European Association of Urology

GUIDELINES ON TESTICULAR CANCER*

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1. BACKGROUND

Testicular cancer represents between 1% and 1.5% of male neoplasms and 5% of urological tumours in general, with 3-6 new cases/occurring per 100,000 males/per year in Western society (1,2). An increase in the incidence of testicular cancer was detected during the 1970's and 1980's, particularly in Northern European countries. Only 1-2% of cases are bilateral. The histological type varies, although there is a clear predominance (90-95%) of germ cell tumours (1). Peak incidence is in the third decade of life for non-seminoma and in the fourth decade for pure seminoma. Familial clustering has been observed, particularly among siblings (3). Genetic changes have been described in patients with testicular cancer. A specific genetic marker (an isochromosome of the short arm of chromosome 12), i(12p), has been described in all histological types of germ cell tumours (3). Intratubular germ cell neoplasia (Tin) shows the same chromosomal changes, and recently alterations in the p53 locus have been found in 66% of cases of testicular Tin (4).

Currently, testicular tumours show excellent cure rates. The main factors contributing to this are: careful staging at the time of diagnosis; adequate early treatment based on chemotherapeutic combinations, with or without radiotherapy and surgery; and very strict follow-up and salvage therapies. In the last decade, a decrease in the mean time delay to diagnosis and to treatment has been observed (5). In the treatment of Testicular Cancer the choice of the Center where this treatment is going to be administered is of capital importance. Although early stages can be succesfully treated in a non reference Center, the relapse rate is higher, suggesting that the high survival rate is due to the Chemo and Radiosensitivity of the early stages rather than the compliance achieved in the non reference Center (6). In poor prognosis non Seminomatous Germ Cell Tumors overall survival is significantly different (worse) depending on the number of patients treated at the Institution (< 5) (7).

2. CLASSIFICATION

The recommended pathological classification (modified World Health Organization) is shown below.

1. Germ cell tumours
    - Intratubular germ cell neoplasia
    - Seminoma (including cases with syncytiotrophoblastic cells)
    - Spermatocytic seminoma (mention if there is sarcomatous component)
    - Embryonal carcinoma
    - Yolk sac tumour:
        - Reticular, solid and polyvesicular patterns
        - Parietal, intestinal, hepatoid and mesenchymal differentiation
    - Choriocarcinoma
    - Teratoma (mature, immature, with malignant component)
    - Tumours with more than one histological type (specify % of individual components)

2. Sex cord stromal tumours
    - Leydig cell tumour
    - Sertoli cell tumour (typical, sclerozing, large cell calcifying)
    - Granulosa (adult and juvenile)
    - Mixed
    - Unclassified

3. Mixed germ cell/sex cord stromal tumours

2.1 Staging

There are multiple staging systems, including the; tumour, node, visceral metastasis (TNM) system, the Peckham classification (Royal Marsden Hospital), the Walter Reed Hospital classification and staging systems from the European Organization for Research and Treatment of Cancer (EORTC), Memorial Sloan Ketering (MMSK) and Indiana University Hospital. It appears that each group working in the field of testicular cancer has its own staging system. The most commonly used systems are the TNM and the Peckham classification. The staging systems are generally based on the quantity of tumoural volume at diagnosis and take into account known risk factors.

The staging system recommended in these guidelines is the 1997 TNM (Table 1). This includes: determination of the anatomical extent of disease; assessment of serum tumour markers: including nadir

values of beta-human chorionic gonadotrophin (beta-hCG), alpha-fetoprotein (AFP) and lactate dehydrogenase (LDH) after orchiectomy (S category); clear definition of regional nodes; and some N category modifications related to the node size (8). Nevertheless for practical purposes, treatment and follow-up (outlined in) the Peckham classification are still mentioned in this report.
According to the 1997 TNM classification, stage I testicular cancer includes the following substages:

Stage IA	pT1	N0	M0	S0
Stage IB	pT2, pT3 or pT4	N0	M0	S0
Stage IS	Any pT/TX	N0	M0	S1-3

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. 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, which is evidence of subclinical metastatic disease (or possibly a second germ cell tumour in the remaining testis). If serum tumour marker levels are declining according to the expected half-time decay after orchiectomy, the patient is usually followed up until normalization.

In large, population-based patient series, 75-80% of seminoma patients and about 55% of patients with non-seminomatous germ cell testicular cancer (NSGCT) have stage I disease at diagnosis (9,10). True stage IS (persistently elevated or increasing serum marker levels after orchiectomy) is found in about 5% of non-seminoma patients. If a staging retroperitoneal lymph nodes dissection (RPLND) is performed in stage IS patients, nearly all patients have pathological stage II disease (pN+) (1-3,10).

Table 1: The 1997 TNM staging system for testicular cancer

pT	**Primary tumour**				
pTx	Primary tumour cannot be assessed (if no radical orchiectomy has been performed Tx is used)				
pTo	No evidence of primary tumour (e.g. histological scar in testis)				
pTis	Intratubular germ cell neoplasia (carcinoma in situ)				
pT1	Tumour limited to testis and epididymis without vascular/lymphatic invasion; tumour may invade tunica albuginea, but not tunica vaginalis				
pT2	Tumour limited to testis and epididymis with vascular/lymphatic invasion, or tumour extending through tunica albuginea with involvement of tunica vaginalis				
pT3	Tumour invades spermatic cord with or without vascular/lymphatic invasion				
pT4	Tumour invades scrotum with or without vascular/lymphatic invasion				
pN	**Regional lymph nodes**				
pNx	Regional lymph nodes cannot be assessed				
pN0	No regional lymph node metastasis				
pN1	Metastasis with a lymph node mass 2 cm or less in greatest dimension and five or fewer positive nodes, none more than 2 cm in greatest dimension				
pN2	Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension, or more than five positive nodes positive, none more than 5 cm in greatest dimension, or evidence of extranodal extension of tumour				
pN3	Metastasis with a lymph node mass more than 5 cm in greatest dimension				
pM	**Distant metastasis**				
The pM category corresponds to the M category					
S	**Serum tumour markers**				
Sx	Serum marker studies not available or not performed				
So	Serum marker study levels within normal limits				
	LDH (U/L)		**Beta-hCG (mIU/ml)**		**AFP (ng/ml)**
S1	< 1.5 x N[a]	and	< 5.000	and	< 1,000
S2	1.5–	or	5,000–50,000	or	1.0–10.0
S3	> 10 x N	or	50,000	or	>10,000

LDH = lactate dehydrogenase; beta-hCG = beta-human chorionic gonadotrophin; AFP = alpha-fetoprotein.
[a] Indicates the upper limit of normal for the LDH assay.

3. RISK FACTORS

In addition to the well-known epidemiological and clinical risk factors, a series of pathological risk factors have been identified in all staging systems, which consequently have a bearing on the prognosis. The classification of risk factors into epidemiological, clinical and pathological categories is shown in Table 2 (11-16). For clinical stage I, the most important risk factors are the histological type (seminomatous or non-seminomatous) and the presence of peri-tumoural vascular and lymphatic invasion (17). Recently, the International Germ Cell Collaborative Group (IGCCG) analysed data on 5,202 patients with NSGCT and on 660 patients with seminoma and identified some clinical independent adverse factors for metastatic disease. They devised a prognostic based staging system based on this data, on which the presence or absence of the aforementioned risk factors and the degree of elevation of serum tumour markers determined subgroups of good, intermediate or poor prognosis for NSGCT, and of good and intermediate risk for seminoma (18). The value of scrotal surgery as a risk factor remains controversial (19,20).

Table 2: Classification of risk factors for testicular cancer

Epidemiological
- Cryptorchidism
- Klinefelter's syndrome
- Familial history
- Contralateral tumour
- Tin
- Infertility

Pathological (for stage I)
- Histopathological type
- Tumour size
- Vascular/lymphatic peri-tumoural invasion

Clinical (for metastatic disease)
- Primary location
- Elevation of tumour marker levels
- Presence of non-pulmonary visceral metastasis[a]

[a] Only clinical predictive factor for metastatic disease in seminoma.

3.1 Screening

Although there are no surveys proving the advantages of screening programmes, it has been demonstrated that stage and prognosis are directly related to early diagnosis. In the presence of clinical risk factors, some self-physical examination by the affected individual is advisable.

4. DIAGNOSIS

Testicular cancer generally affects young men in the third or fourth decade of life. It normally appears as a painless, unilateral mass in the scrotum or the casual finding of an intrascrotal mass. In approximately 20% of cases the first symptom is scrotal pain and up to 27% of patients with testicular cancer have local pain (1). Occasionally, trauma to the scrotum may reveal the presence of a testiscular mass. Gynaecomastia appears in 7% of cases and is more common in non-seminomatous tumours. Back and flank pain are present in about 11% of cases (5). Reduction in testis size can precede a testicular tumour (12).

In about 10% of cases, a testicular tumour can mimic an orchioepididymitis, with consequent delay of the correct diagnosis (1,2). Ultrasound must be performed in any doubtful case. Physical examination reveals the features of the mass and must always be carried out in conjunction with a general examination in order to find possible (supraclavicular) distant metastases, a palpable abdominal mass or gynaecomastia. A correct diagnosis must be established in all patients with an intrascrotum mass (16).

4.1 Diagnostic tools

Staging represents the cornerstone on which testicular cancer treatment is based; treatment will vary according

to the extent and histology of the tumour. It is mandatory to determine:

- Pre- and post-orchiectomy levels of serum tumour markers
- Pathology of the testis
- Status of abdominal and supraclavicular nodes, and the liver
- Presence or absence of mediastinal nodal involvement and lung metastases
- Status of brain and bone if any suspicious symptoms are present

The recommended tests for staging at diagnosis are shown in Table 3.

Table 3: Recommended tests for staging at diagnosis

Test	Mandatory	Advisable	Optional
Tumour markers	Alpha-fetoprotein Beta-human chorionic gonadotrophin Lactate dehydrogenase		Neuro-specific enolase Placental alkaline phosphatase
Abdominal computed tomography	Young men		Slim adolescents and children
Chest X-ray	Seminoma[a]		NSGCT
Chest computed tomography	Non-seminomatous germ cell tumour		Seminoma[a]
Abdominal ultrasound	Slim adolescents and children		Young men
Testes ultrasound	Clinically suspicious and normal scrotum	Patients at risk	Abnormal testis examination
Magnetic resonance imaging			All cases
Other		If suspicious of metastatic disease	

[a] If negative abdominal computed tomography (CT) scan.

4.2 Serum tumour markers

Serum tumour markers are prognostic factors and contribute to diagnosis and staging (24). The following markers should be determined:

- AFP (produced by yolk sac cells)
- Beta-hCG (b-hCG) (expression of trophoblasts)
- LDH (marker of tissue destruction)

The mean serum half-life of AFP is 5-7 days and that of beta-hCG approximately 1 day (25).
Globally, there is an increase in these markers in 51% of cases of testicular cancer (5). AFP increases in 50-70% of patients with NSGCT and a rise in beta-hCG is seen in 40-60% of patients with NSGCT. About 90% of non-seminomatous tumours present with a rise in one or two of the markers. Up to 30% of seminomas can present or develop an elevated beta-hCG level during the course of the disease (25,26). LDH is a less specific marker, and its concentration is proportional to tumour volume. Its level may be elevated in 80% of patients with advanced testicular cancer (25). It should be noted that negative markers levels do not exclude the diagnosis of a germ cell tumour, and normalization of marker levels after treatment does not necessarily mean the absence of a tumour.

Other markers studied include neuro-specific enolase (NSE) and placental alkaline phosphatase (PLAP). NSE and/or PLAP may be of limited value in monitoring patients with pure seminoma. Cytogenetic and

molecular markers are available in specific centres, but at present only contribute to research studies.

Measurement of serum AFP, beta-hCG and LDH is mandatory. NSE and PLAP are optional.

4.3 Inguinal exploration and orchiectomy

Every patient with a suspected testicular mass must undergo inguinal exploration with exteriorization of the testis within its tunics, and immediate orchiectomy with division of the spermatic cord at the internal inguinal ring has to be performed if a tumour is found.

The spermatic cord is isolated at the external ring and clamped with a soft vascular clamp. The testis is then exteriorized with its tunics. The surgical field is protected with surgical sponges, the tunica vaginalis is opened, and the testis is carefully inspected and palpated. If the diagnosis is not clear, a testicular biopsy is taken for frozen section histological examination. Once the diagnosis of testicular tumour has been established, the testis is enveloped into the sponges which protected the surgical field, gloves are changed, the inguinal channel is opened and the spermatic cord is divided at the level of the internal ring. The specimen is sent for definitive histology.

4.3.1 Organ sparing surgery

Although Organ Sparing Surgery is not indicated it can be attempted in special cases with all the necessary precautions.

In bilateral testicular tumors or in a tumor in a solitary testis, organ preserving surgery can be performed when the tumor measures less than 2 cm and surgical rules are respected. In those cases, the rate of associated Tin is high (up to 82%) and can be treated with Radiotherapy (27).

4.4 Diagnosis of testicular carcinoma in SITU

Contralateral biopsy has been advocated to rule out the presence of Tin. Although this is routine policy in some countries, the low incidence of Tin and contralateral asynchronic testicular tumours, up to 5% and approximately 2.5% respectively, (12-15), the morbidity of Tin treatment and the fact that most of these asynchronic tumours are at a low stage at presentation makes it controversial to recommend a systematic contralateral biopsy (21,22).

It is stil difficult to reach a consensus whether the existence of contralateral Tin has to be indentified in all cases. However biopsy of the contralateral testis is recommended if there is testicular athrophy, in the cases of azoospermia or if the patient is less than 30 years of age (14).

Once Tin is diagnosed, local Radiotherapy (up to 18 Gy) is the treatment of choice. Because this may produce infertility, the patient must be carefully counselled before treatment commences (14,23)

4.5 Pathology of the testis

After surgical ablation of the testis, pathological assessment is mandatory and determination of serum tumour markers is advisable.

Mandatory pathological requirements

- Macroscopic features: side, testis size, tumoural maximum size and macroscopic features of epididymis, spermatic cord and tunica vaginalis.
- Sampling: 1 cm^2 section for every cm of maximal tumoural diameter, including normal macroscopic parenchyma (if present), albuginea and epididymis selection of suspected areas. At least one proximal and one distal section of spermatic cord plus any suspected area.
- Microscopic features and diagnosis: histological type (specify individual components and estimate amount as percentage). Presence or absence of peri-tumoral venous and/or lymphatic invasion. Presence or absence of albuginea, tunica vaginalis, epididymis or spermatic cord invasion. Presence or absence of intratubular germinal neoplasia (Tin) in non-tumoral parenchyma.
- Category pT category according to TNM 1997.
- Immunohistochemical studies: in seminoma and mixed germ cell tumour, AFP and beta-hCG.

Advisable immunohistochemical markers

- In seminoma: cytokeratins (CAM 5.2), PLAP
- In intratubular germ cell neoplasia: PLAP
- Other advisable markers: Chromogranine A (Cg A), Ki 1, and NSE

4.6 Abdominal, mediastinal and supraclavicular nodes, and state of the viscera

Supraclavicular nodes

The supraclavicular nodes are best assessed by physical examination.

Abdominal computed tomography (CT) scan

CT scanning has clear advantages over lymphography; it offers a sensitivity of 70-80% in the determination of the state of retroperitoneal nodes. Its accuracy depends on the size of the nodes; sensitivity and negative predictive value increase using a 3-mm threshold to define metastatic nodes in the landing zones (28). Those figures decrease slightly in stages I and II (29-30), with a rate of understaging of 25-30% (32). New generations of CT scans do not seem to improve the sensitivity. An abdominal CT scan is mandatory but can be considered optional in very slim young men and children, in whom ultrasound must be performed due to lack of retroperitoneal fat.

Chest X-ray

Chest X-ray is the routine thorax examination. It is usually performed before orchiectomy in the surgical protocol. An antero-posterior and lateral chest X-ray could be considered the only thoracic examination in seminoma when retroperitoneal and pelvic CT scans are negative (33).

Chest CT scan

A chest CT scan is the most sensitive way to evaluate the thorax. This exploration has to be recommended in patients with NSGCT because up to 10% of cases can present with small subpleural nodes that are not visible radiologically (1). The CT scan has high sensitivity but low specificity (33). A chest CT is mandatory in all patients with NSGCT and in those with seminoma and positive abdominal CT scan (33).

Ultrasound

Currently, diagnostic ultrasound serves to confirm the presence of a testicular mass and to explore the contralateral testis. Its sensitivity in detecting a testicular tumour is almost 100%, and it has an important role in determining whether a mass is intra- or extratesticular (34). Ultrasound is an inexpensive test, but it is unnecessary when the presence of a testicular tumour is clinically evident (35). Ultrasound of the testis has to be performed in young men without a palpable testicular mass who have retroperitoneal or visceral masses or elevated serum beta-hCG or AFP (36-39).

The main uses of ultrasound are as a screening test of the contralateral testis in the follow-up of patients at risk (406) and as a substitute for abdominal CT in slim young men or children.

Magnetic resonance imaging (MRI)

MRI offers higher sensitivity and specificity than ultrasound for diagnosing tumours (41-43) and may be able to differentiate seminomatous from non-seminomatous tumours. MRI of the scrotum offers a sensitivity of 100% and a specificity of 95-100% (44), but its high cost does not justify its use for diagnosis. In detection of retroperitoneal nodal enlargement, MRI produces similar results to CT scanning (45). Again, the main objections to its routine use are high cost and limited access. Nevertheless, MRI can be very helpful when abdominal CT or ultrasound are inconclusive (45) , when CT scan is contraindicated because of allergy to contrast media or when the physician or the patient are concerned about radiation dose. MRI is an optional test and there are currently no indications for its systematic use in the staging of testicular cancer.

PET scan

There is not yet enough evidence to support the use of the FDG-PET scan in early stages, it can nevertheless be recommended in Seminoma post-Chemotherapy residual masses bigger than 3 cm in order to decide Watchul Waiting or active treatment therapy (46-48).

Other examinations

Other examinations, such as brain or spinal CT, bone scan or liver ultrasound, should be performed if there is suspicion of metastases to these organs. CT scan or MRI of the skull are advisable in patients with NSGCT and widespread lung metastases.

4.7 GUIDELINES ON DIAGNOSIS AND STAGING OF TESTICULAR CANCER

1. Physical examination may be sufficient for the diagnosis of testicular cancer.
2. Testicular ultrasound is mandatory when a tumour is clinically suspected but the examination of the scrotum is normal, or if there is any doubt about the clinical findings in the scrotum.
3. Pathological examination of the testis is necessary to confirm the diagnosis and define the local extension (pT category).
4. Serum determination of tumour markers (AFP, beta-hCG, LDH) must be performed before and after orchiectomy for staging and prognostic reasons.
5. Retroperitoneal, mediastinal and supraclavicular nodes and visceral state have to be assessed in testicular cancer. In seminoma, a chest CT scan is not necessary if abdominal nodes are negative.

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5. TREATMENT: STAGE I GERM CELL TUMOURS

5.1 Stage I seminoma

After modern staging procedures, about 15-20% of stage I seminoma patients have subclinical metastatic disease, usually in the retroperitoneum, and will relapse after orchiectomy alone (1).

Prophylactic radiotherapy

Seminoma cells are extremely radiosensitive. Prophylactic radiotherapy to a para-aortic (PA) field or to a hockey stick field (para-aortic and ipsilateral iliacal nodes), with moderate doses (total 20-24 Gy), will reduce the relapse rate to only 1-3% (2-5). After modern radiotherapy nearly all relapses will first occur outside the irradiated field (supradiaphragmatic lymph nodes or in the lungs) (2,5). Based upon the results of a large randomized Medical Research Council (MRC) trial, Fosså et al. (2,3) recommended radiotherapy to an ipsilateral para-aortic field as standard treatment for patients with testicular seminoma stage I, T1-T3 and with undisturbed lymphatic drainage. The acute toxicity was reduced and the sperm count within the first 18 months was significantly higher after unilateral para-aortic irradiation than after irradiation of the traditional dog-leg field. On the other hand, the relapse rate in the iliac lymph nodes was about 2% (all of them on the right side) after para-aortic and 0% after dog-leg irradiation. Another possible site of failure is in the left renal hilum. Para-aortic irradiation should be tailored according to the site of the primary tumour. Prophylactic irradiation of supradiaphragmatic lymph nodes is not indicated in seminoma stage I.

The rate of severe radiation-induced long-term toxicity is less than 2%. Moderate chronic gastrointestinal (GI) side-effects are seen in about 5% of patients and moderate acute GI toxicity in about 60% (2). The main concern surrounding prophylactic radiotherapy is the potentially increased risk of radiation-induced secondary non-germ-cell malignancies, including leukaemia (6-8). A scrotal shield can be of benefit during prophylactic radiotherapy in order to prevent toxicity in the contralateral testis (9). At this point in time it is difficult to evaluate the increased risk after prophylatic radiotherapy for stage I seminoma since former treatment procedures included larger fields, higher doses of radiotherapy and/or the use of alkylating chemotherapy.

Because the retroperitoneum does not need to be intensily monitorized during follow-up Prophylactic Radiotherapy is the cheaper treatment option per life saved (10).

Surveillance

Several prospective non-randomized studies of surveillance have been conducted during the last decade, several of which comprised more than 100 patients. The actuarial relapse rate is of the order of 15-20% at 5 years, and most of the relapses are first detected in infra-diaphragmatic lymph nodes (1,11). About 70% of the patients relapsing after surveillance are suitable for treatment with radiotherapy alone. Only about 20% of these patients relapse after salvage radiotherapy and need salvage chemotherapy. The overall cancer-specific survival rate reported by experienced centres is 98-100% for seminoma stage I after surveillance (11).

A pooled (multivariate) analysis based on the three largest studies of testicular seminoma stage I managed by surveillance indicates that a primary tumour of over 4 cm in size and invasion of the rete testis are important prognostic factors for relapse, with hazard ratios of 1.9 and 2.0, respectively (12).

The main drawback of surveillance is the need for more intensive follow-up, especially with repeated imaging examinations of the retroperitoneal lymph nodes, for at least 5 years after orchiectomy. This compares with the very low risk of subdiaphragmatic relapse after prophylactic radiotherapy. About 20% of the relapses seen after surveillance occur more than 4 years after orchiectomy (11).

Cost analyses of surveillance compared with radiotherapy indicate that it is more expensive (13), but estimates vary depending basically on the follow-up schedules (10,14).

Prophylactic chemotherapy
Chemotherapy is very effective in advanced seminoma and may be an alternative to radiotherapy or surveillance in stage I seminoma (11). One or two courses of adjuvant carboplatin seem to reduce the relapse rate to the order of 1-2% (15,16), but further experience and long-term observations are needed before such adjuvant chemotherapy can be recommended as a routine option. A joint MRC and EORTC trial (MRC TE 19 trial) is currently comparing adjuvant radiotherapy with one course of carboplatin, but the results are not yet available (2).

RPLND
In a prospective, non-randomized study comparing radiotherapy and RPLND in stage I seminoma, there was a trend towards a higher incidence of retroperitoneal relapses (9.5%) after RPLND as primary treatment. Therefore this policy should not be recommended in stage I seminoma (15).

5.2 GUIDELINES FOR THE TREATMENT OF SEMINOMA STAGE I

1. Prophylactic radiotherapy to a para-aortic or a hockey stick field, to a total dose of 20-24 Gy.
2. Surveillance (if available facilities).
3. Awaiting the results of current comparative studies, Carboplatin based chemotherapy can only be recommended in the setting of clinical trials.

5.3 NSGCT stage I
If true stage IS cases are excluded, up to 30% of NSGCT patients with clinical stage I (CS1) disease have subclinical metastases and will relapse if surveillance alone is applied after orchiectomy.

RPLND
If RPLND is performed, about 30% of patients are found to have retroperitoneal lymph node metastases, that to say pathological stage II (PS2) disease. If no retroperitoneal metastates are found at RPLND (PS1), approximately 10% of the PS1 patients relapse at distant sites (16-19). The main predictor of relapse in CS1 NSGCT managed by surveillance, and both for having PS2 disease and for relapse in PS1 after RPLND, is histopathological evidence of vascular invasion by tumor cells near the primary tumor in the testis (17,19-21). The presence of vascular invasion seems to be a very robust parameter, and is clinically usable even without centralized review by an expert panel (19,22).

Patients without vascular invasion constitute about 70% of the CS1 population, and these patients have only a 15-20% risk of relapse on surveillance, compared with a 50% relapse rate in patients with vascular invasion. The risk of relapse for PS1 patients is less than 10% for those without vascular invasion and about 30% for those with vascular invasion (19,22-24).

If CS1 patients with PS2 are only followed up after RPLND, about 30% relapse, mainly at sites outside the abdomen and pelvis. The risk of relapse depends upon the amount of retroperitoneal disease resected (25-27). If two (or more) courses of cisplatin-based chemotherapy are given adjuvant to RPLND in the PS2 cases, the relapse rate is reduced to less than 2%, including teratoma relapse (17,20,28).

The risk of retroperitoneal relapse after a properly performed nerve-sparing RPLND is very low (less than 2%), as is the risk of ejaculatory disturbance or other significant side-effects (20,25,26). The follow-up after RPLND is much simpler and less costly than that carried out during post-orchiectomy surveillance due to the reduced need for abdominal CT scans (20).

A laparoscopic RPLND may become a good alternative to an open RPLND, but can currently not be recommended as a standard treatment (29-32).

Surveillance
Improvements in clinical staging and follow-up methods, and the availability of effective salvage treatment with cisplatin-based chemotherapy and post-chemotherapy surgery, have led to studies of only close surveillance after orchiectomy in CS1 NSGCT patients. The largest reports of the surveillance strategy indicate a cumulative relapse rate of about 30%, with 80% of the relapses occurring during the first 12 months of follow-up, 12% during the second year and 6% during the third year, decreasing to 1% during the fourth and fifth years, and occasionally even later (21,33,34). About 45% of relapsing patients have normal levels of serum tumour markers at relapse. About 60% of the relapses are detected clinically in the retroperitoneum. Despite very close follow-up, 11% of relapsing patients presented with large-volume recurrent disease. Half of the deaths reported were attributable to the relapse or to salvage therapy. The somewhat lower relapse rates reported from surveillance studies compared with those expected in patients staged by RPLND (17) can be explained by the fact that some patients (presumably at risk) are excluded once surveillance is advised.

Primary chemotherapy

Several studies involving two courses of chemotherapy with bleomycin, etoposide and cisplatin, (BEP) as primary treatment for high-risk patients (having about 50% risk of relapse) have been reported (35-39). In these series, involving more than 200 patients, some with a median follow-up of nearly 8 years (36), a relapse rate of only 2.7% was reported, with very little long-term toxicity. Two cycles of Cisplatinum based adjuvant Chemotherapy do not seem to adversely affect fertility or sexual activity (40)

It is important to be aware of the risk of slow-growing retroperitoneal teratomas after primary chemotherapy and of the risk of chemoresistant cancer relapse. The need for repeated and long-term follow-up with imaging (CT or ultrasound) of the retroperitoneum after primary chemotherapy is not yet clear.

The results of cost analyses comparing surveillance, RPLND and primary chemotherapy show different results among the reported studies, possibly because of differences in intensity and costs related to follow-up procedures. Overall costs for the different options in treating CS1 may be of the same order of magnitude although a unique cost-benefit analysis shows that adjuvant chemotherapy is the cheaper option per life saved (10,13,14,41).

Risk-adapted treatment

As with primary chemotherapy, a policy of stratifying patients with CS1 NSGCT according to their presumed risk of relapse may be a rational option. Several studies have reported similar survival rates and a final cure rate close to 100% (22,35-38,42). The main selection criterion for high-risk patients was the presence of vascular invasion in those treated with primary chemotherapy or RPLND, and that for low-risk patients was the absence of vascular invasion following surveillance.

5.4 CS1S with (persistently) elevated serum tumour markers

Serum tumour markers should be followed closely until it is clear whether or not levels are falling according to the expected half-time values for AFP and beta-hCG. If the marker level does not fall and/or increases after orchiectomy, the patient has residual disease. If RPLND is performed, up to 87% of these patients have pathologically documented nodes in the retroperitoneum (43). An ultrasound examination of the contralateral testicle must be performed, if this has not been done initially.

The treatment of true CS1S patients is still controversial. They may be treated with either three courses of primary BEP chemotherapy, with follow-up as for CS1B (high risk; see below) patients after primary chemotherapy (44), or by RPLND (41). The presence of vascular invasion may strengthen the indication for primary chemotherapy as most CS1S with vascular invasion will need chemotherapy sooner or later anyway.

5.5 GUIDELINES FOR THE TREATMENT OF NSGCT STAGE I

CS1A (pT1, no vascular invasion); low risk

1. If the patient is willing and able to comply with a surveillance policy and long-term (at least 5 years) close follow-up is feasible, surveillance is equivalent to nerve-sparing RPLND.
2. If RPLND reveals PN+ (nodal involvement) disease, we are facing a Pathological Stage II and consequently adjuvant chemotherapy with two courses of BEP should be considered.

CS1B (pT2-pT4); high risk

One of the following active treatments is recommended.

1. Nerve-sparing RPLND, which must be bilateral if PN+ disease is revealed perioperatively (nerve-sparing on the opposite side). If Pathological Stage II is revealed further chemotherapy should be considered.
2. Primary chemotherapy with two courses of BEP.

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Table 4: Prognostic-based staging system for metastatic germ cell cancer (International Germ Cell Cancer Collaborative Group)

Good prognosis group	
Non-seminoma	
56% of cases 5-year PFS 89% 5-year survival 92%	*All of the following criteria:* • Testis/retroperitoneal primary • No non-pulmonary visceral metastases • AFP < 1,000 ng/ml • β-hCG < 5,000 mIU/L (1,000 ng/ml) • LDH < 1.5 x ULN
Seminoma	
90% of cases 5-year PFS 82% 5-year survival 86%	*All of the following criteria:* • Any primary site • No non-pulmonary visceral metastases • Normal AFP • Any β-hCG • Any LDH
Intermediate prognosis group	
Non-seminoma	
28% of cases 5 years PFS 75% 5-year survival 80%	*All of the following criteria:* • Testis/retroperitoneal primary • No non-pulmonary visceral metastases • AFP > 1,000 and < 10,000 ng/ml or • β-hCG > 5000 and < 50,000 mIU/l or • LDH > 1.5 and < 10 x ULN
Seminoma	
10% of cases 5-year PFS 67% 5-year survival 72%	*Any of the following criteria:* • Any primary site • Non-pulmonary visceral metastases • Normal AFP • Any β-hCG • Any LDH
Poor prognosis group	
Non-seminoma	
16% of cases 5-year PFS 41% 5-year survival 48%	*Any of the following criteria:* • Mediastinal primary • Non-pulmonary visceral metastases • AFP > 10,000 ng/ml or • β-hCG > 50,000 mIU/L (10,000 ng/ml) or • LDH > 10 x ULN
Seminoma	
No patients classified as poor prognosis	

PFS = progression-free survival; AFP = alpha-fetoprotein; β-hCG = beta-human chorionic gonadotrophin; LDH = lactate dehydrogenase.

6. TREATMENT: METASTATIC GERM CELL TUMOURS

Treatment of metastatic germ cell tumours depends on:

- Histology of the primary tumour
- Prognostic groups as they have been defined by the International Germ Cell Collaborative Group based on 5,202 non-seminoma and 660 seminoma cases (Table 4) (1).

There is a general consensus that treatment should start with initial chemotherapy in all cases except for low-volume stage II disease, which alternatively can be treated with primary bilateral RPLND for non-seminoma (eventually followed by two cycles of chemotherapy or by surveillance) or radiotherapy for pure seminoma (2,3). In stage II a-b NSGCT primary Chemotherapy and primary RPLND are comparable options in terms of outcome but side effects and toxicity are different leading the patients to be involved in the treatment´s choice (4).

6.1 Primary chemotherapy

The primary treatment of choice for advanced disease is four courses of BEP (or PEB) combination chemotherapy (Table 5). These regimens have proven superiority to cisplatin, vinblastine and bleomycin (PVB) in patients with advanced disease (5,6).

Table 5: British BEP and PEB regimens (every 3 (4) weeks)

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

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

For patients with ”good prognosis”, according to the International Germ Cell Consensus Classification (IGCCC) (1) standard treatment consists of three cycles of PEB or in case of contraindication against bleomycin of four cycles of PE (1,7-9). Therapy should be given without reduction of the doses in 22-day intervals; delaying the folowing chemotherapy cycle is justified only in case of fever with granulocytopenia < 1.000/mm^3 or thrombopenia < 100.000/ul. There is no indication for prophylactic application of hematopoetic growth factors as G-CSF for example. However, if infectious complications have occurred under chemotherapy, prophylactic administration of G-CSF is recommended for the following cycles (9,10).
With the “intermediate prognosis” group in the IGCCC a group of patients has been defined, which reaches a 5-year survival rate of about 80%. The available data support four cycles of PEB as standard treatment (1, 11). Due to the generally less favourable prognosis of this patient group, in comparison to patients with “good prognosis”, they may be treated in prospective trials like for example in the EORTC GU Group trial with PEB vs PEB+paclitaxel (12).
For patients with “poor prognosis” standard treatment consists of four cycles of PEB; four cycles of PEI are of the same effect but more toxic (13). The 5-year progression-free survival is between 45 and 50%. It has not yet been proven that high-dose chemotherapy increases the survival rate. Since a matched-pair analysis resulted in a better survival rate (14,15), these patients should be treated in the ongoing prospective randomized trial, investigating the value of high-dose chemotherapy. Patients meeting “poor-prognosis” criteria should therefore be transferred to a reference Centre.
Any general recommendations for treatment modifications for patients with a poor general condition (Karnofsky <50%), extended liver infiltration (>50%) and extended pulmonary infiltration do not exist.

6.2 Restaging and Further Treatment

Restaging
After termination of two courses of chemotherapy reevaluation is performed by imaging investigations and determination of tumor markers. At marker decline and stable or regressive tumor manifestation chemotherapy will be completed (three or four cycles depending on the initial stage) (1,16,17). In case of marker decline, but growing metastases, resection of the tumor is obligatory after termination of induction therapy, unless in case of emergency according to local tumor growth. Only with documented marker growth after 2 courses of chemotherapy an early crossover of therapy is indicated. These patients are usually candidates for new drugs

trials (15,18). Patients with a low-level marker plateau post treatment will be observed whether or not complete normalisation occurs. Salvage chemotherapy is indicated for documented marker rise only (19).

Residual Tumor Resection
A residual mass of seminoma will not be resected, irrespective of the size, but controlled by imaging investigations and tumor markers (20-26). On progression, salvage chemotherapy will be given, if necessary including surgery and radiotherapy (27-29).
In case of non-seminoma and complete remission after chemotherapy, secondary RPLND is not indicated (30-35).
In case of residual mass and marker normalisation surgical resection is indicated (30,36-43).
Histology in different organ sites may be different. Overall, following BEP induction chemotherapy, only 10% of residual masses contain viable cancer, 50% contain mature teratoma and 40% contain necrotic-fibrotic tissue. As yet no imaging investigation including PET or prognosis model are able to predict histological differentiation of the residual tumor. Residual tumor resection is mandatory (31-33,44-47).

Consolidation Chemotherapy after Secondary Surgery
After resection of necrosis or mature teratoma no further treatment is required. In case of complete resection of vital carcinoma or immature teratoma two adjuvant cycles of conventionally dosed cisplatinum-based chemotherapy should be given (cave: cumulative dosis of bleomycine). The prognosis will definitely deteriorate if vital carcinoma is found in resection specimens after second and third line chemotherapy. In this latter situation postoperative chemotherapy is not indicated and unable to improve the prognosis (41,46).
Two courses of cisplatin, vinblastine and bleomycin (PVB), vinblastine, adriamycin and, bleomycin (VAB) or BEP given post-operatively following lymphadenectomy for ‘radically’ resected retroperitoneal metastases containing viable cancer have been followed by nearly no relapses (48-52). This adjuvant treatment has been questioned by some authors (49-53), who reported equivalent results in 60 radically resected patients with, or without, such treatment. Furthermore, it has been demonstrated in a co-operative retrospective study (54) that the major success factors in these patients are complete surgical resection and percentage of viable cancer in the residual mass, with the effect of adjuvant chemotherapy being borderline. Nevertheless, the results with adjuvant chemotherapy are not statistically superior to those resulting from very careful observation and deferred treatment in the case of relapse (55).

Table 6: Standard VIP (VeIP)

Drug	**VIP (VeIP)**
Cisplatin	20 mg/m^2, days 1–5[a]
Etoposide (vinblastine)	75 mg/m^2, days 1–5 (0.11 mg/kg, days 1, 2)
Ifosfamide[c]	1.2 g/m^2, days 1–5

VIP = VP-16 (vinblastine) ifosfamide and cisplatin; VeIP = velban, ifosfamide and cisplatin;
[a] Plus hydration.

6.3 Systemic Salvage Treatment for Relapse or Refractory Disease

Seminoma
Cisplatin based combination salvage chemotherapy will result in long-term remissions for about 50% of patients who relapse after first-line chemotherapy (56). Regimens of choice are: four cycles of PEI/VIP or four cycles of VeIP. At present it is impossible to determine whether conventionally dosed cisplatin based combination chemotherapy is sufficient as first salvage treatment or whether early intensification of first-salvage treatment with high-dose chemotherapy should be attempted (57). Therefore treatment of these rare patients within clinical trials and at experienced centres is of outmost importance.

Non-Seminoma
Standard salvage treatment after first-line chemotherapy consists of either four cycles of PEI/VIP or four cycles of VeIP, respectively (Table 6). Conventionally dosed salvage chemotherapy may achieve long-term remissions

in 15 to 40% of patients, depending on individual risk factors (58,59). Salvage therapy with VeIP is probably not superior to other conventionally dosed cisplatin based combination regimens (57,59). The use of conventionally dosed combination regimens with more than three agents will increase toxicity without improving treatment outcome (60).
Depending on the presence of adverse prognostic factors, the results of salvage therapy after first-line cisplatin based treatment are unsatisfactory (58,61). Although some Phase II trials indicate a 10% improvement in survival with early intensification of first salvage treatment using high-dose chemotherapy, others fail to demonstrate such improvement (62,63). Recently, taxol and gemcitabine have proved to be active in the treatment of refractory germ cell tumours; both drugs are synergistic with cisplatin (64-66).
However, all of these patients should be entered into ongoing multicentre studies to define the optimal approach to salvage treatment and should be referred to centers experienced in caring for relapse and/or refractory patients (57).

6.4 Salvage Surgery

Residual tumors after salvage chemotherapy should be resected within four to six weeks after marker normalisation or when a marker plateau is reached. In case of marker progression after salvage treatment and lack of other chemotherapeutic options, resection of residual tumors ("desperation surgery") should be considered if complete resection of all tumor seems feasible (about 25% long-term survival may be achieved) (39,47,58,67-77).

6.5 GUIDELINES FOR THE TREATMENT OF METASTATIC GERM CELL TUMOURS

1. Low volume NSGCT stage II can be treated either by RPLND (plus surveillance or two cycles of chemotherapy) or by primary chemotherapy.
2. In metastatic NSGCT with a good prognosis, three courses of BEP is the primary treatment of choice.
3. In metastatic NSGCT with an intermediate or poor prognosis, the primary treatment of choice is four courses of standard BEP.
4. Surgical resection of residual masses after chemotherapy in NSGCT is indicated when serum levels of tumour markers are normal or normalizing.
5. Metastatic seminoma with less than N3M1 disease can be treated initially with radiotherapy. When necessary, chemotherapy can be used as a salvage treatment with the same schedule as for the corresponding prognostic groups of NSGCT.
6. Advanced seminoma (N3 or M1) should be treated with primary chemotherapy according to the same principles used for NSGCT.

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7. FOLLOW-UP: STAGE I NON-SEMINOMA

7.1 Why?

Approximately 5% of patients with clinical stage I NSGCT present with elevated levels of tumour markers after orchiectomy and up to 25-30% relapse during the first 2 years (1-9). The aim of follow-up is two-fold: to detect relapse and the rare possibility of asynchronous contralateral carcinoma of the testis in an early phase, and to avoid unnecessary treatment.

7.2 When and how?

The follow-up schedule will differ depending on which of the three possible treatment strategies was chosen: surveillance, nerve-sparing retroperitoneal lymphadenectomy (RLND) or primary chemotherapy.

Follow-up after surveillance

The results of a surveillance policy depend upon a careful pre-operative staging procedure and follow-up management. Half of the relapses will occur in the first 6 months; however, recurrent disease has been detected as late as 6 years after orchiectomy. In a “wait and see” policy, relapses will occur in 30% of cases. Of these relapses, 80% will occur in the first 12 months after orchiectomy and approximately 12% during the seond year. The median time to relapse is 6 months (range 1-62 months), but relapses after 3-5 years, and even later, may still occur, with an annual rate of 4% (10-11). Relapse occurs mainly in the retroperitoneum; approximately 20% of patients have evident metastases in the retroperitoneum and 10% in the mediastinum and lungs (12). Sometimes the only indication is an elevated level of tumor markers.

Table 7: Recommended follow-up schedule in a surveillance policy: – stage I non-seminoma

Procedure	Year			
	1	**2**	**3–5**	**6–10**
Physical examination	Six times (monthly for the first 6 months[a])	Four times (six times[a])	Twice/year	Once/year[a]
Tumour markers	Six times (monthly for the first 6 months[a])	Four times (six times[a])	Twice/year	Once/year[a]
Chest X-ray	Six times (monthly for the first 6 months[a])	Four times (six times[a])	Twice/year	Once/year[a]
Abdominal computed tomography scan	Three times (four times[a])	Twice (three times[b])	Once/year	If indicated

[a] = Advisable, [b] = Optional.

Careful observation during the first 6 months after orchiectomy is mandatory; thereafter, the interval may be longer. Surveillance should continue for a minimum of 6 years and indefinite yearly follow-up is advocated by some. There is no universally accepted protocol for surveillance. A recommended follow-up schedule is shown in Table 7. It is particularly difficult to establish recommendations for those patients with negative pre-operative tumour markers levels. If RLND is not performed, patients may require closer follow-up. Currently, not enough data are available in the literature from which to derive strict recommendations.

Follow-up after nerve-sparing RLND

Retroperitoneal relapse after a properly performed nerve-sparing RLND is extremely rare. RLND should eliminate the retroperitoneal nodes as a site of relapse, and thus the need for repeated abdominal CT scans. The USA Intergroup data show retroperitoneal relapse in 7/264 patients with pathological stage I disease (and 20 pulmonary relapses); four of these seven had no marker elevation (13). In the Indiana series, only one relapse in 559 cases was reported (14). If a relapse occurs, it is generally in the chest, neck or at the margins of the surgical field. Pulmonary relapses occur in 10-12% of patients and more than 90% of those relapses occur within 2 years of RLND (15,16). The recommended follow-up schedule is shown in Table 8.

Follow-up after adjuvant chemotherapy

Although the number of patients treated using adjuvant chemotherapy is still small, some prospective reports with long-term follow-up show a very low relapse rate (1-3,17) of about 3%. The need for repeated and long-term assessment of the retroperitoneum is still not clear. Primary chemotherapy in the treatment of NSGCT cannot be regarded as investigational, but still has to be offered in the setting of clinical trials. The follow-up schedule will depend on the results of these studies, but will probably be similar to that recommended for RPLND (Table 8). Owing to the risk of developing a late, slow-growing teratoma in the retroperitoneum after adjuvant chemotherapy, an abdominal CT or an ultrasound examination should also be performed (at least) annually during the third to fifth year.

It should be noted that these recommendations represent the minimum standard of follow-up. Any other

tests (e.g. hormonal determinations, spermiograms, neurological examinations) or more frequent schedules of evaluation may be performed on the basis of clinical protocol or investigative purposes.

Table 8: Recommended follow-up schedule after retroperitoneal lymphadenectomy or adjuvant chemotherapy - stage I non-seminoma

Procedure	Year			
	1	2	3–5	5–10
Physical examination	Six times	Three times	Twice/year	Once/year[a]
Tumour markers	Six times	Three times	Twice/year	Once/year[a]
Chest X-ray	Six times	Three times	Twice/year	Once/year[a]
Abdominal computed tomography scan	Twice	Once	If indicated[b]	If indicated
Abdominal ultrasound	Twice[ac]	Twice[ac]	Twice/year	Once/year

[a] = Advisable.
[b] Due to a risk of late, slow-growing teratoma in the retroperitoneum after adjuvant chemotherapy.
[c] Alternating with abdominal CT scan.

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8. FOLLOW-UP: STAGE I SEMINOMA

8.1 Why?

The majority of patients with seminoma (70-80%) present with clinical stage I disease at diagnosis (1). In 15-20% of cases, there is nodal radiological involvement at the level of the retroperitoneum and 5% of patients present with distant metastasis (1). The relapse rate varies between 1% and 20%, depending on the post-orchiectomy therapy chosen. Only up to 30% of seminomas present with elevation of beta-hCG at diagnosis or in the course of the disease. Consequently, in most cases, measurement of blood markers will not be an un-reliable test for follow-up (2). The aim of follow-up is to detect early recurrence and contralateral testiculars tumours and to avoid unnecessary treatment.

The treatment options post-orchiectomy in stage I seminoma are retroperitoneal radiotherapy, surveillance and adjuvant chemotherapy. Due to extreme radio- and chemosensitivity, high cure rates of almost 100% are reached with each of the approaches, even in case of relapse.

The costs of the different therapies vary, as do the expected side-effects (3-5). Of major importance is the identification of potential prognostic factors, both clinical and pathological, for occult metastasis and consequent relapse.

Risk factors for relapse

Although there is no total agreement among different groups, the size of the tumour seems to be the most important risk factor for relapse in uni- and multivariate analyses. Vascular and lymphatic invasion has also proved to be an important risk factor in univariate analysis. Other risk factors are age and histological subtype (anaplastic), and local tumoural extension (6-8).

8.2 When and how?

The optimal schedule of follow-up has yet to be defined and will differ according to the treatment chosen. Different tests have to be performed according to the relapse time and pattern of relapse.

Follow-up after radiotherapy

Low doses of radiotherapy (20-24 Gy) limited to the retroperitoneal or the hockey stick field achieve an overall survival rate of approximately 99% at 5-10 years (9-13). The rate of relapse is 1- 2% and the most common time of presentation is within 18 months after treatment (4,10,14,15,16), although late relapses have also been described (17). The site of relapse is mainly at the supradiaphragmatic lymph nodes, mediastinum, lungs or bones. In a small proportion of cases, the tumour will relapse in the inguinal or external iliac nodes (1).

The side-effects of radiotherapy include impaired spermatogenesis, gastrointestinal symptoms (peptic ulceration) and induction of second malignancies (4,18,19). Up to 50% of patients can develop moderate toxicity Grade I-II (9). The schedule of follow-up is described in Table 9.

Table 9: Follow-up for post-orchiectomy radiotherapy or chemotherapy – stage I seminoma

Procedure	Year			
	1	2	3	4–5
Physical examination	Four times	Three times	Three times	Twice/year
Chest X-ray	Four times	Three times	Three times	Twice/year
Tumour markers	Four times	Three times	Three times	Twice/year
Abdominal computed tomography scan	Once	Once	If indicated	If indicated
Abdominal ultrasound	Once[a]	Once[a]	Once	If indicated

[a] Alternating with abdominal computed tomography scan.

Follow-up after surveillance

The main goal of the surveillance policy is to avoid unnecessary therapy. It must be recognized that there is a somewhat higher need for salvage chemotherapy if prophylactic radiotherapy is omitted. Alternatively, at least 80% of patients will receive unnecessary radiotherapy if this is given prophylactically to all those with seminoma stage I. There are already prospective, but not randomized, studies of surveillance showing that the actuarial risk of relapse at 5 years ranges between 15% and 20% (6,8,20-22). Nevertheless, there is no increased risk of death. The median time to relapse ranges from 12-18 months, but up to 29% of relapses can develop later (1). The sites of relapse are the PA lymph nodes in up to 82% of cases; the pelvic lymph nodes, inguinal nodes and lungs can also be affected (1). Due to the high and often late rate of relapse, close and active follow-up is mandatory for at least 5 years. The major disadvantages of this policy are lack of long-term follow-up data, high cost and patient compliance. The schedule of follow-up is described in Table 10.

Follow-up after adjuvant chemotherapy

One or two courses of carboplatin-based chemotherapy is an effective alternative treatment in stage I seminoma. The relapse rate is less than 2%, but the number of patients treated in a prospective setting is still low and the length of follow-up is also limited in most studies. In general, this treatment is well tolerated, with only mild, acute and intermediate-term toxicity (23,24). As the relapse rate is low, the follow-up schedule can be the same as the one proposed for post-orchiectomy radiotherapy (Table 9).

Table 10: Follow-up in surveillance policy

Procedure	Year				
	1	2	3	4–5	6–10
Physical examination	Six times	Four times	Three times	Twice/year	Once/year
Tumour markers	Six times	Four times	Three times	Twice/year	Once/year
Chest X-ray	Six times	Four times	Three times	Twice/year	Once/year
Abdominal computed tomography scan	Four times	Four times	Twice	Once/year	If indicated
Abdominal ultrasound	[a]	[a]	Twice[b]	Once/year[b]	If indicated

[a] Not required.

[b] Alternating with abdominal computed tomography scan.

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9. FOLLOW-UP: STAGE II AND ADVANCED (METASTATIC) DISEASE

9.1 Why?

The more advanced the nodal stage of the disease, the higher the likelihood of recurrence (1). In general, the primary tumour bulk governs the outcome for patients with NSGCT (2). In stage II NSGCT, regardless of the treatment policy adopted, excellent survival rates of 97% are reached provided that relapse is identified as soon as possible (3-5).

In advanced metastatic germ cell tumours, the extent of the disease is correlated with the response to therapy and with survival. The combination of cisplatin-based chemotherapy and surgery (aggressive multimodality) achieves cure rates between 65% and 85%, depending on the initial extent of disease (2,6). Complete response rates to chemotherapy are in the order of 50-60% (2); another 20-30% of patients could be rendered disease free with post-chemotherapy surgery (7).

The main reasons for failure of therapy in advanced NSGCT are (2,8,9):

- The presence of bulky disease not responding completely to chemotherapy
- Unresectable residual teratoma after chemotherapy
- Presence or development of chemoresistant non-germ elements, which account for 8.2% of cases

9.2 When and how?

The rate and timing of relapse will determine the intensity of the follow-up schedule. The pattern of relapse dictates the most appropriate tests to be performed during follow-up. There is a lack of randomized trial results from which to plan evidence-based follow-up, and the different schedules used by various centres have a higher variability and are more individualized than for stage I.

As for less advanced stages, the methods of follow-up are:

- Physical examination, including a search for neck and abdominal masses, for gynaecomastia, examination of groins, superficial nodes and the remaining testis
- Tumour markers: AFP, beta-hCG and LDH
- Chest X-ray
- Abdominal and pelvic CT or abdominal ultrasound
- Chest CT
- Brain CT (in case of neurological symptoms)

9.3 Clinical and pathological stage II NSGCT

Relapse after primary RPLND

Two different situations can occur:

1. About 23-28% of clinical stage II patients will have pathological stage I disease and should be followed up accordingly (see follow-up for NSGCT stage I) (10,11).
2. Between 72% and 77% of clinical stage II patients will be of pathological stage II, having a different relapse rate depending on the type of treatment. Whatever the treatment policy chosen, the majority of relapses occur within the first 2 years and outside the surgical field.

Relapse after RPLND followed by two immediate cycles of chemotherapy:

The relapse rate for this group is 6% at 4 years (1,6). In non-randomized series, with a mean follow-up ranging from 30-72 months, this treatment policy results in a high overall disease-free survival rate of 98-100% (3,12). The main disadvantage of adjuvant chemotherapy is that it represents an overtreatment in approximately 50% of patients with stage II disease.

Relapse after RPLND followed by surveillance:
The average relapse rate in this group is 35% (range 8-49%) at a mean of 4 years (1,13,14). Nevertheless, the relapse rate depends on pathological stage; pathological stage IIa presents a risk of relapse of less than 50%, while pathological stage IIb presents a risk of relapse of at least 50% (1,3,6,15).

Following primary RPLND the retroperitoneal CT scan can be replaced by a less expensive abdominal ultrasound, although a baseline post-RPLND CT scan is recommended (Table 11). *When primary RPLND is followed by surveillance* (generally in cases of low-volume lymph node involvement or pathological stage IIa), a stricter schedule of follow-up is needed than with adjuvant chemotherapy. A physical examination, tumour marker assessment and chest X-ray are performed more frequently than in the former treatment policy. The follow-up outlined in Table 11 can be used, but the tests have to be performed:

- *Monthly during the first year*
- *Bimonthly during the second year*
- *Three-monthly during the third year*
- *Every 4 months during the fourth year*
- *Twice in the fifth year*
- *Yearly thereafter*

B. Relapse after primary chemotherapy
Between 68% and 78% of patients (average 75%) will reach a clinical complete response (5,16,17). The relapse rate is then around 5%, and most relapses occur in the first 8 months after chemotherapy, continuing up to 2 years. Nevertheless, later relapses in the range 2-5% may occur depending on several prognostic factors (e.g. whether the metastasis is: > 3 cm or < 3 cm in size, histology of the primary tumour/teratoid elements). Mature teratomas have been described at 5-8 years of follow-up (3). Generally, the relapse rate at a median follow-up of 5.5 years is approximately 8%. The progression-free survival rate is approximately 92% and the overall survival rate is 97% (5).

Although this treatment policy avoids RPLND in 68-78% of patients, depending on whether the clinical stage is IIa or IIb (5,16,18), it requires extended follow-up. After primary chemotherapy, retroperitoneal CT scans cannot be omitted from the follow-up schedule. The follow-up schedule is basically the same as that for primary RPLND plus adjuvant chemotherapy, although after primary chemotherapy an abdominal and pelvic CT scan has to be performed at least twice during the first 2 years (Table 11).

Table 11: Follow-up of NSGCT stage IIa–IIb after RPLND plus chemotherapy or primary chemotherapy

Procedure	Year					
	1	**2**	**3**	**4**	**5**	**Thereafter**
Physical examination	Bimonthly	Four times	Twice	Twice	Twice	Once/year
Tumour markers	Bimonthly	Four times	Twice	Twice	Twice	Once/year
Chest X-ray	Bimonthly	Four times	Twice	Twice	Twice	Once/year
Abdominal CT[ab]	Baseline, then as indicated	As indicated	If indicated	If indicated	If indicated	If indicated
Abdominal ultrasound	Twice	Twice	If indicated	If indicated	If indicated	If indicated

RPLND = retroperitoneal lymph node dissection; NSGCT = non-seminomatous germ cell tumour; CT = computed tomography.
[a] After RPLND, a baseline CT scan of the abdomen and pelvis is obtained, and repeated if clinically indicated thereafter.
[b] After primary chemotherapy, the retroperitoneum has to be monitored by means of CT scan at least twice during the first 2 years.

9.4 Clinical stage II seminoma

Relapse rates following radiotherapy for clinical stages IIa and IIb are in the range 5-15%. Most relapses occur within the first 2 years and present with a supraclavicular or mediastinal mass, while relapses in the irradiated

Table 12: Follow-up of seminoma stage IIa–IIb after radiotherapy

Procedure	Year					
	1	2	3	4	5	> 5
Physical examination	Six times	Four times	Three times	Twice	Twice	Once/year
Tumour markers	Six times	Four times	Three times	Twice	Twice	Once/year
Chest X-ray	Six times	Four times	Three times	Twice	Twice	Once/year
CT abdomen and pelvis[a]	If indicated	If indicated	If indicated	If indicated	If indicated	If indicated
CT chest[b]	If indicated	If indicated	If indicated	If indicated	If indicated	If indicated

CT = computed tomography.
[a] Baseline CT of the abdomen/pelvis post-treatment and repeated only if indicated.
[b] Only if there is an abnormal chest X-ray or if clinical symptoms indicate.

field are rare (6).

During follow-up, attention must be paid to the specific sites of relapse (Table 12).

9.5 Clinical stage IIc and III seminoma and non-seminoma

In advanced disease following the IGCCG classification, the overall survival rate is in the order of 92% for patients in the good prognostic category, 80% for those in the intermediate category and 48% for those in the poor prognostic category (19). Stage IIc is generally grouped in the subset of patients with good prognosis (3).

After chemotherapy, careful follow-up observation is recommended if there is a decrease of at least 90% in the volume of retroperitoneal masses, provided there was no evidence of teratomatous elements in the primary tumour. Nevertheless, to date there are no reliable CT scan criteria to distinguish tumour or teratoma from necrotic debris in the post-chemotherapy setting; false-negative CT scan rates range from 8-37% (8).

In advanced NSGCT, despite statistical correlation with a variety of factors (e.g. degree of shrinkage, size of residual mass, pre-chemotherapy tumour marker levels, teratomatous components in orchiectomy specimen), the risk of a false-negative prediction based on a CT scan is still currently approximately 20% (8). In advanced seminoma, the rate of 'in-site' failure is 3% when the CT scan is normal or shows a residual

Table 13: Follow-up of advanced NSGCT and seminoma

Procedure	Year					
	1	2	3	4	5	Thereafter
Physical examination	Monthly	Bimonthly	Four times	Three times	Twice	Once/year
Tumour markers	Monthly	Bimonthly	Four times	Three times	Twice	Once/year
Chest X-ray	Monthly	Bimonthly	Four times	Three times	Twice	Once/year
Abdominal CT[ab]	As indicated	As indicated	As indicated	As indicated	As indicated	As indicated
Chest CT[bc]	As indicated	As indicated	As indicated	As indicated	As indicated	As indicated
Brain CT[d]	As indicated	As indicated	As indicated	As indicated	As indicated	As indicated

CT = computed tomography.
[a] Abdominal CT scan has to be performed at least annually if teratoma is found in retroperitoneum.
[b] If the post-chemotherapy evaluation shows any mass > 3 cm, the appropriate CT scan should be repeated 2 and 4 months later to ensure that the mass is continuing to regress.
[c] Chest CT is indicated if abnormality is detected on chest X-ray and after pulmonary resection.
[d] In patients with headaches, focal neurological findings or any CNS symptom.

abnormality less than 3 cm in diameter (20-23).

The follow-up schedule for advanced disease (seminoma and non-seminoma) is presented in Table 13. A brain CT has to be performed during follow-up if neurological symptoms are present, because up to 5% of patients with advanced disease present with or develop brain metastases (6). An abdominal CT scan has to be performed at least annually, because of the ominous significance of teratoma, if found in the retroperitoneum.

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* These EAU Guidelines on Testicular Cancer are endorsed by all members of the EAU Oncological Urology Group (Chairman: C. Abbou). Members of the Oncological Urology Group are the EAU Working parties on: Bladder Cancer, Renal Cell Cancer, Penile Cancer, Prostate Cancer & Testis Cancer.

10. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive for the most common abbreviations.

AFP:	alpha-fetoprotein
BEP:	bleomycin, etoposide and cisplatin
beta-hCG:	beta-human chorionic gonadotrophin
CgA:	Chromogranine A
CT:	Computed tomography
EP:	etoposide and cisplatin
EORTC:	European Organization for Research and Treatment of Cancer
IGCCG:	International Germ Cell Collaborative Group
LDH:	lactate dehydrogenase
MMSK:	Memorial Sloan Ketering
MRC:	Medical Research Council
MRI:	Magnetic resonance imaging
NSE:	neuro-specific enolase
NSGCT:	non-seminomatous germ cell tumour
PEB:	cisplatin, etoposide and bleomycin
PEI:	cisplatin, etoposide, ifosfamide
PVI:	cisplatin, vinblastine, ifosfamide
PLAP:	placental alkaline phosphatase
PVB:	cisplatin, vinblastine and bleomycin
RPLND:	retroperitoneal lymph node dissection
Tin:	intratubular germ cell neoplasia
TNM:	Tumour Node Metastasis
VAB:	vinblastine, adriamycin and bleomycin
VelP:	velvan, ifosfamide and cisplatin