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Guidelines on Testicular Cancer

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Abstract

Objective: To up-date the 2001 version of the EAU testicular cancer guidelines.

Methods: A non-structured literature review until January 2005 using the MEDLINE database has been performed. Literature has been classified according to evidence-based medicine levels.

Results: Testicular cancer is a highly curable disease. Excellent cure rates have been achieved by standardization of treatment, interdisciplinary management, and tremendous success in performing clinical trials. Currently, the aims of testicular cancer treatment are as follows: for patients with low-stage disease, a reduction in treatment is proposed to improve long-term toxicity in these patients with unaltered life expectancy; for about 10% of patients with advanced disease and poor prognosis, intensification of treatment (including high-dose chemotherapy and new drugs as well as aggressive surgical approaches) is being investigated to improve long-term cure rates.

Conclusion: Guidelines will improve clinical practice only if they are regularly updated. This update presents the state-of-the-art management of testicular cancer patients in 2005.

Keywords: Consensus; Guidelines; Testicular cancer

1. Background

Testicular cancer represents between 1% and 1.5% of male neoplasms and overall 5% of urological tumours, with 3–6 new cases occurring per 100,000 males/per year in Western society and up to 10 new cases per 100,000 males/per year in Denmark and Norway. An increased incidence over the last 30 years has clearly been observed in industrialized countries [1,2].

Epidemiological risk factors for the development of testicular tumours are: a history of cryptorchidism or undescended testis, a hypotrophic (<12 ml) or atrophic testicle, Klinefelter's syndrome, familial history of testicular tumours among first-grade relatives (brothers, father), the presence of a contralateral tumour or TIN and infertility [3].

Currently, testicular tumours show excellent cure rates in the order of 95% for low stages and somewhat less for the more advanced stages of disease. The main factors contributing to this are: careful staging at the time of diagnosis; adequate early treatment based on an interdisciplinary management including chemotherapy,

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radiotherapy and surgery; and very strict follow-up and salvage therapies. For the treatment of testicular cancer, the choice of the treatment centre is of paramount importance. In poor-prognosis, non-seminomatous, germ cell tumours, it has been shown that overall survival within a clinical trial depended upon the number of patients enrolled from the participating centre (worse survival: <5 patients enrolled) [4].

1.1. Methods

This publication represents a condensed version of the EAU guidelines published on the internet (www.uroweb.org) and is based on a non-structured review of the literature by using the MEDLINE database through 2005. In addition, data from meta-analysis studies, Cochrane evidence and the recommendations of the European Germ Cell Cancer Collaborative Group, as well as other available guidelines, have been included [5–12]. It focuses on changes in diagnosis and treatment compared to the previously published version [13]. For further information, the reader is referred to the 2001 EAU guideline version [13] and to the extended guidelines text of the EAU.

2. Diagnosis, pathology and classifications

Testicular cancer is usually diagnosed by physical examination and generally appears as a painless, unilateral intrascrotal mass. A correct diagnosis must be established in all patients with an intrascrotal mass. In addition to the clinical examination, the following investigations are therefore mandatory.

2.1. Scrotal ultrasound

A 7.5 MHz transducer is necessary to image the testis correctly. The sensitivity of scrotal ultrasound to detect a testicular tumour is almost 100%, and ultrasound has an important role in determining whether a mass is intra- or extratesticular [14]. In young men with either a retroperitoneal mass, visceral metastasis or elevated beta-human chorionic gonadotrophin (β-hCG) and/or alpha-fetoprotein (AFP), an ultrasound of the testes is mandatory. Magnetic resonance imaging (MRI) of the scrotum offers a sensitivity of 100% and a specificity of 95–100%, but its use for diagnosis cannot be justified because of its high cost.

2.2. Serum tumour markers

Serum tumour markers are prognostic factors and contribute to diagnosis and staging [15]. The mean serum half-life of AFP is 5–7 days and that of β-hCG approximately 2–3 days. Therefore, the following markers should be determined before orchidectomy and thereafter in weekly intervals until normalization:

- AFP (produced by yolk sac cells)
- β-hCG (expression of trophoblasts)
- lactate dehydrogenase (LDH) (marker of tissue destruction).

Overall, there is an increase in these markers in 51% of cases of testicular cancer [15]. The level of AFP increases in 50–70% of patients with non-seminomatous germ cell tumour (NSGCT) and a rise in β-hCG occurs in 40–60% of patients with NSGCT. About 90% of NSGCTs present with a rise in the levels of either AFP and/or β-hCG markers. It should be noted that negative marker levels do not exclude the diagnosis of a germ cell tumour. Other markers studied include neuro-specific enolase (NSE) and placental alkaline phosphatase (PLAP) and may be of limited value in monitoring patients with pure seminoma. The measurement of serum AFP, β-hCG and LDH is mandatory, while NSE and PLAP are optional.

2.3. Inguinal exploration and orchidectomy

Every patient with a suspected testicular mass must undergo inguinal exploration with exteriorization of the testis within its tunics. Immediate orchidectomy with division of the spermatic cord at the internal inguinal ring has to be performed if a tumour is found. If the diagnosis is not clear, an intra-operative testicular biopsy or the completely resected tumour is taken for frozen section histological examination before orchidectomy to avoid unnecessary orchidectomy in benign tumours. In the case of disseminated disease and life-threatening metastases, up-front chemotherapy can be started and orchidectomy delayed until clinical stabilization.

2.3.1. Organ-sparing surgery

Although organ-sparing surgery is not generally indicated, it can be attempted in the following special situations with all the necessary precautions [16]:

- in suspicion of a benign lesion
- in synchronous, bilateral testicular tumours
- in metachronous, contralateral tumours, with normal preoperative testosterone levels
- in a tumour in a solitary testis, with normal preoperative testosterone levels.

The tumour volume in these cases should be less than about 30% of the testicular volume. In all patients, remaining TIN can safely be treated with adjuvant

radiotherapy using a dose of 20 Gy [16]. Infertility will result after radiotherapy. The option has to be carefully discussed with the patient and surgery performed in a centre with experience [16].

2.4. Pathological examination of the testis

Mandatory pathological requirements [17] are:

- Macroscopic features: side, testis size, tumoural maximum size and macroscopic features of epididymis, spermatic cord and tunica vaginalis.
- Sampling: 1 cm^2 section for every centimetre of maximal tumoural diameter, including normal macroscopic parenchyma (if present), albuginea and epididymis selection of suspected areas. At least one proximal and one distal section of spermatic cord plus any suspected area.
- Microscopic features and diagnosis: histological type according to WHO 2004 (specify individual components and estimate amount as percentage).
- Presence or absence of peri-tumoural venous and/or lymphatic invasion.
- Presence or absence of albuginea, tunica vaginalis, rete testis, epididymis or spermatic cord invasion.
- Presence or absence of TIN in non-tumoural parenchyma.
- pT category according to TNM 2002 [18].
- Immunohistochemical studies: in seminoma and mixed germ cell tumour, AFP and β-hCG.

2.5. Staging and clinical classification

Staging represents the cornerstone on which testicular cancer treatment is based. To determine the presence of metastatic or occult disease, half-life kinetics of serum tumours markers have to be assessed (see above and Section 4.3), the nodal pathway has to be screened and the presence of visceral metastases excluded. Consequently, in addition to tumour marker half-life kinetics, it is mandatory to assess:

- status of abdominal and supraclavicular nodes, and the liver
- presence or absence of mediastinal nodal involvement and lung metastases
- status of brain and bone if any suspicious symptoms are present.

Abdominal and pulmonary, extra-pulmonary, and mediastinal nodes are best assessed by means of computerized tomography (CT) scan. The supraclavicular nodes are best assessed by physical examination and CT scan if suspicious. Other examinations, such as brain or spinal CT, bone scan or liver ultrasound, should be performed if there is suspicion of metastases to these organs. CT scan or MRI of the skull are advisable in patients with NSGCT and widespread lung metastases.

Based on the tumour marker level and the results of CT scanning, patients have to be classified according to the 2002 TNM classification of the UICC (International Union Against Cancer) [18]. Patients with metastatic disease (TNM stage $\geq$2) additionally have to be classified according to the International Germ Cell Cancer Collaborative Group (IGCCCG) staging system, defined as a prognostic-factor based staging system for metastatic testicular tumour (Table 1).

3. Diagnosis and treatment of TIN

Contralateral biopsy has been advocated to rule out the presence of TIN. The low incidence of TIN and contralateral asynchronic testicular tumours (up to 5% and approximately 2.5%, respectively), the morbidity of TIN treatment and the fact that most of these asynchronic tumours are at a low stage at presentation make it controversial to recommend a systematic contralateral biopsy [20]. It is still difficult to reach a consensus whether the existence of contralateral TIN has to be identified in all cases. However, biopsy of the contralateral testis should be offered to all patients and is advised to be performed for exclusion of contralateral TIN in high-risk patients with a testicular volume less than 12 ml, a history of cryptorchidism and age under 30 years [20].

Once TIN is diagnosed, local radiotherapy (20 Gy in single fractions of 2 Gy) is the treatment of choice. Because this will produce infertility, the patient must be carefully counselled before treatment commences. In addition to infertility, Leydig cell function and testosterone production may be impaired long-term after radiotherapy of TIN [21].

4. Treatment: stage I germ cell tumours

4.1. Stage I seminoma

After modern staging procedures, about 15–20% of stage I seminoma patients have subclinical metastatic disease, usually in the retroperitoneum, and will relapse after orchidectomy alone.

4.1.1. Adjuvant radiotherapy

Seminoma cells are extremely radiosensitive. Adjuvant radiotherapy to a para-aortic (PA) field with a total

Table 1
Prognostic-based staging system for metastatic germ cell cancer (IGCCCG) [19]

Good-prognosis group	
Non-seminoma (56% of cases)	All of the following criteria:
5-year PFS 89%	Testis/retroperitoneal primary
5-year survival 92%	No non-pulmonary visceral metastases
	AFP <1,000 ng/ml
	β-hCG <5,000 IU/l (1,000 ng/ml)
	LDH <1.5 × ULN
Seminoma (90% of cases)	All of the following criteria:
5-year PFS 82%	Any primary site
5-year survival 86%	No non-pulmonary visceral metastases
	Normal AFP
	Any β-hCG
	Any LDH
Intermediate-prognosis group	
Non-seminoma (28% of cases)	All of the following criteria:
5-year PFS 75%	Testis/retroperitoneal primary
5-year survival 80%	No non-pulmonary visceral metastases
	AFP > 1,000 and <10,000 ng/ml or
	β-hCG > 5,000 and <50,000 IU/l or
	LDH > 1.5 and <10 × ULN
Seminoma (10% of cases)	Any of the following criteria:
5-year PFS 67%	Any primary site
5-year survival 72%	Non-pulmonary visceral metastases
	Normal AFP
	Any β-hCG
	Any LDH
Poor-prognosis group	
Non-seminoma (16% of cases)	Any of the following criteria:
5-year PFS 41%	Mediastinal primary
5-year survival 48%	Non-pulmonary visceral metastases
	AFP > 10,000 ng/ml or
	β-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: alpha-fetoprotein; β-hCG: beta-human chorionic gonadotrophin; LDH: lactate dehydrogenase; and ULN: upper limit of normal range.

target volume of 20 Gy will reduce the relapse rate to only 1–3% [22].

After modern radiotherapy, nearly all relapses will first occur outside the irradiated field (supradiaphragmatic lymph nodes or in the lungs) [23]. Based upon the results of a large randomized Medical Research Council (MRC) trial, Fossa et al. [24] recommended radiotherapy to a PA field as standard treatment for patients with testicular seminoma stage I, T1–T3 and with undisturbed lymphatic drainage. Para-aortic 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.

Concerning the dose of irradiation, the MRC has recently finished a large randomized trial of 20 Gy versus 30 Gy PA irradiation in stage I seminoma that showed equivalence for both doses regarding recurrence rates [22].

4.1.2. Surveillance

Meta-analysis of the four largest prospective non-randomized studies of surveillance shows an actuarial 5 years relapse-free rate of 82.3%. On multivariate analysis, tumour size (≤4 cm) and invasion of the rete testis remained the most important predictors for relapse [25].

The actuarial relapse rate is of the order of 15–20% at 5 years. The overall cancer-specific survival rate reported by experienced centres is 97–100% for seminoma stage I after surveillance [25]. The main drawback of surveillance is the need for more intensive follow-up, especially with repeated imaging examinations of the retroperitoneal lymph nodes, for at least 5 years after orchidectomy.

4.1.3. Adjuvant chemotherapy

A joint MRC and European Organization for Research and Treatment of Cancer (EORTC) trial

(MRC TE19 trial, EORTC Trial 30942) comparing one cycle of carboplatin (AUC 7) to adjuvant radiotherapy has recently been finished. Single-agent carboplatin therapy showed no significant difference to radiotherapy concerning recurrence rate, time to recurrence and survival after a median follow-up of 3 years [26]. Thus, adjuvant carboplatin therapy is an alternative to radiotherapy or surveillance in stage I seminoma. Two courses of adjuvant carboplatin seem to further reduce the relapse rate to the order of 1–3%, but further experience and long-term observations are needed.

4.1.4. Retroperitoneal lymph node dissection (RPLND)

In a prospective, non-randomized study comparing radiotherapy and RPLND in stage I seminoma, there was a trend towards a higher incidence of retroperitoneal relapses (9.5%) after RPLND as primary treatment. This policy should therefore not be recommended in stage I seminoma [27] (Table 2).

4.2. NSGCT stage I

If stage IS cases are excluded, up to 30% of NSGCT patients with clinical stage I (CS1) disease have subclinical metastases and will relapse if surveillance alone is applied after orchiectomy. However, patients can be stratified according to risk factors into different prognostic groups with different recurrence rates.

4.2.1. Prognostic factors

The main predictor of relapse in CS1 NSGCT managed by surveillance, and both for having pathological stage II (PS2) disease and for relapse in pathological stage I (PS1) after RPLND, is histopathological evidence of vascular invasion by tumour cells in, or near, the primary tumour in the testis [28].

4.2.2. Risk-adapted treatment

Risk-adapted treatment is recommended as treatment of first choice in NSGCT I. Risk assessment is currently based on the risk factor of vascular invasion alone. Stratifying patients with CS1 NSGCT according to their presumed risk of relapse is a rational option since several studies have reported similar survival rates and a final cure rate close to 100% with all available treatment options using the risk-stratifying approach [29]. Patients with vascular invasion are recommended to undergo adjuvant chemotherapy with two cycles of cisplatin, etoposide and bleomycin (PEB) and patients without vascular invasion are recommended to undergo surveillance. Only if patients or doctors are not willing to accept the relevant risk-adapted treatment or if there are conditions against the risk-adapted treatment option, the remaining treatments should be considered.

Table 2
Guidelines for the treatment of seminoma stage 1

1. Adjuvant radiotherapy to a para-aortic field to a total dose of 20 Gy (Grade A recommendation)
2. Surveillance (if available facilities) (Grade B recommendation)
3. Carboplatin-based chemotherapy (one course at AUC 7) can be recommended as alternative to radiotherapy and surveillance (Grade A recommendation)

4.2.2.1. Surveillance. Eighty percent of relapses occur during the first 12 months 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 [30,31]. About 35% of relapsing patients have normal levels of serum tumour markers at relapse.

4.2.2.2. Adjuvant chemotherapy. Several studies involving two courses of chemotherapy with PEB as primary treatment for high-risk patients (having about 50% risk of relapse) have been reported [29,32] showing a relapse rate of only 2.7%, with very little long-term toxicity. It is important to be aware of the risk of slow-growing retroperitoneal teratomas after chemotherapy and of the risk of chemoresistant cancer relapse.

4.2.3. Retroperitoneal lymph node dissection (RPLND)

If RPLND is performed without risk assessment, about 30% of patients are found to have retroperitoneal lymph node metastases (PS2 disease) [33]. If no retroperitoneal metastases are found at RPLND (PS1), approximately 10% of the PS1 patients relapse at distant sites.

If CS1 patients with PS2 are only followed up after RPLND, about 30% relapse, mainly at sites outside the abdomen and pelvis. The risk of relapse depends upon the amount of retroperitoneal disease resected. If two (or more) courses of cisplatin-based chemotherapy are given adjuvant to RPLND in the PS2 cases, the relapse rate is reduced to less than 2%, including teratoma relapse [34]. The follow-up after RPLND is much simpler and less costly than that carried out during post-orchiectomy surveillance due to the reduced need for abdominal CT scans.

4.3. CS1S with (persistently) elevated serum tumour markers

Serum tumour markers should be followed closely until it is clear whether or not levels are falling

Table 3
Guidelines for the treatment of NSGCT stage I

CS1A (pT1, no vascular invasion); low risk
1. If the patient is willing and able to comply with a surveillance policy and long-term (at least 5 years), close follow-up should be recommended (Grade B recommendation)
2. Adjuvant chemotherapy or nerve-sparing RPLND in low-risk patients remain options for those not willing to undergo surveillance. If RPLND reveals PN+ (nodal involvement) disease, chemotherapy with two courses of PEB should be considered (Grade A recommendation)
CS1B (pT2–pT4); high risk
1. Primary chemotherapy with two courses of PEB should be recommended (Grade B recommendation)
2. Surveillance or nerve-sparing RPLND in high-risk patients remain options for those not willing to undergo adjuvant chemotherapy. If pathological stage II is revealed at RPLND, further chemotherapy should be considered (Grade A recommendation)

according to the expected half-time values for AFP and β-hCG. If the marker level increases after orchiectomy, the patient has residual disease. If RPLND is performed, up to 87% of these patients have pathologically documented nodes in the retroperitoneum [35]. An ultrasound examination of the contralateral testicle must be performed if this has not been done initially.

The treatment of true CS1S patients is still in debate. Currently, three courses of primary PEB chemotherapy seem appropriate since all of these patients will present with metastatic disease if followed-up only (Table 3).

5. Treatment: metastatic germ cell tumours

5.1. Stage II A/B seminoma

The standard treatment of stage II A/B seminoma is radiotherapy. The radiation dose delivered in stage IIA and IIB is 30 Gy and 36 Gy, respectively. The standard radiation field compared to stage I will be extended from the PA region to the ipsilateral iliac field (''hockey-stick''). In stage IIB, the lateral borders should include the metastatic lymph nodes with a safety margin of 1.0–1.5 cm. This technique yields a relapse-free survival after 6 years for stage IIA and IIB of 95% and 89%, respectively. Overall survival is almost 100% [36].

In stage IIB, chemotherapy with three cycles of PEB or four cycles of EP (''good prognosis'') is an alternative for patients not willing to undergo radiotherapy.

5.2. NSGCT stage II A/B

There is a general consensus that treatment should start with initial chemotherapy in all advanced cases of NSGCT except for stage II NSGCT disease without elevated tumour markers, which alternatively can be treated with primary RPLND or surveillance [5]. These rare cases of Stage IIA/B without marker elevation may represent metastatic differentiated teratoma.

Stage II A/B non-seminoma with elevated markers should be treated according to IGCCCG ''good or intermediate prognosis'' NSGCT according to marker levels (three or four cycles PEB for good- and intermediate-prognosis patients, respectively, followed by residual tumour resection). About 30% of patients will not achieve a complete remission after chemotherapy and will need a residual tumour resection.

Patients not willing to undergo primary chemotherapy have the option of primary nerve-sparing RPLND with adjuvant chemotherapy (two cycles PEB) in case of metastatic disease (pII A/B). Primary chemotherapy and primary RPLND are comparable options in terms of outcome but side effects and toxicity are different, allowing for involvement of the patient in selecting the treatment of choice.

The cure rate with either approach will be close to 98% [34,37].

5.3. Advanced metastatic disease

5.3.1. Primary chemotherapy

The primary treatment of choice for advanced disease is three or four cycles of either bleomycin, etoposide and cisplatin (BEP) or PEB combination chemotherapy depending on IGCCCG risk classification (Table 1). These regimens have proven superiority to cisplatin, vinblastine and bleomycin (PVB) in patients with advanced disease [38] (Table 4).

For patients with a ''good prognosis'' according to the IGCCCG, standard treatment consists of three cycles of PEB or, where bleomycin is contraindicated, four cycles of PE [39]. Therapy should be given without reduction of the doses in 22-day intervals; delaying

Table 4
British BEP and PEB regimens (every 3 weeks)

Drug	BEP	PEB
Cisplatin	20 mg/m^2, days 1–5[a]	20 mg/m^2, days 1–5[a]
Etoposide	120 mg/m^2, days 1, 3, 5	100 mg/m^2, days 1–5
Bleomycin	30 mg, days 2, 9, 16	30 mg, days 1, 8, 15

BEP: bleomycin, etoposide and cisplatin; and PEB: cisplatin, etoposide and bleomycin.
[a] Plus hydration.

the following chemotherapy cycle is justified only in cases of fever with granulocytopenia <1000/mm^3 or thrombopenia <100,000/Ul.

With the ''intermediate-prognosis'' group in the IGCCCG, a group of patients has been defined, which achieve a 5-year survival rate of about 80%. The available data support four cycles of PEB as standard treatment [40]. Due to the generally less favourable prognosis of this patient group, in comparison to patients with a ''good prognosis'', they may be treated in prospective trials such as the EORTC GU Group trial with PEB versus PEB plus paclitaxel.

For patients with a ''poor prognosis'', standard treatment consists of four cycles of PEB. Four cycles of PEI (cisplatin, etoposide, ifosfamide) have the same effect but are more toxic. The 5-year progression-free survival is between 45% and 50%. It has not yet been proven that high-dose chemotherapy increases the survival rate. General recommendations for treatment modifications for patients with a poor general condition (Karnofsky performance status <50%), extended liver infiltration (>50%) and extended pulmonary infiltration do not exist [41].

5.4. Restaging and further treatment

5.4.1. Restaging

After termination of two courses of chemotherapy, re-evaluation is performed by imaging investigations and determination of tumour markers. At marker decline and stable or regressive tumour manifestation chemotherapy will be completed (three or four cycles depending on the initial stage) [42]. In cases of marker decline, but growing metastases, resection of the tumour is obligatory after termination of induction therapy, unless in the case of emergency according to local tumour growth.

5.4.2. Residual tumour resection

A residual mass of seminoma will not be resected, irrespective of the size, but controlled by imaging investigations and tumour markers [5,43]. Positron emission tomography scan in metastatic seminoma after chemotherapy is a valid tool with which to detect vital residual tumour. In cases of vital tumour after first-line chemotherapy, salvage chemotherapy is given, if necessary including surgery and radiotherapy.

In cases of non-seminoma and complete remission after chemotherapy, residual tumour resection is not indicated [5]. In cases of residual mass (greater than 1 cm in transverse CT diameter) and marker normalization, surgical resection is indicated [44,45]. As yet no imaging investigations including PET or prognosis models, are able to predict histological differentiation of the non-seminomatous residual tumour. Thus, residual tumour resection is mandatory [46].

5.4.3. Consolidation chemotherapy after secondary surgery

After resection of necrosis or mature teratoma, no further treatment is required. In the case of complete resection of vital carcinoma or immature teratoma, two adjuvant cycles of conventionally dosed cisplatinum-based chemotherapy may be given in certain subgroups (e.g. ''poor prognosis'' patients, (cave: cumulative doses of bleomycin). The prognosis will definitely deteriorate if vital carcinoma is found in resection specimens after second- and third-line chemotherapy. In the latter situation, postoperative chemotherapy is not indicated and is unable to improve the prognosis [47].

5.5. Systemic salvage treatment for relapse or refractory disease

5.5.1. Seminoma

Cisplatin-based combination salvage chemotherapy will result in long-term remissions for about 50% of patients who relapse after first-line chemotherapy [48]. Regimens of choice are: four cycles of PEI/VIP (cisplatin, etoposide, ifosfamide), or four cycles of VeIP (vinblastin, ifosfamide, cisplatin).

5.5.2. Non-seminoma

Standard salvage treatment after first-line chemotherapy (Table 5) consists of four cycles of PEI/VIP. Conventionally dosed salvage chemotherapy may achieve long-term remissions in 15–40% of patients, depending on individual risk factors. Prognostic indicators of response to salvage therapy are:

- location and histology of the primary tumour
- response to first line treatment
- duration of remissions
- level of AFP and β-hCG at relapse.

Table 5
Standard PEI/VIP and VeIP chemotherapy

PEI/VIP	Dosage	Duration of cycles
Cisplatin	20 mg/m^2, days 1–5[a]	21 days
Etoposide	75–100 mg/m^2, days 1–5	
Ifosfamide[b]	1.2 g/m^2, days 1–5	
VeIP	**Dosage**	**Duration of cycles**
Vinblastin	0.11 mg/kg, days 1 + 2	21 days
Ifosfamide[b]	1.2 g/m^2, days 1–5	
Cisplatin	20 mg/m^2, days 1–5[a]	

[a] Plus hydration.
[b] Plus mesna protection.

Salvage therapy with VeIP is probably not superior to other conventionally dosed cisplatin-based combination regimens. The use of conventionally dosed combination regimens with more than three agents will increase toxicity without improving treatment outcome.

Depending on the presence of adverse prognostic factors, the results of salvage therapy after first-line cisplatin-based treatment are unsatisfactory [49]. New agents such as paclitaxel, docetaxel, gemcitabine, irinotecan, and oxaliplatin have been tested in the salvage setting. Recently, paclitaxel and gemcitabine have shown to be active in the treatment of refractory germ cell tumours; both drugs are synergistic with cisplatin. Oxaliplatin seems to have activity even in truly cisplatin-refractory patients. For patients with good performance status and adequate bone marrow function, combination regimens of these new agents (e.g. gemcitabine plus oxaliplatin [50]) are currently recommended, since at least a small percentage of patients may again reach long-lasting remissions.

5.6. Salvage surgery

Residual tumours after salvage chemotherapy should be resected within 4–6 weeks after marker normalization or when a marker plateau is reached. In the case of marker progression after salvage treatment and lack of other chemotherapeutic options, resection of residual tumours (''desperation surgery'') should be considered if complete resection of all tumour seems feasible (about 25% long-term survival may be achieved) [51].

5.7. Treatment of brain metastases

Brain metastases occur in the frame of a systemic relapse and rarely as an isolated relapse. The long-term survival of patients presenting with brain metastasis at initial diagnosis is poor (30–40%), but even poorer with the development of brain metastasis as recurrent disease (5-year survival 2–5%) [52]. Chemotherapy is the initial treatment in this case and some data support the use of consolidation radiotherapy even in the case of a total response after chemotherapy. Surgery can be considered in the case of a persistent solitary metastasis depending on the systemic state, the histology of the primary tumour and the location of the metastasis (Table 6).

6. Follow-up after curative therapy

The following considerations apply in a general manner to selecting an appropriate schedule and investigations in the follow-up of all stages of testicular tumours. For detailed follow-up, it is recommended that the reader refers to the previously published version of these guidelines [13].

- Most recurrences after curative therapy will occur in the first 2 years; consequently surveillance should be most frequent and intensive during this time.
- Late relapses can occur beyond 5 years; annual follow-up for life may therefore be advocated [53].
- After RPLND, relapse in the retroperitoneum is rare, the most likely site of recurrence being the chest.
- The value of chest X-ray has been recently questioned in the follow-up of patients with disseminated disease after complete remission [54].
- CT of the chest has a higher predictive value than chest X-ray.
- The results of therapy are dependent on the bulk of disease, thus an intensive strategy to detect presymptomatic disease may be justifiable [55].
- After chemotherapy or radiotherapy, there is a small long-term risk of secondary malignancies.

Table 6
Guidelines for the treatment of metastatic germ cell tumours

1. Low-volume NSGCT stage IIA/B with elevated markers should be treated like ''good'' or ''intermediate prognosis'' advanced NSGCT with three and four cycles of PEB, respectively. Stage II without marker elevation (in suspicion of differentiated teratoma) can be treated either by RPLND or close surveillance with delayed surgery
2. In metastatic NSGCT ($\geq$ stage IIC) with a good prognosis, three courses of PEB is the primary treatment of choice (Grade A recommendation)
3. In metastatic NSGCT with an intermediate or poor prognosis, the primary treatment of choice is four courses of standard PEB (Grade A recommendation)
4. Surgical resection of residual masses after chemotherapy in NSGCT is indicated in the case of a residual mass >1 cm and when serum levels of tumour markers are normal or normalizing (Grade B recommendation)
5. Metastatic seminoma with less than N3M1 disease can be treated initially with radiotherapy. When necessary, chemotherapy can be used as a salvage treatment with the same schedule as for the corresponding prognostic groups of NSGCT (Grade A recommendation)
6. Advanced seminoma (N3 or M1) should be treated with primary chemotherapy according to the same principles used for NSGCT (Grade A recommendation)

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