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Introduction

A germ cell tumour of the testis is a rare disease although it is the most common tumour in men aged 20–35 years. The incidence of testicular cancer is about 4–5 per 100 000 men per year, but there is a geographical and racial variation. Most patients present themselves with a painless lump in the testicle. Sometimes the first symptoms are related to retroperitoneal lymph node metastasis (back pain) or to lung metastasis (haemoptysis or breathlessness). A few patients present with gynaecomastia as a result of an elevated level of the tumour marker human chorionic gonadotrophin (HCG).

The diagnosis is established after an inguinal orchiectomy, and germ cell tumours are distinguished into seminomas and non-seminomas, each accounting for about 50% of the total. Staging includes, next to physical examination, computed tomographic (CT) scanning of the chest, the abdomen and the pelvis and determination of the serum levels of lacto-dehydrogenase (LDH), alpha-fetoprotein (AFP) and HCG. The Royal Marsden staging system is widely used [1]. In stage I there is no evidence of metastatic disease and the tumour is confined to the testicle. In stage II there is abdominal metastasis and in stage III supradiaphragmatic metastasis. In stage IV extralymphatic metastasis are present. Furthermore, this staging system also quantifies the volume of metastatic disease. In 1997, the International Germ Cell Cancer Collaborative Group published a prognostic classification system for patients with disseminated disease based on histology (seminoma vs non-seminoma), origin of the primary (gonadal vs extra-gonadal), place of metastases and the level of serum tumour markers. Patients can be divided into three prognostic groups: good, intermediate and poor [2] (Table 13.1).

Because the histopathology of testicular cancer is complex, as is the treatment, referral to a specialist centre is frequently advised [3], especially because survival of patients with testicular cancer appears to be related to the experience of the treating institution [4] and because of the need for long-term medical care of survivors [5].

Table 13.1 Staging and classification of testicular cancer [2,60,61]

Royal Marsden Hospital staging (seminoma and non-seminoma)		International Germ Cell Consensus classification	
		Non-seminoma	Seminoma
I	Testicular involvement alone, no evidence of metastases	Good prognosis: all of the following	Good prognosis: all of the following
		αFP < 1000 ng/ml and βHCG < 5000 IU/L	Normal αFP, any βHCG and any LDH
		LDH < 1.5 × upper limit of normal (ULN)	Any primary site
		Non-mediastinal primary and no non-pulmonary visceral metastases present	No non-pulmonary visceral metastases present
Im+	Stage I on CT scan but marker-positive	Intermediate prognosis: all of the following	Intermediate-prognosis:
II	Infradiaphragmatic lymph node involvement	αFP 1000–10 000 ng/ml or βHCG 5000–50 000 IU/L or LDH 1.5–10 × ULN	Non-pulmonary visceral metastases present
	Stage IIA/B/C: maximum diameter < 2 cm/2–5 cm/> 5 cm	Non-mediastinal primary site and no non-pulmonary visceral metastases present	
III	Supradiaphragmatic lymph node involvement Stages IIIA/B/C as for stage II		
IV	Extranodal metastases	Poor prognosis: any of the following αFP > 10 000 ng/ml or βHCG > 50 000 IU/L or LDH > 10× ULN Mediastinal primary site Non-pulmonary visceral metastases present	

Seminoma stage I

Radiation to the para-aortic and ipsilateral lymph nodes is the standard treatment for stage I seminoma, the so-called 'dogleg' field. Doses of 25–30 Gy are given and provide excellent local control. In order to reduce haematologic, gastrointestinal and gonadal toxicity and to maintain efficacy, a recent randomized prospective trial compared the conventional 'dogleg' field with a field limited to the para-aortic region alone. It was found that the limited field produced statistically less significant morbidity

while the 3-year relapse-free survival was identical (96%), as was the overall survival (99–100%). The more limited field radiation, however, had a nonsignificant increased risk of pelvic recurrences (1.8% vs 0%) [6].

Concerns regarding acute and chronic toxicity of radiation have resulted in interest in surveillance for stage I seminoma. Several large surveillance series showed a recurrence rate in the range of 15–20% with a median follow-up of 4–6 years, but nearly all patients with recurrent disease can be cured by radiation therapy or cisplatin-containing chemotherapy, leading to a survival rate of more than 99% [7]. The risk of recurrence in patients on surveillance seems to be related to several adverse prognostic factors, such as tumour size, tumour invasion of small vessels and age at presentation, but in a multivariate analysis tumour size (more than 4 cm) and invasion of the rete testis were the only important factors [7]. Nevertheless, surveillance is not yet an accepted alternative to radiation.

The effectiveness of one or two courses of adjuvant chemotherapy with the single-agent carboplatin in stage I seminoma has been studied in 160 patients [8]. Although only two patients developed a recurrence, the use of adjuvant carboplatin should be considered as investigational until the results of randomized trials are available.

Standard treatment options

For patients with stage I: Radical inguinal orchiectomy, followed by radiation to para-aortic and ipsilateral lymph nodes, 'dogleg' field, with a dose range from 25 to 30 Gy.

Seminoma stage IIA/B with lymph node metastasis < 5 cm

In stage II seminomatous testicular cancer, retroperitoneal or para-aortic lymph nodes are usually present in the region of the kidney. Retroperitoneal involvement should be further characterized by the size of the involved nodes. For treatment planning and estimation of prognosis, stage II seminoma is divided into bulky (IIC) and nonbulky (IIA/B) disease. Radiotherapy alone is standard in seminoma stage IIA/B. The risk of recurrence after radiotherapy is increased if more than five nodes are involved, or if the maximal size of the lymph node metastasis is greater than 5 cm in diameter [9]. Stage IIA/B disease has a cure rate of more than 90% with radiation alone and chemotherapy cures more than 90% of patients who have a relapse after radiation therapy [10].

Bulky stage II (IIC) disease describes patients with extensive retroperitoneal nodes (< 5 cm) who require primary chemotherapy and who have a less favourable prognosis.

Standard treatment options

For patients with stage IIA/B: Radical inguinal orchiectomy followed by radiation to the retroperitoneal and ipsilateral pelvic lymph nodes. (Radiation to inguinal nodes is not standard unless there has been some damage to the scrotum, putting inguinal lymph nodes at risk.)

Seminoma advanced disease: stage IIC with lymph node metastasis > 5 cm to stage IV

Patients with stage IIC seminomatous testicular cancer have metastatic tumours greater than 5 cm on a CT scan. Historically, radiotherapy was used for all stages of seminoma; however, the success of the radiation is inversely related to the bulk of the disease. These studies suggest that radiotherapy had a high failure rate if the abdominal mass was more than 5 cm in diameter. Higher risk of relapse can amount to 35% for abdominal masses larger than 10 cm in diameter [9]. Another problem with the use of radiotherapy in the initial management of patients with an abdominal mass of more than 5 cm in diameter is the extent of the kidney within the radiation field. These considerations lead most authors to recommend primary chemotherapy for patients with bulky disease (IIC) [9]. Combination chemotherapy with cisplatin is an effective therapy in patients with stage IIC seminomas, leading to a probability of progression-free survival of ± 90%. Patients with stage III and IV disease are also treated primarily with combination chemotherapy. Chemotherapy combinations include BEP (bleomycin + etoposide + cisplatin) for four courses [11,12] and EP (etoposide + cisplatin) for four courses in good-prognosis patients only [13]. Other regimens, such as VIP (etoposide + ifosfamide + cisplatin), appear to produce similar survival outcomes but are less commonly used. A randomized study comparing four courses of BEP with four courses of VIP showed equivalent overall survival and time-to-treatment failure for the two regimens in patients with advanced disseminated germ cell tumours who had not received prior chemotherapy [14]. Haematologic toxic effects, however, were substantially worse with the VIP regimen. A recent study in patients with good-risk germ cell cancer (including seminoma) showed equivalence of three versus four courses of BEP chemotherapy [15]. Four hundred and six patients were compared in both arms; 23% of the randomized patients had seminoma in both arms. The projected 2-year progression-free survival was 90.4% for three cycles and 89.4% for four cycles of BEP.

Because of the toxicity of these cisplatin regimens in relatively old patients with seminoma, there is a need for less toxic treatments. Although monotherapy with carboplatin has a relatively high failure rate of about

23% [16], combinations of carboplatin-based chemotherapy have been propagated as active [17].

Residual radiologic abnormalities are common at the completion of chemotherapy, but many gradually regress over a period of months. Some clinicians advocate empiric radiation of persistent residual abnormalities or attempt to resect residual masses if the diameter is 3 cm or more [18]. Either approach is controversial. In a combined retrospective series of 174 seminoma patients with postchemotherapy residual disease treated in ten centres, empiric radiation was not associated with any significant improvement in progression-free survival after completion of the chemotherapy [19]. In some other series, surgical resection of specific masses has yielded a significant number with residual seminoma that requires additional therapy [20]. Nevertheless, other reports indicate that size of the residual mass does not correlate well with active residual disease; most residual masses do not grow and frequent marker and CT scan evaluation is a viable option even when the residual mass is 3 cm or more in diameter.

Table 13.2 Common chemotherapy regimens for patients with disseminated non-seminomatous testicular cancer in different prognostic groups

Prognosis group	Regimen	Days of administration	Interval (weeks)	Number of courses
Good prognosis	**BEP***		3	3
	Bleomycin 30 mg	Days 2, 8 and 15		
	Etoposide 100 mg/m^2	Days 1–5		
	Cisplatin 20 mg/m^2	Days 1–5		
	Bleomycin 30 mg	Days 2, 8 and 15	3	3
	Etoposide 165 mg/m^2	Days 1–3		
	Cisplatin 50 mg/m^2	Days 1 and 2		
	EP		3	4
	Etoposide 100 mg/m^2	Days 1–5		
	Cisplatin 20 mg/m^2	Days 1–5		
Intermediate and poor prognosis	**BEP**		3	4
	Bleomycin 30 mg	Days 2, 8 and 15		
	Etoposide 100 mg/m^2	Days 1–5		
	Cisplatin 20 mg/m^2	Day 1–5		
	VIP**		3	4
	Etoposide 75 mg/m^2	Days 1–5		
	Ifosfamide 1.2 g/m^2	Days 1–5		
	Cisplatin 20 mg/m^2	Days 1–5		

*de Wit *et al.* [15].
**Nichols *et al.* [14]

Standard treatment options

For seminoma patients with stage IIC–IV: Radical inguinal orchiectomy followed by combination chemotherapy (with a cisplatin-based regimen). Chemotherapy combinations include BEP for three or four courses in good- or intermediate-prognosis patients (Table 13.2) or EP for four courses in good-prognosis patients. There is controversy whether any residual masses present at the completion of chemotherapy should be empirically irradiated, or whether masses greater than 3 cm should be resected.

Non-seminoma stage I

The cure rate for patients with non-seminomatous tumours in clinical stage I exceeds 95%. About 20% of patients with stage I disease without lymphatic or vascular invasion or without invasion into the tunica albuginea, spermatic cord or scrotum are discovered to have regional lymph node metastases at surgery. Nerve-sparing retroperitoneal lymph node dissection and surveillance are both standard treatment options [1].

Nerve-sparing retroperitoneal lymph node dissection

A primary retroperitoneal lymph node dissection after orchiectomy allows careful pathological staging, while at the same time offering a therapeutic benefit if the retroperitoneal lymph nodes are positive. A nerve-sparing retroperitoneal lymphadenectomy (RPL) that preserves ejaculation in virtually every clinical stage I patient appears to be as effective as the standard RPL. Despite the improved accuracy of clinical staging methods about 20% of patients with clinical stage I have pathological stage II disease at RPL. Many of these patients are cured surgically without subsequent chemotherapy. However, approximately 80% of clinical stage I patients who undergo primary RPL are found to have pathological stage I disease and do not benefit from the surgical procedure [21].

In case of a pathological stage I after RPL, patients can go into follow-up without additional treatment. In a large study, 15% of patients with a negative lymph node dissection experienced recurrence, usually pulmonary and usually within 18 months [22]. The overall survival rate of patients with pathological stage I is about 99% [23].

In case of tumour in the resected lymph nodes in patients with a clinical stage I, a pathological stage II is documented. The relapse rate of a pathological stage II not treated with adjuvant chemotherapy is related to the volume of retroperitoneal disease up to 30% [21]. These patients are therefore further treated with two courses of adjuvant cisplatin-combination chemotherapy [24].

Prognostic factors for patients with stage I disease that may predict the likelihood of occult metastases are the presence of lymphatic or venous invasion in the primary tumour, the presence of embryonal cell carcinoma and the absence of yolk sac elements in the primary tumour [23]. A more sophisticated way to stain proliferating tumour cells in testicular tumours with a monoclonal antibody MIB-1 against Ki-67 in combination with the volume of embryonal cell carcinoma and the transaxial diameter of retroperitoneal lymph nodes in the predicted landing zone allows a low-risk clinical stage I classification [25]. However, none of these strategies reliably predicts the presence of occult metastases in clinical stage I disease.

If performed, surgery should be followed by monthly determination of serum markers and chest X-rays for the first year and 1- to 2-month determinations for the second year, every 6 months in years 3 to 5, and follow-up is then indicated yearly thereafter [26].

Surveillance

Approximately 75–80% of patients with clinical stage I disease who undergo RPL have negative lymph nodes [26]. The rational for surveillance is to avoid surgical 'overtreatment' of patients with clinical stage I disease. In this strategy, radical inguinal orchiectomy without retroperitoneal node dissection is followed by regular follow-up (e.g. every 1–2 months) consisting of history, physical examination, determination of serum tumour markers, and during the first year, abdominal CT scans [27]. Intervals for abdominal CT scans have varied from every 2 months to scans only at 3 and 12 months post-orchiectomy, with apparently similar outcomes [27]. Disease recurrence is rarely detected by chest X-ray alone, so chest X-ray may play little or no role in routine surveillance [28]. In a Medical Research Council (MRC) surveillance study of non-seminomatous germ cell tumours (NSGCTs), 396 patients with a median follow-up of 4 years had a 25% recurrence rate and a mortality rate of less than 2% [29]. Long-term follow-up is important, since relapses have been reported more than 5 years after the orchiectomy in patients who did not undergo a retroperitoneal dissection.

Surveillance should be considered only if:

1 CT scan and serum markers are normal;

2 the patient and the physician accept the need for repeating CT scans as necessary to continue the periodic monitoring of the retroperitoneal lymph nodes up to 24 months;

3 the patient diligently follows a programme of regular check-ups, which includes history, physical examination, radiology and determination of serum markers;

4 the physician accepts responsibility for seeing that a follow-up schedule is maintained as noted for 2 years and then periodically beyond 2 years.

Data suggest that relapse rates are higher in patients with histological evidence of lymphatic or venous invasion and lower when the primary tumour contains mature teratoma [30]. Some investigators have reported higher relapse rates in patients with embryonal cell histology and recommend RPL for such patients [22,29]. Other investigators have not found a higher relapse rate for this subgroup [30]. Additionally, some investigators recommend RPL in patients with a normal pre-orchiectomy AFP, because they feel this marker cannot be used as an indicator of relapse during follow-up [22,29]. However, since marker-negative patients may be marker-positive at relapse and marker-positive patients may be marker-negative at relapse, other investigators do not view a normal pre-orchiectomy AFP as a contraindication to a surveillance policy.

Adjuvant therapy consisting of two courses of BEP has been administered to patients with clinical stage I disease who were considered at high risk of relapse (about 50% predicted relapse rate based on presence of vascular invasion and histologic type) [31]. In 114 such patients, the relapse-free survival at 2 years was 98%. Another study of high-risk clinical stage I patients treated with two adjuvant courses of BEP [32] reported a relapse rate of less than 5%, while in historical series of high-risk patients followed without adjuvant chemotherapy the relapse rate was 50%. However, in the historical series, cure rates have also been 95% and greater after chemotherapy is given for relapse. Given the present criteria, high-risk patients will relapse, at most, around 50% of the time, and thus approximately 50% of patients who would not have relapsed would receive chemotherapy 'unnecessarily'.

It is unclear which approach is superior in outcome. The adjuvant chemotherapy series are too small to draw definite conclusions about ultimate efficacy and about the risk of chemotherapy-induced long-term toxicity, secondary malignancies, impact on fertility or risk of late relapse.

Standard treatment options

For patients with non-seminoma stage I: Radical inguinal orchiectomy followed by either retroperiotoneal lymph node dissection (in case of pathological stage I: follow-up, in case of pathological stage II: two adjuvant courses of BEP) or surveillance.

Non-seminoma stage II–IV

Disseminated non-seminoma is highly curable. In most patients, an orchiectomy is performed before starting chemotherapy. However, if the

diagnosis has been made by biopsy of a metastatic site and chemotherapy initiated, subsequent orchiectomy is generally performed due to the fact that chemotherapy may not eradicate the primary cancer. This is illustrated by case reports in which viable tumour was found on postchemotherapy orchiectomy despite complete response of metastatic lesions [33].

After the introduction of cisplatin, vinblastine and bleomycin (PVB) combination chemotherapy, consisting of a remission–induction part and a maintenance part, the strategy for treatment outcome improvement had focused on less toxicity with similar efficacy. It was shown that the dosage of vinblastine could be reduced (0.3 mg/kg vs 0.4 mg/kg) and that maintenance chemotherapy does not prevent relapses but adds significantly to the toxicity [34]. Later on vinblastine has been replaced by etoposide; based on the efficacy of etoposide in salvage therapy, and based on the results of a randomized study with BEP, this combination became the new standard [34].

Other centres have developed their own combinations such as the Memorial Sloan–Kettering Cancer Center, New York, using the so-called VAB schemes [35], or Charing Cross Hospital, London, using the POMB-ACE combination [36], but most often the BEP regimen is used.

The success of treatment of disseminated testicular cancer has led to refinements in treatment, with a greater importance on prognostic factors. Several groups have devised schema for stratifying patients into prognostic groups. Although each prognostic system has advantages and disadvantages, several characteristics are common. On the other hand, substantial differences occur between the various classifications in their use of prognostic variables and in their ability to separate patients into good-and poor-prognostic groups. This means that the description of a good prognosis differs, depending on the prognostic system used. To achieve more uniformity in classifying the prognosis of patients with metastatic disease, the International Germ Cell Cancer Collaborative Group (IGCCCG) recently developed a prognostic classification for germ cell tumours based on a large analysis of more than 5000 patients who were treated in prospective studies in North America, Europe, New Zealand and Australia. Primary tumour site, degree of elevation of serum tumour markers (AFP, HCG and LDH) and the presence or absence of non-pulmonary visceral metastases were identified as the most important independent prognostic variables. Integration of these prognostic factors produced three groupings of testicular cancer patients with good, intermediate and poor prognosis, with 5-year overall survival rates of 92%, 80% and 48%, respectively [2]. Since then this system is used by all collaborative groups.

Good-risk patients with metastatic non-seminomatous testicular cancer

The strategy for treatment outcome improvement in 'good-risk patients' has focused on less toxicity with the same efficacy compared with the standard treatment of BEP. Attempts to improve the toxicity profile have focused on the role of bleomycin (especially because of bleomycin-induced pulmonary fibrosis). The European Organization of Research and Treatment of Cancer (EORTC) compared four courses of BEP with four courses of EP in patients with a 'good prognosis'. The total dose of etoposide per course, however, was 360 mg/m^2 compared with 500 mg/m^2, as is the US standard. In total, 419 patients were randomized. In the EP arm 87% of the patients achieved a complete response, if necessary followed by surgical resection of residual disease; in the BEP arm this was the case in 95% of the patients. This difference is significant. Due to the low number of relapses (4%) no difference in progression-free survival was found [37]. An Eastern Cooperative Oncology Group (ECOG) study compared three cycles of BEP with three cycles of EP [38]. In the BEP arm 94% of the patients achieved a complete response versus 88% in the EP arm. The progression-free survival of the BEP group was significantly higher than that of the EP group (86% vs 68% after 5 years). So bleomycin is an essential part of the standard BEP regimen.

To address the question whether cisplatin can be replaced by the less-toxic analogue carboplatin, an MRC–EORTC study was performed. Almost 600 patients with a 'good prognosis' were randomized between four courses of BEP and four courses of carboplatin–etoposide–bleomycin (CEB) [39]. Significantly less patients in the CEB arm achieved a complete response (94% vs 88%). After 1 year, the progression-free survival was significantly lower in the CEB arm compared with the BEP arm. These data demonstrate that cisplatin cannot be substituted by carboplatin. To assess the optimal number of courses of BEP (Table 13.2) a study was performed in which three courses of BEP have been shown to be equivalent to four courses in patients with minimal or moderate extent of disseminated germ cell tumours [40]. To estimate equivalence of three and four courses of BEP, an EORTC–MRC study was performed randomizing three courses of BEP with three courses of BEP plus one course of EP [15]. The median 2-year progression-free survival was 90.4% versus 89.4%. Therefore it can be concluded that for good-risk patients based on the IGCCCG criteria these regimens are equivalent.

One question remaining is whether in good-risk patients three courses of BEP are equivalent to four courses of EP (Table 13.2). Probably this question will never be answered and the choice is based on personal preferences.

The standard treatment options for 'good-prognosis' patients

Radical inguinal orchiectomy followed by chemotherapy. Chemotherapy regimens include BEP for three courses or EP for four courses (Table 13.2). If these patients do not achieve a complete radiological response on chemotherapy, surgical removal of all residual masses should be performed.

'Intermediate- and poor-risk' patients with metastatic non-seminomatous testicular cancer

Compared with good-risk non-seminoma patients, patients with intermediate or poor risk have a worse prognosis. This is a strong argument for treating patients as soon as possible after being diagnosed as having metastatic disease. IGCCCG data show that intermediate prognosis accounts for ± 28% of the non-seminomatous testicular cancer patients and the 5-year survival of this group is 80%. The non-seminomatous testicular cancer patients with a poor prognosis (± 16% of the patients) have a 5-year survival of 48% [2]. The patients who are not cured with standard chemotherapy usually have widespread visceral metastases, high tumour marker levels or mediastinal primary tumours at presentation. Some retrospective data suggest that the experience of the treating institution may impact the outcome of non-seminoma. Data from 380 patients treated from 1990 to 1994 on the same study protocol at 49 institutions were analysed [4]. Overall, 2-year survival for the patients treated at institutions that entered less than five patients onto the protocol was 62% (95% CI = 48–75%) versus 77% (95% CI = 72–81%) in the institutions that entered at least five patients. As in any nonrandomized study design, patient selection factors and factors leading patients to choose treatment at one centre over another can make interpretation of results difficult.

Although the standard treatment for patients with an intermediate or poor prognosis has been four courses of BEP chemotherapy, the strategy for treatment outcome improvement has focused on non-cross-resistant chemotherapy combinations, and dose escalation or intensification. A study in which 244 patients were randomized between four courses of BEP and four alternating courses of PVB and BEP showed no significant differences in complete remission numbers: 72% versus 76%, respectively. The progression-free survival was 80% in both groups [41]. Because of its activity in second-line treatments, ifosfamide was incorporated into first-line treatments. A randomized study comparing four courses of BEP with four courses of VIP showed equivalent overall survival (83% vs 85%, respectively) and time-to-treatment failure for the two regimens in patients with advanced disseminated germ cell tumours who had not received prior chemotherapy. Haematologic toxic effects were substantially worse with the VIP regimen [14].

In patients with poor-risk germ cell tumours, the standard dose cisplatin regimen has been shown to be equivalent to high-dose cisplatin (40 mg/m^2 daily $\times$ 5 per course) in terms of complete response, cure rates and survival; moreover, patients in the high-dose cisplatin regimen experienced significantly more toxic effects [42]. A randomized comparison of an intensive induction-sequential chemotherapy schedule BOP/VIP-B (bleomycin, vincristine, cisplatin, etoposide, ifosfamide) with BEP in patients with poor-prognosis non-seminomatous testicular cancer showed more toxicity without evidence of an improved response rate or survival for the BOP/VIP-B regimen [43].

Based on its activity in patients with a relapsed or refractory germ cell tumour, paclitaxel is an interesting drug to add to the first-line regimen in patients with intermediate- or poor-prognosis disease [44]. The EORTC is currently performing a study in which intermediate-risk patients are treated with standard BEP versus BEP plus paclitaxel (T-BEP).

More intensive approaches are explored in several studies, including high-dose chemotherapy with peripheral stem cell transplantation. This approach has been fuelled by results from small studies in patients who failed second- or third-line cisplatin-containing regimens. Long disease-free periods were established in 10–20% of patients who were treated with high-dose chemotherapy and peripheral stem cell rescue [45,46]. This approach has also been used in a French study in which patients with poor prognostic factors were randomized between conventional dose chemotherapy and conventional dose combined with high-dose chemotherapy as first-line treatment [47]. The 2-year survival rate was not different in both treatment arms; however, the trial was inconclusive because the dose of cisplatin was lower in the experimental arm compared with the standard arm. A dose-intense regimen using the VIP combination has been exploited by a German study group [48]. The dose intensity of etoposide was three times higher and that of ifosfamide two times higher compared with standard VIP. The EORTC is currently performing a randomized study in poor-prognosis testicular cancer patients, comparing standard BEP with high-dose VIP and peripheral stem cell rescue. Patients who present with brain metastases as a poor prognostic factor should be treated with chemotherapy and simultaneous whole-brain irradiation (5000 cGy/25 fractions) [49].

The standard treatment options for 'intermediate- and poor-prognosis' patients

Radical inguinal orchiectomy followed by chemotherapy with postchemotherapy surgery for removal of residual masses (if present). Chemotherapy regimens include BEP for four courses and VIP for four courses (Table 13.2).

Surgery after chemotherapy

If patients do not achieve a complete radiological response after chemotherapy, surgical removal of residual masses should be performed. The timing of such surgery requires clinical judgement, but occurs most often after three or four cycles of combination chemotherapy and after normalization of serum marker levels. The probability of finding residual teratoma or carcinoma after chemotherapy may depend on the histology of the primary tumour [50]. However, others have reported that irrespective of initial histology there is a significant risk of teratoma or carcinoma in residual masses. Moreover, neither size of the initial metastasis nor degree of shrinkage while on therapy appears to accurately identify patients with residual teratoma or carcinoma. This has led some authors to recommend surgery with resection of all residual masses apparent on scans in patients who have normal or normalized markers after chemotherapy [51]. The presence of persistent viable tumour cells in the resected specimen seems to be an indication for additional chemotherapy [52], although this strategy may not improve overall survival [53]. Surgical removal of residual masses is also necessary to prevent regrowth of teratomas and growth of non-germ cell elements present in some of these masses [54]. Some patients may have discordant pathological findings (fibrosis/necrosis, teratoma or carcinoma) in residual masses in the abdomen versus the chest; some medical centres therefore perform simultaneous retroperitoneal and thoracic operations. However, most centres do not perform simultaneous retroperitoneal and thoracic resections. Although the agreement among the histologies of residual masses above, versus below, the diaphragm is only moderate, there is some evidence that if retroperitoneal resection is performed first, results can be used to guide decisions about whether to perform a thoracotomy [55]. In a multi-institutional case series of surgery to remove postchemotherapy residual masses in 159 patients, only necrosis was found at thoracotomy in about 90% of patients who had also only necrosis in their retroperitoneal masses. This figure was about 95% if the original testicular primary tumour did not contain teratomatous elements. Conversely, the histology of residual masses at thoracotomy was not nearly as good a predictor of the histology of retroperitoneal masses [55].

The standard treatment options

If patients with disseminated non-seminomatous testicular cancer do not achieve a complete radiological response on chemotherapy, surgical removal of residual masses should be performed. The timing of such surgery should be done after three or four cycles of combination chemotherapy and after normalization of serum tumour marker levels.

Treatment of recurrent disease

Deciding on further treatment in case of recurrent testicular cancer depends on many factors, including the histology, prior treatment, site of recurrence, as well as individual patient considerations. Salvage regimens consisting of ifosfamide, cisplatin and either etoposide or vinblastine can induce long-term complete responses in about one quarter of patients with disease that has persisted or recurred following first-line cisplatin-based regimens. Patients who have had an initial complete response to first-line chemotherapy and those without extensive disease have the most favourable outcome [56]. The VIP regimen is now the standard initial salvage regimen [56]. However, few, if any, patients with recurrent NSGCTs of an extragonadal origin achieve long-term disease-free survival using VIP if their disease recurs [56]. High-dose chemotherapy with autologous stem cell transplantation has also been used with some success in the setting of refractory disease [46]. Durable complete remissions may be achievable in 10–20% of patients. The durable complete remission rate may even exceed 50% in selected patients if high-dose chemotherapy is used as salvage chemotherapy at the first relapse of primary testicular cancer [57]. In general, patients with progressive tumours during frontline or after salvage treatment and those with refractory mediastinal germ cell tumours do not appear to benefit as much from high-dose chemotherapy with autologous stem cell transplantation as those who relapse after an initial response [58]. In some highly selected patients with chemorefractory disease confined to a single site, surgical resection may yield long-term disease-free survival [52]. The choice of salvage surgery versus high-dose chemotherapy with autologous stem cell transplantation for refractory disease is based on resectability, the number of sites of metastatic disease and the degree to which the tumour is refractory to cisplatin.

A special case of late relapse may be patients who relapse more than 2 years after achieving complete remission; this population represents less than 5% of patients who are in complete remission after 2 years. Results with chemotherapy are poor and surgical treatment appears to be superior, if technically feasible [59]. This may be because mature teratoma may be amenable to surgery at relapse and also has a better prognosis than carcinoma. Mature teratoma is a relatively resistant histologic subtype, so chemotherapy may not be appropriate.

Clinical trials are appropriate and should be considered whenever possible, including phase I and II studies for those patients not achieving a complete remission with induction therapy or not achieving a complete remission following salvage treatment for their first relapse or for patients who have a second relapse.

Patients who relapse with brain metastases after a complete initial response to chemotherapy require further chemotherapy, with simultaneous whole-brain irradiation and consideration of surgical excision of solitary lesions [49].

The standard treatment options

Patients with recurrent non-seminomatous testicular cancer can be treated with a salvage VIP regimen. However, since only few of these relapsed patients achieve a long-term disease-free survival, high-dose chemotherapy with autologous stem cell transplantation can also be used. Participation of these patients in clinical trials should be considered whenever possible.

Follow-up

The aim of follow-up care in patients treated for testicular cancer is to detect a relapse at a stage where salvage treatment has the best chance of being effective, to monitor and treat treatment-related toxicity, to detect cancers in the contralateral testicle and to offer support and counselling about issues such as fertility and employment. Recently minimal recommendations have been published by the European Society for Medical Oncology (ESMO) [60,61], but the optimal timing of clinical, biochemical and radiological follow-up is still under investigation.

Early detection of recurrence of testicular cancer after successful treatment with cisplatin combination chemotherapy is beneficial if there is a chance of achieving another durable remission with salvage treatment [58]. The possibility of early recognition of recurrence and subsequent treatment prolonging survival will increase with more effective salvage therapies [57]. However, the optimal regimen of physical examination, tumour marker estimations and chest X-rays for use in the follow-up of patients after initial treatment has not been determined. The widely used follow-up strategies come from large multi-institutional chemotherapy trials that defined the optimal chemotherapy combination for disseminated non-seminomatous testicular cancer during the last 2 decades. However, the primary focus of this particular follow-up was to define the efficacy of the first-line treatment regimen and not to evaluate the value of follow-up examinations. Furthermore, there are few data in the medical literature concerning the effectiveness of these follow-up regimens. In daily practice, the aim of follow-up after successful chemotherapy is to detect a tumour relapse in time without unnecessary procedures. Recent data suggest that routine chest X-rays (CXR) have limited or no additional value in the detection of a relapse during follow-up in patients who have a complete biochemical response and

no residual masses [62]. The value of CXR in follow-up of clinical stage I patients with non-seminomatous testicular cancer also does not show additional value in detection of disease recurrence [28]. So tumour marker measurements, medical history and physical examination seem to be of key value.

From an oncologic point of view, recent data and recommendations suggest that it is reasonable to discharge patients with stage I non-seminomatous testicular tumours and all stages of seminoma from follow-up after 5 years [28,60,61]. Metastatic non-seminomatous testicular cancers seem to have a continuing annual relapse rate of 1–2% even after 10 years, suggesting that life-long follow-up might be needed [1,60]. However, an important part of the long-term follow-up is surveillance of long-term toxicity of administered treatment. Since most of the cured patients are men in their twenties or early thirties, long-term treatment-related toxicity is of growing importance.

Treatment toxicity and long-term side-effects

Chemotherapy with cisplatin causes significant side-effects both in the short and the long term. Acute side-effects include nausea and vomiting, alopecia, bone marrow suppression with risk for neutropenic fever, fatigue, renal toxicity and acute cardiovascular toxicity. A particular complication of the BEP combination chemotherapy is lung toxicity associated with bleomycin [63]; in most studies, 0.5–1% developed fatal bleomycin-induced pneumonitis. Bleomycin combined with cisplatin is also associated with the risk of developing Raynaud's phenomenon [64]. Cisplatin may also cause damage to both peripheral and auditory sensory nerves. This resolves in most patients over 6–12 months but long-term studies suggest persistent damage in a proportion of patients.

Infertility is one of the most distressing adverse effects of cancer therapy. Patients with germ cell tumour may have azoospermia related to the disease itself or to the sterilizing effects of chemotherapy [65]. Fertility is an important predictor of long-term health-related quality of life in testicular cancer survivors. Testicular patients undergoing chemotherapy are usually counselled about the risks of infertility and offered the opportunity for sperm banking before commencing therapy. For the azoospermic germ cell cancer survivor, donor insemination and adoption have historically been the main reproductive options. A recent report by Damani *et al.* explores the possibilities of testis sperm extraction in testicular cancer survivors. This assisted reproductive technology, initially developed for conditions such as congenital absence of the vas deferens, resulted in successful retrieval of sperm in approximately two-thirds of the patients [66]. Rather, it should be considered

a reproductive option for the azoospermic cancer survivor without banked sperm. This technique represents the development of an effective intervention for an established treatment-related adverse effect, with the potential to improve the long-term well-being of the cancer survivor. For many other physiologic adverse effects of cancer treatment, the situation is not so clear.

The prevalence and time course for development of certain other late effects have not been well defined. The main concerns relate to the increased risk of second malignancies that can occur after treatment with chemotherapy or radiotherapy or of cardiovascular events in long-term survivors [67,68].

Cisplatin-containing chemotherapy for germ cell cancer has been associated with Raynaud's phenomenon, and serious vascular complications, including myocardial infarction, stroke and thromboembolic disease, have been reported [64]. Some, but not all, studies have suggested that after cisplatin-containing chemotherapy, patients may be at increased risk for the premature development of hypertension and lipid abnormalities, well-known major cardiovascular risk factors [68,69,70]. Testicular cancer survivors develop a metabolic syndrome or syndrome X-like state after chemotherapy, which makes them more prone to cardiovascular events [71,72]. However, does cisplatin combination chemotherapy result in an increased risk for early cardiovascular events? In one study of testicular cancer patients treated with surgery or surgery plus chemotherapy, no increase in cardiovascular events was noted in the chemotherapy group at a median follow-up of 5 years [73]. A more recent study reported an increased risk of cardiovascular events for testicular cancer survivors younger than 50 years of age who had received chemotherapy and were in remission for 10 or more years [68]. Further studies are needed to better define the actual risk, if any, of early cardiovascular events in these patients. What do these data tell us regarding the education and counselling of testicular cancer survivors concerning cardiovascular risk? Are there rational early intervention possibilities?

Who will be following the cancer survivor when these adverse effects become manifest? While the oncologist might be the most knowledgeable about the potential late adverse effects of cancer treatment, many survivors may not regularly see an oncologist once the risk of tumour recurrence is unlikely. Probably many of these patients are followed by primary care physicians, who may not be fully aware of the details of the patient's oncologic history and may not be familiar with the long-term sequelae of cancer and its treatment. Other patients may exit the health care system altogether. For uncommon cancers such as germ cell tumours, few centres have enough patients to define a large enough long-term cohort for studies. Our preference is to undertake the long-term follow-up at a cancer centre to

allow the build-up of well-documented databases on the well-being and actual health status of testicular cancer survivors facilitating cancer survivor research.

For future well-defined health care problems of testicular cancer survivors, either primary care physicians with knowledge of testicular cancer and treatment sequelae or a cancer specialist with knowledge of general internal medicine should take care of treatment sequelae or risk factors for disease.

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