiectomy is carried out through an inguinal incision [III, A].
- Testis-sparing surgery is feasible in experienced centres for selected patients [III, A].
- If a GCT is diagnosed during testis-sparing surgery, completion orchiectomy or post-resection testicular RT (if solitary testis) is mandatory due to a high risk of GCNIS in the remaining testis [III, A].

Seminoma stage I

- Inform patients about the post-orchiectomy management options: surveillance or adjuvant carboplatin; as well as treatment-specific recurrence rates and acute and long-term side-effects [II, A].
- Explain the impact of risk factors for the risk of micrometastases and the rationale of adjuvant carboplatin for patients with larger tumour and/or rete testis infiltration [III, B].
- Do not offer adjuvant carboplatin to patients without risk factors [III, D].
- Patient autonomy should be taken into account for selecting the post-orchiectomy management following thorough provision of the pros and cons of surveillance as opposed to one cycle of carboplatin [III, B].
- Do not offer or apply RT as an adjuvant post-orchiectomy management option [II, D].

Seminoma stage IIA

- Minimise overtreatment by histological/cytological verification of metastasis or at minimum, an observed radiological progression over time [III, B].
- Participation in ongoing clinical trials should be encouraged [III, B].
- Treat patients with seminoma stage IIA with either RT (30 Gy in 2 Gy fractions) or cisplatin-based ChT (three cycles of BEP or four cycles of EP) according to IGCCCG recommendations [II, A].

Non-seminoma stage I

- Inform patients with stage I non-seminoma about surveillance and adjuvant ChT as post-orchiectomy management options including treatment-specific recurrence rates as well as acute and long-term side-effects [II, A].
- Patient autonomy should be taken into account for selecting the post-orchiectomy management following thorough provision of the pros and cons of surveillance as opposed to one cycle of adjuvant BEP [III, B].
- RPLND is not recommended [II, D].

Non-seminoma stage IIA marker-negative

- Careful assessment is recommended to avoid overtreatment as ~15%-35% of clinical stage IIA patients do not harbour metastases in the enlarged lymph nodes [II, A].

Non-seminoma stage IIA-IIB marker-positive

- Treat patients with marker-positive non-seminoma stage IIA-IIB according to IGCCCG recommendations, e.g. three cycles of BEP or four cycles of EP if contraindications against bleomycin in good-risk patients [II, A].

MANAGEMENT OF METASTATIC DISEASE

First-line treatment

Seminoma stage II-III. Whereas patients with limited retroperitoneal lymph node metastases only, i.e. stage IIA, may be managed by RT, treatment of more advanced seminoma consists principally of ChT according to the IGCCCG classification for advanced/metastatic disease.[33-35] Three cycles of BEP represents the standard therapy for seminoma patients categorised as good prognosis and four cycles of BEP for intermediate prognosis (see updated IGCCCG classification).[33-35]

If there are contraindications against bleomycin, e.g. reduction in lung capacity (diffusing capacity of lung for carbon monoxide score), emphysema or heavy smoking (including former smokers), four cycles of EP are recommended in good-prognosis patients and four cycles of etoposide, ifosfamide and cisplatin (VIP) in intermediate-prognosis patients (Figure 1).[58,59] Only patients unfit for cisplatin-based ChT should be treated with carboplatin-based ChT (carboplatin, etoposide and bleomycin), which is inferior to BEP.[60] Inadequate renal function due to compression of one or both ureters requires nephrostomy and may impact on the application of cisplatin and bleomycin. Furthermore, renal function should be continuously followed and the regeneration of adequate renal function should prompt application of cisplatin-based ChT for the remaining cycles, if relevant.

Seminoma post-ChT management. Patients with complete response after ChT do not require further treatment and are candidates for follow-up [II, A]. In case of residual tumour >3 cm, an FDG-PET scan at least 6 weeks after completion of ChT is recommended [III, B].

Based on the negative predictive value >90%, negative PET lesions require no further management and these patients can be followed routinely by repeated imaging. Seventy-five percent of positive PET scans are falsely positive, i.e. no vital seminoma present, such that a biopsy is recommended before RT or resection.[61] Perioperative complications, however, are more common in seminoma than in non-seminoma due to desmoplastic reactions of ChT-exposed seminoma metastases.[61] Alternatively, further follow-up is recommended with biopsy before treatment in case of repeated positivity or growth of the lesion.[61]

Metastatic non-seminoma stage IIA marker-positive and stage IIB-III. Patients with IGCCCG good prognosis should receive three cycles of BEP or four cycles of EP, if contraindications against bleomycin exist [II, A]. Four cycles of BEP represent the standard treatment of patients with intermediate or poor prognosis [I, A].[33-35] In case of

contraindications against bleomycin, four cycles of VIP with granulocyte colony-stimulating factor (G-CSF) support are used.

A European Organisation for Research and Treatment of Cancer (EORTC) study randomising poor-risk patients to either four cycles of BEP or high-dose (HD) VIP therapy achieved a significant PFS but no OS benefit.[62] The GETUG 13 study used a more individualised approach and identified 80% of poor-risk non-seminoma patients (203 of 254) to have unfavourable marker decline after the first cycle of BEP.[58] These patients were randomised to either continue with standard BEP or to shift to a dose-dense regimen (continuous bleomycin infusions over 5 days with additional paclitaxel, ifosfamide and oxaliplatin, with G-CSF support), which demonstrated a significantly improved 3-year PFS of 59% versus 48% [hazard ratio (HR) 0.66, 95% CI 0.44-1.00]. The trend to improved OS did not reach statistical significance (HR 0.78, 95% CI 0.46-1.31). The dose-dense regimen caused relevant neurotoxicity and haematotoxicity but did not show an increase in grade 1-2 febrile neutropaenia or toxic deaths.

The 3-year PFS of patients undergoing four cycles of BEP was 70% versus 48%, HR 0.66 for those with favourable versus unfavourable marker decline, respectively.

Marker decline can be undertaken using an online calculation tool:

https://www.gustaveroussy.fr/calculation-tumour/NSGCT.html.

AFP and β-hCG decline should be assessed after the first cycle of BEP in poor-risk non-seminoma patients and patients with poor decline should be considered for treatment intensification in a high-volume expert centre [II, A].

Similarly, non-seminoma patients with CNS metastases or primary mediastinal tumours should always be treated at high-volume expert centres [II, A].

Poor-prognosis patients with significantly symptomatic disease, including extensive metastatic lung and/or liver involvement, have a significant risk of toxicity with standard BEP ChT.[63] A first cycle with adapted cisplatin and etoposide doses should be considered.[63] In that case, the full number of cycles should be applied after this induction cycle and orchidectomy may be carried out after finishing first-line ChT. In order to reduce intercycle treatment delay and to avoid dose reduction due to neutropaenia, prophylactic G-CSF should be considered to maintain the dose intensity in patients with intermediate and poor prognosis and in particular when using the VIP regimen.[33]

Prevention of thromboembolic events

Thromboembolic events (TEEs) occur more frequently in GCT patients receiving ChT than in young males under ChT for other cancers.[64] In Denmark, comparison of TEE incidence between 5185 GCT patients and 51 850 men without GCT revealed that GCT patients undergoing BEP ChT had significantly more TEEs within the first year with HRs of 6.3, 6.0 and 24.7 for myocardial infarction, cerebrovascular accident and venous thromboembolism, respectively.[65] Several retrospective studies identified increasing stage and size of retroperitoneal lymph nodes (different cut-offs reported, e.g. 3.5 cm and 5 cm), as well as Khorana score $\geq$3 and most importantly, indwelling vascular access device (VAD) as TEE risk factors [III, A].[66]

Data regarding the efficacy of thromboprophylaxis are conflicting[67]; however, the proportion of GCT patients developing a deep vein thrombosis was nearly halved by low molecular weight heparin (LMWH) prophylaxis to 9 out of 97 (9.2%) as compared with 9 out of 54 (16.6%) patients undergoing ChT without LMWH, although not statistically significant. With the exception from one patient with intratumour haemorrhage due to progressive brain metastases, no serious adverse events were observed in patients treated with preventive LMWH.

Despite lacking level I evidence, TEE prevention should be considered in GCT patients receiving cisplatin-based ChT for metastatic disease. The benefit of this preventive treatment is expected to be most pronounced in patients with retroperitoneal lymph nodes >3.5 cm and those with stage III or poor-risk features.[66,68] VADs should be avoided whenever possible.[69]

Non-seminoma post-ChT management

In case of complete response, no further treatment is necessary. Residual lymph nodes >1 cm in axial diameter should be removed preferentially by open nerve-sparing RPLND [II, A].[70] Laparoscopic or robotic post-ChT RPLND should preferably be carried out within clinical studies and otherwise only for select patients with low-volume disease at highly experienced centres.[71]

Patients with complete resection of differentiated teratoma or fibrotic tissue require no further treatment. Patients with completely resected viable malignant tumour, comprising <10% of the specimen, do not benefit from adjuvant ChT [IV, C].[72] In patients with IGCCCG intermediate or poor prognosis, >10% viable tumour in the specimen and/or incomplete resection, consolidation ChT, e.g. two cycles of VIP, may be considered, although surveillance appears justified as well.[72,73]

Patients with multiple visceral metastases should always be evaluated at expert centres for the possibility of radical resection, even in case of plateauing tumour markers [II, A]. Patients with rising tumour markers indicative of progressive disease usually require salvage ChT. The post-ChT management of multisite residual disease without elevated tumour markers should be carried out by highly specialised multidisciplinary teams.

Salvage treatment

Salvage can be achieved with HD-ChT or standard-dose cisplatin-based regimens such as cisplatin, ifosfamide and paclitaxel (TIP), VIP or cisplatin, ifosfamide and vinblastine (Figure 2).[74,75] Several major retrospective series with multicycle HD-ChT showed that this could be the preferred treatment option. The International Prognostic Factor Study Group (IPFSG) categorised GCT patients relapsing after first-line ChT into five prognostic groups, with 2-year survival rates ranging from 75% (very low risk) to 6% (very high risk)

[IV, C].[76] Superior survival rates after HD-ChT compared with standard-dose ChT demonstrated a 10% survival benefit in nearly all prognostic subgroups.[76] A randomised trial of intensification with a single course of HD-ChT after response to three versus four cycles of VIP, however, did not confer a survival advantage.[77] The ongoing TIGER study randomising first-line relapsing patients to either four cycles of TIP or one mobilising course of paclitaxel-ifosfamide followed by three HD-ChT cycles will yield level I evidence. Until this is achieved, the evidence from the admittedly large IPFSG meta-analyses supporting HD-ChT as potentially superior to conventional ChT is not sufficient for its recommendation as first-salvage regimen.

HD-ChT should be employed in third-line therapy, if not already used earlier, and might still cure selected patients in this setting [II, A].[74] Experience with HD-ChT and the accompanying side-effects require management by highly experienced GCT oncologists.

In patients with relapse after salvage HD-ChT or with cisplatin-refractory disease, cure is infrequently achieved. The combination of gemcitabine and oxaliplatin (plus paclitaxel if not used in earlier lines) achieved remission response rates of up to 40% and if responding patients become resectable, long-term survival is reached in about 10%-15% of these patients.[78]

Surgery should be part of the salvage strategy whenever possible, particularly in those patients with localised or late relapse, and with poor response to ChT. Multimodal approaches are especially important for management of rare localisations of metastases, e.g. the brain.[79] Principally, all ablative therapies, including stereotactic RT and radiofrequency ablation, should be considered within a multidisciplinary approach with an expert centre.

Late relapse

A late relapse is defined as re-occurrence of tumour >2 years after complete response to at least three cycles of ChT. Late relapses occur in 2%-3% of patients and often comprise yolk-sac tumour or slow-growing teratoma [IV, C].[49] Radical surgical resection of all lesions, if feasible, is the recommended approach in marker-negative patients. ChT must be individualised based on the histology of the late relapse and tumour marker development. If salvage ChT is the first late-relapse treatment, radical post-ChT surgery should be conducted whenever possible.

Recommendations

Seminoma stage II-III
- Cisplatin-based ChT according to the IGCCCG classification is standard for seminoma stage IIB-IIC and III [II, A].
- Patients with stage IIB seminoma unsuitable for ChT should receive para-aortic and ipsilateral iliac field RT up to 36 Gy in 2 Gy fractions [II, A].

Seminoma post-ChT management
- Patients with complete response after ChT do not require further treatment [II, A].
- FDG-PET scan at least 6 weeks after completion of ChT is recommended for residual tumours >3 cm [III, B].

Metastatic non-seminoma stage IIA marker-positive and stage IIB-III
- IGCCCG good-prognosis patients should receive three cycles of BEP or four cycles of EP, if contraindications against bleomycin exist four cycles of VIP with G-CSF support are used [II, A].
- AFP and β-hCG decline should be assessed after the first cycle of BEP in poor-risk non-seminoma patients for treatment intensification at high-volume expert centres [II, A].
- Non-seminoma patients with CNS metastases or primary mediastinal tumours should always be treated at high-volume expert centres [II, A].

Prevention of TEEs
- Prophylaxis of TEEs should be considered in MGCT patients for the ChT duration, especially when presenting with one or more of the established risk factors: retroperitoneal lymph nodes >3.5 cm, stage III disease, central venous access catheter, intermediate or poor-risk features or immobilisation [III, B].
- Peripheral venous access should be used instead of an indwelling VAD [III, A].

Non-seminoma post ChT management
- Residual lymph nodes >1 cm in axial diameter should be surgically removed preferentially by open nerve-sparing RPLND [II, A].
- Patients with multiple visceral metastases should always be evaluated at expert centres [II, A].

Salvage treatment
- Second-line conventional dose ChT (e.g. TIP) at a specialist centre is recommended [II, A].
- HD-ChT might cure selected patients in third or later line [II, A].
- Surgery is an important part of the salvage strategy [III, A].

Late relapse
- The 2%-3% of patients developing a late relapse should be managed in expert centres only [II, A].
- ChT should be based on the histology of the late relapse and tumour marker development [II, A].
- Surgery should be an integral part of curative treatment [II, A].

PERSONALISED MEDICINE

TGCTs are known for significant intra-tumoural and inter-tumoural heterogeneity which has made innovative research challenging. Moreover, as a result of the excellent prognosis in TGCTs, research in uro-oncology has drifted away from testis cancer and high-throughput research has not been tested or applied to GCTs.

Therefore, there are numerous challenges and pitfalls in testis cancer care for how a reliable set of biomarkers could be useful to help[80]:
- Diagnose TGCTs (either seminoma or non-seminoma);

- Identify clinical stage I patients benefitting from adjuvant treatment after orchiectomy, i.e. identification of micrometastases;
- Monitor ChT response and guide possible treatment (de) escalation;
- Predict histology of post-ChT residual lesions;
- Identify platinum-refractory disease and select better treatment options.

Serum miRNA showed promising clinical applicability: miR-371a-3p expression was associated with clinical stage, primary lesion size and burden and could differentiate seminoma from non-seminoma lesions.[81-86] Further, miR-371a-3p correlates with ChT response and the presence of active germ-cell malignancy in surgical specimens in post-ChT RPLND patients.[83,87-89] Nevertheless, miR-371a-3p is not expressed by mature teratoma lesions. Ongoing multi-institutional prospective studies aim to validate miRNA as a clinical biomarker.

Management of metastatic refractory and platinum-resistant germ-cell cancers is challenging. The extraordinary histological and biological heterogeneity of TGCTs poses an obstacle for uniform treatment recommendation as well as biomarker research required for more individually tailored treatment.[90] So far, gemcitabine, oxaliplatin and paclitaxel followed by surgical resection has been considered the standard treatment, however, with poor outcomes.[78,91]

Phase I-II trials with tyrosine kinase inhibitors, anti-angiogenic agents, cyclin-dependent kinase inhibitors, antibody-drug conjugates, immune checkpoint inhibitors and poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitors failed to achieve significant clinical responses—but were not based on molecular treatment selection.[90,92]

Palbociclib (or other cyclin-dependent kinase 4 and 6 inhibitors) postponed progression in patients with unresectable, growing teratoma, by median 23 weeks with acceptable toxicity in a small phase II trial.[93]

Treatment-resistant TGCTs are found to harbour genomic alterations of the Ras and PI3K/AKT/mTOR pathways and alterations in *p53-MDM2* axis.[94,95] Unveiling specific alterations might guide clinical research to identify therapeutic targets, select patients and provide tailored therapies aiming for clinically meaningful responses.

Poor-risk as well as relapsed TGCT patients should always be referred to high-volume centres with GCT experts.

Recommendation

- Serum miRNA shows promising clinical applicability but cannot be recommended yet in routine clinical care [III, D].

FOLLOW-UP, LONG-TERM IMPLICATIONS AND SURVIVORSHIP

The high cure rates of the usually young TGCT patients render late effects and long-term sequelae a particular concern. During follow-up of TGCT survivors, the gradual shift from relapse detection to identification of late effects and promotion of a healthy lifestyle is greatly supported by survivorship plans.

Follow-up

The main aim of the initial follow-up is the timely diagnosis of recurrent disease to ensure the possibility of curative treatment.[73] Many published follow-up recommendations might expose TGCT survivors to unnecessary radiation, which is of concern with its inherent risk of carcinogenesis. Most guidelines have subsequently reduced the number of CT scans. One recent randomised trial and one prospective trial of MRI in stage I seminoma have indicated that MRI is equivalent to CT in the detection of recurrent disease in the abdomen [I, A].[96,97]

Recommendations for the follow-up schedule need to be adapted according to national and institutional requirements which can be found in Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2022.01.002.

Long-term and late effects

The most serious late effects after treatment of GCT are cardiovascular disease and secondary cancers, which typically evolve many years after treatment. Cisplatin-based ChT is associated with increased risk for metabolic syndrome and cardiovascular disease, and might accelerate the cardiovascular ageing process. The risk of developing a secondary non-germ-cell cancer malignancy is increased after RT or ChT for GCT. Importantly, counselling with regard to maintaining a healthy lifestyle to reduce the risk of these serious late effects is important.[98]

All GCT survivors are at long-term risk of hypogonadism, in particular after treatment for metastatic disease. Testosterone replacement therapy should only be offered to testicular cancer survivors with testosterone levels below the normal range and clinical symptoms of hypogonadism [III, B].[13]

Fatigue is a distressing and common symptom among GCT survivors. For men who present with moderate or severe fatigue, an adequate assessment should be carried out.[99]

Survivorship care plan

During follow-up of TGCT patients, there is a gradual shift of focus from detection of tumour recurrence to identification of late effects of treatment and promotion of general health in TGCT survivors.[100] Patients are to be encouraged to maintain a healthy lifestyle to reduce the risk of serious late effects such as secondary cancers and cardiovascular disease. Every cancer patient should have an informative end-of-treatment summary at completion of the treatment, together with a survivorship care plan. A survivorship care plan can be implemented in addition to the routine oncological follow-up or when the routine follow-up with the oncologist is terminated and taken over by another healthcare giver including cardiovascular risk management.

Currently, the distribution of survivorship plans is recommended in a number of European countries.

Recommendations

- GCT survivors should be followed with regular hormonal assessments regarding their long-term risk of hypogonadism [II, A].
- Testosterone replacement therapy should only be offered to testicular cancer survivors with testosterone levels below the normal range and clinical symptoms of hypogonadism [III, B].
- A healthy lifestyle should be encouraged for better well-being and minimisation of cardiovascular disease and secondary cancers, which are the most serious long-term toxicities [II, A].

METHODOLOGY

This Clinical Practice Guideline has been developed by ESMO in partnership with EURACAN, the European Reference Network for rare adult solid cancers, in accordance with the ESMO standard operating procedures for Clinical Practice Guidelines development (http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology). The relevant literature has been selected by the expert authors.

The guideline is conceived to provide a standard approach to diagnosis, treatment and survivorship of testicular cancer. Recommended interventions are intended to correspond to the 'standard' approaches, according to current consensus among the European multidisciplinary testicular cancer community of experts. These are represented by the members of the ESMO Genitourinary Faculty and experts appointed by all institutions belonging to the genitourinary domain of EURACAN. Experimental interventions considered to be beneficial are labelled as 'investigational'. Other non-standard approaches may be proposed to the single patient as 'options' for a shared patient-physician decision in conditions of uncertainty, as long as some supporting evidence (though not conclusive) is available. Algorithms accompany the text, covering the main typical presentations of disease, and are meant to guide the user throughout the text. Levels of evidence and grades of recommendation have been applied using the system shown in Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2022.01.002.[101] Statements without grading were considered justified standard clinical practice by the authors.

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