



## Review – Testis Cancer

# European Consensus Conference on Diagnosis and Treatment of Germ Cell Cancer: A Report of the Second Meeting of the European Germ Cell Cancer Consensus Group (EGCCGG): Part II

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## Abstract

**Objectives:** The first consensus report that had been presented by the European Germ Cell Cancer Consensus Group (EGCCCG) in 2004 has found widespread approval by many colleagues throughout the world. In November 2006, the group met a second time under the auspices of the Department of Urology of the Amsterdam Medical Center, The Netherlands.

**Methods:** Medical oncologists, urologic surgeons, radiation oncologists as well as pathologists from several European countries reviewed and discussed the data that had emerged since the 2002 conference and incorporated the new data into updated and revised guidelines. As for the first meeting the methodology of evidence-based medicine (EBM) was applied. The results of the discussion were compiled by the writing committee. All participants have agreed to this final update.

**Results:** The second part of the consensus paper includes the treatment of metastasised disease, residual tumour resection, salvage therapy, follow-up, and late toxicities.

**Conclusions:** Whereas the vast majority of the recommendations made in 2004 remain valid 3 yr later, refinements in the treatment of early-stage as well as of advanced-stage testicular cancer have emerged from clinical trials. Despite technical improvements, expert clinical skills will continue to be one of the major determinants for the prognosis of patients with germ cell cancer. In addition, the particular needs of testicular cancer survivors have been acknowledged.

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## 1. Treatment of patients with seminoma clinical stage (CS) IIA/B

Until now the standard treatment in CS IIA/B seminoma has been radiotherapy. Total doses in the range of 30–36 Gy seem reasonable. In CS IIA 30 Gy and in CS IIB 36 Gy, respectively, are administered homogeneously with single doses of 2 Gy at five fractions per week [EBM IIB: 1–3]. With modern radiation techniques this treatment results in a relapse-free survival at 6 yr of 95% for stage IIA and

89% for stage IIB [EBM IIB: 1]. Overall survival is close to 100% [EBM IIB: 1–3; EBM III: 4]. The target volume includes the para-aortal and ipsilateral iliac lymphatics. The upper field margin is the upper border of thoracic vertebra 11; the lower field margin is the upper border of the ipsilateral acetabulum. In CS IIA, the lateral field margins for the para-aortic fields are identical to those for CS I. In CS IIB the lateral field margins are individually modified according to the extension of the lymph nodes with a safety margin of 1.0–1.5 cm. To reduce the risk of impairment of

**Table 1 – Chemotherapy protocols for treatment of advanced germ cell cancer**

	Cisplatin, mg/m <sup>2</sup>	Etoposide, mg/m <sup>2</sup>	Ifosfamide, mg/m <sup>2</sup>	Bleomycin, mg absolute	Interval, day	No. of cycles according to prognosis	
						Good	Intermediate/poor
BEP "5 d"	20 d 1-5	100 d 1-5	—	30 (bolus) d 1, 8, 15	21	3	4
BEP "3 d"	50 d 1, 2	165 d 1, 2, 3	—	30 (bolus) d 1, 8, 15	21	3	—
EP	20 d 1-5	100 d 1-5	—	—	21	4	—
VIP	20 d 1-5	75 d 1-5	1200 d 1-5	—	21	—	4

BEP (PEB) = cisplatin, etoposide, bleomycin; EE = cisplatin, etoposide; VIP = etoposide, ifosfamide, cisplatin.

fertility due to scatter radiation dose, shielding of the remaining testicle during irradiation is mandatory. Three months after radiation therapy, abdominal and pelvic computed tomography (CT) scans should be performed to document the treatment effect [EBM III: 5–10] and as a basis for follow-up (Table 1).

Extension of the radiation target volume to the contralateral iliac, inguinal, or scrotal region for prior testicular maldescent, inguinal or scrotal violation, or pT3–4 primary tumours is unnecessary because there is no evidence for a different outcome if such an extension is made [EBM IIA: 11; EBM III: 12–14]. The role of combined radiation and chemotherapy is currently under investigation [EBM IIB: 15,16] and is not recommended outside clinical trials.

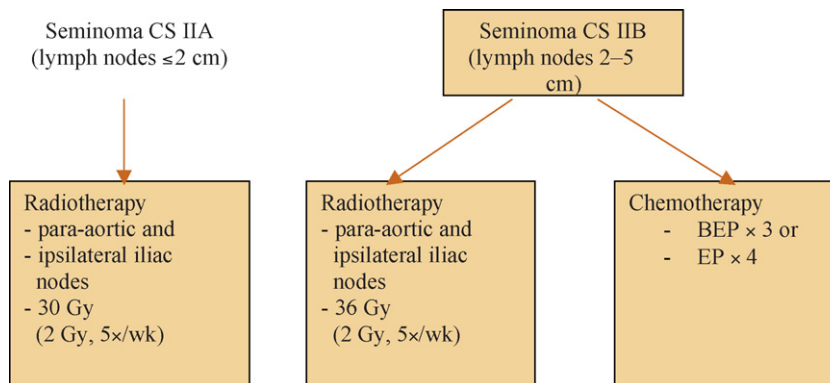
In stage IIA radiotherapy remains the preferred treatment option over chemotherapy. In stage IIB chemotherapy with three cycles of standard-dose bleomycin, etoposide, and cisplatin (BEP), or four cycles of etoposide (EP), represents a treatment alternative to radiotherapy, particularly in patients with larger multinodal retroperitoneal disease (Fig. 1), but may be associated with a higher risk

of acute toxicity as compared to radiotherapy [EBM IIB: 17]. Single-agent carboplatin has not been shown to safely eradicate retroperitoneal metastases in patients with stage II seminoma despite a dosage of area under the curve (AUC) 7 [EBM IIB: 18].

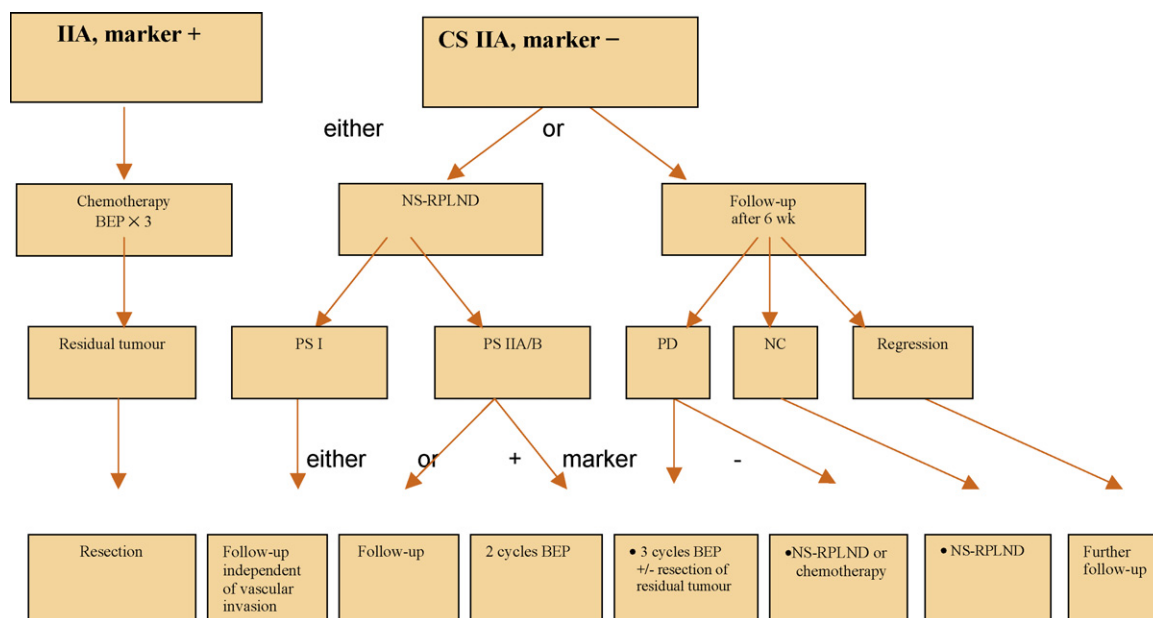
## 2. Treatment of patients with non-seminoma CS IIA/B

The cure rate for CS IIA and IIB non-seminoma is close to 98%. The vast majority of patients with marker elevations of  $\alpha$ -fetoprotein (AFP), human chorionic gonadotropin (HCG), or lactic dehydrogenase (LDH) in CS IIA/B are treated according to the algorithms for patients with advanced disease, according to the International Germ Cell Cancer Consensus Group (IGCCCG) recommendations [19].

Only a few patients without marker elevations but with retroperitoneal lymph nodes 1–2 cm, suspected to have CS IIA, represent a particular problem. Some of these patients will have benign lymph node enlargement. Some of them, however, will have teratoma, pure embryonal carcinoma, or



**Fig. 1 – Treatment algorithm in seminoma clinical stage (CS) IIA/B. BEP = bleomycin, etoposide, cisplatin; EP = etoposide.**



**Fig. 2 – Treatment options in patients with non-seminoma clinical stage (CS) IIA. NC = no change; PD = progressive disease; BEP = cisplatin, etoposide, bleomycin; RPLND = retroperitoneal lymph node dissection; PS = pathologic stage; NS = nerve-sparing.**

mixed tumours. Therefore, patients with primary pure embryonal carcinoma should undergo primary chemotherapy immediately or after a period of surveillance. In patients with primary teratoma or mixed tumours two options can be considered: retroperitoneal lymph node dissection (RPLND) or surveillance. With RPLND the pathologic stage can be verified immediately; if surveillance is chosen, one follow-up after 6 wk is indicated to document whether the lesion grows, remains stable, or shrinks. A shrinking lesion is likely to not be of malignant origin and should be further observed. A stable or growing lesion indicates either teratoma or undifferentiated malignant tumour. If the lesion grows without a corresponding increase of the tumour markers AFP or  $\beta$ -HCG, RPLND should be performed by an experienced surgeon because of suspected teratoma. Patients with a growing lesion and a concomitant increase of the tumour markers AFP or  $\beta$ -HCG should not undergo surgery; they require chemotherapy with BEP according to the treatment algorithm for patients with metastatic disease and IGCCCG recommendations [EBM III: 20–22] (Fig. 2). There is no proven role for positron emission tomography (PET) scans in this situation.

When RPLND is performed, it should be done using a nerve-sparing technique [EBM III: 23,24]. However, depending on the experience of the surgeon, RPLND may result in loss of antegrade ejaculation in 5–32% of patients despite a nerve-sparing approach [EBM IB: 25, EBM IIA: 26, EBM IIB:

14, EBM III: 15]. Other morbidity related to surgery may occur in up to 10% of patients [EBM III: 27]. Surgical exploration at the time of RPLND will reveal pathologic stage (PS) I in 12–13% of patients [EBM IIA: 26, EBM III: 28]; the remaining 87–88% of patients will have PS IIA/B. In the patients at PS IIA/B, further options after RPLND are surveillance or adjuvant chemotherapy [EBM IB: 29, EBM IIA: 30, EBM IIB 31, EBM III: 32–34]. Surveillance after RPLND has a risk of relapse in about 30–50% patients, who will then require three to four cycles of BEP [EBM IB: 29, EBM IIA: 30, EBM III: 21,32,33]. Relapses occur almost exclusively outside the retroperitoneum [EBM IB: 29, EBM III: 24,33–35]. Adjuvant chemotherapy in all patients at PS IIA/B after RPLND reduces this risk of recurrence to about 0–7%. Yet, adjuvant chemotherapy represents an over-treatment in 50–70% of radically operated PS IIA/B patients with the resulting treatment-related toxicity and possible late sequelae [EBM IB: 36, EBM III: 37–42].

An alternative to open RPLND is a laparoscopic approach [EBM III: 43]. However, laparoscopic RPLND has not been validated in a randomised fashion and cannot be recommended as standard treatment.

### 3. Treatment of patients with advanced disease (Table 1)

For patients with a good prognosis, according to IGCCCG criteria [19], standard treatment is three



cycles of BEP. In cases of contraindications against bleomycin four cycles of cisplatin and EP can be given [EBM IA: 19, EBM IB: 44-46, EBM IIA: 47, EBM III: 48]. The efficacy of BEP, given for 5 d with EP 100 mg/m<sup>2</sup> and cisplatin 20 mg/m<sup>2</sup> each day, is equivalent to BEP with EP 165 mg/m<sup>2</sup> applied during 3 d and cisplatin 50 mg/m<sup>2</sup> during 2 d [EBM IB: 49]. However, BEP given over 3 d has increased long-term toxicity including ototoxicity, peripheral neurotoxicity, or Raynaud syndrome when four cycles are applied [EBM IB: 50, EBM IIA: 47, EBM III: 51]. Therefore, the original 5-d BEP regimen remains standard treatment for four cycles required in patients with intermediate and poor prognosis. Chemotherapy should be given without dose reductions at 22-d intervals. Dose reductions are highly discouraged, even in the setting of a critically ill patient. Postponing treatment, that is, maximal of 3 d for each decision, should only rarely be considered, for example, in cases of existing fever, neutrophil counts <500/μl, or platelet counts <100,000/μl at day 1 of a subsequent cycle.

There is no indication for routine prophylactic application of haematopoietic growth factors, such as granulocyte colony-stimulating factor (G-CSF). However, if serious infectious complications have occurred during one preceding chemotherapy cycle, prophylactic administration of G-CSF is recommended in subsequent cycles [EBM IIA: 52,53]. Because dose reductions due to neutropenia should be avoided, prophylactic G-CSF should also be used if prolonged neutropenia occurs for maintenance of the required dose intensity. Prophylactic antibiotic treatment reduces febrile neutropenia during chemotherapy; however, in one study, there was no increased mortality in the control group [EBM IB: 54]. In the EGCCCG panel no consensus could be achieved on this issue.

With the introduction of a group with an intermediate prognosis by the IGCCCG classification, a group of patients has been defined who may reach a 5-yr survival of 80%. Available data support four cycles BEP as standard treatment in these patients [EBM IB: 50]. To design more effective treatment, all patients with an intermediate prognosis should preferably be treated in prospective trials [EBM III: 55]. For patients with a poor prognosis, standard treatment consists of four cycles of BEP. Four cycles of EP, ifosfamide, and cisplatin (VIP) are equally effective, but cause more acute myelotoxicity and are not recommended as standard therapy [EBM IB: 56]. In the IGCCCG analysis, 5-yr progression-free and overall survival were 41% and 48%, respectively. In individual patients VIP may be preferred to BEP to avoid possible bleomycin-induced lung injury in

patients with compromised pulmonary function. Patients with extensive liver, pulmonary, or central nervous system (CNS) involvement may benefit from an immediate brief course of reduced-dose chemotherapy before full-dose chemotherapy cycles are started.

Orchiectomy must not delay the initiation of curative chemotherapy in patients with acute life-threatening poor-prognosis disease [EBM IB: 57]. There is no evidence that high-dose chemotherapy plus autologous haematopoietic stem cell support given as part of first-line therapy increases survival. Two randomised studies have shown no advantage from high-dose chemotherapy for the overall group of patients with a poor prognosis [EBM IB: 58,59]. Evidence from three trials, including one prospective trial, indicates that the decline rate of tumor marker is of prognostic relevance in patients with a poor prognosis according to the IGCCCG criteria [EBM IB: 58, EBM III: 60,61]. These patients should therefore be included in further clinical trials, but they should not receive high-dose chemotherapy in first-line therapy outside such trials [EBM IB: 62; EBM IIB: 63; EBM III: 64].

To maintain the highest chance of cure, patients with a poor prognosis should be transferred to a specialised centre without any delay to benefit from optimal interdisciplinary management and supportive care [EBM III: 65].

#### 4. Treatment of patients with brain metastases

Approximately 10% of all patients with advanced germ cell cancer present with brain metastases (ie, 1-2% of all patients with testicular cancer). At relapse, metastases in the CNS usually occur as part of a systemic relapse and rarely as an isolated sanctuary-site relapse after previously successful treatment. Patients who present with brain metastases at initial diagnosis have a long-term survival probability of 30-40%, whereas patients who develop metastases during first-line treatment or in the context of recurrent disease outside of the brain have a 5-yr survival rate of only 2-5% [EBM IIB: 66]. The best prognostic group consists of patients with a solitary brain lesion discovered by initial staging investigations [EBM III: 67,68]. The presence of metastatic choriocarcinoma indicates a poor prognosis independent from any form of treatment [EBM III: 67-69].

The optimal sequence of treatment modalities (chemotherapy, radiotherapy, surgery) has not yet been finally defined. Curative-intent chemotherapy

is necessary in all patients with brain metastases [EBM III: 69]. In a multivariate analysis cranial irradiation added to systemic chemotherapy improved the overall prognosis of patients who present with brain metastasis [EBM III: 70], which contrasts with earlier reports demonstrating no benefit from additional cranial irradiation [EBM III: 68]. Radiotherapy is commonly applied as whole-brain irradiation, use of single dose of 2 Gy up to a total dose of 40–45 Gy, eventually followed by boost irradiation of the metastatic region. Chemotherapy and radiotherapy can be applied either synchronously or sequentially (chemotherapy followed by radiotherapy). It has not yet been defined whether postchemotherapy irradiation of the CNS is required after complete remission has been achieved by chemotherapy alone. It also remains unclear whether or not secondary resection of a solitary residual mass is required after chemotherapy (magnetic resonance tomography scans are mandatory for detection of micrometastases). Finally, primary cerebral surgery might be considered in patients with solitary brain metastases, though the sparse existing data do not demonstrate any survival benefit.

## 5. Monitoring of treatment results and further treatment

The prognostic value of a transient increase of tumour markers after initiation of first-line treatment as well as a delayed decrease of tumour markers according to their usual half-life is equivocal [EBM III: 71]. In patients with slow tumour marker decline and stable or regressing tumours, chemotherapy should be completed with three to four cycles, depending on the initial stage [EBM IIA: 19,72,73]. Patients with an unequivocal tumour marker increase during chemotherapy must be switched to salvage treatment even if the tumour marker progression does not coincide with radiologic progression. It is important that the marker be measured directly before each treatment cycle; otherwise, the marker can be falsely increased due to release of markers from necrotic tumour cells (Fig. 3).

Patients with elevated tumour markers at diagnosis, who arrive at a low-level marker plateau after four cycles of BEP or VIP, should be followed at short intervals. Salvage chemotherapy should be initiated only if an unequivocal tumour marker increase is observed (Fig. 3). In patients with persistent plateau or further marker regression, all residual radiologic lesions should be resected [EBM III: 74].

The monitoring of tumour markers prior to each treatment cycle is mandatory. Radiologic restaging should be performed after completion of first-line chemotherapy. In patients with slow marker decline or clinical evidence of tumour progression radiologic restaging should be considered earlier. In those rare patients with unequivocally progressive tumours, immediate modification of the first-line treatment strategy is required. Progression with tumour markers despite first-line chemotherapy requires the immediate initiation of salvage treatment [EBM IIB: 75]. However, patients who experience tumour marker progression during or within 4 wk of cisplatin-based first-line treatment have a very poor prognosis [EBM IIB: 76].

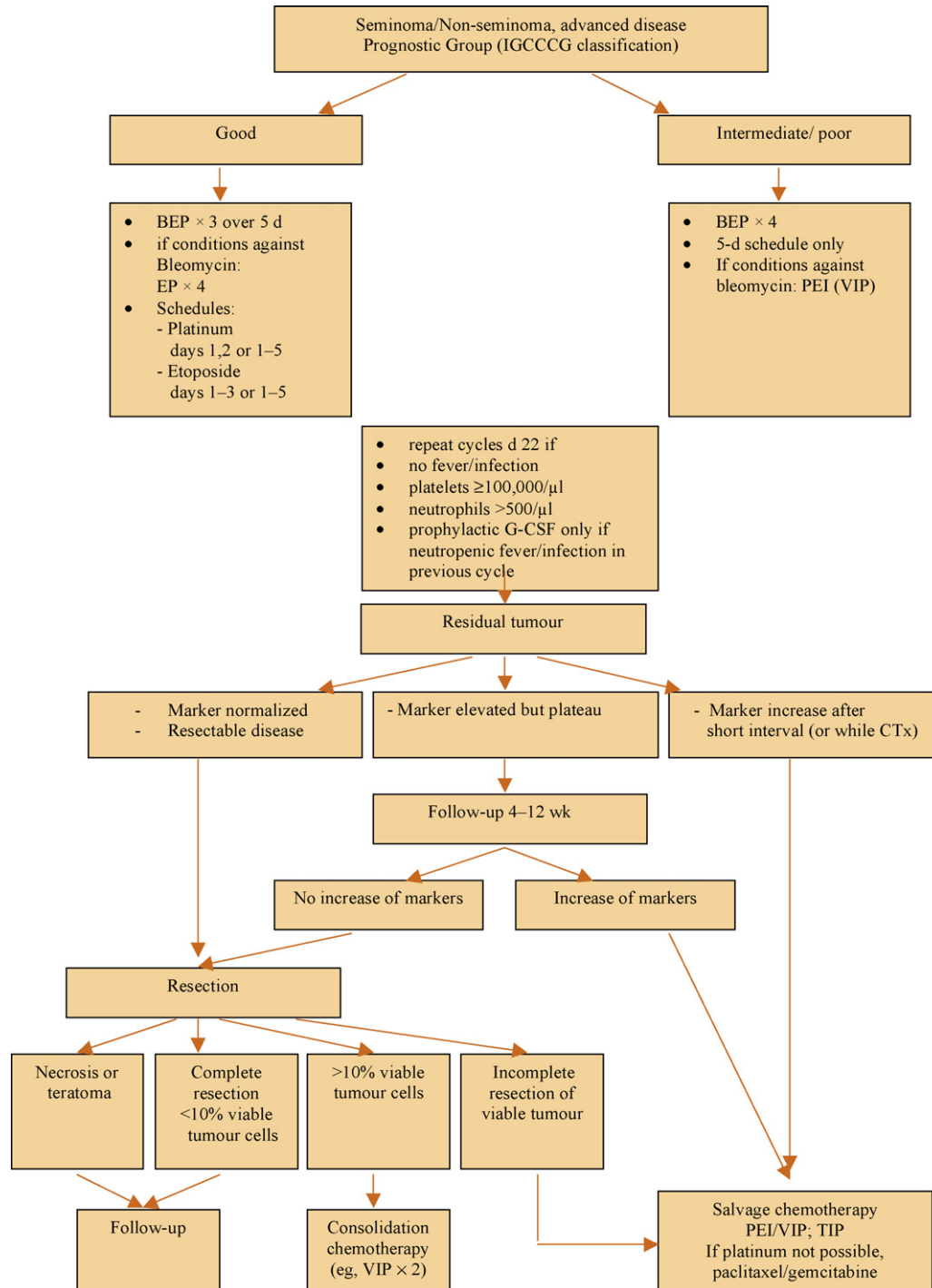
If progression occurs with growing metastases, despite declining tumour markers, the presence of a “growing teratoma syndrome” is highly probable, and complete resection of all residual tumour manifestations is required after the end of first-line chemotherapy [EBM III: 77]. Only in the rare event of rapid radiologic tumour progression should immediate surgery be performed before completion of chemotherapy.

Resection of residual masses should be performed in patients with tumour markers persisting at low levels after completion of first-line treatment. Salvage chemotherapy is required for any documented increase in tumour markers after first-line treatment [EBM III: 51].

## 6. Resection of residual tumour

### 6.1. Seminoma

In patients with seminoma, residual masses present after chemotherapy and after radiotherapy should not necessarily be resected, irrespective of their size, but should be closely followed by imaging investigations and tumour marker determinations [EBM IIB: 78,79; EBM III: 80–82]. Fluorodeoxyglucose (FDG)-PET has a high prognostic value in patients with residual masses after treatment of seminoma. Patients with residual lesions of >3 cm in size that do not regress after therapy should undergo FDG-PET scanning to gain more information about the viability of these residuals. In patients with residual lesions of <3 cm in size, the use of FDG-PET scanning is optional. No resection or any other treatment modality is necessary in patients with a negative PET scan, whereas a positive PET scan, if performed >4–6 wk after day 21 of the last chemo/radiotherapy, is a strong and reliable predictor of viable tumour tissue in patients with residual



**Fig. 3 – Treatment algorithm for advanced germ cell tumour. IGCCCG = International Germ Cell Cancer Consensus Group; BEP = bleomycin, etoposide, cisplatin; EP = etoposide; PEI (VIP) = Platino, etoposide, ifosfamide (etoposide, ifosfamide, cisplatin); TIP = paclitaxel, ifosfamide, and cisplatin; G-CSF = granulocyte colony-stimulating factor; CTx = chemotherapy.**

lesions [EBM IIB: 83,84]. In patients with positive FDG-PET, histology should be obtained by biopsy or preferably by resection. Further treatment should be based on the results of histology and may include observation, surgery, radiation, or

further chemotherapy. In patients with progressive disease after first-line chemotherapy, histology should be obtained and salvage chemotherapy given after confirmation of malignancy [EBM III: 85; EBM IV: 86].



## 6.2. Non-seminoma

Patients who achieve complete remission, that is, normalised tumour markers and no visible residual lesions after chemotherapy, postchemotherapy surgery is not required [EBM IIB: 87,88; EBM III: 89]. No imaging procedures (including PET) nor any prognostic model has been able to reliably predict residual mass histology [EBM IIB: 90; EBM III: 74,91–98]. Therefore, in patients with any residual mass and normalisation of tumour markers the residual masses should be resected [EBM IIA: 99,100; EBM IIB: 101; EBM III: 89,102,103]. In patients with residual lesions >1 cm, there is an increased risk of residual teratoma, if teratoma was present in the initial histology. Histology of residual masses after first-line chemotherapy will show necrosis, mature teratoma, and vital cancer in about 50%, 35%, and 15% of patients, respectively. The incidence of vital cancer may be even higher after salvage chemotherapy.

If technically feasible, all residual masses should be resected. In persistent retroperitoneal disease, retroperitoneal surgery should include all areas of initial metastatic sites. All areas should be completely resected within 4–6 wk after completion of chemotherapy. If technically feasible, a nerve-sparing procedure should be performed. Resection of residual tumours outside the retroperitoneum should also be resected because discordant histology is found in 35–50% of patients [EBM III: 95,104]. Only if the histology of the primarily resected mass, which is located in the retroperitoneum in the majority, is complete necrosis, small (1–1.5 cm) residual lesions in other organs might be actively observed. Nevertheless, larger lesions should be resected. Similarly, surveillance is acceptable in patients with multiple pulmonary lesions in whom necrosis is found in one side of the lung. Due to the high treatment-related acute morbidity, surgery of residual masses should be performed only at specialised centres. Postchemotherapy laparoscopic RPLND remains experimental and should not be used outside clinical trials [EBM III: 43,105,106].

## 7. Consolidation chemotherapy after secondary surgery

After resection of necrosis or teratoma no further treatment is required. When viable undifferentiated tumour is found, the role of further consolidation chemotherapy is uncertain. A retrospective analysis demonstrated an improved progression-free survival with adjuvant chemotherapy but failed to show

an improvement in overall survival. Therefore, a wait-and-watch strategy may also be justified [EBM III: 107]. Patients in the good prognosis group, according to the IGCCCG classification, with complete resection of residual masses and with <10% vital tumour cells in the resected specimens have a favourable outcome even without adjuvant chemotherapy. If completely resected tumour presents >10% of viable cancer, or if completeness of the resection is in doubt, consolidation chemotherapy might be justified (cave: cumulative dose of bleomycin).

## 8. Salvage chemotherapy for relapsed or refractory disease

In patients who relapse or progress after first-line chemotherapy, the localisation and histology of the primary tumour, response to first-line treatment, duration of previous remissions as well as the levels of the tumour markers AFP and HCG at the time of relapse or progression are prognostic indicators [EBM IIB: 76, EBM III: 71] (Table 2).

### 8.1. Seminoma

Patients who relapse after first-line radiotherapy have a cure rate of >90% and should receive cisplatin-based chemotherapy comparable to the treatment strategy in advanced seminoma (Fig. 1). Conventional doses of cisplatin-based salvage chemotherapy after first-line therapy with BEP or EP result in long-term remissions in >50% of patients [EBM IIB: 108]. The regimens of choice are four cycles of VIP, vinblastine, ifosfamide, and cisplatin (VeIP), or paclitaxel, ifosfamide, and cisplatin (TIP) [EBM IIB: 109]. No conventional-dose salvage regimen has shown unequivocal superiority so far over another conventional-dose cisplatin-containing salvage regimen [EBM IIB: 110,111]. Some experts believe that in individual patients radiation treatment may be used instead of or in addition to chemotherapy in patients with small and localised relapses [EBM IV].

### 8.2. Non-seminoma

Patients with recurrent disease after surgery alone have a good prognosis with a cure rate >90% and should receive cisplatin-based chemotherapy comparable to the treatment strategy in metastatic non-seminoma. Salvage treatment after first-line chemotherapy for metastatic disease should comprise four cycles of VIP, VeIP, or TIP. Paclitaxel has shown single-agent activity in patients refractory to

**Table 2 – Reported prognostic factors for relapsed or refractory germ cell tumours [71,109–113]**

	Good	Poor
Histology	Seminoma	Non-seminoma
Localisation of primary tumour	Gonadal	Extragenadal
Response to first-line treatment	CR or marker-negative PR	Marker-positive PR, SD, or PD
Progression-free interval	>6 mo from last treatment	<6 mo from last treatment
Metastatic sites prior to salvage treatment	Only nodal or pulmonary manifestations; no extrapulmonary organ metastases	Extrapulmonary metastases
Marker levels prior to salvage treatment	Low (e.g. AFP <1000 ng/ml) (e.g. HCG < 1000 U/l)	High (e.g. AFP ≥ 1000 ng/ml) (e.g. HCG ≥ 1000 U/l)

CR = complete remission, PR = partial remission; SD = stable disease; PD = progressive disease; AFP =  $\alpha$ -fetoprotein; HCG = human chorionic gonadotropin.

conventional cisplatin-based chemotherapy. In addition, a high response rate of >50% to TIP was observed in patients with a good prognosis. Results from randomised trials specifically addressing the role of paclitaxel are not yet available [EBM IIB: 109]. Conventional-dose cisplatin-based salvage chemotherapy can achieve long-term remissions in 15–60% of patients, depending on individual risk factors (Table 10) [EBM IIB: 76,110; EBM III: 71]. In the absence of randomised trials, no conventional-dose salvage regimen has shown unequivocal superiority [EBM IIB: 110]. The use of more than three drugs in salvage chemotherapy increases toxicity without improving overall treatment outcome.

The results of salvage therapy after first-line cisplatin-based treatments are unsatisfactory and depend largely on the presence or absence of vital malignant tumour tissue [EBM IIB 76; EBM III: 71]. Patients with good prognostic features in the first-salvage situation have a favourable prognosis [EBM IIA: 112]. No advantage from high-dose chemotherapy was observed according to the results of the randomised IT 94 trial [EBM IB: 113]. Therefore, patients with good prognostic features should be offered conventional-dose salvage chemotherapy as the first salvage treatment. In patients with poor prognostic features several phase 2 trials as well as one retrospective matched-pair analysis have shown an improvement in survival with early intensification of first-line salvage treatment using high-dose chemotherapy [EBM IIB: 114,115]. Yet, no consensus for the role of high-dose chemotherapy as first-salvage treatment could be reached. High-dose chemotherapy still represents a curative option for patients with second or subsequent relapses [EBM IIB 115,116; EBM III: 117]. Options for third-line chemotherapy are monotherapy with oral etoposide, paclitaxel, gemcitabine, or oxaliplatin or combinations of these drugs usually given as palliative treatment. However, in individual patients even third-line combinations incorporating new

agents and multimodality treatment can still result in long-term remissions or even cure [EBM III: 118]. Therefore, all patients with relapsed seminoma and non-seminoma as well as patients undergoing palliative treatment should preferably be treated at experienced centres and preferably within prospective randomised trials.

## 9. Salvage surgery

Residual masses after salvage chemotherapy should be resected within 4–6 wk after the normalisation of tumour markers or after a low-level marker plateau has been reached. The prognosis is markedly worse in patients after second- or third-line chemotherapy whose resected residual masses contain vital undifferentiated tumour. In these patients postoperative adjuvant chemotherapy does not improve survival and is therefore not indicated [EBM III: 96,102].

Occasional patients with rising tumour markers and no curative chemotherapy option will be candidates for salvage surgery, sometimes referred to as “desperation surgery,” if complete resection of all tumour manifestations seems feasible. With this approach long-term survival may be achieved in about 25% of patients [EBM IIB: 76; EBM III: 119–124]. Results are better in patients who have a late relapse, moderately elevated AFP level, and localised (mainly retroperitoneal) metastatic deposits. Salvage surgery should not be attempted in rapidly progressive disease with increased  $\beta$ -HCG levels.

## 10. Late relapse

Late relapse is defined as any disease recurrence >2 yr after completion of first-line treatment. A pooled analysis of larger series published between 1989 and 2006 results in a crude incidence of 3.2% and 1.4% for patients with non-seminoma and seminoma,

respectively [EBM III: 125]. Patients with late relapse after chemotherapy are particularly difficult to treat and should be managed differently from all other groups. If technically feasible, all patients with late relapse after chemotherapy should undergo immediate radical surgical resections of all lesions irrespective of the level of their tumour markers to completely resect all undifferentiated germ cell tumour, teratoma, or secondary non-germ-cell cancer [EBM III: 126; 127–131]. If the lesions are not completely resectable, biopsies should be obtained for histologic assessment and salvage chemotherapy should be initiated according to the histologic results. If the patient responds to salvage chemotherapy, secondary surgery should be conducted whenever possible. To avoid excess mortality, late relapses should only be treated at centres experienced in managing such patients.

## 11. Follow-up and late toxicity

The aims of follow-up of patients with germ cell cancer are detection of relapse (including late relapse), diagnosis of second cancers as well as prevention, early diagnosis, and treatment of physical and psychological morbidity related to germ cell cancer or its therapy.

During the initial posttreatment phase follow-up consists of regular clinical examinations, monitoring of serum tumour markers, and imaging investigations. The frequency and type of examinations depend on the estimated risk of relapse, the chosen treatment strategy, and the time that has elapsed

since completion of therapy and should be modified according to these risks. However, only limited information about the optimal follow-up strategy exists, and at the present time recommendations can only be given for seminoma (Table 3) [132]. Table 4 summarises the diagnostic imaging procedures based on the treatment chosen and the resulting pattern of relapse [EBM IB: 133]. Nevertheless, the most effective time schedule still remains to be defined. For low-risk stage I non-seminoma two abdominopelvic CT scans during the first year seem sufficient to detect relapses at an early stage [EBM IB: 134]. The significance of additional CT scans remains uncertain. No studies are available that address the optimal monitoring of such patients by serum tumour markers (AFP,  $\beta$ -HCG).

Clinicians and patients should be aware of the risk of a contralateral second testicular primary tumour. This risk depends on a patient's age and exposure to chemotherapy and varies between 2% and 5% during the first 15 yr [EBM III: 135]. Patients aged <30 yr with seminoma display the highest risk, whereas older men with non-seminoma disease have the lowest risk. In case of biopsy-proven untreated testicular intraepithelial neoplasia (TIN) in the contralateral testis the cumulative probability for development of testicular cancer ranges between 30% and 70% after 7–15 yr. All second testicular tumours should be detected at an early stage by regular controls including self-examination of the testis, which should be encouraged in all patients [EBM III: 136]. Regular ultrasound should be performed in patients with high-risk factors (testicular

**Table 3 – Recommendations for frequency of follow-up visits in seminoma stage I [132]**

Annual hazard rate	Frequency of visits/yr	Duration of follow-up		
		Surveillance	Radiotherapy	Carboplatin $\times$ 1
>5%	3 $\times$	1st–2nd yr	NA	NA
1–5%	2 $\times$	3rd–4th yr	1st–3rd yr	1st–3rd yr
0.3–5%	1 $\times$	5th–10th yr	4th–6th yr	No recommendation possible so far
<0.3%	Cease	After 10 yr	After 6 yr	

NA = not available.

**Table 4 – Recommendations for investigations at follow-up in seminoma stage I**

Investigation	Surveillance	Para-aortic RT	Carboplatin $\times$ 1
History and examination <sup>a</sup>	Yes	Yes	Yes
CT abdomen	Yes	No	Yes
CT pelvis	Yes	Yes	Yes
Chest x-ray	Yes	Yes	Yes

CT = computed tomography; RT = radiotherapy.

<sup>a</sup> Plus human chorionic gonadotropin.

maldescent, atrophy of the remaining testicle, infertility) who have not had a testicular biopsy for exclusion of TIN. If regular ultrasound of the contralateral testicle is performed one should be aware that microlithiasis is common after chemotherapy and should not be regarded as an abnormality [EBM IV].

The relative risk (RR) of a treatment-induced non-germ-cell solid cancer depends on the patient's age at diagnosis, type of treatment, and duration of follow-up [EBM III: 137]. In 10-yr survivors significantly increased RRs have been demonstrated after initial radiotherapy alone (RR = 2.0), chemotherapy alone (RR = 1.8), and, in particular, after the combination of chemotherapy and radiotherapy (RR = 2.9). Cases of leukemia after cumulative doses of EP <2 g (reported incidence 0.6%) and etoposide doses  $\geq$ 2 g (reported incidence 2%) occur most frequently during the first decade after treatment decade [EBM III: 138].

Clinical or subclinical late effects comprise cardiovascular disease and metabolic syndrome and should be actively monitored and treated if present. Risk factors for cardiovascular disease are hypercholesterolaemia and hypertension. Patients should be strongly encouraged to stop smoking [EBM III: 139–144]. Other potential late effects such as nephrotoxicity, hypogonadism, persistent neurotoxicity, Raynaud phenomena, and ototoxicity may occur in 15–25% of long-term survivors and should be adequately addressed [EBM III: 140,144]. The risk of hypogonadism may be as high as 10–16% and requires regular monitoring of luteinising hormone, follicle-stimulating hormone, and testosterone particularly in patients with sexual problems and those experiencing involuntary infertility [EBM III: 145,146]. After abdominal radiotherapy slight persistent gastrointestinal symptoms are relatively common (increased stool frequency, meteorism) [EBM III: 147]. After use of older radiation techniques, significantly increased standardised mortality rates (SMR = 1.61) due to benign digestive disorders were reported [EBM III: 144]. It is uncertain whether the risks of gastrointestinal disorders are maintained using modern radiotherapy, with reduced field size and target doses of only 20 Gy. Long-term follow-up requires education of practitioners about potential late effects. It is recommended to provide survivors of germ cell tumours with a "Patient Care Plan" that summarises treatment, complications from this treatment, and the risks of future morbidity.

### Conflicts of interest

The authors have nothing to disclose.

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