clinical practice guidelines

Testicular seminoma and non-seminoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up[†]

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epidemiology

Germ cell tumours (GCT) represent a rare malignancy affecting mostly Caucasian males aged between 15 and 40 years. Among these young men, testicular GCT (TGCT) is the most common cancer with noted geographic differences [1]. Cure rates approximate 100% in stage I disease and exceed 80% in metastatic cases.

Approximately 50% of the TGCTs are pure seminomas and 50% are non-seminomas. The vast majority of GCT arise in the testicles with ∼5% occurring outside of the gonads, i.e. extragonadal germ cell tumour (EGGCT). EGGCTs are usually found in the body's mid-line, e.g. retroperitoneum, mediastinum or cerebrum, sometimes posing diagnostic difficulties.

diagnosis

In patients with a testicular mass, testicular sonography (7.5 MHz transducer) should be carried out, also noting the size and any structural alterations of the contralateral testis. Diagnosis of a testicular germ cell cancer (TGCC) is based on histology of the testicular mass. Elevation of 'tumour markers', i.e. serum levels of α-fetoprotein (AFP) and/or human chorionic gonadotropin (HCG) support the diagnosis. Biopsy of mid-line extragonadal tumours is mandatory, unless the patient is very sick and has high tumour markers. The biopsy should be preceded by testicular sonography to exclude a TGCT.

Histology of GCT should be reported according to the World Health Organisation (WHO) classification, specifying tumour size, multiplicity, extension of tumour (e.g. in rete testis or other tissue), pT category (according to the American Joint Committee on Cancer, AJCC, Union for International Cancer Control, UICC), all histological components with corresponding percentages, and presence or absence of vascular invasion and testicular intraepithelial neoplasia (TIN). In seminomas, the presence of syncytiotrophoblasts should be reported. Increased copy numbers of iso-chromosome 12p are found in both TGCT and EGGCT and provide a pathognomonic test, which might be useful in challenging histologic diagnoses, e.g. somatically transformed teratoma.

management of the primary tumour

'Radical orchiectomy' provides the histological diagnosis and should be carried out before any further treatment, unless the clinical situation requires immediate chemotherapy in patients with a clear germ cell malignancy based on elevated tumour markers. Any testicular mass of uncertain ranking must be explored by the inguinal approach to verify or exclude malignancy. As benign testicular lesions are recognised with increasing frequency, frozen section analysis should be considered intra-operatively, which differentiates malignant from benign testicular lesions [IV, B] [2]. Tumour marker analysis should be carried out 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, 'organ-preserving 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. However, mandatory postresection testicular radiotherapy renders the residual testicular tissue azoospermic but retains some testosterone production [IV, B] [3].

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biopsy for diagnosis of TIN in the contralateral testis and subsequent management

In 2%–5% of TGCT patients, a contralateral TGCT is diagnosed either metachronously or synchronously. Accordingly, between 3% and 5% of testicular cancer patients have TIN in the contralateral testis with the highest risk (∼30%) in men with testicular atrophy (volume <12 ml) and age <40 years, and in patients with EGGCT.

The majority of European Germ Cell Cancer Consensus group (EGCCCG) experts did not consider a routine biopsy of the contralateral testis as indicated [V, C] [4]. If a biopsy is carried out and TIN is diagnosed, however, the condition may be managed by surveillance, irradiation with 20 Gy in 2 Gy fractions (with potential damage to the contralateral, non-affected testis by scattered radiation) or orchiectomy, depending on fertility issues.

In patients with metastatic disease treated with three or more cycles of cisplatin-based chemotherapy, TIN in the contralateral non-resected testicle may be eradicated or progression may be slowed down, although the risk of developing an invasive tumour is still substantial.

post-orchiectomy staging and risk assessment

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

'Staging and risk group categorisation' are carried out according to the AJCC/UICC and the International Germ Cell Cancer Collaborative Group (IGCCCG), reflecting the extent of the disease based on clinical and radiological examinations and the results of serum tumour markers after orchiectomy, including serum lactate dehydrogenase (LDH) [5].

For stage I disease different risk factors have been identified for seminoma and non-seminoma based on histological features in the primary tumour. For metastatic cases the IGCCCG has identified three prognostic groups (see Table 1). If treatment is carried out correctly, the 5-year survival rate of patients with TGCT approximates 99% in stage I, and 91%, 79% and 48% in metastatic disease with good, intermediate and poor prognosis, respectively.

The IGCCCG provided prognostic information for chemotherapy-treated metastatic disease. For patients with non-seminoma, a good, intermediate or poor risk group is identified. Patients with seminoma are categorised as either good or intermediate risk (there is no poor-risk group). However, not all patients with metastases receive chemotherapy, e.g. radiotherapy for seminoma IIA or retroperitoneal lymph node dissection (RPLND) for non-seminoma IIA (Figures 1 and 2).

Imaging: computed tomography (CT) scan of the abdomen and pelvis [III, B] is mandatory. Thoracic CT should be carried out in case of non-seminoma, but can be omitted in seminoma patients without infradiaphragmatic metastases. Magnetic resonance imaging (MRI) of the central nervous system is indicated in advanced stages, particularly in case of choriocarcinoma/high HCG, or in those with cerebral symptoms. Positron emission tomography (PET) scanning does not contribute to initial staging [II, D].

Blood tests: tumour markers (AFP, HCG, LDH) should be determined before orchiectomy and followed until normalisation or lack of further decrease. The half-life for HCG is up to 3 days and 5–7 days for AFP. Serum levels of total testosterone, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) should be determined. Semen analysis and sperm banking should be discussed with all patients.

post-orchiectomy treatment

Before any treatment (Figures 1 and 2), the patient should be informed about the potential treatment modalities, their acute

Table 1. Post-orchiectomy staging of metastatic seminoma and non-seminoma according to AJCC/UICC and IGCCCG classification

Clinical stage	TNM (AJCC/UICC)			Serum tumour markers (S) to be determined after orchiectomy				IGCCCG prognostic group
	T^a	N	M	S	LDH	HCG	AFP (ng/ml)	
IS	T_{any}	N0	M0	S1	<1.5xN and	<5000 and	<1000	Good
				S2	1.5–10xN or	5000–50 000 or	1000–10 000	Intermediate
				S3	>10xN or	>50 000 or	>10 000	Poor
IIA	T_{any}	N1	M0	S0	Normal	Normal	Normal	Good
		(≤2 cm)		S1	<1.5xN and	<5000 and	<1000	
IIB	T_{any}	N2	M0	S0	Normal	Normal	Normal	Good
		(>2–5 cm)		S1	<1.5xN and	<5000 and	<1000	
IIC	T_{any}	N3	M0	S0	Normal	Normal	Normal	Good
		(>5 cm)		S1	<1.5xN and	<5000 and	<1000	
IIIA	T_{any}	N_{any}	M1a	S0	Normal	Normal	Normal	Good
				S1	<1.5xN and	<5000 and	<1000	
IIIB	T_{any}	N1-3	M0	S2	1.5–10xN or	5000–50 000 or	1000–10 000	Intermediate
		N_{any}	M1a					
IIIC	T_{any}	N1-3	M0	S3	>10xN or	>50 000 or	>10 000	Poor
		N_{any}	M1a	S3	>10xN or	>50 000 or	>10 000	Poor
			M1b	S_{any}	Any level	Any level	Any level	Poor
	Primary mediast EGGCT	N_{any}	M_{any}	S_{any}	Any level	Any level	Any level	Poor

^{a}Primary retroperitoneal EGGCT is staged like TGCT (T_{any}).

	Stage I	Stage IIA	Stage IIB/IIC/III

First line	Low risk*
	Preferred :
	  • Surveillance
	
	Alternatively :
	  ▪ Carboplatin x 1 (AUC 7)
	  ▪ Radiotherapy (20 Gy)
	
	High risk#
	Preferred:
	  • Surveillance
	  • Carboplatin x 1 (AUC 7)
	Alternatively:
	  • Radiotherapy (20 Gy)
		▪ BEPx3
		    (or EPx4)
		
		  ▪ Radiotherapy
			• BEPx3-4
			  (VIPx3-4)

Residual disease	n/a	Observation Consider biopsy or resection of lesion > 3 cm, particularly if PET positive	

Relapse	Post-surveillance/carboplatin
	  ▪ Localised: Radiotherapy
	  ▪ Otherwise: BEPx3-4
	
	Post-radiotherapy
	  ▪ BEPx3 (EPx4)
		Salvage chemotherapy
		
		In localised lesions: consider radiotherapy
		
		Surgery in case of a single resectable lesion	

*Low risk: absence of rete testis invasion and tumour <4 cm
#High risk: rete testis invasion or tumour ≥4 cm

Figure 1. Standard treatment strategies for seminoma.

and late toxicity, and the overall outcome. Based on multiple clinical studies, three or four cycles with bleomycin, etoposide, cisplatin (BEP) (Table 2) represent the standard treatment of metastatic patients.

In order to maintain treatment intensity, chemotherapy cycles should be repeated every 3 weeks, independent of leukocyte count. However, infection at day 22 warrants delay of chemotherapy until recovery.

Tumour markers are to be determined immediately before the start of each new chemotherapy cycle.

seminoma

stage I

Approximately 80% of the patients with seminoma present with stage I disease, with a survival of ~99%, independent of the chosen strategy, if accepted by the patient. In light of this very high cure rate, minimising toxicity is the priority. Surveillance is considered the preferred strategy. The predictive value of 'risk factors', such as rete testis infiltration and tumour size ≥4 cm, is controversial, but these factors are sometimes used to apply one course of carboplatin (AUC 7) or radiotherapy (20 Gy/10 fractions to para-aortic target volume) as adjuvant treatment. Compared with radiotherapy, one course of carboplatin results

in similar relapse rates, but less protracted treatment-related lethargy, sick leave and probably treatment-induced malignancies [I, A] [6, 7], although the true long-term adverse effects after >10 years are still unknown.

If a relapse occurs, it is usually located in the retroperitoneal or iliac lymph nodes. Rarely, late occurring relapses may contain non-seminoma components [IV, B] [8].

stage IIA (lymph nodes 1–2 cm)

The treatment options consist of either cisplatin-based chemotherapy or radiotherapy to para-aortic and ipsilateral iliac lymph nodes with 30 Gy in 2 Gy fractions (Figure 1). A recent study reported three relapses among 29 irradiated stage IIA patients (10.9%), compared with no relapses after cisplatin-based chemotherapy among six stage IIA and 79 stage IIB patients [II, B] [9]. Neoadjuvant carboplatin before radiotherapy may further reduce relapse rates, according to a recent single centre pilot study in 51 seminoma patients, but this strategy needs further validation [III, B] [10].

stage IIB/IIC

Three cycles of BEP represent the standard therapy. If there are arguments against bleomycin, e.g. reduction in lung capacity, emphysaema, heavy smoking (including former smokers) or

	Stage I	Stage II/III		
		Good	**Intermediate**	**Poor**
First line	Vascular invasion present Preferred: • Surveillance Alternatively: ▪ 1-2xBEP ▪ RPLND (rarely) Vascular invasion absent Preferred: ▪ 1-2xBEP ▪ Surveillance Alternatively: ▪ RPLND (rarely)	▪ BEPx3 (EPx4) ▪ RPLND (if marker negative stage IIA)	▪ BEPx4 ▪ VIPx4	▪ BEPx4 ▪ VIPx4
Residual disease	n/a	Resection in case of lesion > 1 cm Observation in case of lesion < 1 cm		
Relapse	Post-surveillance or post-RPLND: ▪ BEPx3-4 Surgery in case of a single resectable lesion Post-chemotherapy: ▪ Salvage chemotherapy Surgery in case of a single resectable lesion	Salvage chemotherapy Surgery in case of a single resectable lesion		

Figure 2. Standard treatment strategies for non-seminoma.

poor renal function, four cycles of etoposide, cisplatin (EP) are used (Table 2).

Patients unsuitable for chemotherapy should receive para-aortic and ipsilateral iliac field radiotherapy to 36 Gy in 2 Gy fractions.

stage III

Chemotherapy with BEP is standard treatment: three cycles for good prognosis patients according to IGCCCG (alternatively four cycles of EP) and four cycles for intermediate prognosis patients according to IGCCCG (alternatively four cycles of etoposide, ifosfamide and cisplatin (VIP), if there are arguments against bleomycin) [5, 11].

post-chemotherapy management

Patients with complete response do not require further treatment and are followed-up. In case of residual tumour, a 2-fluor-2-deoxy-D-glucose PET (FDG-PET) scan a minimum of 6 weeks after ending chemotherapy may be carried out:

- in lesions >3 cm, FDG-PET is the recommended approach
- in lesions <3 cm, FDG-PET may be considered, but its positive predictive value is lower and surveillance is preferred.

Based on the negative predictive value >90%, a negative PET scan of a non-growing or regressing lesion may substitute a

biopsy [IV, B] [12]. If PET is unavailable, lesions >3 cm can either be biopsied, resected or followed until resolution or progression.

A negative PET scan warrants follow-up only. In the case of a positive PET scan, the possibility of residual seminoma is high, though a false-positive result cannot be excluded [IV, B] [12]. A biopsy might be carried out before treatment by irradiation or resection. However, perioperative complications are more common than in non-seminoma due to desmoplastic reactions of the chemotherapy-exposed seminoma metastases.

non-seminoma

stage I

Stage I disease implies excellent survival rates of 98%–100% and is categorised by absence or presence of vascular invasion into 'low risk' (20% relapse rate) or 'high risk' (40%–50% relapse rate), respectively.

low-risk non-seminoma stage I

Surveillance is the standard for low-risk disease. If surveillance is not feasible, e.g. due to difficulties with repeated imaging, low compliance or patient's preference, adjuvant chemotherapy with one or two cycles of BEP is given. Efficacy appears to be similar between one and two cycles of BEP [III, C] [13]. In patients not

Table 2. Chemotherapy regimens in metastatic seminoma and non-seminoma

BEP[a]	(Repeat cycles every 3 weeks)	
Cisplatin	20 mg/m^2	Day 1–5
Etoposide	100 mg/m^2	Day 1–5
Bleomycin	30 mg	Day 1, 8, 15
EP[b]	(Repeat cycles every 3 weeks)	
Cisplatin	20 mg/m^2	Day 1–5
Etoposide	100 mg/m^2	Day 1–5
VIP/PEI[c]	(Repeat cycles every 3 weeks)	
Cisplatin	20 mg/m^2	Day 1–5
Etoposide	75 mg/m^2	Day 1–5
Ifosfamide	1.2 g	Day 1–5
TIP[d]	(Repeat cycles every 3 weeks)	
Paclitaxel	250 mg/m^2	Day 1
Cisplatin	25 mg/m^2	Day 2–5
Ifosfamide	1.5 g	Day 2–5
VeIP[e]	(Repeat cycles every 3 weeks)	
Vinblastine	0.11 mg/kg	Day 1 + 2
Ifosfamide	1.2 g/m^2	Day 1–5
Cisplatin	20 mg/m^2	Day 1–5
TI-CE[f]	(TI cycles 1–2 every 2 weeks)	
Paclitaxel	200 mg/m^2	Day 1
Ifosfamide	2.0 g	Day 2–4
	(CE cycles 3–5 every 3 weeks)	
Carboplatin	AUC = 7	Day 1–3
Etoposide	400 mg/m^2	Day 1–3
CE[g]	(Two cycles, may be preceded by VeIP)	
Carboplatin	700 mg/m^2	Day 1
Etoposide	750 mg/m^2	Day 1–3

[a]Three cycles BEP in IGCCCG good prognosis, four cycles BEP in IGCCCG intermediate or poor prognosis.

[b]Four cycles EP only in IGCCCG good prognosis in case of contra-indications to bleomycin.

[c]Four cycles VIP only in IGCCCG intermediate or poor prognosis in case of contra-indications to bleomycin as first-line chemotherapy; or as salvage chemotherapy. PEI is synonymous to VIP.

[d]Four cycles TIP, typically as conventional dose salvage chemotherapy.

[e]Four cycles VeIP, typically as conventional dose salvage chemotherapy.

[f]Two cycles TI before stem cell harvesting, thereafter three cycles CE as high-dose treatment.

[g]Two cycles CE as high-dose treatment, may be preceded by cyto-reductive VeIP.

suitable for surveillance or adjuvant chemotherapy, open nerve-sparing RPLND in highly experienced centres is an option. Some experts consider nerve-sparing RPLND the preferred treatment of patients with teratoma and somatic transformation in the primary tumour.

high-risk non-seminoma stage I

There are two standard treatment options: surveillance with 40%–50% relapse rate or adjuvant chemotherapy (one or two cycles of BEP, relapse rate of 3%–4%). Survival is the same whichever option is used. Nerve-sparing RPLND may be carried out in case of contra-indications against the strategies recommended above. Some experts consider nerve-sparing RPLND the preferred treatment of patients with teratoma and somatic transformation in the primary tumour.

stage IIA (IIB), marker-negative

Metastatic non-seminoma not purely consisting of teratoma should be treated according to the IGCCCG's recommendations (Figure 2).

Small lymph nodes might not represent metastases thus implying the risk of over-treatment, which may be avoided by the following two 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, and the presence of normal markers suggestive of teratoma or chemotherapy. In case of multiple progressive lymph nodes and/or rising tumour markers suggestive of non-teratomatous TGCT, chemotherapy (3 cycles of BEP) is indicated.
- Lymph node biopsy or primary nerve-sparing RPLND. The latter approach comprising both diagnostic and therapeutic potential. Adjuvant chemotherapy post-RPLND in form of two cycles BEP may be considered, in case of vital GCT in the specimen. Completely resected teratoma warrants follow-up only.

Stage IS/II/III

Patients with good prognosis should receive three cycles of BEP or four cycles of EP if contra-indications against bleomycin exist. BEP can be substituted by VIP (Table 2). Four cycles of BEP still represent standard treatment of patients with intermediate or poor prognosis [I, A] [5, 14]. In case of contra-indication against bleomycin, four cycles of VIP are used. First-line high-dose chemotherapy has not been proven superior to standard dose chemotherapy in three randomised trials.

A prospective randomised trial has indicated that poor prognosis patients with an insufficient tumour marker decline after the first cycle of BEP might benefit from dose intensification of first-line therapy, rather than continuation of standard BEP treatment [15], though the evidence of an optimal dose-dense regimen is still needed.

post-chemotherapy management

Four (to eight) weeks after the last cycle, determination of tumour markers as well as imaging (chest X-ray, CT scan or MRI of the initial sites) should be carried out.

In case of complete response (normal tumour markers, no residual tumour lesions, no retroperitoneal lymph nodes ≥10 mm), no further treatment is necessary. Residual lymph nodes, exceeding 10 mm in diameter, should be removed by open nerve-sparing RPLND [III] [16, 17].

Principally, any residual tumour with normal markers should be resected if technically feasible. This applies in particular to liver and lung metastases after chemotherapy. Patients with multiple visceral metastases should be discussed with experts

and treated at specialised centres. Patients in whom all residual lesions are deemed resectable should be operated by surgeons with appropriate experience and without delay, also in case of plateauing tumour markers.

Also, patients with elevated tumour markers should receive treatment based on individualised recommendations by experts. Elevated tumour markers should be assessed at least once weekly: rising tumour markers indicate progressive GCT, usually requiring highly specialised multi-disciplinary therapy (see salvage treatment). A laparoscopic RPLND should only be carried out within clinical studies since not all potentially affected lymph nodes can be assessed by this approach.

Patients with complete response or with complete resection of differentiated teratoma or fibrotic tissue only, require no further treatment. Good prognosis patients with completely resected viable malignant tumour, comprising <10% of the specimen, do not benefit from adjuvant chemotherapy [IV, C] [18].

However, in patients with IGCCCG intermediate or poor prognosis, >10% viable tumour in the specimen, and/or incomplete resection, consolidation chemotherapy, e.g. two cycles of VIP, may be considered, although a surveillance strategy is also justified according to ∼30% of EGCCCG experts [4].

salvage treatment of seminoma and non-seminoma

Conclusive recommendations as to an optimal salvage approach in patients relapsing after cisplatin-based first-line treatment cannot be made at present. The prognosis of relapsing GCC patients is variable as shown by the 'International Prognostic Factor Study Group' who categorised 1594 relapsing GCC patients into five prognostic groups, with 2-year survival rates ranging from 75% (very low risk) to 6% (very high risk), Table 3 [IV, C] [19]. The same group demonstrated superior survival rates for patients treated with high-dose chemotherapy [$n = 812$, 51.2% 5-year overall survival (OS)] compared with conventional dose chemotherapy ($n = 773$, 5-year OS 42.8) [IV, C] [20]. The retrospective nature of this study limits its conclusive power, such that an international prospective study randomising relapsing patients to either four cycles of paclitaxel, ifosfamide,

cisplatin (TIP) or high-dose chemotherapy with three cycles of paclitaxel, ifosfamide, carboplatin and etoposide (TI-CE) is under preparation.

In 2005, Pico et al. reported on 280 relapsing TC patients randomised to either four cycles of cisplatin, ifosfamide and etoposide/vinblastine or three such cycles followed by high-dose carboplatin, etoposide and cyclophosphamide (CarboPEC) with haematopoietic stem cell support without significant differences of OS or progression-free survival (PFS) [II, D] [21] Alternative conventional dose cisplatin-based regimens with similar efficacy comprise TIP, VeIP (vinblastine, ifosfamide, cisplatin) or VIP/PEI (etoposide, ifosfamide, cisplatin) [14]. Carboplatin-based high-dose chemotherapy has been reported to achieve complete remissions in relapsing patients as third line or later and is the preferred option of some authorities, despite absence of randomised trials in this area. [III, B] [22].

In refractory patients, i.e. those not reaching a marker-negative complete response after first-line treatment or those without favourable response to salvage treatment, further treatment must be individualised by GCT experts [V, B] [23]. These patients should be included in clinical trials, if available. Surgery should be part of the strategy whenever possible, particularly in those patients with localised or late relapse, and with poor response to chemotherapy.

late relapse

A late relapse occurs in 2%–3% of survivors and is defined as new tumour growth >2 years after at least three cycles of preceding chemotherapy. These relapses do not respond so well to new chemotherapy (often yolk sac tumour, usually AFP-positive, or slow-growing teratoma) [IV, C] [24].

In particular, in marker-negative relapses histological assessment of the relapsing lesions should be carried out by radical surgical resection of all lesions, if technically feasible. Further chemotherapy must be individualised based on the histology of the late relapse and tumour marker development. If salvage chemotherapy is the first treatment option of a late relapse, radical post-chemotherapy surgery should be conducted whenever possible.

Table 3. Prognostic score for patients with relapsing non-seminoma or seminoma. From Lorch et al. [19]. Reprinted with permission. @2010 American Society of Clinical Oncology. All rights reserved.

Parameter	Score points				
	0	1	2	3	Score
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 prognostic score (−1 = very low risk; 0 = low risk; 1 = intermediate risk; 2 = high risk; 3 = very high risk)					

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

Table 4. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System[a]

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

[a]Dykewicz CA. Summary of the guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. Clin Infect Dis 2001; 33: 139–144. By permission of the Infectious Diseases Society of America.

late toxicity

Besides early detection of relapse, follow-up should be directed towards prevention, detection and treatment of late toxicity for the increasing number of GCC survivors.

Semen cryopreservation should be considered in each patient. Compared with the general population the 10-year post-treatment paternity rate is significantly reduced, in part due to pre-existing fertility problems. Nevertheless, the 15-year fatherhood rate among testicular cancer survivors wishing to father a child is ~70%, with a strong association with treatment intensity [IV, B] [25]. Hypogonadism is present in 11%–35% of TGCT survivors, depending on cut-off levels of testosterone used, age, cumulative cisplatin dose and follow-up duration. Therefore, determination of testosterone levels is recommended during follow-up, although it is not always clear when and at what testosterone level replacement should be offered. Compared with the general population, there is about a twofold increased risk of late post-chemotherapy cardiovascular disease (coronary heart disease, myocardial infarction, congestive heart failure and stroke) among TGCT survivors. Early-onset (starting 3–5 years after treatment) metabolic syndrome occurs in about 20%–30% of long-term survivors [IV, C] [26]. Therefore, survivors need to be counselled on a healthy lifestyle (no smoking, regular physical exercise) and screened for other known risk factors such as hypertension, dyslipidaemia and excessive weight gain. Pulmonary and renal toxicity, oto- and neurotoxicity are further dose-related sequelae.

The relative risk (RR) of a second solid non-germ cell tumour, particularly in the gastro-intestinal and urinary tract, is approximately doubled after radiotherapy (latency ≥10 years) and is probably also increased after chemotherapy. The estimated cumulative risk of leukaemia depends on the cumulative etoposide dose and occurs earlier in the course of follow-up, i.e. usually <10 years.

Health-related quality of life in long-term TGCT survivors appears to be similar to the normal male population, but persisting long-term treatment-related side-effects show a strong association with both impaired physical and mental quality of life. Furthermore, anxiety levels are higher in GCC survivors than in the general male population.

Perhaps most importantly, TGCT survivors and their family doctors should be adequately informed (verbally and using written information) about potential late toxicity and their prevention, both during and at the end of treatment and in the course of specialised follow-up.

personalised medicine

In this disease setting, more research is needed to identify molecular markers which could lead to advances in personalised medicine.

follow-up

Early detection and treatment of relapse represents the primary objective of follow-up visits during the first 5–10 years. Recommendations for the follow-up schedule need to be adapted according to national and institutional requirements. Many follow-up recommendations that have been published most likely expose TGCT survivors to unnecessary radiation, increasing the risk of a radiation-induced second cancer. Replacing CT by MRI scan would reduce this risk, but is not considered feasible for the majority of European countries. However, effort should be made to reduce the frequency of CT scans and limit their overall number. PET-CT scanning has no role in the routine follow-up of TGCT patients.

note

Levels of evidence and grades of recommendation have been applied using the system shown in Table 4. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty.

conflict of interest

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