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European Association of Urology

Guidelines

# Guidelines on Testicular Cancer: 2015 Update

*Peter Albers*[a,*], *Walter Albrecht*[b], *Ferran Algaba*[c], *Carsten Bokemeyer*[d], *Gabriella Cohn-Cedermark*[e], *Karim Fizazi*[f], *Alan Horwich*[g], *Maria Pilar Laguna*[h], *Nicola Nicolai*[i], *Jan Oldenburg*[j]

[a] *Department of Urology, Medical Faculty, Düsseldorf University, Düsseldorf, Germany;* [b] *Department of Urology, Mistelbach, Austria;* [c] *Department of Pathology, Fundacio Puigvert, Barcelona, Spain;* [d] *Department of Oncology, Hematology and Bone Marrow Transplantation with section Pneumology, Universitätskliniken Eppendorf, Hamburg, Germany;* [e] *Department of Oncology-Pathology, Karolinska Institute and Karolinska University Hospital, Stockholm, Sweden;* [f] *Department of Medicine, University of Paris XI, Villejuif, France;* [g] *Academic Unit of Radiotherapy and Oncology, Royal Marsden NHS Trust and The Institute of Cancer Research, Sutton, UK;* [h] *Department of Urology, Amsterdam Medical Centre, Amsterdam University, Amsterdam, The Netherlands;* [i] *Department of Surgery, Urology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy;* [j] *Health Sciences, Høgskolen i Buskerud og Vestfold, Kongsberg, Norway*

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**Abstract**

***Context:*** This is an update of the previous European Association of Urology testis cancer guidelines published in 2011, which included major changes in the diagnosis and treatment of germ cell tumours.
***Objective:*** To summarise latest developments in the treatment of this rare disease. Recommendations have been agreed within a multidisciplinary working group consisting of urologists, medical oncologists, and radiation oncologists.
***Evidence acquisition:*** A semi-structured literature search up to February 2015 was performed to update the recommendations. In addition, this document was subjected to double-blind peer review before publication.
***Evidence synthesis:*** This publication focuses on the most important changes in treatment recommendations for clinical stage I disease and the updated recommendations for follow-up.
***Conclusions:*** Most changes in the recommendations will lead to an overall reduction in treatment burden for patients with germ cell tumours. In advanced stages, treatment intensification is clearly defined to further improve overall survival rates.
***Patient summary:*** This is an update of a previously published version of the European Association of Urology guidelines for testis cancer, and includes new recommendations for clinical stage I disease and revision of the follow-up recommendations. Patients should be fully informed of all the treatment options available to them.


* Corresponding author. Department of Urology, Medical Faculty, University Hospital, Heinrich-Heine University Düsseldorf, Moorenstrasse 5, D-40225 Düsseldorf, Germany. Tel. +49 21 18118110; Fax: +49 21 18118676.
E-mail address: urologie@uni-duesseldorf.de (P. Albers).

## 1. Introduction

Testicular cancer is a rare disease, with an incidence of up to 10 in 100 000 men. In Europe, cure rates of up to 97% for all stages have been achieved [1]. However, cure is dependent on excellent diagnosis, treatment facilities, and specialised expertise for patients with advanced disease. In the overwhelming group of patients with low-stage disease, the main goal of treatment is to reduce treatment-related long-term toxicities, including secondary cancers. Thus, regular updates of current treatment guidelines are necessary to achieve the best possible treatment outcome.

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Current evidence suggests that the best results are obtained in high-volume reference centres, not only for patients with advanced disease but also for patients with early-stage disease. Although early stages can be successfully treated in a nonreference centre, the relapse rate is higher [2]. In poor-prognosis nonseminomatous germ-cell tumours, overall survival (OS) within a clinical trial depends on the number of patients treated at the participating centre (poorer if fewer than five patients are enrolled) [3]. In the same context, the frequency of postchemotherapy residual tumour resection is associated with perioperative mortality and OS [4,5].

First analyses of a recently introduced internet-based second-opinion portal suggest that up to 40% of primary diagnoses were incorrect and treatment was changed in a considerably high number of patients after a second opinion [6].

## 2. Evidence acquisition

A multidisciplinary team of urologists, medical oncologists, radiation oncologists, and a pathologist were involved in producing this document, which is based on a semi-structured review of the literature up to February 2015. This publication focuses on the most important changes and relevant clinical recommendations. For unchanged recommendations, the reader is referred to the previous publication of the guidelines in *European Urology* [7]. The full version of the 2015 guidelines is available on the European Association of Urology (EAU) website (http://uroweb.org/guideline/testicular-cancer/). References were assessed according to their level of scientific evidence, and guideline recommendations were graded according to a system modified from the Oxford Centre for Evidence-based Medicine levels of evidence [8].

**Table 1 – Recommended tests for staging at diagnosis**

| Test | Recommendation | GR |
|---|---|---|
| Serum tumour markers | α-Fetoprotein<br>hCG<br>Lactate dehydrogenase | A |
| Abdominopelvic CT | All patients | A |
| Chest CT | All patients | A |
| Testis ultrasound (bilateral) | All patients | A |
| Bone scan or spinal MRI | In the case of symptoms | |
| Brain scan (CT/MRI) | In the case of symptoms and patients with metastatic disease with multiple lung metastases and/or high β-hCG levels | |
| **Further investigations** | | |
| Fertility investigations:<br>Total testosterone<br>Luteinising hormone<br>Follicle-stimulating hormone<br>Semen analysis | | B |
| Sperm banking | Should be offered | A |

GR = grade of recommendation; hCG = human chorionic gonadotrophin; CT = computed tomography; MRI = magnetic resonance imaging.

## 3. Evidence synthesis

### 3.1. Diagnosis of testicular cancer

It is very important to correctly classify a patient with a newly diagnosed germ-cell cancer. Ultrasound (US) of both testis remains the cornerstone of primary imaging in patients with testicular tumours followed by computed tomography (CT) of the abdomen and chest as subsequent staging tools (Table 1). Correct interpretation of tumour markers before and after orchiectomy in conjunction with CT findings allows correct patient classification according to TNM and Union for International Cancer Control staging (Tables 2 and 3) [9]. Patients with metastatic disease should be classified according to the International Germ Cell Cancer Collaborative Group (IGCCCG) [10] to tailor further treatment (Table 4).

### 3.2. Diagnosis and treatment of testicular intraepithelial neoplasia (TIN)

Contralateral biopsy has been advocated to rule out the presence of TIN [11]. Although systematic contralateral biopsy is routine policy in some countries, the low incidence of TIN (up to 9%) and contralateral metachronous testicular tumours (~2.5%) [12,13], the morbidity associated with TIN treatment, and the low stage of most metachronous tumours at presentation mean that biopsy recommendation for all patients is controversial.

It is still difficult to reach a consensus on whether the existence of contralateral TIN must be identified in all cases. However, biopsy of the contralateral testis should be offered to patients at high risk of contralateral TIN (testicular volume <12 ml, history of cryptorchidism, or poor spermatogenesis with Johnson score 1–3). A contralateral biopsy is not necessary in patients older than 40 yr without risk factors [14,15]. A double biopsy increases sensitivity [14]. Patients should be informed that a testicular tumour may arise in spite of a negative biopsy.

When TIN is diagnosed, local radiotherapy (16–20 Gy in fractions of 2 Gy) is the treatment of choice in the case of a solitary testis. Testicular radiotherapy in a solitary testis will result in infertility and a higher long-term risk of Leydig cell insufficiency [16,17]. Fertile patients who wish to father children may delay radiation therapy and can be followed with regular testicular US [14].

If TIN is diagnosed and the contralateral testis is healthy, the options for management are orchiectomy or close observation (with a 5-yr risk of developing testicular cancer of 50%).

### 3.3. Prognostic factors for progression and recurrence in clinical stage I

In stage I seminoma, tumour size (>4 cm) and invasion of the rete testis have been identified as predictors of relapse in a pooled analysis. However, these risk factors have not been validated in a prospective setting, although the

**Table 2 – TNM classification of testicular cancer [9]**

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

IGD = in greatest dimension; LDH = lactate dehydrogenase; hCG = human chorionic gonadotrophin; AFP = α-fetoprotein; ULN = upper limit of normal range.
[a] Except for pTis and pT4, for which radical orchiectomy is not always necessary for classification purposes, the extent of the primary tumour is classified after radical orchiectomy. In other circumstances, TX is used if no radical orchiectomy has been performed.

**Table 3 – Stage grouping for cancer**

| | | | | |
|---|---|---|---|---|
| Stage 0 | pTis | N0 | M0 | S0, SX |
| Stage I [a] | pT1–T4 | N0 | M0 | SX |
| Stage IA | pT1 | N0 | M0 | S0 |
| Stage IB | pT2–T4 | N0 | M0 | S0 |
| Stage IS | Any patient/TX | N0 | M0 | S1–3 |
| Stage II | Any patient/TX | N1–N3 | M0 | SX |
| Stage IIA | Any patient/TX | N1 | M0 | S0, S1 |
| Stage IIB | Any patient/TX | N2 | M0 | S0, S1 |
| Stage IIC | Any patient/TX | N3 | M0 | S0, S1 |
| Stage III | Any patient/TX | Any N | M1a | SX |
| Stage IIIA | Any patient/TX | Any N | M1a | S0, S1 |
| Stage IIIB | Any patient/TX | N1–N3 | M0 | S2 |
| | Any patient/TX | Any N | M1a | S2 |
| Stage IIIC | Any patient/TX | N1–N3 | M0 | S3 |
| | Any patient/TX | Any N | M1a | S3 |
| | Any patient/TX | Any N | M1b | Any S |

[a] Stage I testicular cancer includes the following substages:
Stage IA: patients have primary tumours limited to the testis and epididymis, with no evidence of microscopic vascular or lymphatic invasion by tumour cells on microscopy, no sign of metastases on clinical examination or imaging, and post-orchiectomy serum tumour marker levels within normal limits. Marker decline in patients with clinical stage I disease should be assessed until normalisation.
Stage IB: patients have a more locally invasive primary tumour, but no sign of metastatic disease.
Stage IS: patients have persistently elevated (and usually increasing) serum tumour marker levels after orchiectomy, indicating subclinical metastatic disease (or possibly a second germ-cell tumour in the remaining testis).

absence of both factors indicated a low recurrence rate (6%) [18].

For stage I nonseminoma, vascular invasion by the primary tumour into blood or lymphatic vessels is the most important predictor of occult metastatic disease. The proliferation rate and the percentage of embryonal carcinoma are additional predictors that increase the positive and negative predictive values, respectively, for vascular invasion [19].

### 3.4. *Treatment of clinical stage I seminoma*

Staging procedures reveal that approximately 15–20% of stage I seminoma patients have subclinical metastatic disease, usually in the retroperitoneum, and will relapse after orchiectomy alone. The decision regarding adjuvant treatment should always be based on a thorough discussion with the patient, taking into account the advantages and disadvantages described and the patient's individual situation.

#### 3.4.1. *Surveillance*

Several prospective nonrandomised surveillance studies have been conducted during the past decade. The largest study, with >1500 patients, showed an overall relapse rate

**Table 4 – Prognostic-based staging system for metastatic germ cell cancer (International Germ Cell Cancer Collaborative Group)** [a]

| Group | Type | Criteria |
|---|---|---|
| Good prognosis | Nonseminoma (56% of cases)<br>5-yr PFS 89%<br>5-yr survival 92% | All of the following criteria:<br>• Testis/retroperitoneal primary<br>• No nonpulmonary visceral metastases<br>• AFP <1000 ng/ml<br>• hCG <5000 IU/l (1000 ng/ml)<br>• LDH <1.5 × ULN |
| | Seminoma (90% of cases)<br>5-yr PFS 82%<br>5-yr survival 86% | All of the following criteria:<br>• Any primary site<br>• No nonpulmonary visceral metastases<br>• Normal AFP<br>• Any hCG<br>• Any LDH |
| Intermediate prognosis | Nonseminoma (28% of cases)<br>5-yr PFS 75%<br>5-yr survival 80% | All of the following criteria:<br>• Testis/retroperitoneal primary<br>• No nonpulmonary visceral metastases<br>• AFP 1000–10 000 ng/ml or<br>• hCG 5000–50 000 IU/l or<br>• LDH 1.5–10 × ULN |
| | Seminoma (10% of cases)<br>5-yr PFS 67%<br>5-yr survival 72% | All of the following criteria:<br>• Any primary site<br>• Nonpulmonary visceral metastases<br>• Normal AFP<br>• Any hCG<br>• Any LDH |
| Poor prognosis | Nonseminoma (16% of cases)<br>5-yr PFS 41%<br>5-yr survival 48% | Any of the following criteria:<br>• Mediastinal primary<br>• Nonpulmonary visceral metastases<br>• AFP >10 000 ng/ml or<br>• hCG > 50 000 IU/l (10 000 ng/ml) or<br>• LDH > 10 × ULN |
| | Seminoma | No patients classified as poor prognosis |

PFS = progression-free survival; AFP = α-fetoprotein; hCG = human chorionic gonadotrophin; LDH = lactate dehydrogenase; ULN = upper limit of normal range.
[a] Prechemotherapy serum tumour markers should be assessed immediately before administration of chemotherapy (same day).

of 16.8% in unselected patients. In patients with low risk (tumour size ≤4 cm and no rete testis invasion), the recurrence under surveillance is as low as 6% [20]. Chemotherapy, according to the IGCCCG classification, is a possible treatment for seminoma relapse under surveillance. However, 70% of patients with relapse are suitable for treatment with radiotherapy alone because of small-volume disease at the time of recurrence. Patients who experience relapse after salvage radiotherapy can be effectively treated with chemotherapy [21]. The combination of carboplatin chemotherapy and modern radiotherapy for treatment of low-stage seminoma relapse (IIA/IIB) is under investigation.

The overall cancer-specific survival rate under surveillance performed by experienced centres is 97–100% for stage I seminoma [21,22]. The main drawback of surveillance is the need for more intensive follow-up, especially with repeated imaging examinations of the retroperitoneal lymph nodes.

#### 3.4.2. *Adjuvant chemotherapy*

A joint trial by the Medical Research Council (MRC) and the European Organisation for Research and Treatment of Cancer (trial MRC TE19), which compared one cycle of carboplatin (dosage of area under the curve [AUC] × 7) with adjuvant radiotherapy, did not show a significant difference with regard to recurrence rate, time to recurrence, and survival after a median follow-up of 4 yr [23–25]. Therefore, adjuvant carboplatin therapy with one course at a dosage of AUC × 7 is an alternative to radiotherapy or surveillance in stage I seminoma [22–25]. Two courses of adjuvant carboplatin seem to further reduce the relapse rate to the order of 1–3% [18,26]; however, additional experience and long-term observation are needed.

#### 3.4.3. *Adjuvant radiotherapy*

Adjuvant radiotherapy to a paraaortic field with moderate doses (total 20–24 Gy) will reduce the relapse rate to 1–3% [27–29]. The main concern regarding adjuvant radiotherapy is the higher risk of radiation-induced second non–germ-cell malignancies [30,31]. Therefore, adjuvant radiotherapy should no longer be used in young patients.

#### 3.4.4. *Risk-adapted treatment*

Using tumour size >4 cm and rete testis invasion, patients with stage I seminoma may be subdivided into group with low and high risk of occult metastatic disease. Patients with and without both risk factors have a 32% and 12% risk of occult disease, respectively. A prospective trial based on these risk factors (no risk factors, surveillance; both risk factors, two courses of carboplatin AUC × 7) showed the feasibility of a risk-adapted approach, and patients without either risk factor had a 6.0–14.8% risk of relapse at 5 yr. This is why adjuvant treatment is not recommended for patients with very low risk (Table 5). Patients in the high-risk group

**Table 5 – Guidelines for the treatment of stage I seminoma**

| | GR |
|---|---|
| Surveillance is a recommended management option (if facilities are available and the patient is compliant) | A * |
| Carboplatin-based chemotherapy (one course at AUC × 7) is recommended | A |
| Adjuvant treatment is not recommended for patients at very low risk | A |
| Radiotherapy is not recommended as adjuvant treatment | A |

* Upgraded following panel consensus.
GR = grade of recommendation; AUC = area under curve.

treated with carboplatin experienced a relapse rate of 1.4–3.2% at a mean follow-up of 34 mo [20,32].

### 3.5. *Treatment of clinical stage I nonseminoma*

Up to 30% of patients with clinical stage I nonseminomatous germ cell tumour (NSGCT) have subclinical metastases and will relapse if surveillance alone is undertaken after orchiectomy.

The decision regarding adjuvant treatment should always be based on a thorough discussion with the patient, taking into account the advantages and disadvantages described and the patient's individual situation.

#### 3.5.1. *Surveillance*

The largest studies on a surveillance strategy indicate a cumulative relapse rate of ~30%, with 80% of relapses occurring during the first 12 mo of follow-up, 12% during the second year, and 6% during the third year, decreasing to 1% thereafter [33–36]. Approximately 35% of patients who experience relapse have normal levels of serum tumour markers at relapse. Some 60% of relapses are in the retroperitoneum. According to overall cancer-specific survival data, surveillance within an experienced surveillance programme can be safely offered to patients with non–risk-stratified clinical stage I nonseminoma as long as they are compliant and informed about the expected recurrence rate and the salvage treatment [37,38].

#### 3.5.2. *Adjuvant chemotherapy*

Patients with clinical stage I NSGCT have a 14–48% risk of recurrence within 2 yr after orchiectomy. Adjuvant chemotherapy with two courses of cisplatin, etoposide, and bleomycin (BEP) was introduced in 1996 in a prospective MRC trial [39]. Subsequently, adjuvant chemotherapy was mainly given to patients with high risk (vascular invasion present) [39,40]. In these series involving more than 200 patients, some with a median follow-up of nearly 7.9 yr [39], a relapse rate of only 2.7% was reported, with very little long-term toxicity.

Two cycles of cisplatin-based adjuvant chemotherapy do not seem to adversely affect fertility or sexual activity [41]. However, the very long-term (>20 yr) side effects of adjuvant chemotherapy in this setting are currently unknown, especially the long-term cardiovascular effects [42]. In a randomised trial, one course of adjuvant BEP in patients with clinical stage I nonseminoma significantly increased the 2-yr recurrence-free survival to 99.41% compared to primary retroperitoneal lymph node dissection (RPLND). Of 174 patients who received one course of BEP, 43% had high-risk features (>pT1) [43]. In a community-based prospective nonrandomised study, the relapse rate at 5 yr among 490 patients who received BEP × 1 was 3.2% for patients with lymphovascular invasion (LVI) and 1.6% for patients without LVI [44]. After a median follow-up of 8.1 yr, the relapse rate was 2.3% for all patients, 3.4% for those with LVI, and 1.3% for those without LVI [45]. A reduction from two to one BEP cycle considerably improves the risk-benefit ratio of adjuvant chemotherapy (Table 6).

#### 3.5.3. *Risk-adapted treatment*

Risk-adapted treatment is an alternative to surveillance for all patients with stage I NSGCT. Risk-adapted treatment is based on vascular invasion. Similar survival rates and a final cure rate close to 100% can be achieved (Table 7 and Fig. 1) [39,40,44–47].

#### 3.5.4. *RPLND*

In view of the high cancer-specific survival rates for surveillance with salvage treatment in cases of relapse and the low relapse rates if adjuvant chemotherapy is chosen, the role of primary diagnostic RPLND has diminished. Higher rates of in-field recurrences and of

**Table 6 – Guidelines for the treatment of stage I nonseminomatous germ cell tumour (NSGCT)**

| | LE | GR |
|---|---|---|
| Patients with stage I NSGCT should be informed about all adjuvant treatment options after orchiectomy (surveillance, adjuvant chemotherapy, and RPLND) including treatment-specific recurrence rates and acute and long-term side effects | 2a | A * |
| Surveillance and risk-adapted treatment based on vascular invasion (Table 6) are the recommended treatment options | 2a | A * |
| If patients are not willing to undergo surveillance, one course of BEP as adjuvant treatment was superior to RPLND in terms of recurrence rate in a community-based study | 1b | A * |
| Salvage treatment of patients with recurrence during surveillance consists of three or four courses of BEP chemotherapy followed by postchemotherapy RPLND if necessary | 2a | A |

GR = grade of recommendation; LE = level of evidence; RPLND = retroperitoneal lymph node dissection.

**Table 7 – Risk-adapted treatment for clinical stage I based on vascular invasion**

| Stage | LE | GR |
|---|---|---|
| **Stage IA (pT1, no vascular invasion): low risk** | | |
| Surveillance is recommended if the patient is willing and able to comply | 2a | A |
| For patients not willing (or suitable) to undergo surveillance, adjuvant chemotherapy with one course of BEP is recommended | 2a | A * |
| **Stage IB (pT2–pT4): high risk** | | |
| Primary chemotherapy with one course of BEP is recommended | 2a | A * |
| Patients should be informed about the advantages and disadvantages of one course of BEP | | |
| Surveillance and nerve-sparing RPLND are options for those not willing to undergo adjuvant chemotherapy; if RPLND reveals pathologic stage II, further chemotherapy and observation should be discussed with each patient | | A * |

* Upgraded following panel consensus.
BEP = cisplatin, etoposide, bleomycin; GR = grade of recommendation; LE = level of evidence; RPLND = retroperitoneal lymph node dissection.

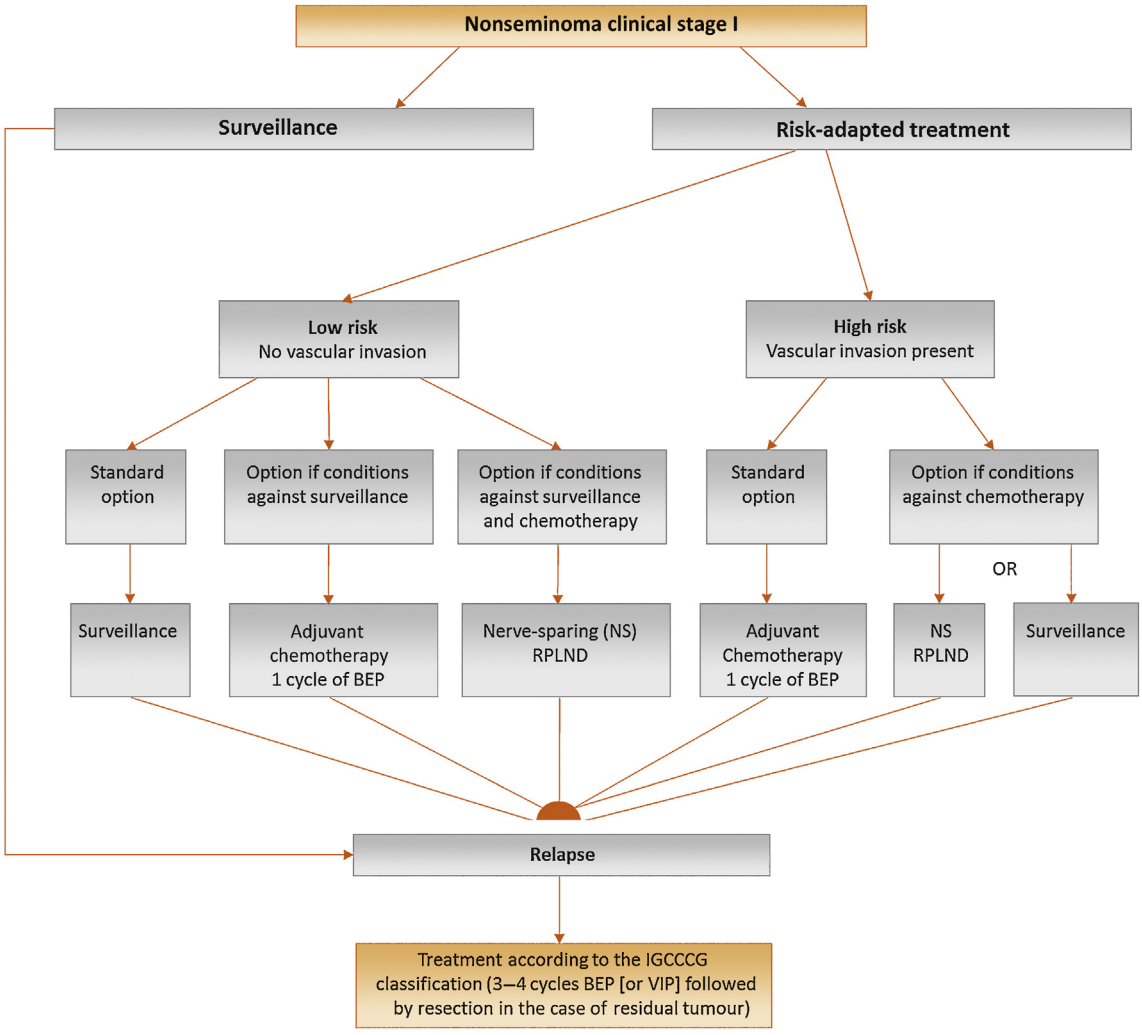


**Fig. 1 – Risk-adapted treatment in patients with clinical stage I nonseminoma. All treatment options need to be discussed with individual patients to allow them to make an informed decision as to their further care. BEP = cisplatin, etoposide, bleomycin; CS = clinical stage; IGCCCG = International Germ Cell Cancer Collaborative Group; RLNPD = retroperitoneal lymph node dissection; VIP = etoposide, cisplatin, ifosfamide.**

complications have been reported for RPLND performed in a multicentre setting [43,48]. Thus, nerve-sparing RPLND, if indicated, should be performed by an experienced surgeon in a specialised centre. If there is an indication to perform a staging RPLND, laparoscopic or robot-assisted RPLND is feasible in expert hands. This minimally invasive approach is not recommended as the standard approach outside of a specialised laparoscopic centre with particular expertise in testis tumour management [49].

### 3.6. *Treatment of patients with metastatic disease*

First-line treatment of metastatic germ-cell tumours depends on the histology of the primary tumour and prognostic groups as defined by the IGCCCG (Tables 4 and 8) [10].

**Table 8 – Guidelines for the treatment of metastatic germ-cell tumours**

| | LE | GR |
|---|---|---|
| Low-volume stage IIA/B NSGCT with elevated markers should be treated similarly to advanced NSGCT with good or intermediate prognosis, with three or four cycles of BEP | 2 | A |
| In stage IIA/B NSGCT without marker elevation, histology can be obtained by RPLND or biopsy; staging can be repeated after 6 wk of surveillance before the final decision on further treatment | 3 | B |
| In metastatic NSGCT (stage ≥IIC) with good prognosis, three courses of BEP is the primary treatment of choice | 1 | A |
| In metastatic NSGCT with intermediate prognosis, the primary treatment of choice is four courses of standard BEP | 1 | A |
| In metastatic NSGCT with poor prognosis, the primary treatment of choice is one cycle of BEP, followed by tumour marker assessment after 3 wk; in the case of an unfavourable decline, chemotherapy intensification can be initiated; in the case of a favourable decline, BEP should be continued up to a total of four cycles | 1 | A |
| Surgical resection of residual masses after chemotherapy in NSGCT is indicated in the case of visible residual masses and when serum levels of tumour markers are normal or normalising | 2 | A |
| Stage IIA/B seminoma can be treated initially with radiotherapy; when necessary, chemotherapy can be used as a salvage treatment according to the same schedule as for the corresponding NSGCT prognostic groups | 2 | B |
| In stage IIA/B seminoma, chemotherapy (3 × BEP or 4 × EP with good prognosis) is an alternative to radiotherapy; 3 × BEP and 4 × EP appear to achieve similar levels of disease control | 1 | A |
| Stage ≥IIC seminoma should be treated with primary chemotherapy according to the same principles used for NSGCT | 1 | A |

BEP = cisplatin, etoposide, bleomycin; EP = etoposide, cisplatin; GR = grade of recommendation; LE = level of evidence; NSGCT = nonseminomatous germ cell tumour; BEP = cisplatin, etoposide, bleomycin; RPLND = retroperitoneal lymph node dissection.

**Table 9 – Construction of the International Germ Cell Cancer Collaborative Group-2 prognostic score [50]**

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

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

In patients with relapse, a new prognostic score including response to first-line therapy can be used to estimate patient outcome following salvage chemotherapy (Tables 9 and 10) [50].

### 3.6.1. *Stage IIA/B seminoma*

An observation period of 8 wk with a second staging is recommended for patients with enlarged lymph nodes without marker elevation, unless a biopsy verifies metastatic disease. Treatment should not be initiated unless metastatic disease is unequivocal, (eg, growth or positive biopsy). To date, the standard treatment for stage IIA/B seminoma has been radiotherapy, with relapse rates of 9–24% reported [51,52]. Accumulating data on long-term morbidity, such as a higher risk of cardiovascular events and risk of second malignancies following radiotherapy, have led to concern. Most reports refer to patients irradiated with larger target volumes and higher doses, but there are also more recent studies on patients treated with more modern radiotherapy [53]. The radiation dose delivered for stage IIA and IIB is approximately 30 and 36 Gy, respectively, and the field size is enlarged. This technique yields relapse-free survival of 92% for stage IIA and 90% for stage IIB, with OS of almost 100% [51,52].

For stage IIA/B, chemotherapy with three courses of BEP or four courses with etoposide and cisplatin (EP) is an alternative to radiotherapy. There are no randomised studies comparing radiotherapy and chemotherapy. Although more toxic than radiotherapy in the short-term, three courses of BEP or four courses of EP achieves a similar level of disease control.

Single-agent carboplatin is not an alternative to standard EP or BEP chemotherapy for metastatic disease (Fig. 2) [54].

**Table 10 – Progression-free survival (PFS) and overall survival (OS) estimates for all patients according to the International Germ Cell Cancer Collaborative Group-2 prognostic score [50]**

| Score ($n$ = 1435) | Patients $n$ (%) | HR | 2-yr PFS (%) | 3-yr OS (%) |
|---|---|---|---|---|
| Very low | 76 (5.3) | 1 | 75.1 | 77.0 |
| Low | 257 (17.9) | 2.07 | 52.6 | 69.0 |
| Intermediate | 646 (45.0) | 2.88 | 42.8 | 57.3 |
| High | 351 (24.5) | 4.81 | 26.4 | 31.7 |
| Very high | 105 (7.3) | 8.95 | 11.5 | 14.7 |
| Missing | 159 | | | |

HR = hazard ratio.

### 3.6.2. *Stage IIA/B non-seminoma*

Patients with clinical stage II NSGCT and elevated marker levels should receive chemotherapy according to the

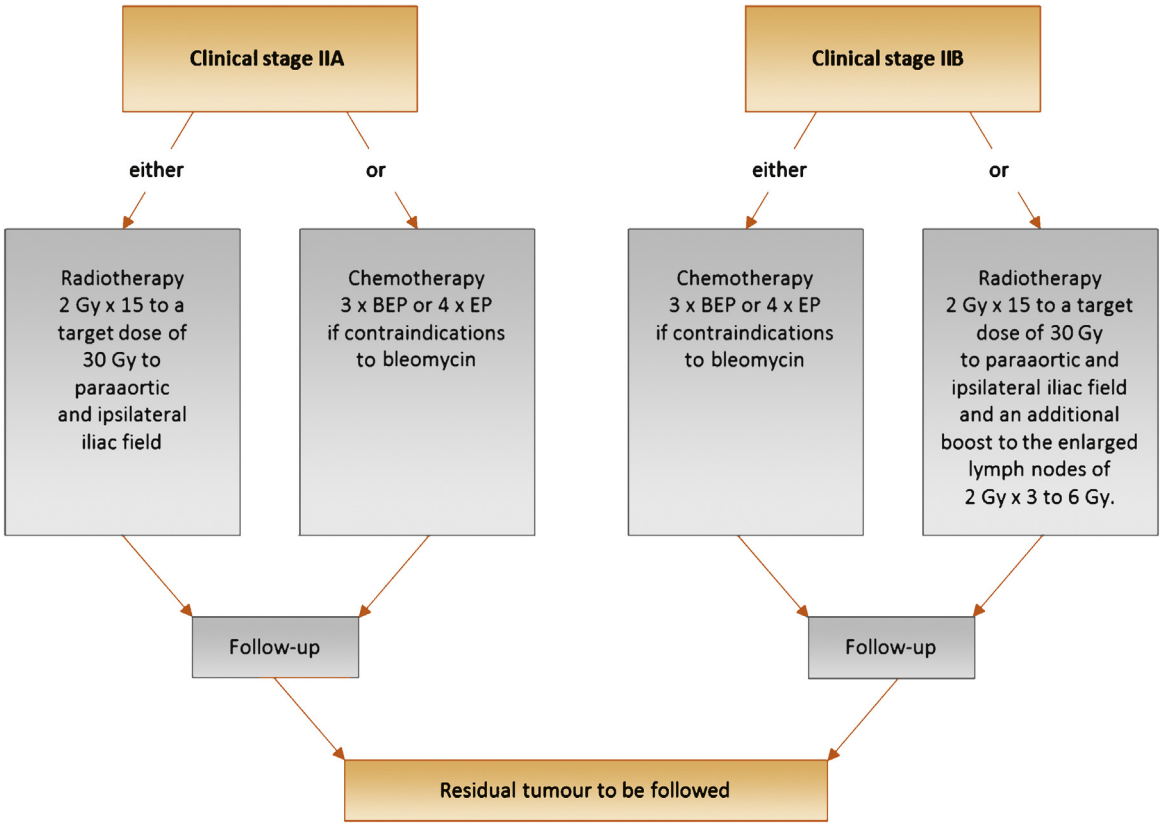


**Fig. 2 – Treatment options for patients with clinical stage IIA and IIB seminoma. BEP = cisplatin, etoposide, bleomycin; EP = etoposide, cisplatin.**

IGCCCG classification, followed by residual tumour resection if indicated (Table 8). Patients without elevated tumour marker levels can be managed by primary RPLND or surveillance to clarify the clinical stage [55].

A stable or growing lesion indicates either teratoma or an undifferentiated malignant tumour. An alternative to surveillance for marker-negative stage IIA/B nonseminoma with suspicion of an undifferentiated malignant tumour is a (CT-guided) biopsy, if technically possible. There are insufficient data on positron emission tomography (PET) scans in this situation. When primary chemotherapy is contraindicated or is refused by the patient, primary nerve-sparing RPLND represents a viable option.

Primary chemotherapy and primary RPLND are comparable options in terms of outcome, but differ in their side effects and toxicity, so the patient should be involved in selecting the treatment of choice [55,56]. The cure rate for either approach is close to 98% [57,58].

### 3.6.3. *Metastatic disease (stages IIC and III)*

*3.6.3.1. Seminoma with good prognosis.* For metastatic seminoma, very limited data are available from randomised trials and they indicate that a cisplatin-based regimen is preferable to carboplatin chemotherapy [59]. Recent data indicate that EP × 4 results in cure in almost all cases of seminomatous germ-cell cancers with good prognosis [60]. Standard treatment in this setting should therefore be BEP × 3 or EP × 4. In the case of contraindications to bleomycin, EP × 4 should be given. Postchemotherapy masses should be managed as described in Section 3.7.

*3.6.3.2. Seminoma with intermediate prognosis.* For patients with intermediate-risk seminoma, four cycles of BEP or etoposide, cisplatin, and ifosfamide (VIP) are recommended, although no randomised trial has focused specifically on this rare group of patients.

*3.6.3.3. Nonseminoma with good prognosis.* For nonseminoma, the primary treatment of choice for metastatic disease in patients with good prognosis according to the IGCCCG risk classification is three cycles of BEP combination chemotherapy. This regimen is superior to cisplatin, vinblastine, and bleomycin (PVB) in patients with advanced disease. While data show that a 3-d regimen of combination chemotherapy is equally effective as a 5-d regimen, it is associated with higher toxicity when four cycles are used [61], so the 5-d BEP regimen is recommended. In selected cases in which bleomycin is contraindicated, four cycles of EP can be given [9]. Therapy should be given without dose reductions at 21-d intervals; delaying the subsequent chemotherapy cycle is justified only in cases of fever with granulocytopaenia $<1000/mm^3$ or thrombocytopaenia $<100\ 000$/IU. There is no indication for prophylactic administration of haematopoietic growth factors. However, if infectious complications occur during chemotherapy or the treatment interval is delayed because of myelotoxicity,

prophylactic administration of granulocyte-colony stimulating factor (G-CSF) is recommended in subsequent cycles.

*3.6.3.4. Nonseminoma with intermediate prognosis.* Patients with intermediate IGCCCG prognosis have a 5-yr survival rate of approximately 80%. The available data support four cycles of BEP as standard treatment [10]. A randomised trial comparing four cycles of BEP without and with addition of paclitaxel (T-BEP) found no significant improvement in OS [62].

*3.6.3.5. Nonseminoma with poor prognosis.* For patients with poor-prognosis nonseminoma as defined by the IGCCCG and favourable marker decline, standard treatment consists of four cycles of BEP. Four cycles of cisplatin, etoposide, and ifosfamide (PEI) have the same effect, but the myelotoxicity is higher. The 5-yr progression-free survival (PFS) is between 45% and 50%. Three randomised trials showed no OS advantage for high-dose chemotherapy in the overall group of patients with poor prognosis [35,63,64].

However, patients with a slow decline in tumour marker levels after the first or second cycle represent a prognostically inferior subgroup [63].

An international randomised phase 3 trial conducted in 263 patients with IGCCCG poor-risk NSGCT demonstrated that intensifying treatment with dose-dense chemotherapy improves PFS but not OS in patients with an early unfavourable decline in tumour marker levels [65]. On the basis of results from this trial, patients with an unfavourable decline in tumour marker levels after one cycle of BEP should be switched to a more intensive chemotherapy regimen [66]. Further prospective trials and registries are planned to further validate this approach. A matched-pair analysis comparing high-dose to conventional treatment revealed a better survival rate [67], so patients with poor prognosis should still be treated in ongoing prospective trials or registries whenever available.

Patients meeting poor-prognosis criteria should be transferred to a reference centre, as better outcomes were observed for patients with intermediate or poor prognosis when treated in a clinical trial in a high-volume centre [3,68]. There are no general recommendations for treatment modifications for patients with poor general condition (Karnofsky performance score <50%) or extended liver infiltration (>50%), but two small studies indicate that a first cycle of dose-reduced therapy may reduce acute mortality without compromising long-term outcome [69,70]. However, the number of subsequent cycles of full-dose therapy should not be reduced after a first low-dose induction cycle.

*3.6.3.6. Restaging and further treatment.* Restaging involves imaging investigations and reevaluation of tumour markers. If marker levels decline and a stable or regressive tumour is observed, chemotherapy is completed (three or four cycles, depending on the initial stage) [10]. If marker levels decline but metastases continue to grow, tumour resection is obligatory after termination of induction therapy, other than in an emergency, according to local tumour growth. Early therapy crossover to a completely new regimen is only indicated for a documented increase in marker levels after two courses of chemotherapy. Such patients are usually candidates for new drug trials.

Patients with a low-level human chorionic gonadotrophin (hCG) plateau after treatment should be observed to see whether complete normalisation occurs. In patients with a low serum α-fetoprotein (AFP) plateau after chemotherapy, surgery of residual masses is indicated, with postsurgical AFP monitoring. Salvage chemotherapy is only indicated for a documented increase in marker level.

### 3.7. Residual tumour resection

#### 3.7.1. Seminoma

A residual seminoma mass, irrespective of size, should not be primarily resected but should be controlled using imaging investigations and tumour markers.

Fluorodeoxyglucose (FDG)-PET has a high negative predictive value in patients with residual masses after treatment of seminoma. False-positive results are less frequent when scans are scheduled >2 mo after chemotherapy [71].

In the case of a postchemotherapy mass that is still positive at reclassification FDG-PET with no volume increase, a second FDG-PET scan should be performed 6 wk later. Alternatively, a biopsy should be carried out to ascertain if persistent disease is present. In such cases and in cases with progressive disease, salvage therapy is indicated (usually chemotherapy or radiotherapy). Patients with persistent and progressing hCG elevation after first-line chemotherapy should immediately undergo salvage chemotherapy. Patients with progressing disease without hCG progression should undergo histologic verification (eg, biopsy or mini-invasive or open surgery) before salvage chemotherapy is administered. When RPLND is indicated, this should be performed in referral centres, as residual seminoma masses may be difficult to remove because of extensive fibrosis. Ejaculation may be preserved in these cases.

#### 3.7.2. Nonseminoma

Following first-line BEP chemotherapy, only 6–10% of residual masses contain viable cancer, 50% contain mature teratoma, and 40% contain necrotic-fibrotic tissue [72].

FDG-PET is not indicated for restaging after chemotherapy [73]. In cases of complete remission after first-line chemotherapy (no visible tumour), tumour resection is not indicated [74,75]. Residual tumour resection is mandatory for all patients with a residual mass >1 cm along the short axis at cross-sectional CT imaging [76]. The role of surgery in patients with retroperitoneal residual lesions <1 cm is debated. There is still a risk of residual cancer or teratoma, although the vast majority of patients (>70%) harbour fibronecrotic tissue [77]. Proponents of postchemotherapy RPLND for all patients refer to the fact that both teratoma and vital malignant germ-cell tumours are still found after radiologic complete remission in lesions <10 mm [78]. The alternative is to place patients with residual disease

**Table 11 – Standard PEI/VIP, TIP, and GIP chemotherapy regimens (interval 21 d)**

| Regimen | Chemotherapy agents | Dosage | Cycle duration |
|---|---|---|---|
| PEI/VIP | Cisplatin [a] | 20 mg/m$^2$ | Days 1–5 |
| | Etoposide | 75–100 mg/m$^2$ | Days 1–5 |
| | Ifosfamide [b] | 1.2 g/m$^2$ | Days 1–5 |
| TIP | Paclitaxel | 250 mg/m$^2$ [c] | 24-h continuous infusion day 1 |
| | Ifosfamide [b] | 1.5 g/m$^2$ | Days 2–5 |
| | Cisplatin [a] | 25 mg/m$^2$ | Days 2–5 |
| GIP | Gemcitabine | 1000 mg/m$^2$ | Days 1 and 5 |
| | Ifosfamide | 1200 mg/m$^2$ | Days 1–5 |
| | Cisplatin | 20 mg/m$^2$ | Days 1–5 |

PEI/VIP = cisplatin, etoposide, ifosfamide; TIP = paclitaxel, ifosfamide, cisplatin; GIP = gemcitabine, ifosfamide, cisplatin.
[a] Plus hydration.
[b] Plus mesna protection.
[c] A Medical Research Council schedule uses paclitaxel at 175 mg/m$^2$ in a 3-h infusion.

of <1 cm on an observation protocol, for which the recurrence rate is 6–9%, depending on the follow-up time [74,75]. Patients treated with first-line chemotherapy should be informed about a lifelong risk of recurrence of approximately 10% before consenting to observation of residual lesions of <1 cm. Patients after salvage chemotherapy or high-dose chemotherapy in first or subsequent salvage situations harbour vital tumour at a much higher rate. Therefore, there is an indication to perform surgery in salvage patients even with residual disease <1 cm [74,75]. If residual surgery is indicated, all areas of primary metastatic sites must be completely resected within 2–6 wk of chemotherapy completion. If technically feasible, a bilateral nerve-sparing procedure should be performed. There is growing evidence that template resection with unilateral preservation of nerves in selected patients yields equivalent long-term results to bilateral systematic resection in all patients. Mere resection of the residual tumour (so-called lumpectomy) should not be performed [75,77,79–82]. Laparoscopic RPLND may yield similar outcomes to the open procedure in very selected cases with small residual disease and in experienced hands, but this strategy is not recommended outside specialised laparoscopic centres with particular expertise in testis tumour management [83–85].

#### 3.7.3. *Surgical timing in the case of multiple sites*

In general, surgery for residual masses should start at the location with the highest volume of residual disease. The histology may diverge in different organ sites. In cases with retroperitoneal and lung residual masses, the presence of fibronecrotic tissue in the retroperitoneum is associated with a probability as high as 90% that lung masses contain the same histology. Resection of contralateral pulmonary lesions is not mandatory if pathologic examination of lesions from the first lung shows complete necrosis. However, discordant histology between the two lungs may occur in up to 20% of patients [86,87].

#### 3.7.4. *Surgical quality and intensity*

Postchemotherapy surgery is always demanding. Approximately one third of patients may require a planned intervention in which organs affected by the disease (eg, kidney, psoas muscle, or gross vessels) are removed, followed by ad hoc reconstructive surgery (eg, vascular interventions such as vena cava or aortic prostheses) [88,89]. In patients with intermediate or poor risk and residual disease of >5 cm, the probability of vascular procedures is as high as 20% [90]. This intense (“maximal”) surgery must therefore be referred to specialised centres capable of interdisciplinary surgery (hepatic resections, vessel replacement, spinal neurosurgery, thoracic surgery). Patients treated within such centres benefit from a significant reduction in perioperative mortality from 6% to 0.8% [4]. In addition, specialised urologic surgeons are capable of reducing the local recurrence rate from 16% to 3% with a higher rate of complete resections [5]. Surgery of resectable disease even after (multiple) salvage treatments remains a potentially curative option with durable complete remissions in the order of 20% [91,92].

### 3.8. *Systemic salvage treatment for relapsing or refractory disease*

Cisplatin-based combination salvage chemotherapy will result in long-term remissions in approximately 50% of patients with relapse after first-line chemotherapy, but the results are highly dependent on several prognostic factors. The regimens of choice are four cycles of a triplet regimen including cisplatin and ifosfamide plus etoposide, paclitaxel, or potentially gemcitabine as a third agent (Table 11) [93]. No randomised trial has ever compared these regimens. Owing to their potentially lethal risk of haematologic toxicity, these regimens should be used with G-CSF support and by well-trained oncologists. At present it is impossible to determine whether conventional dosing for cisplatin-based combination chemotherapy is sufficient as first-salvage treatment or whether early intensification of first-salvage treatment with high-dose chemotherapy should be used. However, there is evidence from large retrospective analyses that there are different prognostic groups in the case of relapse after first-line chemotherapy [50,94,95], and the Lorch-Beyer score has resulted in five prognostic subgroups (Table 9). A second large analysis in this cohort of 1600 patients showed an OS improvement of approximately 10–15% among patients from all prognostic subgroups for high-dose salvage therapy compared to standard-dose therapy. If high-dose chemotherapy is used

**Table 12 – Recommended minimum follow-up schedule in a surveillance policy for stage I nonseminoma [103]**

| Procedure | Year | | | |
|---|---|---|---|---|
| | 1 | 2 | 3 | 4–5 |
| Physical examination | Four times | Four times | Four times | Once/yr |
| Tumour markers | Four times | Four times | Four times | Once/yr |
| Plain radiography of the chest | Twice | Twice | Twice | Twice |
| Abdominopelvic computed tomography | Twice (at 3 and 12 mo) | Once (at 24 mo) | Once (at 36 mo) | |

**Table 13 – Recommended minimum follow-up schedule after retroperitoneal lymphadenectomy or adjuvant chemotherapy for stage I nonseminoma**

| Procedure | Year | | | | |
|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4–5 | 6–10 |
| Physical examination | Four times | Four times | Four times | Once/yr | Once/yr |
| Tumour markers | Four times | Four times | Four times | Once/yr | Once/yr |
| Plain radiography of the chest | Twice | Twice | Twice | | |
| Abdominopelvic computed tomography | Once | Once | Once | Once/yr | |

**Table 14 – Recommended minimum follow-up schedule for post-orchiectomy surveillance, radiotherapy, or chemotherapy for stage I seminoma [36]**

| Procedure | Year | | |
|---|---|---|---|
| | 1 | 2 | 3–5 |
| Physical examination | Three times | Three times | Once/yr |
| Tumour markers | Three times | Three times | Once/yr |
| Plain radiography of the chest | Twice | Twice | |
| Abdominopelvic computed tomography | Twice | Twice | At 36 and 60 mo |

**Table 15 – Recommended minimum follow-up schedule in metastatic nonseminomatous germ cell tumour and seminoma**

| Procedure | Year | | | |
|---|---|---|---|---|
| | 1 | 2 | 3–5 | Thereafter |
| Physical examination | Four times | Four times | Twice/yr | Once/yr |
| Tumour markers | Four times | Four times | Twice/yr | Once/yr |
| Plain radiography of the chest | Four times | Four times | Twice/yr | Once/yr |
| Abdominopelvic CT [a] | Twice | Twice | Once/yr | As indicated |
| Chest CT [b,c] | Once/yr | Once/yr | Once/yr | As indicated |
| Brain CT [d] | Once/yr | Once/yr | Once/yr | As indicated |

CT = computed tomography.
[a] Abdominal CT must be performed at least annually if teratoma is found in the retroperitoneum.
[b] If postchemotherapy evaluation in a seminoma patient shows any mass >3 cm, the appropriate CT should be repeated 2 and 4 mo later to ensure that the mass is continuing to regress. If available, fluorodeoxyglucose positron emission tomography/CT can be performed.
[c] Chest CT is indicated if an abnormality is detected on a plain chest x-ray and after pulmonary resection.
[d] In patients with headaches, focal neurological findings, or any central nervous system symptoms.

as a salvage treatment, sequential cycles of high-dose carboplatin and etoposide should be preferred over a single high-dose regimen because the former is associated with fewer toxicity-related deaths [96]. It is clearly of the utmost importance that these rare patients with relapse are treated within clinical trials and at experienced centres.

### 3.9. *Late relapse*

Late relapse is defined as recurrence >2 yr after cure following chemotherapy for metastatic testicular cancer, with or without surgery for residual tumour surgery. According to a pooled analysis, late relapse occurs in 1.4% of seminoma and 3.2% of nonseminoma cases [97,98]. If feasible, all lesions in late-relapsing nonseminoma cases should be removed by radical surgery. Patients with rapidly rising hCG may benefit from induction salvage chemotherapy before complete resection, but in most patients surgery should be performed irrespective of the level of their tumour markers to completely resect all undifferentiated germ-cell tumour and mature teratoma with or without somatic transformation [99–101]. To minimise mortality,

late relapses should be treated only at centres experienced in managing such patients [102].

### 3.10. Follow-up schedules

Tables 12–15 list the recommended follow-up schedules.

## 4. Conclusions

For all stages of testicular cancer, the best cure rates are obtained in high-volume reference centres. Patients diagnosed with testicular cancer should be informed about the short- and long-term side effects of radiotherapy and chemotherapy. The aim of risk-adapted treatment is to reduce long-term treatment-related sequelae without compromising therapeutic efficacy.

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*Study concept and design:* Albers.
*Acquisition of data:* Albers, Albrecht, Cohn-Cedermark, Algaba, Bokemeyer, Fizazi, Horwich, Laguna, Nicolai, Oldenburg.
*Analysis and interpretation of data:* Albers, Albrecht, Cohn-Cedermark, Algaba, Bokemeyer, Fizazi, Horwich, Laguna, Nicolai, Oldenburg.
*Drafting of the manuscript:* Albers.
*Critical revision of the manuscript for important intellectual content:* Albers, Albrecht, Cohn-Cedermark, Algaba, Bokemeyer, Fizazi, Horwich, Laguna, Nicolai, Oldenburg.
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