



Guidelines

EAU Guidelines on Testicular Cancer: 2011 Update

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Article info

Article history:

Accepted May 13, 2011

Published online ahead of
print on May 25, 2011

Keywords:

EAU Guidelines
Testicular cancer
Assessment
Diagnosis
Treatment
Follow-up

Abstract

Context: On behalf of the European Association of Urology (EAU), guidelines for the diagnosis, therapy, and follow-up of testicular cancer were established.

Objective: This article is a short version of the EAU testicular cancer guidelines and summarises the main conclusions from the guidelines on the management of testicular cancer.

Evidence acquisition: Guidelines were compiled by a multidisciplinary guidelines working group. A systematic review was carried out using Medline and Embase, also taking Cochrane evidence and data from the European Germ Cell Cancer Consensus Group into consideration. A panel of experts weighted the references, and a level of evidence and grade of recommendation were assigned.

Results: There is a paucity of literature especially regarding longer term follow-up, and results from a number of ongoing trials are awaited. The choice of treatment centre is of the utmost importance, and treatment in reference centres within clinical trials, especially for poor-prognosis nonseminomatous germ cell tumours, provides better outcomes. For patients with clinical stage I seminoma, based on recently published data on long-term toxicity, adjuvant radiotherapy is no longer recommended as first-line adjuvant treatment. The TNM classification 2009 is recommended.

Conclusions: These guidelines contain information for the standardised management of patients with testicular cancer based on the latest scientific insights. Cure rates are generally excellent, but because testicular cancer mainly affects men in their third or fourth decade of life, treatment effects on fertility require careful counselling of patients, and treatment must be tailored taking individual circumstances and patient preferences into account.

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1. Introduction

Testicular cancer is a relatively rare cancer that accounts for about 1–1.5% of male cancers and mainly affects younger men in the third or fourth decade of life [1–3]. It can be classified into three categories: germ cell tumours (90–95%), cord stromal tumours, and miscellaneous germ cell/sex cord stromal tumours (Table 1) [4].

The cure rates for low and intermediate risk testicular tumours are excellent, which is mainly due to careful staging at the time of diagnosis; adequate early treatment based on chemotherapeutic combinations, with or without radiotherapy and surgery, and very strict follow-up and salvage therapies.

In testicular cancer, the choice of treatment centre is of utmost importance. Although early stages can be successfully treated in a nonreference centre, the relapse rate is higher [5]. In poor-prognosis nonseminomatous germ cell tumours (NSGCTs), overall survival within a clinical trial depended on the number of patients treated at the participating centre (worse survival with fewer than five patients enrolled) [6]. Similarly, the likelihood of residual tumour resection following chemotherapy has been associated with perioperative mortality and overall survival [7,8].

2. Evidence acquisition

A multidisciplinary team of urologists, medical oncologists, radiotherapists, and a pathologist were involved in producing this document, which is based on a structured review of the literature from January 2008 until December 2010 for both the germ cell tumour and non-germ cell sections. Also, data from meta-analysis studies, Cochrane evidence, and the

recommendations of the European Germ Cell Cancer Consensus Group Meeting in Amsterdam in November 2006 have been included [9–11]. Medline and Embase on the Dialog-DataStar platform were searched for original and review articles. The non-germ cell section of the testicular cancer guidelines is not included in this overview. The full version of the 2011 guidelines is available through the European Association of Urology (EAU) Central Office and the EAU Web site (www.uroweb.org).

References have been assessed according to their level of scientific evidence, and guideline recommendations have been graded according to a system modified from the Oxford Centre for Evidence-Based Medicine levels of evidence [12]. The aim of grading recommendations is to provide transparency between the underlying evidence and the recommendation given.

3. Diagnosis of testicular cancer

The epidemiologic, pathologic, and clinical risk factors for testicular cancer are well known [13,14] (Table 2). Diagnosis of testicular cancer is based on (1) clinical examination of the testis, (2) general examination to exclude enlarged nodes or abdominal masses, and (3) ultrasound to confirm a testicular mass.

3.1. Clinical and general examination

Testicular cancer usually appears as a painless unilateral mass in the scrotum or the casual finding of an intrascrotal mass. Gynaecomastia is present in 7% of men, more commonly in nonseminomatous tumours. Back and flank pain are present in about 11% of cases [1].

3.2. Imaging of the testis

Diagnostic ultrasound confirms the presence of a testicular mass and is used to explore the contralateral testis.

Table 1 – Recommended pathologic classification*

<p>Germ cell tumours</p> <ul style="list-style-type: none"> • Intratubular germ cell neoplasia, unclassified type • Seminoma (including cases with syncytiotrophoblastic cells) • Spermatocytic seminoma (mention if there is a sarcomatous component) • Embryonal carcinoma • Yolk sac tumour • Choriocarcinoma • Teratoma (mature, immature, with malignant component) • Tumours with more than one histologic type (specify percentage of individual components) <p>Sex cord/gonadal stromal tumours</p> <ul style="list-style-type: none"> • Leydig cell tumour • Malignant Leydig cell tumour • Sertoli cell tumour (lipid-rich variant, sclerosing, large cell calcifying) • Malignant Sertoli cell tumour • Granulosa (adult and juvenile) • Thecoma/fibroma group of tumours • Other sex cord/gonadal stromal tumours (incompletely differentiated, mixed) • Tumours containing germ cell and sex cord/gonadal stromal (gonadoblastoma) <p>Miscellaneous nonspecific stromal tumours</p> <ul style="list-style-type: none"> • Ovarian epithelial tumours • Tumours of the collecting ducts and rete testis • Tumours (benign and malignant) of nonspecific stroma

* Modified from the World Health Organisation (2004).

Table 2 – Risk factors for testicular cancer

<p>Epidemiologic risk factors</p> <ul style="list-style-type: none"> • History of cryptorchidism • Klinefelter syndrome • Testicular cancer in first-grade relatives • Contralateral tumour • TIN or infertility <p>Pathologic prognostic risk factors for occult metastatic disease (stage I)</p> <p>Seminoma</p> <ul style="list-style-type: none"> • Tumour size (≥ 4 cm) • Invasion of the rete testis <p>Nonseminoma</p> <ul style="list-style-type: none"> • Vascular/lymphatic invasion or peritumoural invasion • Proliferation rate (MIB-1) $>70\%$ • Percentage embryonal carcinoma $>50\%$ <p>Clinical risk factors (metastatic disease)</p> <ul style="list-style-type: none"> • Primary location • Elevation of tumour marker levels • Nonpulmonary visceral metastasis*

TIN = testicular intraepithelial neoplasia.

* Only clinical predictive factor for metastatic disease in seminoma.

Testicular ultrasound is inexpensive and should be performed even if there is clinically evident tumour [15]. It should always be performed in a young man without a palpable scrotal mass who has retroperitoneal or visceral masses or elevated tumour serum markers, or in men presenting with fertility problems [16,17].

3.3. Serum tumour markers

Serum tumour markers are prognostic factors used in diagnosis and staging, which include α -fetoprotein (AFP), human chorionic gonadotrophin (hCG), and lactate dehydrogenase (LDH). Marker levels are increased in testicular cancer; however, the lack of an increase does not exclude testicular cancer [18]. LDH levels are elevated in 80% of patients with advanced testicular cancer and should therefore always be measured in advanced cancer [19].

3.4. Inguinal exploration and orchidectomy

Every patient with a suspected testicular mass must undergo inguinal exploration with exteriorisation of the testis within its tunics. Orchidectomy with division of the spermatic cord at the internal inguinal ring must be performed if a malignant tumour is found. If the diagnosis is unclear, a testicular biopsy (enucleation of the intraparenchymal tumour) should be taken for frozen-section histopathology.

In disseminated disease and life-threatening pulmonary metastases, chemotherapy should be started immediately and orchidectomy delayed until there is clinical stabilisation.

3.5. Organ-sparing surgery

Organ-preserving surgery can be performed in synchronous bilateral testicular tumours, metachronous contralateral tumours, or in a tumour in a solitary testis with normal preoperative testosterone levels, provided tumour volume is <30% of testicular volume and surgical rules are respected. However, there is a high rate (up to 82%) of associated testicular intraepithelial neoplasia (TIN), and eventually all patients receive adjuvant radiotherapy (16–20 Gy). Radiotherapy may be delayed in fertile patients who wish to father children. This option must be carefully discussed with the patient and surgery should be performed in an experienced centre.

3.6. Pathologic examination of the testis

Following orchidectomy, pathologic examination of the testis includes the investigations listed in Table 3 [4,20].

3.7. Testicular intraepithelial neoplasia

Contralateral biopsy has been advocated to exclude TIN and is routine policy in some countries. However, a systematic contralateral biopsy cannot be recommended in all patients due to the low incidence of TIN (up to 9%) and the morbidity of TIN treatment, as well as the low incidence of contralateral metachronous testicular tumours (about 2.5%), most of which present at a low stage [21,22]. However, biopsy of the

Table 3 – Pathologic examination of the testis

<p>Macroscopic features</p> <ul style="list-style-type: none"> • Testis side • Testis size • Maximum tumour size • Epididymis • Spermatic cord • Tunica vaginalis <p>Sampling</p> <ul style="list-style-type: none"> • 1-cm² section for every centimetre of maximum tumour diameter, including normal macroscopic parenchyma (if present), albuginea, and epididymis, with selection of suspected areas • At least one proximal and one distal section of the spermatic cord, plus any suspected area <p>Microscopic features and diagnosis</p> <p>Histologic type</p> <ul style="list-style-type: none"> • Specify individual components and estimate amount as a percentage • Presence or absence of peritumoural venous and/or lymphatic invasion • Presence or absence of albuginea, tunica vaginalis, rete testis, epididymis, or spermatic cord invasion • Presence or absence of intratubular germinal neoplasia (TIN) in nontumoural parenchyma • Intratubular germ cell neoplasia <p>pT category</p> <ul style="list-style-type: none"> • According to TNM 2009 <p>Immunohistochemical studies</p> <ul style="list-style-type: none"> • In seminoma and mixed germ cell tumour, AFP and hCG
<p>TIN = testicular intraepithelial neoplasia; AFP = α-fetoprotein; hCG, human chorionic gonadotropin.</p>

contralateral testis should be offered to patients with a high risk of contralateral TIN, testicular volume <12 ml, history of cryptorchidism, or poor spermatogenesis. A contralateral biopsy is not necessary for patients >40 yr of age. Double biopsy increases sensitivity [23].

Once TIN is diagnosed, local radiotherapy (16–20 Gy, in fractions of 2 Gy) is the treatment of choice in solitary testis [24]. Because this may produce infertility, impaired Leydig cell function, and reduced testosterone production, the patient must be carefully counselled. Radiation treatment may be delayed in fertile patients who wish to father children. Patients must be informed that a testicular tumour may exist despite a negative biopsy [25].

If TIN is diagnosed and the contralateral testis is healthy, the options are orchidectomy or close observation (50% risk of testicular cancer at 5 yr).

4. Staging of testicular tumours

To determine the presence of metastatic or occult disease, the half-life kinetics of serum tumour markers must be assessed, the nodal pathway screened, and the presence of visceral metastases ruled out [10,11].

4.1. Postorchidectomy half-life kinetics of serum tumour markers

The mean serum half-life of AFP and hCG is 5–7 d and 2–3 d, respectively. Tumour markers must be reevaluated after orchidectomy to determine half-life kinetics. The persistence of elevated serum tumour markers 3 wk after orchidectomy may indicate the presence of disease, whereas its normalisation does not necessarily indicate an absence of tumour.

Tumour markers should be assessed until they are normal, as long as they follow their half-life kinetics and no metastases are revealed.

Tumour markers should be measured before chemotherapy to classify the patient according to the International Germ Cell Cancer Collaborative Group (IGCCCG) risk classification [26]. During chemotherapy, the markers should decline; persistence has an adverse prognostic value.

4.2. Assessment of retroperitoneal and mediastinal nodes and viscera

Retroperitoneal and mediastinal lymph nodes are best assessed by means of a computed tomography (CT) scan and the supraclavicular nodes by physical examination.

A chest CT scan is the most sensitive way to evaluate the thorax and mediastinal nodes, and it is recommended in all patients with testicular cancer because small subpleural nodes may be present that are not visible radiologically in up to 10% of cases [27].

There is no evidence for using a fluorodeoxyglucose-positron emission tomography (FDG-PET) scan in staging [28]. However, FDG-PET is recommended in patients with seminoma who have any residual mass at least 6 wk after chemotherapy, to help decide between watchful waiting and active treatment [29]. FDG-PET is not recommended in the restaging of patients with NSGCTs after chemotherapy [30].

Brain or spinal CT, bone scan, or liver ultrasound should be performed if metastases are suspected in these organs. A

Table 4 – TNM classification for testicular cancer

	pT	Primary tumour*	
	pTX	Primary tumour cannot be assessed	
	pT0	No evidence of primary tumour (eg, histologic scar in testis)	
	pTis	Intratubular germ cell neoplasia (testicular intraepithelial neoplasia)	
	pT1	Tumour limited to testis and epididymis without vascular/lymphatic invasion: Tumour may invade tunica albuginea but not tunica vaginalis	
	pT2	Tumour limited to testis and epididymis with vascular/lymphatic invasion or tumour extending through tunica albuginea with involvement of tunica vaginalis	
	pT3	Tumour invades spermatic cord with or without vascular/lymphatic invasion	
	pT4	Tumour invades scrotum with or without vascular/lymphatic invasion	
N – Regional lymph nodes clinical			
	NX	Regional lymph nodes cannot be assessed	
	N0	No regional lymph node metastasis	
	N1	Metastasis with a lymph node mass ≤2 cm in greatest dimension or multiple lymph nodes; none >2 cm in greatest dimension	
	N2	Metastasis with a lymph node mass >2 cm but ≤5 cm in greatest dimension or multiple lymph nodes; any one mass >2 cm but ≤5 cm in greatest dimension	
	N3	Metastasis with a lymph node mass >5 cm in greatest dimension	
pN – Pathologic regional lymph nodes			
	pNX	Regional lymph nodes cannot be assessed	
	pN0	No regional lymph node metastasis	
	pN1	Metastasis with a lymph node mass ≤2 cm in greatest dimension and ≤5 positive nodes; none >2 cm in greatest dimension	
	pN2	Metastasis with a lymph node mass >2 cm but <5 cm in greatest dimension; or >5 nodes positive, none >5 cm; or evidence of extranodal extension of tumour	
	pN3	Metastasis with a lymph node mass >5 cm in greatest dimension	
M – Distant metastasis			
	MX	Distant metastasis cannot be assessed	
	M0	No distant metastasis	
	M1	Distant metastasis M1a Nonregional lymph node(s) or lung M1b Other sites	
pM – Pathologic distant metastasis			
	MX	Distant metastasis cannot be assessed	
	M0	No distant metastasis	
	M1	Distant metastasis M1a Nonregional lymph node(s) or lung M1b Other sites	
S – Serum tumour markers			
	Sx	Serum markers studies not available or not performed	
	S0	Serum marker study levels within normal limits	
	LDH, U/l	hCG, mIU/ml	AFP, ng/ml
S1	<1.5 × N and	<5000 and	<1000
S2	1.5–10 × N or	5000–50,000 or	1000–10,000
S3	>10 × N or	>50,000 or	>10,000

LDH = lactate dehydrogenase; N = upper limit of normal for the LDH assay; hCG = human gonadotrophin; AFP = α-fetoprotein.

* Except for pTis and pT4, where radical orchidectomy is not always necessary for classification purposes, the extent of the primary tumour is classified after radical orchidectomy; see pT. In other circumstances, TX is used if no radical orchidectomy has been performed.

Table 5 – Prognostic-based staging system for metastatic germ cell cancer

Good-prognosis group	
Nonseminoma (56% of cases)	All of the following criteria:
5-yr PFS 92%	Testis/retroperitoneal primary
5-yr survival 92%	No nonpulmonary visceral metastases
	AFP <1000 ng/ml
	hCG <5000 IU/l (1000 ng/ml)
	LDH <1.5 × ULN
Seminoma (90% of cases)	All of the following criteria:
5-yr PFS 82%	Any primary site
5-yr survival 86%	No nonpulmonary visceral metastases
	Normal AFP
	Any hCG
	Any LDH
Intermediate-prognosis group	
Nonseminoma (28% of cases)	All of the following criteria:
5-yr PFS 75%	Testis/retroperitoneal primary
5-yr survival 80%	No nonpulmonary visceral metastases
	AFP 1000–10,000 ng/ml, or
	hCG 5000–50,000 IU/l, or
	LDH 1.5–10 × ULN
Seminoma (10% of cases)	Any of the following criteria:
5-yr PFS 67%	Any primary site
5-yr survival 72%	Nonpulmonary visceral metastases
	Normal AFP
	Any hCG
	Any LDH
Poor-prognosis group	
Nonseminoma (16% of cases)	Any of the following criteria:
5-yr PFS 41%	Mediastinal primary
5-yr survival 48%	Nonpulmonary 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	
PFS = progression-free survival; AFP = α -fetoprotein; hCG = human chorionic gonadotrophin; LDH = lactate dehydrogenase; ULN = upper limit of normal range.	

CT or magnetic resonance imaging scan of the skull is advisable in patients with NSGCTs, multiple lung metastases, and poor-prognosis IGCCCG risk factors.

4.3. Staging system

The TNM 2009 staging system is recommended (Table 4) [20]. In large population-based patient series, 75–80% of seminoma patients and about 55% of patients with NSGCT cancer have stage I disease at diagnosis [31]. True stage IS

(persistently elevated or increasing serum marker levels after orchidectomy) occurs in about 5% of NSGCT patients [32].

In 1997, the IGCCCG defined a prognostic factor–based staging system for metastatic germ cell cancer based on the identification of clinically independent adverse factors. The system has been incorporated into the TNM classification and uses histology, location of the primary tumour, location of metastases, and prechemotherapy serum tumour marker levels as prognostic factors to categorise patients into good, intermediate, or poor prognosis [20] (Table 5).

5. Guideline recommendations for diagnosis and staging

Table 6 lists the guidelines for the diagnosis and staging of testicular cancer.

6. Management of stage I germ cell testicular cancer

6.1. Stage I testicular cancer seminoma

According to modern staging methods, about 15–20% of patients with stage I seminoma have subclinical metastatic disease, usually in the retroperitoneum, and relapse after orchidectomy alone [33].

6.1.1. Surveillance

In low-risk patients (tumour size <4 cm, no rete testis invasion), the recurrence rate under surveillance is as low as 6%.

According to the IGCCCG classification, chemotherapy is an option for seminoma relapse under surveillance. However, 70% of relapsed patients are suitable for radiotherapy alone because of small-volume disease at the time of recurrence. Patients who relapse again can be effectively treated with chemotherapy [34]. The overall cancer-specific survival rate for surveillance performed by experienced centres is 97–100% for seminoma stage I [34,35]. The main disadvantage is the need for more intensive follow-up, especially of the retroperitoneal lymph nodes, for at least 5 yr after orchidectomy. This compares with the very low risk of subdiaphragmatic relapse after adjuvant radiotherapy.

Table 6 – Guidelines for the diagnosis and staging of testicular cancer

	GR
Testicular ultrasound is mandatory	B
Orchidectomy and pathologic examination of the testis must be performed to confirm the diagnosis and to define the local extension (pT category); in a life-threatening situation due to extensive pulmonary metastasis, chemotherapy must be started before orchidectomy	B
Serum determination of tumour markers (AFP, hCG, and LDH in metastatic disease) must be performed before and after orchidectomy for staging and prognostic reasons	A
The state of the retroperitoneal, mediastinal, and supraclavicular nodes and visceral state must be assessed in testicular cancer	A
GR = grade of recommendation; AFP = α -fetoprotein; hCG = human gonadotrophin; LDH = lactate dehydrogenase.	

A small but clinically significant risk of relapse >5 yr after orchidectomy for stage I seminoma supports the need for long-term surveillance [36].

6.1.2. Adjuvant chemotherapy

A joint trial by the Medical Research Council (MRC) and the European Organisation for Research and Treatment of Cancer (MRC TE 19 trial), which compared one cycle of carboplatin (area under the curve [AUC] 7) with adjuvant radiotherapy, found no significant difference in recurrence rate, time to recurrence, and survival after a median follow-up of 6.5 yr [37–39]. Adjuvant carboplatin therapy using a dosage of one course AUC 7 is an alternative to radiotherapy or surveillance in stage I seminoma [35,40]. Two courses of adjuvant carboplatin reduced the relapse rate to 1–3%, but further experience and long-term observations are needed [40,41].

6.1.3. Adjuvant radiotherapy

Seminoma cells are extremely radiosensitive. Adjuvant radiotherapy to a para-aortic (PA) field or to a “hockey-stick” field (PA and ipsilateral iliac nodes) with moderate doses (total 20–24 Gy) reduces the relapse rate to 1–3% [37,38]. After modern radiotherapy, nearly all relapses first occur outside the irradiated field (supradiaphragmatic lymph nodes, lungs). Based on the results of a large randomised MRC trial, Fossa et al. recommended radiotherapy to a PA field as standard treatment for patients with testicular seminoma stage I, T1–T3, and with undisturbed lymphatic drainage [37,38]. Acute toxicity was reduced and the sperm count within the first 18 mo was significantly higher after PA irradiation than after irradiation of the traditional “dog-leg” field. However, the relapse rate in the iliac lymph nodes was about 2% (all on the right side) after PA and 0% after dog-leg irradiation. Another possible site of failure is in the left renal hilum. PA irradiation should be tailored according to the site of the primary tumour. Adjuvant irradiation of supradiaphragmatic lymph nodes is not indicated in seminoma stage I.

With regard to the irradiation dose, the MRC finished a large randomised trial of 20 Gy versus 30 Gy PA radiation in stage I seminoma that showed equivalence for both doses in terms of recurrence rates [38]. The rate of severe radiation-induced long-term toxicity was <2%. The main concern surrounding adjuvant radiotherapy has been the increased risk of radiation-induced second non-germ cell malignancies [42–44]. A scrotal shield may be beneficial during adjuvant radiotherapy to prevent scattered radiation toxicity [43]. In view of the published data on long-term toxicity, adjuvant radiotherapy is no longer recommended as first-line adjuvant treatment for patients with CS I seminoma.

6.1.4. Retroperitoneal lymph node dissection

A prospective nonrandomised study of radiotherapy versus retroperitoneal lymph node dissection (RPLND) in stage I seminoma suggested a higher incidence of retroperitoneal relapse (9.5%) after RPLND [45]. RPLND is not recommended as primary treatment in stage I seminoma.

6.1.5. Risk-adapted treatment

Patients with seminoma stage I may be subdivided using tumour size >4 cm and rete testis invasion into low- and high-risk groups of occult metastatic disease. The risk of occult disease is 32% in patients with both risk factors versus 12% in those without these risk factors [9]. A prospective trial based on these risk factors (surveillance for no risk factors versus two courses of carboplatin AUC 7 for both risk factors) showed the feasibility of a risk-adapted approach. Early data with limited follow-up indicate that patients without either risk factor have a 6.0% risk of relapse at 5 yr. Patients at high risk treated with carboplatin experienced a 3.3% relapse rate [41].

However, it is likely that patients are being overtreated, as suggested by the achievement of cure in almost 100% of patients with stage I seminoma, whichever therapy is used (adjuvant radiotherapy, adjuvant chemotherapy, or surveillance), and a relapse rate of 15–20% in large surveillance series not using risk factors. The therapeutic decision should therefore be shared with an informed patient.

Table 7 lists guideline recommendations for treatment of stage I seminoma.

6.2. Nonseminoma germ cell tumour stage I

Up to 30% of NSGCT patients with CS I disease have subclinical metastases and will relapse if surveillance alone is used after orchidectomy.

6.2.1. Surveillance

Improvements in clinical staging and follow-up methods, and the availability of effective salvage treatment with cisplatin-based chemotherapy and postchemotherapy surgery, have led to studies of only close surveillance following orchidectomy in CS I NSGCT patients. The largest reports indicate a cumulative relapse rate of about 30%, with 80% of relapses occurring during the first 12 mo of follow-up, 12% during the second year, and 6% during the third year, decreasing to 1% during the fourth and fifth years, and occasionally even later [46,47]. Despite very close follow-up, 11% of relapsing patients presented with large-volume recurrent disease.

Based on the overall cancer-specific survival data, surveillance within an experienced surveillance programme may be offered to patients with non-risk-stratified

Table 7 – Guidelines for the treatment of testicular cancer seminoma stage I

	GR
Surveillance is the recommended management option (if facilities available and patient compliant)	A*
Carboplatin-based chemotherapy (one course at AUC 7) can be recommended	B
Adjuvant treatment is not recommended for patients at low risk	A
Radiotherapy is not recommended as adjuvant treatment	A
GR = grade of recommendation; AUC = area under the curve. * Upgraded following panel consensus.	

CS1 NSGCT as long as they are compliant and informed about the expected recurrence rate as well as the salvage treatment [48].

6.2.2. Primary chemotherapy

Several studies have involved two cycles of chemotherapy with cisplatin, etoposide, and bleomycin (PEB) as primary treatment for high-risk patients (50% risk of relapse) [49]. A relapse rate of 2.7% has been reported in >200 patients, some with a median follow-up of nearly 8 yr; fertility or sexual activity was unaffected [49–51]. However, the very long-term (>20 yr) side effects of adjuvant chemotherapy in this setting are unknown, which should be considered during decision making, following concern about the long-term cardiovascular effects of chemotherapy in testicular cancer survivors [52]. It remains important to be aware of slow-growing retroperitoneal teratomas after primary chemotherapy [53].

The results of cost analyses comparing surveillance, RPLND, and primary chemotherapy show different results among the reported studies, possibly because of differences in intensity. A low frequency of follow-up CTs (proven effective in surveillance of CS1 NSGCT) considerably reduces follow-up costs [54].

6.2.3. Risk-adapted treatment

Risk-adapted treatment is based on the risk factor of vascular invasion. Stratifying patients with CS1 NSGCT according to their presumed risk of relapse is supported by several studies, with similar survival rates and a final cure rate of almost 100% for all available treatment options using a risk-stratifying approach [49,50,55,56].

Using this approach, patients with vascular invasion undergo adjuvant chemotherapy with two cycles of PEB, whereas patients without vascular invasion undergo surveillance. Only if patients or doctors are not willing to accept the consequent risk-adapted treatment or if there are circumstances that mitigate against the risk-adapted treatment option should other treatments be considered. The patient must be fully informed.

6.2.4. Retroperitoneal lymph node dissection

If RPLND is performed, about 30% of patients are found to have retroperitoneal lymph node metastases that correspond to pathologic stage II (PS2) disease [57]. If no retroperitoneal metastases are found at RPLND (PS1), about 10% of PS1 patients relapse at distant sites [58].

The main predictor of relapse in CS1 NSGCT managed by surveillance, for having PS2 disease and for relapse in PS1 after RPLND, is histopathologic evidence of vascular invasion by tumour cells in, or near, the primary tumour [59–61]. Vascular invasion was the most predictive of stage in a multifactorial analysis; the absence of vascular invasion has a negative predictive value of 77%, permitting surveillance in low-risk compliant patients [59,60].

Patients without vascular invasion constitute about 50–70% of the CS1 population and have only a 15–20% risk of relapse on surveillance, compared with 50% in patients with vascular invasion. The risk of relapse for PS1 patients is

<10% for those without vascular invasion and about 30% for those with vascular invasion [59,62].

A total of 30% of CS1 patients with PS2 followed up without additional treatment after primary RPLND will relapse, mainly at sites outside the abdomen and pelvis. The risk of relapse depends on the volume of retroperitoneal disease resected [63]. If two (or more) courses of cisplatin-based chemotherapy are given adjuvant to RPLND in PS2 cases, the relapse rate is reduced to <2%, including teratoma relapse [64]. There is a very low risk of retroperitoneal relapse (<2%) after a properly performed nerve-sparing RPLND [63].

The follow-up after RPLND is much simpler and less costly than postorchidectomy because of the reduced need for abdominal CT scans [61]. If there is a rare indication to perform a staging RPLND, it can be performed using laparoscopic or robot-assisted RPLND but only at a specialised laparoscopic centre [65].

Research has shown that one course of adjuvant PEB is superior to RPLND with regard to recurrence rates in patients unstratified for risk factors. Research has also shown that one adjuvant cycle of PEB reduced the number of recurrences to 3.2% in high-risk patients and to 1.4% in low-risk patients [66].

6.3. Clinical stage I seminoma with (persistently) elevated serum tumour markers

Serum tumour markers should be followed closely until levels fall to the expected half-life values for AFP and hCG. If the marker level increases after orchidectomy, the patient has residual disease. If RPLND is performed, up to 87% of these patients are found to have pathologically documented nodes in the retroperitoneum [67]. An ultrasound examination of the contralateral testicle must be performed if not done initially.

The treatment of true CS1S patients is still controversial. They may be treated with three courses of primary PEB chemotherapy and with follow-up as for CS1B patients (high risk, Table 8) after primary chemotherapy [68] or by RPLND [54]. The presence of vascular invasion may strengthen the indication for primary chemotherapy because most patients with CS1S with vascular invasion eventually require chemotherapy.

In conclusion, the recommended treatment options for stage I NSGCT are CS1 risk-adapted treatments based on vascular invasion or surveillance without using risk factors (Table 8). Figure 1 provides a treatment algorithm for patients with CS1 NSGCT [11].

7. Metastatic germ cell testicular carcinoma

The treatment of metastatic germ cell tumours depends on the histology of the primary tumour and prognostic groups as defined by the IGCCCG (Table 5).

7.1. Low-volume metastatic disease (stage IIA/B)

7.1.1. Stage IIA/B seminoma

Radiotherapy has been the traditional standard treatment for both stages IIA and IIB seminoma, with a radiation dose

Table 8 – Risk-adapted treatments for clinical stage I based on vascular invasion

Risk-adapted treatments for CS1 based on vascular invasion	GR
CS1A (pT1, no vascular invasion): low risk	
If the patient is willing and able to comply with a surveillance policy, long-term (at least 5 yr) close follow-up should be recommended	A*
In low-risk patients not willing (or suitable) to undergo surveillance, adjuvant chemotherapy or nerve-sparing RPLND are treatment options	
If RPLND reveals PN+ (nodal involvement) disease, chemotherapy with two courses of PEB should be considered	A
CS1B (pT2–pT4): high risk	
Primary chemotherapy with two courses of PEB should be recommended (one course of PEB within a clinical trial or registry)	A
Surveillance or nerve-sparing RPLND in high-risk patients remain options for those not willing to undergo adjuvant chemotherapy	
If pathologic stage II is revealed at RPLND, further chemotherapy should be considered	A

CS 1 = clinical stage I; GR = grade of recommendation; RPLND = retroperitoneal lymph node dissection; PEB = cisplatin, etoposide, bleomycin.
 * Upgraded following panel consensus.

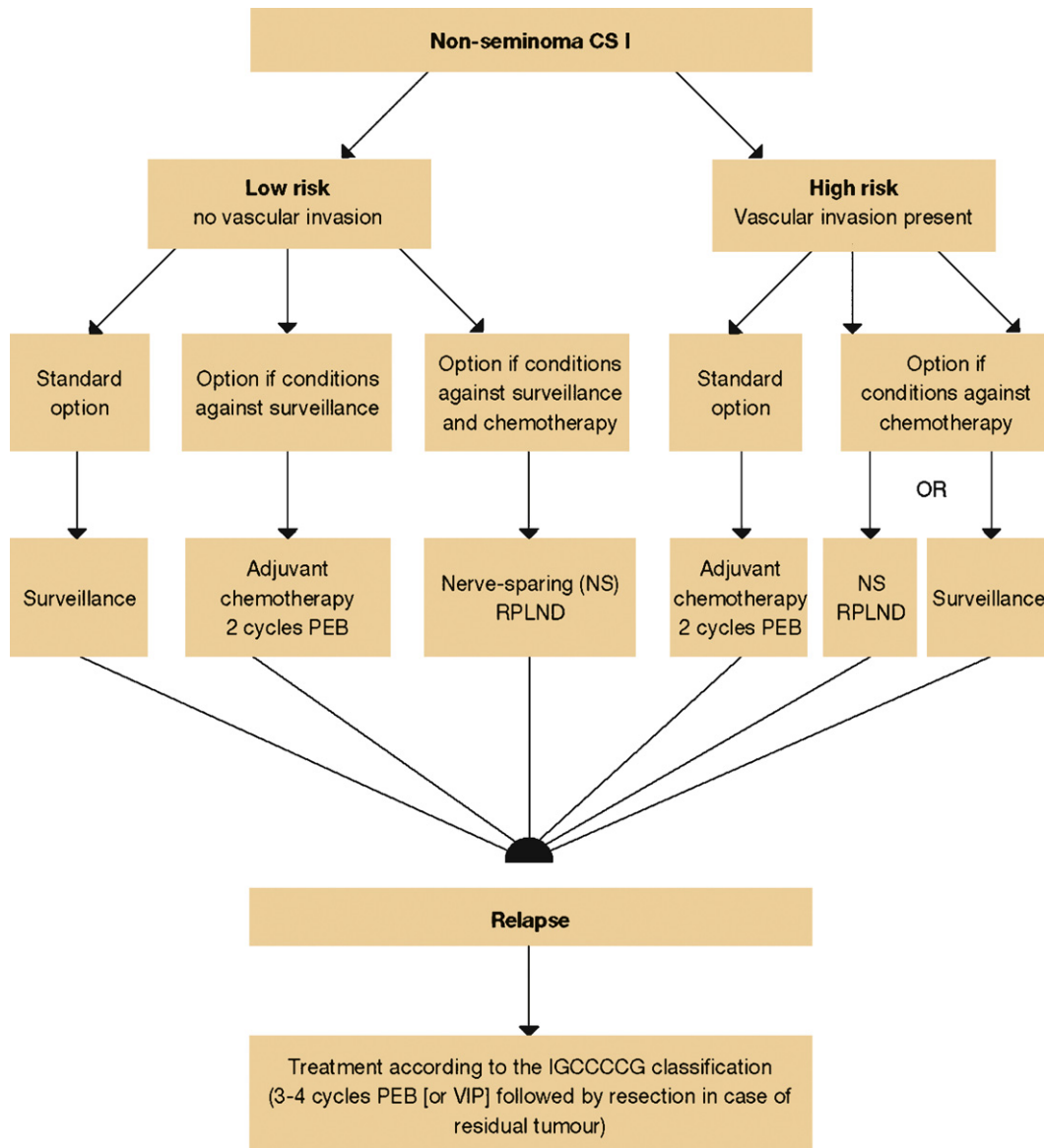


Fig. 1 – Treatment algorithm after orchidectomy according to individual risk factors in patients with clinical stage I nonseminomatous germ cell tumours. PEB = cisplatin, etoposide, bleomycin; CS = clinical stage; IGCCCG = International Germ Cell Cancer Collaborative Group; RLND = retroperitoneal lymph node dissection; VIP = etoposide, cisplatin, ifosfamide.

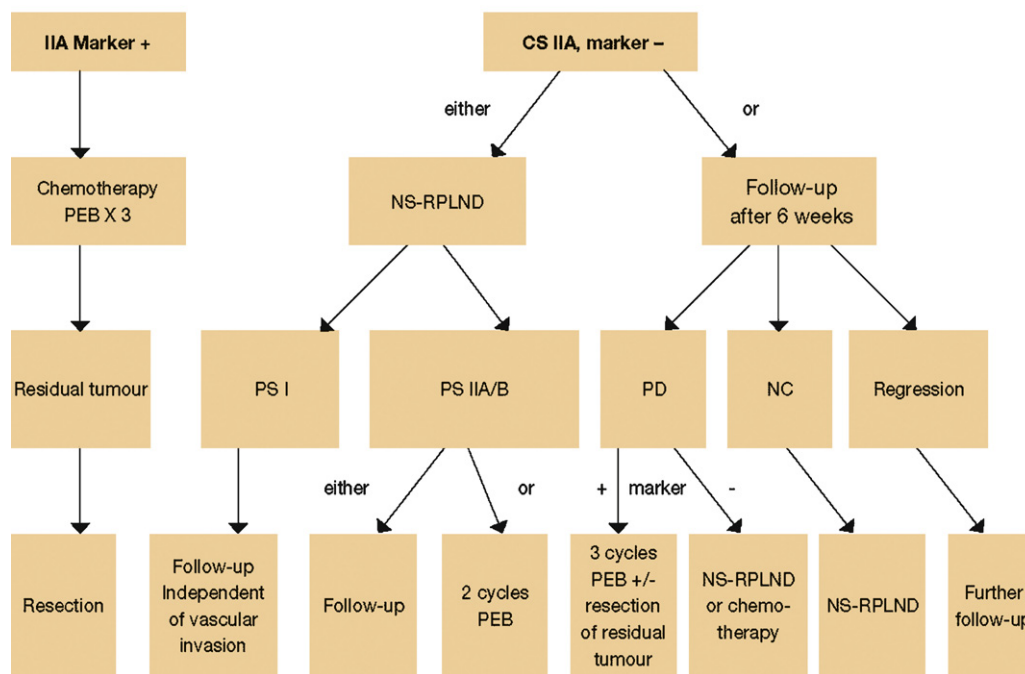


Fig. 2 – Treatment option in patients with clinical stage IIA nonseminoma [23].

PEB = cisplatin, etoposide, bleomycin; NS = nerve sparing; RPLND = retroperitoneal lymph node dissection; PS = pathologic stage; PD = progressive disease; NC = no change.

of 30 Gy in stage IIA and 36 Gy in IIB. The standard radiation field compared with stage I is extended from the PA region to the ipsilateral iliac field (hockey-stick field). In stage IIB, the lateral borders also include the metastatic lymph nodes (safety margin: 1.0–1.5 cm). The relapse-free survival is 90% in stage IIA and 92% in stage IIB; overall survival is almost 100% [69].

In stage IIB, chemotherapy (four cycles of etoposide and cisplatin [EP] or three cycles of PEB in a good prognosis) is an alternative to radiotherapy, with similar disease control [70]. Single-agent carboplatin should not be tried.

7.1.2. Stage IIA/B nonseminoma

Treatment should start with initial chemotherapy in all advanced cases of NSGCT, except for stage II disease without elevated tumour markers, which can be managed by primary RPLND or surveillance.

If surveillance is chosen, one follow-up after 6 wk is needed to determine whether the lesion is growing, stable, or shrinking. A shrinking lesion is probably nonmalignant, requiring continued observation. A stable or growing lesion indicates either a teratoma or undifferentiated malignant tumour. If tumour marker levels have not increased, RPLND should be performed for suspected teratoma. A growing lesion, with increased tumour markers, requires chemotherapy with PEB, according to the treatment algorithm for patients with metastatic disease and IGCCCG recommendations (Fig. 2) [10,11,71]. A (CT-guided) biopsy is an alternative to surveillance in marker-negative IIA/B NSGCT with suspected undifferentiated malignant tumour.

Patients refusing primary chemotherapy can be offered primary nerve-sparing RPLND with adjuvant chemotherapy

(two cycles of PEB). Primary chemotherapy and primary RPLND have comparable outcomes and a cure rate of almost 90% [64,72].

7.2. Advanced metastatic disease

7.2.1. Primary chemotherapy

The primary treatment of choice for advanced disease is three or four cycles of PEB combination chemotherapy (Table 9), depending on the IGCCCG risk classification (Table 5). This regimen has proven superiority to cisplatin, vinblastine, and bleomycin (PVB) in patients with advanced disease [73]. Data support a 3-d regimen of administering combination chemotherapy as equally effective as a 5-d regimen but associated with increased toxicity when four cycles are used [26].

For patients with a “good prognosis,” according to the IGCCCG classification, standard treatment consists of three cycles of PEB [26,74]. In very selected cases, where bleomycin is contraindicated, four cycles of EP can be given. Prophylactic application of haematopoietic growth factors, for example, granulocyte colony-stimulating factor, is only

Table 9 – Cisplatin, etoposide, bleomycin regimen (interval: 21 d)

Drug	Dosage	Duration of cycles
Cisplatin	20 mg/m ²	Days 1–5*
Etoposide	100 mg/m ²	Days 1–5
Bleomycin	30 mg	Days 1, 8, 15

* Plus hydration.

recommended if infectious complications have occurred during earlier cycles of chemotherapy [75].

The “intermediate prognosis” group in the IGCCCG classification are patients with a 5-yr survival rate of about 80% and should receive four cycles of PEB [26].

For patients with a “poor prognosis,” standard treatment consists of four cycles of PEB, with a 5-yr progression-free survival of 45–50%. Patients with a slow marker decline after the first or second cycle may represent a prognostically inferior subgroup, with a potential role for dose-intensified chemotherapy [76]. More aggressive chemotherapy may also be investigated in a very poor prognostic group (eg, primary mediastinal germ cell tumours or synchronous brain metastasis).

Poor-prognosis patients should be treated in ongoing prospective trials investigating dose-intensified or high-dose chemotherapy. There are no general recommendations for patients with a poor general condition (Karnofsky <50%) or extended liver infiltration (>50%). Patients with extended pulmonary infiltration are at risk for acute respiratory distress syndrome. Adapting the doses of the PEB regimen in the first cycle of chemotherapy (only 3 d of EP without bleomycin) has been suggested to reduce the risk of early mortality [77].

7.3. Restaging and further treatment

7.3.1. Restaging

Restaging is performed by imaging and tumour marker reevaluation. If there is marker decline and stable or regressive tumour, chemotherapy is completed [26,78]. If there is marker decline but growing metastases, induction therapy is followed by tumour resection [79].

Early crossover of therapy is only indicated if marker increase continues after two courses of chemotherapy. Patients with a low hCG plateau after chemotherapy should be observed to see if complete normalisation occurs. Patients with a low AFP plateau should undergo surgery of residual masses, with postsurgery AFP monitoring. Salvage chemotherapy is only indicated for a documented marker rise [80].

7.3.2. Residual tumour resection

A residual mass of seminoma should not be primarily resected, irrespective of the size, but observed using imaging, including FDG-PET, and tumour markers [81]. Upon progression, salvage therapy is indicated [82]. In the case of NSGCT and complete remission after chemotherapy (no tumour visible), residual tumour resection is not indicated [83,84]. Long-term relapse rate is 6–9%, although a third of late relapsing patients do not survive [84]. In the case of any visible residual mass and marker normalisation, surgical resection is indicated. If technically feasible, a nerve-sparing procedure should be performed [85].

Overall, following PEB induction chemotherapy, only 10% of residual masses contain viable cancer, 50% contain mature teratoma, and 40% contain necrotic-fibrotic tissue. As yet, no imaging investigations, including PET or a prognosis model, can predict histologic differentiation of the NSGCT residual tumour. Thus residual tumour resection

is mandatory in all patients with residual disease >1 cm [86].

The extent of surgery should be based on the risk of relapse of an individual patient and quality of life [85]. Growing evidence suggests that “template” resections in selected patients yield long-term results equivalent to bilateral systematic resections in all patients [87]. However, mere resection of residual tumour (“lumpectomy”) should not be performed.

Postchemotherapy surgery is demanding and often requires ad hoc vascular interventions (eg, vena cava or aortic prosthesis). Patients referred to specialised centres capable of interdisciplinary surgery show a significant reduction in perioperative mortality; specialised urologic surgeons have a higher rate of complete resections [7].

7.3.3. Consolidation chemotherapy after secondary surgery

After resection of necrosis or mature/immature teratoma, no further treatment is required. In incomplete resection of other germ cell tumour pathologies, two adjuvant cycles of conventionally dosed cisplatin-based chemotherapy may be given in certain subgroups (eg, “poor-prognosis” patients) [88]. After complete resection of “vital” tumour <10% of the total volume, especially in patients with an initially good-prognosis group according to IGCCCG, the relapse rate is very low and adjuvant chemotherapy is not beneficial. The prognosis is worst if vital malignant neoplasm is found in resection specimens after second- and third-line chemotherapy. In this latter situation, postoperative chemotherapy is not indicated and is unable to improve the prognosis [89].

7.3.4. Systemic salvage treatment for relapse or refractory disease

Cisplatin-based combination salvage chemotherapy results in long-term remissions for about 50% of relapses after first-line chemotherapy [90]. Treatment consists of four cycles of etoposide, ifosfamide, cisplatin, four cycles of paclitaxel, ifosfamide, cisplatin, or four cycles of vinblastine, ifosfamide, cisplatin (VeIP) (Table 10).

Table 10 – Standard PEI/VIP, TIP, and VeIP chemotherapy (interval: 21 d)

Chemotherapy agents	Dosage	Duration of cycles
PEI/VIP		
Cisplatin*	20 mg/m ²	Days 1–5
Etoposide	75–100 mg/m ²	Days 1–5
Ifosfamide†	1.2 g/m ²	Days 1–5
TIP		
Paclitaxel	250 mg/m ² xx	24 h continuous infusion day 1
Ifosfamide†	1.5 g/m ²	Days 2–5
Cisplatin*	25 mg/m ²	Days 2–5
VeIP		
Vinblastine	0.11 mg/kg	Days 1 + 2
Ifosfamide†	1.2 g/m ²	Days 1–5
Cisplatin*	20 mg/m ²	Days 1–5

PEI/VIP = cisplatin, etoposide, ifosfamide; TIP = paclitaxel, ifosfamide, cisplatin; VeIP = vinblastine, ifosfamide, cisplatin.

* Plus hydration.

† Plus mesna protection.

xx A Medical Research Council schedule uses paclitaxel 175 mg/m² in a 3-h infusion.

Table 11 – IGCCCG-2 (Lorch-Beyer) score construction

Points/ Variable	–1	0	1	2	3
Histology	Seminoma	Nonseminoma			
Primary site		Gonadal	Retroperitoneal		Mediastinal
Response		CR/PRm–	PRm+/SD	PD	
PFI		> months	≤3 mo		
AFP salvage		Normal	<1000	≥1000	
hCG salvage		<1000	≥1000		
LBB		No	Yes		

IGCCCG = International Germ Cell Cancer Collaborative Group; PFI = progression-free survival; AFP = α -fetoprotein; hCG = human gonadotrophin; LBB = liver, bone, brain metastases; CR = complete remission; PRm– = tumour-marker-negative-partial responder; PRm+ = tumour-marker-positive-partial responder; SD = stable disease.

It is not currently known whether early intensification of first-salvage treatment with high-dose chemotherapy is preferable to conventionally dosed cisplatin-based combination chemotherapy. An international randomised trial of high-dose versus conventional dose chemotherapy in patients with first-line relapse is planned. It is therefore of the utmost importance that these rare patients are treated within clinical trials and at experienced centres.

Conventionally dosed salvage chemotherapy may achieve long-term remissions in 15–40% of patients, depending on individual risk factors [80,91].

The IGCCCG-2 prognostic score is composed of seven important factors (Table 11) [92]. Using these factors, five risk groups (very low risk, –1 point; low risk, 0 points; intermediate risk, 1–2 points; high risk, 3–4 points; and very high risk, ≥5 points) were identified with significant differences in progression-free survival (PFS) and overall survival. Table 12 illustrates the five risk groups and corresponding 2-yr PFS and 3-yr overall survival rates.

Salvage therapy with VeIP is probably not superior to other conventionally dosed cisplatin-based combination regimens [88,90]. Paclitaxel and gemcitabine have proved active in refractory germ cell tumours; both drugs are synergistic with cisplatin [93].

High-dose chemotherapy as first salvage treatment has no additional benefit in good-prognosis patients, who should be offered conventional dose first salvage treatment. However, poor-prognosis patients have shown improved survival with high-dose chemotherapy as first salvage treatment in early clinical trials, and they should be referred to centres experienced in caring for relapse and/or refractory patients [94].

Table 12 – Progression-free survival and overall survival estimates for all patients according to International Germ Cell Cancer Collaborative Group-2 prognostic score

Score (n = 1435)	n	%	HR	2-yr PFS	3-yr OS
Very low	76	5.30	1	75.1	77.0
Low	257	17.9	2.07	52.6	69.0
Intermediate	646	45.0	2.88	42.8	57.3
High	351	24.5	4.81	26.4	31.7
Very high	105	7.3	8.95	11.5	14.7
Missing	159				

HR = hazard ratio; PFS = progression-free survival; OS = overall survival.

7.3.5. Late relapse (≥2 yr after end of first-line treatment)

Late relapses should be treated only at experienced centres. If technically feasible, all nonseminoma patients with late relapse should undergo immediate resection of all undifferentiated germ cell tumours, mature teratomas, or secondary non-germ cell cancer [95]. Patients with a rapidly rising hCG are an exception and may benefit from induction salvage chemotherapy before resection. If complete resection is not possible, salvage chemotherapy should be started. If the patient responds to salvage chemotherapy, secondary surgery should be conducted. In the case of unresectable but localised refractory disease, radiotherapy can be considered.

7.4. Salvage surgery

If there is marker progression after salvage treatment and no other chemotherapeutic options, resection (“desperation surgery”) should be considered if complete resection seems feasible. Long-term survival is possible in about 25% of cases [89,96].

7.5. Brain metastases

The 5-yr survival of patients presenting with brain metastases is poor (30–40%) but only 2–5% for a brain metastasis due to recurrent disease [97]. Chemotherapy is the initial treatment, with some support for consolidation radiotherapy [98]. Surgery may be suitable for a persistent solitary metastasis, depending on the systemic status, primary tumour histology, and location. Table 13 summarises the guidelines for the treatment of metastatic germ cell tumours.

8. Follow-up after curative treatment

The aims of follow-up are to detect the relapse of testicular cancer as early as possible and to monitor the contralateral testis. The following principles should be applied following treatment aimed at cure or prolonging life:

- Ensure that the interval between examinations and duration of follow-up is consistent with the time of maximal risk of recurrence.
- The choice of follow-up tests will depend on the increased risk of second malignancy, both at the primary site and in

Table 13 – Guidelines for the treatment of metastatic germ cell tumours

	Grade
Low-volume NSGCT stage IIA/B with elevated markers should be treated like “good or intermediate prognosis” advanced NSGCT, with three or four cycles of PEB	A
In stage IIA/B without marker elevation, histology can be gained by RPLND or biopsy. A repeat staging can be performed after 6 wk of surveillance before final decision on further treatment	B
In metastatic NSGCT (stage IIC or higher) with a good prognosis, three courses of PEB is the primary treatment of choice	A
In metastatic NSGCT with an intermediate or poor prognosis, the primary treatment of choice is four courses of standard PEB; inclusion in clinical trials is strongly recommended	A
Surgical resection of residual masses after chemotherapy in NSGCT is indicated in the case of visible residual masses and when serum levels of tumour markers are normal or normalising	A
Seminoma CSII A/B can initially be treated with radiotherapy; when necessary, chemotherapy can be used as a salvage treatment with the same schedule as for the corresponding prognostic groups of NSGCT	A
In seminoma stage CS IIB, chemotherapy (four cycles of EP or three cycles of PEB, in good prognosis) is an alternative to radiotherapy; it appears that four cycles of EP or three cycles of PEB achieve a similar level of disease control	B
Seminoma stage IIC and higher should be treated with primary chemotherapy according to the same principles used for NSGCT	A

GR = grade of recommendation; NSGCT = nonseminomatous germ cell tumour; PEB = cisplatin, etoposide, bleomycin; RPLND = retroperitoneal lymph node dissection; CS = clinical stage; EP = etoposide and cisplatin.

Table 14 – Stage I nonseminoma testicular cancer: minimum follow-up schedules for surveillance and following retroperitoneal lymph node dissection or adjuvant chemotherapy

Procedure	Year 1	Year 2	Year 3–5	Year 6–10
Minimum follow-up schedule for a surveillance policy				
Physical examination	Four times	Four times	Annually	Annually
Tumour markers	Four times	Four times	Annually	Annually
Chest x-ray	Twice	Twice		
Abdominopelvic CT	Twice (at 3 mo and 12 mo)			
Minimum follow-up schedule after RPLND or adjuvant chemotherapy				
Physical examination	Four times	Four times	Annually	Annually
Tumour markers	Four times	Four times	Annually	Annually
Chest x-ray	Twice	Twice		
Abdominopelvic CT	Once	Once		

CT = computed tomography scan; RPLND = retroperitoneal lymph node dissection.

Table 15 – Stage I seminoma testicular cancer: minimum follow-up schedule for postorchidectomy surveillance, radiotherapy, or chemotherapy

Procedure	Year 1	Year 2	Year 3	Year 4–5
Physical examination	3 times	3 times	Annually	Annually
Tumour markers	3 times	3 times	Annually	Annually
Chest x-ray	Twice	Twice	–	–
Abdominopelvic CT scan	Twice	Twice	Annually	Annually

CT = computed tomography scan.

Table 16 – Advanced (metastatic) testicular cancer: minimum follow-up schedule

Procedure	Year 1	Year 2	Year 3–5	Thereafter
Physical examination	Four times	Four times	Twice per year	Annually
Tumour markers	Four times	Four times	Twice per year	Annually
Chest x-ray	Four times	Four times	Twice per year	Annually
Abdominopelvic CT ^{†,‡}	Twice	Twice	As indicated	As indicated
Chest CT ^{†,‡}	As indicated	As indicated	As indicated	As indicated
Brain CT [§]	As indicated	As indicated	As indicated	As indicated

CT = computed tomography scan.

^{*} Abdominal CT scanning must be performed at least annually if teratoma is found in the retroperitoneum.

[†] If the postchemotherapy evaluation in a seminoma patient shows any mass >3 cm, the appropriate CT scan should be repeated at 2 and 4 mo later to ensure that the mass is continuing to regress. If available, fluorodeoxyglucose-positron emission tomography scanning can be performed.

[‡] Chest CT scan is indicated if abnormality is detected on chest x-ray and after pulmonary resection.

[§] In patients with headaches, focal neurologic findings, or any central nervous system symptoms.

other tissues that may have been exposed to the same carcinogens, or in which there is epidemiologic evidence of increased risk.

- Follow-up tests should focus on the most likely sites of recurrence and ensure good accuracy.
- Nonmalignant complications of therapy should be considered.

8.1. Stage 1 seminoma and nonseminoma disease

Table 14 provides the minimum follow-up schedules for surveillance of stage I nonseminoma testicular cancer and also following RPLND or adjuvant chemotherapy.

Table 15 provides the minimum follow-up schedules for stage I seminoma testicular cancer following orchidectomy, radiotherapy, or chemotherapy.

8.2. Stage II and advanced (metastatic) disease

Table 16 summarises the minimum follow-up schedule for advanced (metastatic) germ cell testicular cancer.

Author contributions: Peter Albers had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition of data: Albers, Albrecht, Algaba, Bokemeyer, Cohn-Cedermark, Fizazi, Horwich, Laguna

Analysis and interpretation of data: Albers.

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Critical revision of the manuscript for important intellectual content: Albers, Albrecht, Algaba, Bokemeyer, Cohn-Cedermark, Fizazi, Horwich, Laguna.

Statistical analysis: None.

Obtaining funding: None.

Administrative, technical, or material support: None.

Supervision: Albers.

Other (specify): None.

Financial disclosures: I certify that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/ affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Peter Albers receives royalties from Thieme Books. He is a company consultant for Pfizer, MSD, and Novartis. He receives company speaker honorariums from Pfizer, Novartis, Sanofi-Aventis, Amgen, AstraZeneca, and Astellas. He participates in trials for Novacea, Sanofi-Aventis, Bayer, Astra Zeneca, Novartis, and Ferring. He receives research grants from Novartis Oncology. Walter Albrecht receives company speaker honorariums from Takeda, Astellas, and Aesca. Carsten Bokemeyer is a company consultant for Fresenius Biotech, Sanofi Aventis, Ortho Biotech, and MSD. He receives company speaker honorariums from Roche, Sanofi Aventis, Amgen, MSC, Novartis, and Chugai. He has participated in several trials over the years. He has received research grants from Bristol and Lilly. Ferran Algaba, Gabriella Cohn-Cedermark, Karim Fizazi, Alan Horwich, and Maria Pilar Laguna have nothing to disclose.

Funding/Support and role of the sponsor: None.

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