Guidelines on
Testicular Cancer

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1. BACKGROUND

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

Up to 5% of cases are bilateral. In 95% of patients, the histology reveals a germ cell tumour which is characterized by a specific genetic marker (supernumerical copies of the short arm of chromosome 12, isochromosome i(12p) (1,4). Intratubular germ cell neoplasia (testicular intraepithelial neoplasia, TIN) has been shown to be a precursor lesion in the majority of germ cell tumours (5-7).

Epidemiological risk factors for the development of testicular tumours are: a history of cryptorchidism or undescended testis, a hypotrophic (< 12 ml) or atrophic testicle, Klinefelter's syndrome, familial history of testicular tumours among first-grade relatives (brothers, father), the presence of a contralateral tumour or TIN and infertility (8-12).

Currently, testicular tumours show excellent cure rates in the order of 95% for low stages and somewhat less for the more advanced stages of disease. The main factors contributing to this are: careful staging at the time of diagnosis; adequate early treatment based on an interdisciplinary management including chemotherapy, radiotherapy and surgery; and very strict follow-up and salvage therapies. For the treatment of testicular cancer, the choice of the treatment centre is of paramount importance. Although early stages can be successfully treated in a non-reference centre, 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 centre (13). In poor-prognosis, non-seminomatous, germ cell tumours, it has been shown that overall survival within a clinical trial depended upon the number of patients treated at the participating centre (worse survival: < 5 patients enrolled) (14).

1.1 Methods
The present guidelines represent an implementation of previously published texts; the latest edition of the European Association of Urology (EAU) guideline text was formally published in 2001 (15), and the latest update was distributed among EAU members in March 2005. A multidisciplinary team of urologists, medical oncologists, radiotherapists and a pathologist were involved in producing the present text, which is based on a non-structured review of the literature by using the MEDLINE database through 2005. In addition, data from meta-analysis studies, Cochrane evidence and the recommendations of the European Germ Cell Cancer Collaborative Group, as well as other available guidelines, have been included (16-23). Whenever possible, references have been labelled according to the principles of evidence-based medicine (EBM). The nature of the recommendations in the present guidelines is labelled according to grade of evidence. This text focuses on changes in diagnosis and treatment compared to the previously published version (15).

2. DIAGNOSIS, PATHOLOGY AND CLASSIFICATIONS

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

2.1 Scrotal ultrasound
A 7.5 MHz transducer is necessary to image the testis correctly. The sensitivity of scrotal ultrasound to detect a testicular tumour is almost 100%, and ultrasound has an important role in determining whether a mass is intra- or extratesticular (24). In young men with either a retroperitoneal mass, visceral metastasis or elevated human chorionic gonadotrophin (hCG) and/or alpha-fetoprotein (AFP), an ultrasound of the testes is mandatory. Magnetic resonance imaging (MRI) of the scrotum offers a sensitivity of 100% and a specificity of 95-100% (25), but its use for diagnosis cannot be justified because of its high cost.

2.2   Serum tumour markers

Serum tumour markers are prognostic factors and contribute to diagnosis and staging (26). The mean serum half-life of AFP is 5-7 days and that of hCG approximately 2-3 days. Therefore, the following markers should be determined before orchidectomy and thereafter at weekly intervals until normalization:

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

Overall, there is an increase in these markers in 51% of cases of testicular cancer (26). The level of AFP increases in 50-70% of patients with non-seminomatous germ cell tumour (NSGCT) and a rise in hCG occurs in 40-60% of patients with NSGCT. About 90% of NSGCTs present with a rise in the levels of either AFP and/or hCG markers. Up to 30% of seminomas can present or develop an elevated hCG level during the course of the disease (27). Lactate dehydrogenase 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. It should be noted that negative marker levels do not exclude the diagnosis of a germ cell tumour. Other markers studied include neuro-specific enolase (NSE) and placental alkaline phosphatase (PLAP). NSE and/or PLAP may be of limited value in monitoring patients with pure seminoma. The measurement of serum AFP, hCG and LDH is mandatory, while NSE and PLAP are optional.

2.3   Inguinal exploration and orchidectomy

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

2.3.1   Organ-sparing surgery

Although organ-sparing surgery is not generally indicated, it can be attempted in the following special situations with all the necessary precautions (28,29):

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

The tumour volume in these cases should be less than about 30% of the testicular volume. In all patients, remaining TIN can safely be treated with adjuvant radiotherapy using a dose of 20 Gy (29). A few studies have tried to reduce the radiation dose to 16 Gy. However, recurrences have been seen with 14 Gy in a Danish trial (30) and with 16 Gy in a German trial (31). Infertility will result after radiotherapy. The option has to be carefully discussed with the patient and surgery performed in a centre with experience (29).

2.4   Pathological examination of the testis

Mandatory pathological requirements (32) are:

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

2.5   Staging and clinical classification

Staging represents the cornerstone on which testicular cancer treatment is based. To determine the presence of metastatic or occult disease, half-life kinetics of serum tumours markers have to be assessed (see section 2.2 and section 5.3), the nodal pathway has to be screened and the presence of visceral metastases excluded.

Consequently, in addition to tumour marker half-life kinetics, it is mandatory to assess:
- status of abdominal and supraclavicular nodes, and the liver
- presence or absence of mediastinal nodal involvement and lung metastases
- status of brain and bone if any suspicious symptoms are present.

Abdominal and pulmonary, extra-pulmonary, and mediastinal nodes are best assessed by means of a computerized tomography (CT) scan. The supraclavicular nodes are best assessed by physical examination and CT scan if suspicious. CT scanning 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 (33). MRI produces similar results to CT scanning in the detection of retroperitoneal nodal enlargement (34). Again, the main objections to its routine use are high cost and limited access. MRI is a test for special indications; there are currently no indications for its systematic use in the staging of testicular cancer. A chest CT scan is mandatory in all patients with NSGCT and in those with seminoma and a positive abdominal CT scan (35).

There is not enough evidence to support the use of the fluorodeoxyglucose-positron emission tomography (FDG-PET) scan in early testicular tumour stages. It can, however, be recommended in the follow-up of seminoma post-chemotherapy residual masses in order to decide for watchful waiting (WW) or active treatment therapy (36-39).

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

Based on the tumour marker level and the results of CT scanning, patients have to be classified according to the 2002 TNM classification of the UICC (International Union Against Cancer) (Table 1) (40). Patients with metastatic disease (TNM stage $\geq$ 2) have to be classified additionally according to the International Germ Cell Cancer Collaborative Group (IGCCCG) staging system, defined as a prognostic-factor based staging system for metastatic testicular tumour (Table 2). This staging system has been incorporated into the TNM classification and uses histology, location of the primary tumour, location of metastases and serum marker levels as prognostic factors to categorize patients into "good", "intermediate" or "poor" prognosis (41).

Table 1: TNM classification for testicular cancer (UICC, 2002, 6th ed) (40)

pT	**Primary tumour[1]**
pTX	Primary tumour cannot be assessed
pT0	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
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 or less in greatest dimension or multiple lymph nodes, none more than 2 cm in greatest dimension
N2	Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension, or multiple lymph nodes, any one mass more than 2 cm but not more than 5 cm in greatest dimension
N3	Metastasis with a lymph node mass more than 5 cm in greatest dimension

pN Pathological

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 5 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 5 nodes positive, none more than 5 cm; or evidence or extranodal extension of tumour
pN3	Metastasis with a lymph node mass more than 5 cm in greatest dimension

M Distant metastasis

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Non-regional lymph node(s) or lung
M1b	Other sites

S Serum tumour markers

Sx	Serum marker studies not available or not performed
S0	Serum marker study levels within normal limits

	LDH (U/l)	hCG (mIU/ml)	AFP (ng/ml)
S1	< 1.5 x N and	< 5,000 and	< 1,000
S2	1.5-10 x N or	5,000-50,000 or	1,000-10,000
S3	> 10 x N or	> 50,000 or	> 10,000

N indicates the upper limit of normal for the LDH assay.

[1]Except for pTis and pT4, where radical orchiectomy is not always necessary for classification purposes, the extent of the primary tumour is classified after radical orchiectomy; see pT. In other circumstances, TX is used if no radical orchiectomy has been performed.

According to the 2002 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

Table 2: Prognostic-based staging system for metastatic germ cell cancer (IGCCCG) (41)

Good-prognosis group

Non-seminoma (56% of cases)	*All of the following criteria:*
5-year PFS 89%	• Testis/retroperitoneal primary
5-year survival 92%	• No non-pulmonary visceral metastases
	• AFP < 1,000 ng/ml
	• hCG < 5,000 IU/l (1,000 ng/ml)
	• LDH < 1.5 x ULN
Seminoma (90% of cases)	*All of the following criteria:*
5-year PFS 82%	• Any primary site
5-year survival 86%	• No non-pulmonary visceral metastases
	• Normal AFP
	• Any hCG
	• Any LDH

Intermediate-prognosis group

Non-seminoma (28% of cases)	*All of the following criteria:*
5-year PFS 75%	• Testis/retroperitoneal primary
5-year survival 80%	• No non-pulmonary visceral metastases
	• AFP > 1,000 and < 10,000 ng/ml or
	• hCG > 5,000 and < 50,000 IU/l or
	• LDH > 1.5 and < 10 x ULN

Seminoma (10% of cases)	Any of the following criteria:
5-year PFS 67%	• Any primary site
5-year survival 72%	• Non-pulmonary visceral metastases
	• Normal AFP
	• Any hCG
	• Any LDH

Poor-prognosis group

Non-seminoma (16% of cases)	Any of the following criteria:
5-year PFS 41%	• Mediastinal primary
5-year survival 48%	• Non-pulmonary visceral metastases
	• AFP > 10,000 ng/ml or
	• hCG > 50,000 IU/l (10,000 ng/ml) or
	• LDH > 10 x ULN

Seminoma
No patients classified as poor prognosis

PFS: progression-free survival; AFP: alpha-fetoprotein; hCG: human chorionic gonadotrophin;
LDH: lactate dehydrogenase; ULN: upper limit of normal range.

3. DIAGNOSIS AND TREATMENT OF TIN

Contralateral biopsy has been advocated to rule out the presence of TIN (42). 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), the morbidity of TIN treatment and the fact that most of these asynchronic tumours are at a low stage at presentation make it controversial to recommend a systematic contralateral biopsy (43,44). It is still difficult to reach a consensus about whether the existence of contralateral TIN has to be identified in all cases. However, biopsy of the contralateral testis should be offered to all patients and is advised for exclusion of contralateral TIN in high-risk patients with a testicular volume less than 12 ml, a history of cryptorchidism and age under 30 years (44).

Once TIN is diagnosed, local radiotherapy (20 Gy in single fractions of 2 Gy) is the treatment of choice. Because this will produce infertility, the patient must be carefully counselled before treatment commences (45, 46). In addition to infertility, Leydig cell function and testosterone production may be impaired long-term after radiotherapy of TIN (30).

4. IMPACT ON FERTILITY AND FERTILITY-ASSOCIATED ISSUES

Sperm abnormalities are not infrequent in patients with testicular tumours. Furthermore chemotherapy treatment can also impair fertility. In patients of reproductive age, pre-treatment and preferably pre-orchidectomy fertility assessment (testosterone, luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels) and sperm analysis with cryopreservation should be offered. Cryopreservation should be performed before or after orchiectomy, but in any case prior to chemotherapy treatment (47-51).

In cases of bilateral orchidectomy or low testosterone levels after treatment of TIN, life-long testosterone supplementation is recommended (51). For more detailed information the reader is referred to the EAU Male Infertility Guidelines.

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 orchidectomy alone (52).

5.1.1 Adjuvant radiotherapy

Seminoma cells are extremely radiosensitive. Adjuvant radiotherapy to a para-aortic (PA) field with a total target volume of 20 Gy will reduce the relapse rate to only 1-3% (53,54).

After modern radiotherapy, nearly all relapses will first occur outside the irradiated field (supradiaphragmatic lymph nodes or in the lungs) (55,56). Based upon the results of a large randomized Medical Research Council (MRC) trial, Fossa et al. (53) recommended radiotherapy to a PA field as standard treatment for patients with testicular seminoma stage I, T1-T3 and with undisturbed lymphatic drainage. The relapse rate to the iliac nodes was 2% with para-aortic (PA) field irradiation only. The acute toxicity was reduced and the sperm count within the first 18 months was significantly higher after PA irradiation. Para-aortic irradiation should be tailored according to the site of the primary tumour. Adjuvant irradiation of supradiaphragmatic lymph nodes is not indicated in seminoma stage I.

Concerning the dose of irradiation, the MRC has recently finished a large randomized trial of 20 Gy versus 30 Gy PA irradiation in stage I seminoma that showed equivalence for both doses regarding recurrence rates (54). 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%. The main concern surrounding adjuvant radiotherapy is the potentially increased risk of radiation-induced secondary non-germ-cell malignancies (57-59). At this point, it is difficult to evaluate the long-term risks after adjuvant radiotherapy for stage I seminoma since former treatment procedures included larger fields, higher doses of radiotherapy and/or the use of alkylating chemotherapy (59,60).

5.1.2 Surveillance

Several prospective non-randomized studies of surveillance have been conducted during the last decade, several of which comprised more than 100 patients (61-63). Meta-analysis of the four largest studies shows an actuarial 5 years' relapse-free rate of 82.3%. On multivariate analysis, tumour size (> 4 cm) and invasion of the rete testis remained the most important predictors for relapse (64).

The actuarial relapse rate is of the order of 15-20% at 5 years. Most relapses are first detected in infra-diaphragmatic lymph nodes (64). 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 97-100% for seminoma stage I after surveillance (61,62,64). The main drawback of surveillance is the need for more intensive follow-up, especially with repeated imaging examinations of the retroperitoneal lymph nodes, for at least 5 years after orchidectomy. About 70% of the relapses seen during surveillance occur within 2 years after orchidectomy; however, about 7% occur more than 6 years after diagnosis (64).

5.1.3 Adjuvant chemotherapy

A joint Medical Research Council (MRC) and European Organization for Research and Treatment of Cancer (EORTC) trial (MRC TE19 trial, EORTC Trial 30942) comparing one cycle of carboplatin (AUC 7) to adjuvant radiotherapy has recently been finished. Single-agent carboplatin therapy showed no significant difference to radiotherapy concerning recurrence rate, time to recurrence and survival after a median follow-up of 3 years (65). Thus, adjuvant carboplatin therapy is an alternative to radiotherapy or surveillance in stage I seminoma. Two courses of adjuvant carboplatin seem to reduce the relapse rate further to the order of 1-3%, but further experience and long-term observations are needed (66-68).

5.1.4 Retroperitoneal lymph node dissection (RPLND)

In a prospective, non-randomized study comparing radiotherapy and RPLND in stage I seminoma, there was a trend towards a higher incidence of retroperitoneal relapses (9.5%) after RPLND as primary treatment. This policy should therefore not be recommended in stage I seminoma (69).

5.1.5   Risk-adapted treatment

Using tumour size > 4 cm and rete testis invasion, patients with seminoma stage I may be subdivided in a low-and high-risk group of occult metastatic disease. However, these risk factors have only been assessed in a meta-analysis of retrospective trials (64). Patients with, and without, both risk factors have a risk of occult disease of 32% and 12%, respectively.

5.1.6   Guidelines for the treatment of seminoma stage 1

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

5.2   NSGCT stage I

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

5.2.1   Prognostic factors

The main predictor of relapse in CS1 NSGCT managed by surveillance, and both for having pathological stage II (PS2) disease and for relapse in pathological stage I (PS1) after RPLND, is histopathological evidence of vascular invasion by tumour cells in, or near, the primary tumour in the testis (70-76). The presence of vascular invasion seems to be a very robust parameter and is clinically usable even without centralized review by an expert panel.

Vascular invasion was found to be most predictive of stage in a multifactorial analysis. The absence of vascular invasion has a negative predictive value of 77%, thus allowing for surveillance in low-risk compliant patients (70). The combination of the absence of vascular invasion with a low MIB-1 score (proliferation rate < 70) improves the negative predictive value to 87%. However, the presence of vascular invasion has a positive predictive value of 53% for occult metastatic disease. Combining the presence of vascular invasion with a proliferation rate of > 70% MIB-1 positive tumour cells and with > 50% embryonal carcinoma within the tumour increases the patient's risk for occult metastatic disease to 64% (high risk) (70).

5.2.2   Risk-adapted treatment

Risk-adapted treatment is recommended as treatment of first choice in NSGCT I. Risk assessment is currently based on the risk factor of vascular invasion alone. Stratifying patients with CS1 NSGCT according to their presumed risk of relapse is a rational option since several studies have reported similar survival rates and a final cure rate close to 100% with all available treatment options using the risk-stratifying approach (77-80). Patients with vascular invasion are recommended to undergo adjuvant chemotherapy with two cycles of cisplatin, etoposide and bleomycin (PEB) and patients without vascular invasion are recommended to undergo surveillance. Only if patients or doctors are not willing to accept the relevant risk-adapted treatment or if there are conditions against the risk-adapted treatment option, the remaining treatments should be considered. Thus, the treatment decision should be based on a thorough discussion with the patient, taking into account the described advantages and disadvantages, as well as the individual situation of the patient and/or the treatment centre.

5.2.2.1   Surveillance

Eighty per cent of relapses occur during the first 12 months of follow-up, 12% during the second year and 6% during the third year, decreasing to 1% during the fourth and fifth years, and occasionally even later (76,81-86). About 35% of relapsing patients have normal levels of serum tumour markers at relapse. About 60% of the relapses are in the retroperitoneum. Despite very close follow-up, 11% of relapsing patients presented with large-volume recurrent disease.

5.2.2.2   Adjuvant chemotherapy

Several studies involving two courses of chemotherapy with PEB as primary treatment for high-risk patients (having about 50% risk of relapse) have been reported (77-80,87). In these series, involving more than 200 patients, some with a median follow-up of nearly 8 years, 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 (80,88). It is important to be aware of the risk of slow-growing retroperitoneal teratomas after chemotherapy and of the risk of chemoresistant cancer relapse.

5.2.3   Retroperitoneal lymph node dissection
If RPLND is performed without risk assessment, about 30% of patients are found to have retroperitoneal lymph node metastases (PS2 disease) (89-91). If no retroperitoneal metastases are found at RPLND (PS1), approximately 10% of the PS1 patients relapse at distant sites.

If CS1 patients with PS2 are only followed up after RPLND, about 30% relapse, mainly at sites outside the abdomen and pelvis. The risk of relapse depends upon the amount of retroperitoneal disease resected (92-95). 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 (96). 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 (90,97). 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. In experienced hands, a laparoscopic RPLND may become an alternative staging procedure to an open RPLND, but cannot currently be recommended as a standard diagnostic tool (98-101).

5.3   CS1S with (persistently) elevated serum tumour markers
Serum tumour markers should be followed closely until it is clear whether or not levels are falling according to the expected half-time values for AFP and ß-hCG. If the marker level increases after orchiectomy, the patient has residual disease. If RPLND is performed, up to 87% of these patients have pathologically documented nodes in the retroperitoneum (102,103). An ultrasound examination of the contralateral testicle must be performed if this has not been done initially.

The treatment of true CS1S patients is still in debate. Currently, three courses of primary PEB chemotherapy seem appropriate since all of these patients will present with metastatic disease if followed up only (104).

5.3.1   Guidelines for the treatment of NSGCT stage I

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

CS1B (pT2-pT4); high risk
1.   Primary chemotherapy with two courses of PEB should be recommended (grade B recommendation).
2.   Surveillance or nerve-sparing RPLND in high-risk patients remain options for those not willing to
      undergo adjuvant chemotherapy. If pathological stage II is revealed at RPLND, further chemotherapy
      should be considered (grade A recommendation).

6.   TREATMENT: METASTATIC GERM CELL TUMOURS

6.1   Stage II A/B seminoma
The standard treatment of stage II A/B seminoma is radiotherapy. The radiation dose delivered in stage IIA and IIB is 30 Gy and 36 Gy, respectively. The standard radiation field compared to stage I will be extended from the PA region to the ipsilateral iliac field ("hockey-stick"). In stage IIB, the lateral borders should include the metastatic lymph nodes with a safety margin of 1.0-1.5 cm. This technique yields a relapse-free survival after 6 years for stage IIA and IIB of 95% and 89%, respectively. Overall survival is almost 100% (105,106).

In stage IIB, chemotherapy with three cycles of PEB or four cycles of EP ("good prognosis") is an alternative for patients not willing to undergo radiotherapy (107).

6.2 NSGCT stage II A/B

There is a general consensus that treatment should start with initial chemotherapy in all advanced cases of NSGCT except for stage II NSGCT disease without elevated tumour markers, which alternatively can be treated with primary RPLND or surveillance (16). These rare cases of stage IIA/B without marker elevation may represent metastatic differentiated teratoma.

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

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

The cure rate with either approach will be close to 98% (96,108,109).

6.3 Advanced metastatic disease

6.3.1 Primary chemotherapy

The primary treatment of choice for advanced disease is three or four cycles of PEB combination chemotherapy (Table 3) depending on IGCCCG risk classification (see Table 2). This regimen has proven superiority to cisplatin, vinblastine and bleomycin (PVB) in patients with advanced disease (110-112). Data support that a 3-day regimen of administering combination chemotherapy is equally effective as a 5-day regimen but associated with increased toxicity (113).

Table 3: PEB regimen (every 3 weeks)

Drug	PEB
Cisplatin	20 mg/m^2, days 1-5[a]
Etoposide	100 mg/m^2, days 1-5
Bleomycin	30 mg, days 1,8,15

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

For patients with a "good prognosis" according to the IGCCCG, standard treatment consists of three cycles of PEB or, where bleomycin is contraindicated, four cycles of PE (112-114). Therapy should be given without reduction of the doses at 22-day intervals; delaying the following chemotherapy cycle is justified only in cases of fever, neutrophils < 1,000/µl or platelets < 100,000/µl at day one of the subsequent cycle. There is no indication for prophylactic application of haematopoetic growth factor such as granulocyte-colony stimulating factor (G-CSF). However, if infectious complications have occurred during chemotherapy, prophylactic administration of G-CSF is recommended for the following cycles (115,116).

With the "intermediate-prognosis" group in the IGCCCG, a group of patients has been defined that achieves a 5-year survival rate of about 80%. The available data support four cycles of PEB as standard treatment (117). Due to the generally less favourable prognosis of this patient group, in comparison to patients with a "good prognosis", they may be treated in prospective trials such as the EORTC GU Group trial with PEB versus PEB plus paclitaxel (118).

For patients with a "poor prognosis", standard treatment consists of four cycles of PEB. Four cycles of PEI (cisplatin, etoposide, ifosfamide) have the same effect but are more toxic (119). 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 (120-122). Since a matched-pair analysis resulted in a better survival rate (121), these patients should be treated in the ongoing prospective randomized trials investigating the value of high-dose chemotherapy, e.g. EORTC trial 30974. Patients meeting "poor-prognosis" criteria should therefore be transferred to a reference centre. General recommendations for treatment modifications for patients with a poor general condition (Karnofsky performance status < 50%), extended liver infiltration (> 50%) and extended pulmonary infiltration do not exist.

6.4   Restaging and further treatment

6.4.1   Restaging

After termination of two courses of chemotherapy, re-evaluation is performed by imaging investigations and determination of tumour markers. At marker decline and stable or regressive tumour manifestation, chemotherapy will be completed (three or four cycles depending on the initial stage) (123,124). In cases of marker decline, but growing metastases, resection of the tumour is obligatory after termination of induction therapy, unless in the case of emergency according to local tumour growth (125).

An early crossover of therapy is indicated only with documented marker growth after two courses of chemotherapy. These patients are usually candidates for new drugs trials (126). Patients with a low-level marker plateau post treatment will be observed whether or not complete normalization occurs. Salvage chemotherapy is indicated for documented marker rise only (127,128).

6.4.2   Residual tumour resection

A residual mass of seminoma will not be resected, irrespective of the size, but controlled by imaging investigations and tumour markers (16,129-134). Positron emission tomography scan (PET) in metastatic seminoma after chemotherapy is a valid tool with which to detect vital residual tumour (135,136). In cases of vital tumour after first-line chemotherapy, salvage chemotherapy is given, if necessary including surgery and radiotherapy.

In cases of non-seminoma and complete remission after chemotherapy, residual tumour resection is not indicated (16). In cases of residual mass (greater than 1 cm in transverse CT diameter) and marker normalization, surgical resection is indicated (137-149). Overall, following PEB induction chemotherapy, only 10% of residual masses contain viable cancer, 50% contain mature teratoma and 40% contain necrotic-fibrotic tissue. As yet no imaging investigations, including PET or prognosis models, are able to predict histological differentiation of the non-seminomatous residual tumour. Thus, residual tumour resection is mandatory (150-158).

The extent of surgery should be based on the risk of relapse of an individual patient and quality-of-life issues. If possible, all the masses have to be resected because a complete resection, in the setting of viable malignant cells, is more critical than recourse to post-operative chemotherapy (159). Histology in different organ sites may diverge.

6.4.3   Consolidation chemotherapy after secondary surgery

After resection of necrosis or mature teratoma, no further treatment is required. In the case of complete resection of vital carcinoma or immature teratoma, two adjuvant cycles of conventionally dosed cisplatinum-based chemotherapy may be given in certain subgroups (e.g. "poor prognosis" patients, [160]) (cave: cumulative doses of bleomycin). The prognosis will definitely deteriorate if vital carcinoma is found in resection specimens after second- and third-line chemotherapy. In the latter situation, post-operative chemotherapy is not indicated and is unable to improve the prognosis (159). In general, a co-operative retrospective study (159) has demonstrated that, in patients with vital cancer in residual specimens, the major success factors are complete surgical resection and percentage of viable cancer in the residual mass, with the effect of adjuvant chemotherapy being borderline.

6.5   Systemic salvage treatment for relapse or refractory disease

6.5.1   Seminoma

Cisplatin-based combination salvage chemotherapy will result in long-term remissions for about 50% of patients who relapse after first-line chemotherapy (161). Regimens of choice are: four cycles of PEI/VIP (cisplatin, etoposide, ifosfamide), or four cycles of VeIP (vinblastin, ifosfamide, cisplatin). 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. Thus, treatment of these rare patients within clinical trials and at experienced centres is of utmost importance.

6.5.2   Non-seminoma

Standard salvage treatment after first-line chemotherapy (Table 4) consists of four cycles of PEI/VIP. Conventionally dosed salvage chemotherapy may achieve long-term remissions in 15-40% of patients, depending on individual risk factors.

Prognostic indicators of response to salvage therapy are:
- location and histology of the primary tumour
- response to first line treatment
- duration of remissions
- level of AFP and ß-hCG at relapse.

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

Depending on the presence of adverse prognostic factors, the results of salvage therapy after first-line cisplatin-based treatment are unsatisfactory (162,163). Although some phase II trials have indicated a 10% improvement in survival with early intensification of first salvage treatment using high-dose chemotherapy, other trials have failed to demonstrate such improvement (164-166). New agents such as paclitaxel, docetaxel, gemcitabine, irinotecan, and oxaliplatin have been tested in the salvage setting. Recently, paclitaxel and gemcitabine have shown to be active in the treatment of refractory germ cell tumours; both drugs are synergistic with cisplatin (167,168). Oxaliplatin seems to have activity even in truly cisplatin-refractory patients. For patients with good performance status and adequate bone marrow function, combination regimens of these new agents (e.g. gemcitabine plus oxaliplatin [169]) are currently recommended, since at least a small percentage of patients may again reach long-lasting remissions. 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 centres experienced in caring for relapse and/or refractory patients.

Table 4: Standard PEI/VIP and VeIP chemotherapy

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

PEI/VIP = cisplatin, eposide, ifosfamide; VeIP = vinblastin, ifosfamide, cisplatin.
[a] Plus hydration.
[b] Plus mesna protection.

6.6 Salvage surgery
Residual tumours after salvage chemotherapy should be resected within 4-6 weeks after marker normalization or when a marker plateau is reached. In the case of marker progression after salvage treatment and lack of other chemotherapeutic options, resection of residual tumours ("desperation surgery") should be considered if complete resection of all tumour seems feasible (about 25% long-term survival may be achieved) (170-179).

6.7 Treatment of brain metastases
Brain metastases occur in the frame of a systemic relapse and rarely as an isolated relapse. The long-term survival of patients presenting with brain metastasis at initial diagnosis is poor (30-40%), but even poorer with the development of brain metastasis as recurrent disease (5-year survival 2-5%) (180-182). Chemotherapy is the initial treatment in this case and some data support the use of consolidation radiotherapy even in the case of a total response after chemotherapy. Surgery can be considered in the case of a persistent solitary metastasis depending on the systemic state, the histology of the primary tumour and the location of the metastasis.

6.8   Guidelines for the treatment of metastatic germ cell tumours

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

7.   FOLLOW-UP AFTER CURATIVE THERAPY

7.1   General considerations
In spite of the fact that relatively limited information exists on the value of follow-up testing of asymptomatic patients after potentially curative therapy, testis cancer, the most curable human tumour, is an excellent model for post curative therapy surveillance. The selection of the tests to be performed in follow-up should adhere to the following principles (183):

A   *The interval between examinations and duration of testing should be consistent with the time of maximal risk of recurrence and the natural history of the tumour.*

B   *The tests should be directed at the most likely sites of recurrence and should have a high predictive value, both positive and negative.*

C   *Therapy should be available that will result in cure of the recurrence, significant prolongation of life or palliation of symptoms. The initiation of earlier therapy should improve the outcome compared with therapy given when the patient becomes symptomatic from the tumour recurrence.*

D   *The increased risk of second malignancy, both at the primary site and in other tissues that may have been exposed to the same carcinogens or in which there is epidemiological evidence of increased risk, should also guide the selection of the tests. Malignant and non-malignant complications of therapy must also be considered. Such testing should also be performed with a frequency and duration consistent with the nature of the risk and include only tests with high positive and negative predictive values.*

The following considerations apply in a general manner to selecting an appropriate schedule and investigations in the follow-up of all stages of testicular tumours.
*   Most recurrences after curative therapy will occur in the first 2 years; consequently surveillance should be most frequent and intensive during this time.
*   Late relapses can occur beyond 5 years; annual follow-up for life may therefore be advocated (184-187).
*   After RPLND, relapse in the retroperitoneum is rare, the most likely site of recurrence being the chest.
*   The value of chest X-ray has been recently questioned in the follow-up of patients with disseminated disease after complete remission (188).
*   CT of the chest has a higher predictive value than chest X-ray (188).
*   The results of therapy are dependent on the bulk of disease, thus an intensive strategy to detect presymptomatic disease may be justifiable (189,190).
*   After chemotherapy or radiotherapy, there is a small long-term risk of secondary malignancies (59,191).

In testis tumour the aims of follow-up are:
- to detect relapse as early as possible in all stages
- to detect an asynchronous contralateral carcinoma of the testis in an early phase
- to avoid unnecessary treatment in stage I.

Since different treatment policies are available for stage I and low-volume metastatic disease (resulting in the same survival but different recurrence rate), in these stages the intensity of the follow-up should be determined by the rate and timing of relapse. The site of relapse for each one of the policies should dictate the tests to be performed during follow-up.

Whether in early or advanced stages, the tests to be performed during follow-up are:
- physical examination (search for neck and abdominal masses, gynaecomastia, examination of groins, superficial nodes and the remaining testis).
- serum tumour markers determination (AFP, hCG and LDH).
- chest X-ray and/or chest CT, abdominal and pelvic CT or abdominal ultrasound.
- brain CT in case of neurological symptoms, and bone scan in case of bone pain.

Currently, insufficient evidence is available in the literature to provide strict recommendations on timing and testing during follow-up. The nature of the recommendations on follow-up is grade B or C with a consistent lack of randomized studies. Therefore, the authors wish to emphasize that the following 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 a clinical protocol or for investigational purposes.

7.2   Follow-up of stage I non-seminoma

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 (4,77,80,84,85,87,192-194). The follow-up schedule will differ depending on which of the three possible treatment strategies was chosen: surveillance, nerve-sparing RPLND or primary chemotherapy.

7.2.1   Follow-up after surveillance

The results of a surveillance policy depend on 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 second 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% (76,81). Relapse occurs mainly in the retroperitoneum; approximately 20% of patients have evident metastases in the retroperitoneum and 10% in the mediastinum and lungs (86). Sometimes the only indication is an elevated level of tumour markers.

Careful observation during the first 6-12 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 5. It is particularly difficult to establish recommendations for those patients with negative pre-operative tumour markers levels.

Table 5: Recommended follow-up schedule in a surveillance policy - stage I non-seminoma

Procedure	Year			
	1	2	3-5	6-10
Physical examination	Monthly	4-6 times	Twice/year	Once/year
Tumour markers	9-12 times (Monthly for the first 6 months)	4-6 times	Twice/year	Once/year
Chest X-ray	9-12 times (Monthly for the first 6 months)	4-6 times	Twice/year	Once/year
Abdominal CT scan	3-4 times	Twice	Once/year	If indicated

7.2.2 Follow-up after nerve-sparing RPLND

Retroperitoneal relapse after a properly performed nerve-sparing RPLND is extremely rare. RPLND 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 (95). In the Indiana series, only one relapse in 559 cases was reported (195). 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 RPLND (196,197). The recommended follow-up schedule is shown in Table 6.

Table 6: Recommended follow-up schedule after retroperitoneal lymphadenectomy or adjuvant chemotherapy - stage I non-seminoma

Procedure	Year			
	1	2	3-5	6-10
Physical examination	6 times	3 times	Twice/year	Once/year[a]
Tumour markers	6 times	3 times	Twice/year	Once/year[a]
Chest X-ray	6 times	3 times	Twice/year	Once/year[a]
Abdominal CT scan	Twice	Once	If indicated[b]	If indicated
Abdominal ultrasound	Twice[c]	Twice[c]	Twice/year	Once/year

[a] Grade C recommendation.
[b] Due to a risk of late, slow-growing teratoma in the retroperitoneum after adjuvant chemotherapy once a year.
[c] Alternating with abdominal CT scan.

7.2.3 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 (77,78,80,87) 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 6). 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.

7.3 Follow-up of stage I seminoma

The majority of patients with seminoma (70-80%) present with clinical stage I disease at diagnosis (198). In 15-20% of cases, there is nodal radiological involvement at the level of the retroperitoneum and only 5% of patients present with distant metastasis (198). 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 β-hCG at diagnosis or in the course of the disease. Consequently, in most cases, measurement of blood markers will not be a reliable test for follow-up (189). 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 cases of relapse. The costs of the different therapies vary, as do the expected side effects (61,199,200).

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

7.3.1 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 (53,55,201-203). The rate of relapse is 1-2% and the most common time of presentation is within 18 months after treatment (53,56,200,204,205), although late relapses have also been described (185). 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 (198).

The side effects of radiotherapy include impaired spermatogenesis, gastrointestinal symptoms (peptic ulceration) and induction of second malignancies (200,206,207). Up to 50% of patients can develop moderate toxicity grade I-II (202). The schedule of follow-up is described in Table 7.

Table 7: Follow-up for post-orchiectomy radiotherapy or chemotherapy - stage I seminoma

Procedure	Year			
	1	2	3	4-5
Physical examination	6 times	4 times	3 times	Twice/year
Chest X-ray	6 times	4 times	3 times	Twice/year
Tumour markers	6 times	4 times	3 times	Twice/year
Abdominal CT scan	Once	Once	If indicated	If indicated
Abdominal ultrasound	Once[a]	Once[a]	Once	If indicated

[a] Alternating with abdominal CT scan.

7.3.2 Follow-up after surveillance

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% (208-212). 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 (198). 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 (198). 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 costs and patient compliance. The schedule of follow-up is described in Table 8.

Table 8: Follow-up in surveillance policy

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

[a] Not required.
[b] Alternating with abdominal CT scan.

7.3.3 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 (67,68). As the relapse rate is low, the follow-up schedule may be the same as the one proposed for post-orchiectomy radiotherapy (Table 7).

7.4 Follow-up of stage II and advanced (metastatic) disease

The more advanced the nodal stage of the disease, the higher the likelihood of recurrence (96). In general, the primary tumour bulk governs the outcome for patients with NSGCT (213). 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 (109,193,214).

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 (213,215).
Complete response rates to chemotherapy are in the order of 50-60% (213); another 20-30% of patients could be rendered disease-free with post-chemotherapy surgery (216).

The main reasons for failure of therapy in advanced NSGCT are (213,217,218):
• The presence of bulky disease not responding completely to chemotherapy.
• Unresectable residual teratoma after chemotherapy.
• Presence or development of chemoresistant non-germ cell elements, which account for 8.2% of cases.

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 IA.

7.4.1 Clinical and pathological stage II NSGCT
As previously stated in this guideline, low-volume stage II NSCGT can be treated by primary RPLND or primary chemotherapy.

7.4.1.1 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) (219,220).
2. Between 72% and 77% of clinical stage II patients will be 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 primary RPLND followed by two immediate cycles of chemotherapy
The relapse rate for this group is 6% at 4 years (96,215). 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% (214,221).

The main disadvantage of adjuvant chemotherapy is that it represents an overtreatment in approximately 50% of patients with stage II disease.

Relapse after primary RPLND followed by surveillance
The average relapse rate in this group is 35% (range 8-49%) at a mean of 4 years (96,190,222). 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% (96,214,215,223). 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 12). 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 9 can be used, but the tests have to be performed:
• monthly during the first year
• bimonthly during the second year
• quarterly during the third year
• every 4 months during the fourth year
• twice in the fifth year
• annually thereafter.

Table 9:   Follow-up of NSGCT stage IIa-IIb after RPLND plus chemotherapy or primary chemotherapy

Procedure	Year					
	1	2	3	4	5	Thereafter
Physical examination	6 times	4 times	Twice	Twice	Twice	Once/year
Tumour markers	6 times	4 times	Twice	Twice	Twice	Once/year
Chest X-ray	6 times	4 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

[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.

7.4.1.2   Relapse after primary chemotherapy
Between 68% and 78% of patients (average 75%) will reach a complete clinical response (85,109,224). The relapse rate is 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 and the histology of the primary tumour/teratoid elements). Mature teratomas have been described at 5-8 years of follow-up (214). 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% (109).

Although this treatment policy avoids RPLND in 68-78% of patients, depending on whether the clinical stage is IIa or IIb (109,156,224), 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 9).

7.4.2   Clinical stage II seminoma
Relapse rates following radiotherapy for clinical stages IIa and IIb are in the range of 5-15%. Most relapses occur within the first 2 years and present with a supraclavicular or mediastinal mass, while relapses in the irradiated field are rare (215). The recommend follow-up schedule is outlined in Table 10.

Table 10: Follow-up of seminoma stage IIa-IIb after radiotherapy

Procedure	Year					
	1	2	3	4	5	>5
Physical examination	6 times	4 times	3 times	Twice	Twice	Once/year
Tumour markers	6 times	4 times	3 times	Twice	Twice	Once/year
Chest X-ray	6 times	4 times	3 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

[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.

7.4.3   Clinical stage IIc and III seminoma and non-seminoma
In advanced disease following the IGCCCG 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 (41). Stage IIc is generally grouped in the subset of patients with good prognosis (214).

After chemotherapy, careful follow-up is recommended if there is a decrease of at least 90% in the volume of retroperitoneal masses, provided there is 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% (217).

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 currently still approximately 20% (217).

In advanced seminoma, the rate of "in-site" failure is 3% when the CT scan is normal or shows a residual abnormality less than 3 cm in diameter (130-132,225). The follow-up schedule for advanced disease (seminoma and non-seminoma) is presented in Table 11.

In advanced disease, routine estimation of serum tumour markers (hCG and AFP) seems to be the single most important follow-up procedure, followed by physical examination and clinical history (188,226). Some recent studies question the value of routine chest X-ray (188).

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 (215). An abdominal CT scan has to be performed at least annually, because of the ominous significance of teratoma, if found in the retroperitoneum.

Table 11: Follow-up of advanced NSGCT and seminoma

Procedure	Year					
	1	**2**	**3**	**4**	**5**	**Thereafter**
Physical examination	12 times	6 times	4 times	3 times	Twice	Once/year
Tumour markers	12 times	6 times	4 times	3 times	Twice	Once/year
Chest X-ray	12 times	6 times	4 times	3 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

[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 central nervous system symptoms.

8.   TESTICULAR STROMAL TUMOURS

8.1   Background
Testicular stromal tumours are rare and account for only 2-4% of adult testicular tumours. However, only Leydig cell and Sertoli cell tumours are of clinical relevance. As no general recommendations are published to date, the Testicular Cancer Working Group of the EAU decided to include these tumours in the EAU Germ Cell Tumour Guidelines. Recommendations for diagnosis and treatment are given only for Leydig and Sertoli cell tumours.

8.2 Methods

A Medline search for Leydig cell tumours (synonym: interstitial cell tumour) and Sertoli cell tumours (synonym: androblastoma) was performed. Approximately 850 papers were found. After excluding pure laboratory work without clinical data, female and paediatric tumours and animal cases, 371 papers and abstracts were reviewed. Double publications and papers with unclear histology or missing data on clinical course were excluded. The majority of the remaining 285 publications were case reports, with only a few papers reporting series of more than 10 cases, most of them published in the pathology literature. The true incidence of stromal tumours remains therefore uncertain and the proportion of metastatic tumours can only be given approximately.

Nevertheless, the symptoms for pre-operative suspicion of testicular stromal tumours and the characteristics of tumours at high risk for metastases are sufficiently well established (EBM IIA and EBM IIB) to enable recommendations to be made regarding diagnosis and surgical approach. However, no recommendations for appropriate follow-up can be given due to the absence of follow-up data in most reported cases and the fatal outcome of metastatic tumours, irrespective of the therapy chosen.

The individual publications have been rated according to EBM categories (see above).

The literature research for clinical data on **Leydig cell tumours** resulted in 193 publications dealing with more than 480 tumours in adults, including three publications (1-3) reporting larger series on a total of 90 patients. Follow-up data of more than 2 years are available for about 80 patients.

The literature research for clinical data on **Sertoli cell tumours** resulted in 93 publications dealing with more than 260 tumours in adults, including three publications (from the same group) (4-6) reporting on a total of 80 patients. Follow-up data of more than 2 years are available in fewer than 40 patients.

8.3 Classification

The non-germ cell tumours of the testicle include the sex cord/gonadal stromal tumours and the miscellaneous non-specific stromal tumours.

The different histological subtypes of testicular tumours are defined according to the WHO classification 2004 (adapted) (7).

8.4 Leydig cell tumours

8.4.1 Epidemiology

Leydig cell tumours constitute about 1-3% of adult testicular tumours (2,8) and 3% of testicular tumours in infants and children (8). The tumour is most common in the third to sixth decade in adults with a similar incidence observed in every decade. Another peak incidence is seen in children between 3 and 9 years. 3% of Leydig cell tumours are bilateral (2). Occasionally, they occur in patients with Klinefelter's syndrome (8).

8.4.2 Pathology of Leydig cell tumours

Leydig cell tumours are the most common type of sex cord/gonadal stromal tumours. Histopathologically, they are well outlined and usually up to 5 cm in diameter. They are also solid, coloured yellow to tan, with haemorrhage and/or necrosis present in 30% of cases. Microscopically, the cells are polygonal, with eosinophilic cytoplasm with occasional Reinke crystals, regular nucleus, solid arrangement and capillary stroma. The cells express vimentin, inhibin, protein S100, steroid hormones, calretinin and cytokeratin (focally) (7).

About 10% of Leydig cell tumours are malignant tumours, which present with the following parameters:
- large size (> 5 cm)
- cytological atypia
- increased mitotic activity (> 3 per 10 high-power field [HPF])
- increased MIB-1 expression (18.6% vs 1.2% in benign)
- necrosis
- vascular invasion (1)
- infiltrative margins
- extension beyond the testicular parenchyma
- DNA aneuploidy (1,9).

8.4.3 Diagnosis

Patients either present with a painless enlarged testis or the tumour is an incidental ultrasound finding. In up to

80%, hormonal disorders with high oestrogen and oestradiol levels and low testosterone, increased levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) are reported (10,11), while negative results are always obtained for the testicular germ cell tumourmarkers, AFP, HCG, lactate dehydrogenaie (LDH) and PLAP. Approximately 30% of patients present with gynaecomastia (12,13). 3% of tumours are bilateral (2).

Leydig cell tumours must be distinguished from the multinodular tumour-like and often bilaterally occurring lesions of the androgenital syndrome (14). Diagnostic work-up must include markers, hormones (at least testosterone, LH and FSH, if not conclusive: additionally oestrogen, oestradiol, progesterone and cortisol), ultrasound of both testes and CT scan of chest and abdomen.

On ultrasound, it may be possible to observe well-defined, small, hypoechoic lesions with hypervascularization, but the appearance is variable and is indistinguishable from germ cell tumours (15,16).
The proportion of metastatic tumours in all published case reports is only 10%. Within three larger series with longer follow-up, 18 metastatic tumours were found in a total of 83 cases (21.7%) (1-3). Histopathological signs of malignancy have been listed above (see 8.4.2) (1,9). In addition, patients of older age have a greater risk of harbouring a tumour of malignant potential.

8.4.4 Treatment
Asymptomatic testicular tumours of small volume are often misinterpreted as germ cell tumours and inguinal orchiectomy is performed. It is highly recommended to perform an organ-sparing procedure in every small intraparenchymal lesion to gain the histological diagnosis. Especially in patients with symptoms of gynaecomastia or hormonal disorders, a non-germ-cell tumour should be considered and immediate orchiectomy should be avoided (17). In cases of germ cell tumour in either frozen section or paraffin histology, orchiectomy is recommended as long as a contralateral normal testicle is present.

In stromal tumours with histological signs of malignancy, especially in patients of older age, orchiectomy and retroperitoneal lymphadenectomy is recommended to prevent metastases (18).
Without histological signs of malignancy an individualized surveillance strategy after orchiectomy is recommended (CT follow-up may be most appropriate since specific tumour markers are not available).

Tumours that have metastasized to lymph nodes, lung, liver or bone respond poorly to chemotherapy or radiation and survival is poor (18).

8.4.5 Follow-up
Recommendations for appropriate follow-up cannot be given because of the lack of follow-up data in most reported cases and the lethal outcome of metastatic tumours, irrespective of the therapy chosen.

8.5 Sertoli cell tumour

8.5.1 Epidemiology
Sertoli cell tumours account for less than 1% of testicular tumours, the mean age at diagnosis is around
45 years with rare cases under the age of 20 (4,19). On rare occasions, these tumours may develop in patients with the androgen insensitivity syndrome and Peutz-Jeghers syndrome.

8.5.2 Pathology of Sertoli cell tumours
The tumour is well circumscribed, yellow, tan or white, with an average diameter of 3.5 cm (4). Microscopically, the cells are eosinophilic to pale with vacuolated cytoplasm. The nuclei are regular with grooves and there may be inclusions. The arrangement of the cells is tubular or solid; a cord-like or retiform pattern is possible.
The stroma is fine and capillary but in some cases a sclerosing aspect predominates. The cells express vimentin, cytokeratins, inhibin (40%) and protein S-100 (30%) (4).

The rate of malignant tumours ranges between 10% and 22% and fewer than 50 cases are reported (20-22).
Signs of a malignant Sertoli tumour are:
•   large size (> 5 cm)
•   pleomorphic nuclei with nucleoli
•   increased mitotic activity (> 5 per 10 HPF)
•   necrosis
•   vascular invasion.

8.5.2.1 Classification

Three subtypes have been described (19):

- the classic Sertoli cell tumour (4)
- the large cell calcifying form with characteristic calcifications (5,23)
- the rare sclerosing form (6,24).

8.5.3 Diagnosis

Patients present either with an enlarged testis or the tumour is an incidental ultrasound finding (25). Most classic Sertoli tumours are unilateral and unifocal. Hormonal disorders are infrequent, though gynaecomastia is sometimes seen (4). The testicular tumour-markers, AFP, HCG, LDH and PLAP are always negative.

Diagnostic work-up has to include tumour markers, hormones (at least testosterone, LH and FSH, if not conclusive: additionally oestrogen, oestradiol, progesterone and cortisol, ultrasound of both testes and CT scan of chest and abdomen.

Sertoli cell tumours are generally hypoechoic on ultrasound but they can be of variant appearance and therefore cannot be safely distinguished from germ cell tumours (19). Only the large cell calcifying form has a characteristic image with brightly echogenic foci due to calcification (26,27).

The large cell calcifying form is diagnosed in younger men and is associated with genetic syndromes (Carney's complex (28) and Peutz-Jeghers syndrome [29]) or, in about 40% of cases, endocrine disorders. 44% are bilateral, either synchronous or metachronous, and 28% show multifocality (21).

The characteristics of metastatic tumours have been depicted above (21,22). However, among patients whose tumours have been histopathologically classified as "malignant" using these or similar characteristics (i.e. 18.8% of tumours in all reported cases), only 7% showed metastatic disease during follow-up.

In the largest series with the longest follow-up, 7.5% of patients had been classified as "malignant" at primary diagnosis and 11.7% showed metastatic disease long-term (4). In general, affected patients are of higher age, tumours are nearly always palpable and show more than one sign of malignancy (4).

Up to 20% of the large cell sclerosing form are malignant. There are some hints that discrimination between an early and a late onset type may define a different risk for metastatic disease (5.5% compared with 23%) (19). Metastases in the infrequent sclerosing subtype are rare.

8.5.4 Treatment

Testicular tumours of small volume, otherwise asymptomatic, are often misinterpreted as germ cell tumours and inguinal orchiectomy is performed. It is highly recommended to proceed with an organ-sparing approach in small intraparenchymal testicular lesions until final histology is available. Especially, in patients with symptoms of gynaecomastia or hormonal disorders or typical imaging on ultrasound (calcifications, small circumscribed tumours), organ-sparing surgery should be considered. Secondary orchiectomy can be performed, if final pathology reveals a non-stromal (e.g. germ cell) tumour. Organ-sparing surgical approaches are justified as long as the remaining testicular parenchyma is sufficient for endocrine (and in stromal tumours also exocrine) function.

In tumours with histological signs of malignancy, especially in patients of older age, orchiectomy and retroperitoneal lymphadenectomy are recommended to prevent metastases (18). Without signs of malignancy, an individualized surveillance strategy after orchiectomy is recommended (CT scans may be most appropriate since specific tumour markers are not available). Tumours metastasizing to lymph nodes, lung or bone respond poorly to chemotherapy or radiation and survival is poor.

8.5.5 Follow-up

Recommendations for appropriate follow-up cannot be given because of the lack of follow-up data in most reported cases and the lethal outcome of metastatic tumours, irrespective of the therapy chosen.

8.6 Granulosa cell tumour

This is a rare tumour, with two variants - juvenile and adult.

The juvenile type is benign. It is the most frequent congenital testicle tumour and represents 6.6% of all prepuberal testicular neoplasms. The cystic appearance is characteristic of this tumour type (30).

With the adult type, the average age at presentation is 44 years. The typical morphology is of a homogeneous, yellow-grey tumour, with elongated cells, with grooves in micro-follicular and Call-Exner bodies' arrangement.

Malignant tumours represent around 20% of cases. They are usually > 7 cm diameter. Vascular invasion and necrosis are features suggestive of malignant biology (31).

8.7 Thecoma/fibroma group of tumours
These tumours are very rare and benign (7).

8.8 Other sex cord/gonadal stromal tumours
Sex cord/gonadal stromal tumours may be incompletely differentiated or mixed forms.

There is limited experience with incompletely differentiated sex cord/gonadal stromal tumours and no cases of reported metastasis (7). In mixed tumour forms, all the histological components should be reported. However, the clinical behaviour is most likely to reflect the predominant pattern or the most aggressive component of the tumour (32).

8.9 Tumours containing germ cell and sex cord/gonadal stromal (gonadoblastoma)
If the arrangement of the germ cells are in nested pattern and the rest of the tumour is composed of sex cord/gonadal stroma, the term gonadoblastoma is used. It is most frequent in gonadal dysgenesis with ambiguous genitalia. Bilateral tumours are present in 40% of cases. The prognosis is correlated with the invasive growth of the germinal component (33).

In case of a diffuse arrangement of the different components, there are some doubts about the neoplastic nature of the germinal cells and some authors consider them to be entrapped rather than neoplastic (34).

8.10 Miscellaneous tumours of the testis

8.10.1 Tumours of ovarian epithelial types
These tumours resemble the epithelial tumours of the ovary. Cystic appearance with occasional mucinous material can be observed. Microscopically, the aspect is identical to their ovarian counterparts and their evolution is similar to the different epithelial ovarian subtypes. Some Brenner types can be malignant (7).

8.10.2 Tumours of the collecting ducts and rete testis
These tumours are very rare. Benign (adenoma) and malignant (adenocarcinoma) have been reported, with malignant tumours showing local growth with a mortality rate of 56% (17).

8.10.3 Tumours (benign and malignant) of non-specific stroma
These are very uncommon and have a similar criteria, prognosis and treatment as the soft tissue sarcomas.

9. REFERENCES

9.1 Germ cell tumours
1. Richie JP. Neoplasms of the testis. In: Walsh PC et al, editors. *Campbells urology.* 7th ed. Philadelphia: WB Saunders, 1997, pp 2411-2452.
2. Huyghe E, Matsuda T, Thonneau P. Increasing incidence of testicular cancer worldwide: a review. J Urol 2003;170:5-11. EBM III.
    http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12796635&dopt=Abstract
3. McGlynn KA, Devesa SS, Sigurdson AJ, Brown LM, Tsao L, Tarone RE. Trends in the incidence of testicular germ cell tumors in the United States. Cancer 2003;97:63-70. EBM III-IIb.
    http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12491506&dopt=Abstract
4. Bosl GJ, Motzer RJ. Testicular germ-cell cancer. N Engl J Med 1997;337:242-253.
    http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9227931&dopt=Abstract

5. Von der Maase H, Rorth M, Walbom-Jorgensen S, Sorensen BL, Christophersen IS, Hald T, Jacobsen GK, Berthelsen JG, Skakkebaek NE. Carcinoma-in-situ of contralateral testis in patients with testicular germ cell cancer: study of 27 cases in 500 patients. BMJ 1986;293:1398-1401. EBM IIa.
    http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=3026550&dopt=Abstract

6. Giwercman A, Bruun E, Frimotd-Muller C, Skakkebaek NE. Prevalence of carcinoma in situ and other histopathological abnormalities in testes of men with a history of cryptorchidism. J Urol 1989;142:998-1002. EBM IIb.
    http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=2571738&dopt=Abstract

7. Dieckmann KP, Loy V. Prevalence of contralatral testicular intraepithelial neoplasia in patients with testicular germ cell neoplasm. J Clin Oncol 1996;14:3126-3132. EBM IIa-IIb.
    http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8955658&dopt=Abstract

8. Osterlind A, Berthelsen JG, Abildgaard N, Hansen SO, Hjalgrim H, Johansen B, Munck-Hansen J, Rassmussen LH. Risk of bilateral testicular germ cell tumors in Denmark: 1960-1984. J Natl Cancer Inst 1991;83:1391-1395. EBM IIa.
    http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1656057&dopt=Abstract

9. Moller H, Prener A, Skakkebaek NE. Testicular cancer, cryptorchidism, inguinal hernia, testicular atrophy and genital malformations: case-control studies in Denmark. Cancer Causes Control 1996;7:264-274. EBM IIa.
    http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8740739&dopt=Abstract

10. Dieckmann KP, Pichlmeier U. The prevalence of familial testicular cancer. Cancer 1997;80:1954-1960. EBM IIb.
    http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9366298&dopt=Abstract

11. Forman D, Oliver RT, Brett AR, Marsh SG, Moses JH, Bodmer JG, Chilvers CE, Pike MC. Familial testicular cancer: a report of the UK family register, estimation of risk and a HLA class 1 sib-pair analysis. Br J Cancer 1992;65:255-262. EBM IIb.
    http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1739626&dopt=Abstract

12. Westergaard T, Olsen JH, Frisch M, Kroman N, Nielsen JW, Melbye M. Cancer risk in fathers and brothers of testicular cancer patients in Denmark. A population based study. Int J Cancer 1996;66:627-631. EBM IIb.
    http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8647624&dopt=Abstract

13. Jones A, Fergus JN,Chapman J, Houghton L. Is surveillance for stage I germ cell tumours of the testis appropiate outside a specialist centre? BJU Int 1999;84:79-84. EBM III.
    http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10444129&dopt=Abstract

14. Collette L, Sylvester RJ, Stenning SP, Fossa SD, Mead GM, de Wit R, de Mulder PH, Neymark N, Lallemand E, Kaye SB. Impact of the treating institution on survival of patients with "poor-prognosis" metastatic non-seminoma. European Organization for Research and Treatment of Cancer Genitourinary Tract Cancer Collaborative Group and the Medical Research Council Testicular Working Party. J Natl Cancer Inst 1999;91:839-846. EBM III.
    http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10340903&dopt=Abstract

15. Laguna MP, Pizzocaro G, Klepp O, Algaba F, Kisbenedek L, Leiva O: EAU Working Group on Oncological Urology. EAU guidelines on testicular cancer. Eur Urol 2001;40:102-110.
    http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11528185&query_hl=35

16. Schmoll HJ, Souchon R, Krege S, Albers P, Beyer J, Kollmannsberger C, Fossa SD, Skakkebaek NE, de Wit R, Fizazi K, Droz JP, Pizzocaro G, Daugaard G, de Mulder PH, Horwich A, Oliver T, Huddart R, Rosti G, Paz Ares L, Pont O, Hartmann JT, Aass N, Algaba F, Bamberg M, Bodrogi I, Bokemeyer C, Classen J, Clemm S, Culine S, de Wit M, Derigs HG, Dieckmann KP, Flasshove M, Garcia del Muro X, Gerl A, Germa-Lluch JR, Hartmann M, Heidenreich A, Hoeltl W, Joffe J, Jones W, Kaiser G, Klepp O, Kliesch S, Kisbenedek L, Koehrmann KU, Kuczyk M, Laguna MP, Leiva O, Loy V, Mason MD, Mead GM, Mueller RP, Nicolai N, Oosterhof GO, Pottek T, Rick O, Schmidberger H, Sedlmayer F, Siegert W, Studer U, Tjulandin S, von der Maase H, Walz P, Weinknecht S, Weissbach L, Winter E, Wittekind C; European Germ Cell Cancer Consensus Group. European consensus on diagnosis and treatment of germ cell cancer: a report of the European Germ Cell Cancer Consensus Group (EGCCCG). Ann Oncol 2004;15:1377-1399.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15319245&query_hl=38

17. Shelley MD, Burgon K, Mason MD. Treatment of testicular germ-cell cancer: a Cochrane evidence-based systematic review. Cancer Treat Rev 2002;28:237-253.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12435371&dopt=Abstract

18. Krege S, Souchon R, Schmoll HJ; German Testicular Cancer Study Group. Interdisciplinary consensus on diagnosis and treatment of testicular germ cell tumors: result of an update conference on evidence-based medicine (EBM). Eur Urol 2001;40:372-391.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11713391&dopt=Abstract

19. Deutsche Krebsgesellschaft: [Evidence based guideline for the diagnosis and therapy of testicular tumours (EBM).] In: Souchon R, Schmoll HJ, Krege S, for the German Testicular Cancer Study Group editors. [Quality assurance in oncology 1st ed.] Munich, Berne, Wien, New York: Zuckschwerdt, 2002. [German]

20. The Royal College of Radiologists' clinical oncology network in partnership with Scottish Intercollegiate Network 2000: guidelines on the management of adult testicular germ cell tumours. Clin Oncol 2000;12:S173-S210.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11315727&dopt=Abstract

21. US Department of Health and Human Services. Public Health Service, Agency for Health Care Policy and Research 1992, pp 115-127.
http://www.ahrq.gov/clinic/epcindex.htm#methodology

22. Comiter CU, Benson CJ, Capelouto CC, Kantoff P, Shulman L, Richie JP, Loughlin KR. Nonpalpable intratesticular masses detected sonographically. J Urol 1995;154:1367-1369. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=7658540&query_hl=10

23. Rholl KS, Lee JKT, Ling D, Heiken JP, Glazer HS. MR imaging of the scrotum with a high resolution surface coil. Radiology 1987;163:99-103. EBM IIa.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=3547497&dopt=Abstract

24. [Diagnostics and treatment of testicular germ cell tumours]. Guidelines of the Dutch Urological Society. No 14. [Dutch]

25. Segal R, Lukka H, Klotz LH, Eady A, Bestic N, Johnston M; Cancer Care Ontario Practice Guidelines Initiative Genitourinary Cancer Disease Site Group. Surveillance programs for early stage non-seminomatous testicular cancer: a practice guideline. Can J Urol 2001;8:1184-1192.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11268306&dopt=Abstract

26. Klein EA. Tumor markers in testis cancer. Urol Clin North Am 1993;20:67-73.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7679533&dopt=Abstract

27. Javadpour N. The role of biologic markers in testicular cancer. Cancer 1980;45:1755-1761.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=6154517&dopt=Abstract

28. Weissbach L. Organ preserving surgery of malignant germ cell tumors. J Urol 1995;153:90-93. EBM IIb.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7966800&dopt=Abstract

29. Heidenreich A, Weissbach L, Holtl W, Albers P, Kliesch S, Kohrmann KU, Dieckmann KP; German Testicular Cancer Study Group. Organ sparing surgery for malignant germ cell tumor of the testis. J Urol 2001;166:2161-2165. EBM IIb.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11696727&dopt=Abstract

30. Petersen PM , Giwercman A, Daugaard G, Rorth M, Petersen JH, Skakkebaek NE, Hansen SW, von der Maase H. Effect of graded testicular doses of radiotherapy in patients treated for carcinoma-in-situ in the testis. J Clin Oncol 2002;20:1537-1543. EBM IIb.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11896102&dopt=Abstract

31. Classen J, Dieckmann K, Bamberg M, Souchon R, Kliesch S, Kuehn M, Loy V; German Testicular Cancer Study Group. Radiotherapy with 16 Gy may fail to eradicate testicular intraepithelial neoplasia: preliminary communication of a dose-reduction trial of the German Testicular Cancer Study Group. Br J Cancer 2003;88:828-831. EBM IIb.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12644817&query_hl=1

32. WHO histological classification of testis tumours. In: Eble JN, Sauter G, Epstein JI, Sesterhenn IA, editors. *Pathology & genetics: tumours of the urinary system and male genital organs.* Lyon: IARC Press, 2004, pp 218, 250-262.

33. Leibovitch I, Foster RS, Kopecky KK, Donohue JP. Improved accuracy of computerized tomography based clinical staging in low stage nonseminomatous germ cell cancer using size criteria of retroperitoneal lymph nodes. J Urol 1995;154:1759-1763. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7563341&dopt=Abstract

34. Ellis JH, Blies JR, Kopecky KK, Klatte EC, Rowland RG, Donohue JP. Comparison of NMR and CT imaging in the evaluation of metastatic retroperitoneal lymphadenopathy from testicular carcinoma. J Comput Assist Tomogr 1984;8:709-719.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=6539790&dopt=Abstract

35. See WA, Hoxie L. Chest staging in testis cancer patients: imaging modality selection based upon risk assessment as determined by abdominal computerized tomography scan results. J Urol 1993; 150:874-878. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8345604&dopt=Abstract

36. Cremerius U, Wildberger JE, Borchers H, Zimny M, Jakse G, Gunther RW, Buell U. Does positron emission tomography using 18-fluoro-2-deoxyglucose improve clinical staging of testicular cancer? - results of a study in 50 patients. Urology 1999;54:900-904. EBM IIb.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10565755&dopt=Abstract

37. Albers P, Bender H, Yilmaz H, Schoeneich G, Biersack HJ, Mueller SC. Positron emission tomography in the clinical staging of patients with stage I and II testicular germ cell tumours. Urology 1999;53:808-811. EBM IIb.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10197862&dopt=Abstract

38. De Santis M, Bokemeyer C, Becherer A, Stoiber F, Oechsle K, Kletter K, Dohmen BM, Dittrich C, Pont J. Predictive impact of 2-18fluoro-2-deoxy-D-glucose positron emission tomography for residual postchemotherapy masses in patients with bulky seminoma. J Clin Oncol 2001;19:3740-3744. EBM IIb.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11533096&dopt=Abstract

39. Spermon JR, De Geus-Oei LF, Kiemeney LA, Witjes JA, Oyen WJ. The role of (18)fluoro-2-deoxyglucose positron emission tomography in initial staging and re-staging after chemotherapy for testicular germ cell tumours. BJU Int 2002;89:549-556. EBM IIb.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11942962&dopt=Abstract

40. Sobin LH, Wittekind Ch, editors. UICC: TNM classification of malignant tumours. 6th ed. Wiley-Liss, 2002.
www.wiley.com/go/tnm

41.   International Germ Cell Cancer Collaborative Group. International Germ Cell Consensus Classification: a prognostic factor-based staging system for metastatic germ cell cancers. J Clin Oncol 1997;15:594-603. EBM Ia, IIa, IIb, III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9053482&dopt=Abstract

42.   Skakkebaek EN. Possible carcinoma-in-situ of the testis. Lancet 1972;2:516-517. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=4115573&dopt=Abstract

43.   Dieckmann KP, Loy V. Prevalence of contralateral testicular intraepithelial neoplasia in patients with testicular germ cell neoplasms. J Clin Oncol 1996;14:3126-3132. EBM IIb.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=8955658&query_hl=3

44.   Harland SJ, Cook PA, Fossa SD, Horwich A, Mead GM, Parkinson MC, Roberts JT, Stenning SP. Intratubular germ cell neoplasia of contralateral testis in testicular cancer: defining high risk group. J Urol 1998;160:1353-1357. EBM IIa.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=9751353&query_hl=15.

45.   De Santis M, Albrecht W, Holtl W, Pont J. Impact of cytotoxic treatment on long-term fertility in patients with germ-cell cancer. Int J Cancer 1999;83:864-865. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10597213&dopt=Abstract

46.   Jacobsen KD, Fossa SD, Bjoro TP, Aass N, Heilo A, Stenwig AE. Gonadal function and fertility in patients with bilateral testicular germ cell malignancy. Eur Urol 2002;42:229-238. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12234507&dopt=Abstract

47.   Kliesch S, Behre HM, Jurgens H, Nieschlag E. Cryopreservation of semen from adolescent patients with malignancies. Med Pediatr Oncol 1996;26:20-27. EBM IV.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7494508&dopt=Abstract

48.   Giwercman A, von der Maase H, Rorth M, Skakkebaek NE. Semen quality in testicular tumour and CIS in the contralateral testis. Lancet 1993;341:384-385. EBM IV.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8094162&dopt=Abstract

49.   Kliesch S, Bergmann M, Hertle L, Nieschlag E, Behre HM. Semen parameters and testicular pathology in men with testicular cancer and contralateral carcinoma in situ or bilateral testicular malignancies. Hum Reprod 1997;12:2830-2835. EBM IV.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9455863&dopt=Abstract

50.   Spermon JR, Kiemeney LA, Meuleman EJ, Ramos L, Wetzels AM, Witjes JA. Fertility in men with testicular germ cell tumors. Fertil Steril 2003; 79(Suppl 3):1543-1549. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12801557&dopt=Abstract

51.   Nieschlag E, Behre HM. Pharmacology and clinical use of testosterone. In: Nieschlag E, Behre HM, editors. *Testosterone - action, deficiency, substitution.* Berlin, Heidelberg, New York: Springer, 1999, pp 92-114. EBM Ib-IV.

52.   Zagars GK. Management of stage I seminoma: radiotherapy. In: Horwich A, editor. *Testicular cancer: investigation and management.* London: Chapman & Hall Medical, 1999, p 99.

53.   Fossa SD, Horwich A, Russell JM, Roberts JT, Cullen MH, Hodson NJ, Jones WG, Yosef H, Duchesne GM, Owen JR, Grosch EJ, Chetiyawardana AD, Reed NS, Widmer B, Stenning SP. Optimal planning target volume for stage I testicular seminoma: a Medical Research Council randomized trial. J Clin Oncol 1999;17:1146-1154. EBM Ib.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10561173&dopt=Abstract&itool=iconabstr

54.   Jones WG, Fossa SD, Mead GM, Roberts JT, Sokal M, Horwich A, Stenning SP. Randomized trial of 30 versus 20 Gy in the adjuvant treatment of stage I testicular seminoma: a report on Medical Research Council Trial TE18, European Organisation of Research and Treatment of Cancer Trial 30942 (ISRCTN18525328). J Clin Oncol 2005;25:1200-1208. EBM Ib.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15718317&query_hl=6

55. Melchior D, Hammer P, Fimmers R, Schuller H, Albers P. Long term results and morbidity of paraaortic compared with paraaortic and iliac adjuvant radiation in clinical stage I seminoma. Anticancer Res 2001;21:2989-2993. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11712799&dopt=Abstract&itool=iconabstr

56. Livsey JE, Taylor B, Mobarek N, Cooper RA, Carrington B, Logue PJ. Patterns of relapse following radiotherapy for stage I seminoma of the testis: implications for follow-up. Clin Oncol (R Coll Radiol) 2001;13:296-300. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11554630&dopt=Abstract&itool=iconabstr

57. Van Leeuwen FE, Stiggelbout AM, van den Belt-Dusebout AW, Noyon R, Eliel MR, van Kerkhoff EH, Delemarre JF, Somers R. Second cancer risk following testicular cancer: a follow-up study of 1909 patients. Clin Oncol 1993;11:415-424.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8445415&dopt=Abstract&itool=iconabstr

58. Travis LB, Curtis RE, Storm H, Hall P, Holowaty E, Van Leeuwen FE, Kohler BA, Pukkala E, Lynch CF, Andersson M, Bergfeldt K, Clarke EA, Wiklund T, Stoter G, Gospodarowicz M, Sturgeon J, Fraumeni JF Jr, Boice JD Jr. Risk of second malignant neoplasms among long-term survivors of testicular cancer. J Natl Cancer Inst 1997;89:1429-1439. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9326912&dopt=Abstract&itool=iconabstr

59. Zagars GK, Ballo MT, Lee AK, Strom SS. Mortality after cure of testicular seminoma. J Clin Oncol 2004; 22:640-647.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14726503&query_hl=13

60. Horwich A, Bell J. Mortality and cancer incidence following treatment for seminoma of the testis. Radiother Oncol 1994;30:193-198. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8209001&dopt=Abstract&itool=iconabstr

61. Sharda N, Kinsella T, Ritter M. Adjuvant radiation versus observation: a cost analysis of alternate management schemes in early stage testicular seminoma. J Clin Oncol 1996;14:2933-2939. EBM IIb.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8918490&dopt=Abstract&itool=iconabstr

62. Francis R, Bower M, Brunstrom G, Holden L, Newlands ES, Rustin GJS, Seckl MJ. Surveillance for stage I testicular germ cell tumors: results and cost benefit analysis of management options. Eur J Cancer 2000;36:1925-1932. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11000572&dopt=Abstract&itool=iconabstr

63. Warde P, Gospodarowicz M, Panzarella T, Catton C, Sturgeon J, Moore M, Jewett M. Issues in the management of stage I testicular seminoma. Int J Radiat Oncol Biol Phys 1997;39:S156.

64. Warde P, Specht L, Horwich A, Oliver T, Panzarella T, Gospodarowicz M, von der Maase H. Prognostic factors for relapse in stage I seminoma managed by surveillance: a pooled analysis. J Clin Oncol 2002;20:4448-4452. EBM IIa.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12431967&dopt=Abstract

65. Oliver RT, Mason M, von der Maase H et al., on behalf of the MRC Testis Tumor Group and the EORTC GU group. A randomised comparison of single agent carboplatin with radiotherapy in the adjuvant treatment of stage I seminoma of the testis, following orchidectomy: MRC TE19/EORTC 30982. Proc ASCO 2004;23:385. Abstract 4517. EBM Ib.

66. Aparicio J, Garcia del Muro X, Maroto P, Paz-Ares L, Alba E, Saenz A, Terrasa J, Barnadas A, Almenar D, Arranz JA, Sanchez M, Fernandez A, Sastre J, Carles J, Dorca J, Guma J, Yuste AL, Germa JR; Spanish Germ Cell Cancer Cooperative Group (GG). Multicenter study evaluating a dual policy of postorchiectomy surveillance and selective adjuvant single-agent carboplatin for patients with clinical stage I seminoma. Ann Oncol 2003;14:867-872.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12796024&dopt=Abstract&itool=iconabstr

67. Krege S, Kalund G, Otto T, Goepel M, Rubben H. Phase II study: adjuvant single-agent carboplatin therapy for clinical stage I seminoma. Eur Urol 1997;31:405-407. EBM IIb.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9187898&dopt=Abstract

68.   Dieckmann KP, Krain J, Kuster J, Bruggeboes B. Adjuvant carboplatin treatment for seminoma clinical stage I. J Cancer Res Clin Oncol 1996;122:63-66. EBM IIb.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8543595&dopt=Abstract

69.   Warszawski N, Schmucking M. Relapses in early-stage testicular seminoma: radiation therapy versus retroperitoneal lymphadenectomy. Scan J Urol Nephrol 1997;31:335-339. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9290165&dopt=Abstract&itool=iconabstr

70.   Albers P, Siener R, Kliesch S, Weissbach L, Krege S, Sparwasser C, Schulze H, Heidenreich A, de Riese W, Loy V, Bierhoff E, Wittekind C, Fimmers R, Hartmann M; German Testicular Cancer Study Group. Risk factors for relapse in clinical stage I nonseminomatous testicular germ cell tumors: results of the German Testicular Cancer Study Group Trial. J Clin Oncol 2003;21:1505-1512. EBM IIa-Ib.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12697874&dopt=Abstract

71.   Klepp O, Olsson AM, Henrikson H, Aass N, Dahl O, Stenwig AE, Persson BE, Cavallin-Stahl E, Fossa SD, Wahlqvist L. Prognostic factors in clinical stage I nonseminomatous germ cell tumors of the testis: multivariate analysis of a prospective multicenter study. J Clin Oncol 1990;8:509-518. EBM IIa.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1689773&dopt=Abstract&itool=iconabstr

72.   Freedman LS, Parkinson MC, Jones WG, Oliver RT, Peckham MJ, Read G, Newlands ES, Williams CJ. Histopathology in the prediction of patients with stage I testicular teratoma treated by orchiectomy alone. Lancet 1987;ii:294-298.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=2886764&dopt=Abstract&itool=iconabstr

73.   Klepp O, Dahl O, Flodgren P, Stierner U, Olsson AM, Oldbring J,Nilsson S, Daehlin L, Tornblom M, Smaland R, Starkhammar H, Abramsson L, Wist E, Raabe N, Edekling T, Cavallin-Stahl E. Risk-adapted treatment of clinical stage 1 non-seminoma testis cancer. Eur J Cancer 1997;33:1038-1044. EBM IIa.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9376184&dopt=Abstract&itool=iconabstr

74.   Kratzik C, Holtl W, Albrecht W et al. Risk adapted management for NSGCT stage I: long-term results of a multicenter study. J Urol 1996;155:547A. Abstract.

75.   Ondrus D, Matoska J, Belan V. Prognostic factors in clinical stage I nonseminomatous germ cell testicular tumors: rationale for different risk-adapted treatment. Eur Urol 1998;33:562-566. EBM IIa,IIb.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9743698&dopt=Abstract&itool=iconabstr

76.   Read G, Stenning SP, Cullen MH, Parkinson MC, Horwich A, Kaye SB, Cook PA. Medical Research Council prospective study of surveillance for stage I testicular teratoma. J Clin Oncol 1992;10:1762-1768. EBM IIb.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1403057&dopt=Abstract&itool=iconabstr

77.   Cullen MH, Stenning SP, Parkinson MC, Fossa SD, Kaye SB, Horwich AH, Harland SJ, Williams MV, Jakes R. Short-course adjuvant chemotherapy in high-risk stage I nonseminomatous germ cell tumours of the testis: a Medical Research Council report. J Clin Oncol 1996;14:1106-1113. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8648364&dopt=Abstract&itool=iconabstr

78.   Oliver RTD, Raja MA, Ong J, Gallagher CJ. Pilot study to evaluate impact of a policy of adjuvant chemotherapy for high risk stage I malignant teratoma on overall relapse rate of stage I cancer patients. J Urol 1992;148:1453-1456. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1279211&dopt=Abstract&itool=iconabstr

79.   Studer UE, Fey MF, Calderoni A. Adjuvant chemotherapy after orchiectomy in high risk patients with clinical stage I nonseminomatous testicular cancer. Eur Urol 1993;23:444-449. EBM IIb.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7687549&dopt=Abstract&itool=iconabstr

80.   Pont J, Albrecht W, Postner G, Sellner F, Angel K, Holtl W. Adjuvant chemotherapy for high risk clinical stage I nonseminomatous testicular germ cell cancer: long-term results of a prospective trial. J Clin Oncol 1996;14:441-448. EBM IIa.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8636755&dopt=Abstract&itool=iconabstr

81. Colls BM, Harvey VJ, Skelton L, Frampton CM, Thompson PI, Bennett M, Perez DJ, Dady PJ, Forgeson GV, Kennedy IC. Late results of surveillance of clinical stage I nonseminoma germ cell testicular tumours: 17 years' experience in a national study in New Zealand. B J Urol Int 1999;83:76-82. EBM IIb.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10233456&dopt=Abstract&itool=iconabstr

82. Spermon JR, Roeleveld TA, van der Poel HG, Hulsbergen-van de Kaa CA, Ten Bokkel-Huinink WW, van de Vijver M, Witjes JA, Horenblas S. Comparison of surveillance and retroperitoneal lymph node dissection in stage I nonseminomatous germ cell tumors. Urology 2002;59:923-929. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12031382&dopt=Abstract&itool=iconabstr

83. Hendry WF, Norman A, Nicholls J, Dearnaley DP, Peckham MJ, Horwich A. Abdominal relapse in stage 1 nonseminomatous germ cell tumours of the testis managed by surveillance or with adjuvant chemotherapy. BJU Int 2000;86:89-93. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10886090&dopt=Abstract&itool=iconabstr

84. Lowe BA. Surveillance versus nerve-sparing retroperitoneal lymphadenectomy in stage I germ cell tumors. Urol Clin North Am 1993;20:75-83. EBM IIb.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8381999&dopt=Abstract

85. Sternberg CN. Role of primary chemotherapy in stage I and low-volume stage II nonseminomatous germ-cell testis tumors. Urol Clin North Am 1993;20:93-109. EBM IIb.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8382000&dopt=Abstract

86. Gels ME, Hoekstra HJ, Sleijfer DT, Marrink J, de Bruijn HW, Molenaar WM, Freling NJ, Droste JH, Schraffordt Koops H. Detection of recurrence in patients with clinical stage I nonseminomatous testicular germ cell tumors and consequences for further follow-up: a single-center 10-year experience. J Clin Oncol 1995;13:1188-1194. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7537802&dopt=Abstract

87. Bohlen D, Borner M, Sonntag RW, Fey MF, Studer UE. Long-term results following adjuvant chemotherapy in patients with clinical stage I testicular nonseminomatous malignant germ cell tumors with high risk factors. J Urol 1999;161:1148-1152. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10081858&dopt=Abstract&itool=iconabstr

88. Bohlen D, Burkhard FC, Mills R, Sonntag RW, Studer UE. Fertility and sexual function following orchiectomy and 2 cycles of chemotherapy for stage I high risk nonseminomatous germ cell cancer. J Urol 2001;165:441-444. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11176393&dopt=Abstract&itool=iconabstr

89. Pizzocaro G, Salvioni R, Zanoni F. Unilateral lymphadenectomy in intraoperative stage I nonsemino-matous testis cancer. J Urol 1985;134:485-489. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=2993672&dopt=Abstract&itool=iconabstr

90. Donohue JP, Thornhill JA, Foster RS, Rowland RG, Bihrle R. Retroperitoneal lymphadenectomy for clinical stage A testis cancer (1965-1989): modifications of technique and impact on ejaculation. J Urol 1993;149:237-243. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8381190&dopt=Abstract&itool=iconabstr

91. Foster RS, Roth BJ. Clinical stage I nonseminoma: surgery versus surveillance. Semin Oncol 1998; 25:145-153.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9562447&dopt=Abstract&itool=iconabstr

92. Donohue JP, Thornhill JA, Foster RS, Rowland RG, Bihrle R. Clinical stage B nonseminomatous germ cell testis cancer: the Indiana University experience using routine primary retroperitoneal lymph node dissection. Eur J Cancer 1995;31A:1599-1604. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7488408&dopt=Abstract&itool=iconabstr

93. Richie JP, Kantoff PW. Is adjuvant chemotherapy necessary for patients with stage 1B testicular cancer? J Clin Oncol 1991;9:1393-1398.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=2072143&dopt=Abstract&itool=iconabstr

94. Pizzocaro G, Monfardini S. No adjuvant chemotherapy in selected patients with pathological stage II nonseminomatous germ cell tumors of the testis. J Urol 1984;131:677-680. EBM IIa.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=6200611&dopt=Abstract&itool=iconabstr

95. McLeod DG, Weiss RB, Stablein DM, Muggia FM, Paulson DF, Ellis JH, Spaulding JT, Donohue JP. Staging relationships and outcome in early stage testicular cancer: a report from the Testicular Cancer Intergroup Study. J Urol 1991;145:1178-1183. EBM IIa.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1851890&dopt=Abstract

96. Williams SD, Stablein DM, Einhorn LH, Muggia FM, Weiss RB, Donohue JP, Paulson DF, Brunner KW, Jacobs EM, Spaulding JT. Immediate adjuvant chemotherapy versus observation with treatment at relapse in pathological stage II testicular cancer. N Engl J Med 1987;317:1433-1438. EBM Ib.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=2446132&dopt=Abstract&itool=iconabstr

97. Heidenreich A, Albers P, Hartmann M, Kliesch S, Kohrmann KU, Krege S, Lossin P, Weissbach L; German Testicular Cancer Study Group. Complications of primary nerve sparing retroperitoneal lymph node dissection for clinical stage I nonseminomatous germ cell tumors of the testis: experience of the German Testicular Cancer Study Group. J Urol 2003;169:1710-1714. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12686815&dopt=Abstract&itool=iconabstr

98. Bianci G, Beltrami P, Giusti G. Unilateral laparoscopic lymph node dissection for clinical stage I nonseminomatous germ cell testicular neoplasm. Eur Urol 1998;33:190-194. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9519363&dopt=Abstract&itool=iconabstr

99. Rassweiler JJ, Frede T, Lenz E, Seemann O, Alken P. Long-term experience with laparoscopic retroperitoneal lymph node dissection in the management of low-stage testis cancer. Eur Urol 2000;37:251-260. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10720848&dopt=Abstract&itool=iconabstr

100. Janetschek G, Hobisch A, Peschel R, Hittmair A, Bartsch G. Laparoscopic retyroperitoneal lymph node dissection for clinical stage I non-seminomatous testicular carcinoma: long-term outcome. J Urol 2000;163:1793-1796. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10799184&dopt=Abstract&itool=iconabstr

101. LeBlanc E, Caty A, Dargent D, Querleu D, Mazeman E. Extraperitoneal laparoscopic para-aortic lymph node dissection for early stage nonseminomatous germ cell tumors of the testis with introduction of a nerve sparing technique: description and results. J Urol 2001;165:89-92. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11125371&dopt=Abstract&itool=iconabstr

102. Pizzocaro G, Nicolai N, Salvioni R. Marker positive clinical stage I non seminomatous germ cell tumors (NSGCT) of the testis: which primary therapy? J Urol 1996;155(Suppl):328A.

103. Davis BE, Herr HW, Fair WR, Bosl GJ. The management of patients with nonseminomatous germ cell tumors of the testis with serologic disease only after orchiectomy. J Urol 1994;152:111-113. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7515445&dopt=Abstract&itool=iconabstr

104. Saxman SB, Nichols CR, Foster RS, Messemer JE, Donohue JP, Einhorn LH. The management of patients with clinical stage I nonseminomatous testicular tumors and persistently elevated serologic markers. J Urol 1996;155:587-589. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=8558665&query_hl=13

105. Classen J, Schmidberger H, Meisner C, Souchon R, Sautter-Bihl ML, Sauer R, Weinknecht S. Radiotherapy for stages IIA/B testicular seminoma: final report of a prospective multicenter clinical trial. J Clin Oncol 2003;21:1101-1106. EBM IIb.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12637477&query_hl=30

106. Warde P, Gospodarowicz M, Panzarella T, Catton C, Sturgeon J, Moore M, Jewett M. Management of stage II seminoma. J Clin Oncol 1998;16:290-294.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=Abstract&list_uids=9440755&query_hl=94&itool=pubmed_DocSum

107. O'Sullivan JM, Huddart RA, Norman AR, Nicholls J, Dearnaley DP, Horwich A. Predicting the risk of bleomycin lung toxicity in patients with germ-cell tumours. Ann Oncol 2003;14:91-96.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12488299&query_hl=82&itool=pubmed_docsum

108. Weissbach L, Bussar-Maatz R, Fletchner H, Pichlmeier U, Hartmann M, Keller L. RPLND or primary chemotherapy in clinical stage IIA/B nonseminomatous germ cell tumors. Results of a prospective multicenter trial including quality of life assessment. Eur Urol 2000;37:582-594.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10765098&dopt=Abstract

109. Horwich A, Norman A, Fisher C, Hendry WF, Nicholls J, Dearnaley DP. Primary chemotherapy for stage II nonseminomatous germ cell tumors of the testis. J Urol 1994;151:72-77; discussion 77-78.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=8254836&query_hl=18

110. Saxman S, Finch D, Gonin R, Einhorn LH. Long-term follow-up of a phase III study of three versus four cycles of bleomycin, etoposide and cisplatin in favorable-prognosis germ-cell tumors: the Indiana University Experience. J Clin Oncol 1998;16:702-706. EBM Ib.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9469360&dopt=Abstract

111. De Wit R, Stoter G, Kaye SB, Sleijfer DT, Jones WG, ten Bokkel Huinink WW, Rea LA, Collette L, Sylvester R. Importance of bleomycin in combination chemotherapy for good-prognosis testicular nonseminoma: a randomized study of the European Organization for Research and Treatment of Cancer Genitourinary Tract Cancer Cooperative Group. J Clin Oncol 1997;15:1837-1843. EBM Ib.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9164193&dopt=Abstract

112. Horwich A, Sleijfer DT, Fossa SD, Kaye SB, Oliver RT, Cullen MH, Mead GM, de Wit R, de Mulder PH, Dearnaley DP, Cook PA, Sylvester RJ, Stenning SP. Randomized trial of bleomycin, etoposide and cisplatin compared with bleomycin, etoposide and carboplatin in good-prognosis metastatic nonseminomatous germ cell cancer: a multi-institutional Medical Research Council/European Organization for Research and Treatment of Cancer trial. J Clin Oncol 1997;15:1844-1852. EBM Ib.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9164194&dopt=Abstract

113. De Wit R, Roberts JT, Wilkinson PM, de Mulder PH, Mead GM, Fossa SD, Cook P, de Pryck L, Stenning S, Collette L. Equivalence of three or four cycles of bleomycin, etoposide, and cisplatin chemotherapy and of a 3- or 5-day schedule in good-prognosis germ cell cancer: a randomized study of the European Organization for Research and Treatment of Cancer Genitourinary Tract Cancer Cooperative Group and the Medical Research Council. J Clin Oncol 2001;19:1629-1640. EBM Ib.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11250991&dopt=Abstract

114. Xiao H, Mazumdar M, Bajorin DF, Sarosdy M, Vlamis V, Spicer J, Ferrara J, Bosl GJ, Motzer RJ. Long-term follow-up of patients with good-risk germ cell tumors treated with etoposide and cisplatin. J Clin Oncol 1997;15:2553-2558. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9215824&dopt=Abstract

115. Fossa SD, Kaye SB, Mead GM, Cullen M, de Wit R, Bodrogi I, van Groeningen CJ, de Mulder PH, Stenning S, Lallemand E, de Pryck L, Collette L. Filgastrim during combination chemotherapy of patients with poor prognosis metastatic germ cell malignancy. European Organization for Research and Treatment of Cancer, Genito-Urinary Group, and the Medical Research Council Testicular Cancer Working Party. J Clin Oncol 1998;16:716-724. EBM IIa.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9469362&dopt=Abstract

116. Bokemeyer C, Kuczyk MA, Köhne H, Einsele H, Kynast B, Schmoll HJ. Hematopoetic growth factors and treatment of testicular cancer: biological interactions, routine use and dose intensive chemotherapy. Ann Hematol 1996;72:1-9. EBM IIa.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8605273&dopt=Abstract

117. De Wit R, Stoter G, Sleijfer DT, Neijt JP, ten Bokkel Huinink WW, de Pryck L, Collette L, Sylvester R. Four cycles of BEP vs four cycles of VIP in patients with intermediate-prognosis metastatic testicular non-seminoma: a randomized study of the EORTC Genitourinary Tract Cancer Cooperative Group. European Organization for Research and Treatment of Cancer. Br J Cancer 1998;78:828-832. EBM Ib.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9743309&dopt=Abstract

118. De Wit R, Louwerens M, de Mulder PH, Verweij J, Rodenhuis S, Schornagel J. Management of intermediate-prognosis germ-cell cancer: results of a phase I/II study of Taxol-BEP. Int J Cancer 1999;83:831-833. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10597204&dopt=Abstract

119. Nichols CR, Catalano PJ, Crawford ED, Vogelzang NJ, Einhorn LH, Loehrer PJ. Randomized comparison of cisplatin and etoposide and either bleomycin or ifosfamide in treatment of advanced disseminated germ cell tumors: an Eastern Cooperative Oncology Group, Southwest Oncology Group, and Cancer and Leukaemia Group B Study. J Clin Oncol 1998;16:1287-1293. EBM Ib.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9552027&dopt=Abstract

120. Motzer RJ, Mazumdar M, Bajorin DF, Bosl GJ, Lyn P, Vlamis V. High-dose carboplatin, etoposide, and cyclophosphamide with autologous bone marrow transplantation in first-line therapy for patients with poor-risk germ cell tumors. J Clin Oncol 1997;15:2546-2552. EBM IIb.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9215823&dopt=Abstract

121. Bokemeyer C, Kollmannsberger C, Meisner C, Harstrick A, Beyer J, Metzner B, Hartmann JT, Schmoll HJ, Einhorn L, Kanz L, Nichols C. First-line high-dose chemotherapy compared with standard-dose PEB/VIP chemotherapy in patients with advanced germ cell tumors: a multivariate and matched-pair analysis. J Clin Oncol 1999;17:3450-3456. EBM IIb.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10550141&dopt=Abstract

122. Kaye SB, Mead GM, Fossa SD, Cullen M, de Wit R, Bodrogi I, van Groeningen C, Sylvester R, Collette L, Stenning S, de Pryck L, Lallemand E, de Mulder P. Intensive induction-sequential chemotherapy with BOP/VIP-B compared with treatment with BEP/EP for poor prognosis metastatic germ cell tumor: a randomized Medical Research Council/European Organization for Research and Treatment of Cancer study. J Clin Oncol 1998;16:692-701. EBM IIb.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9469359&dopt=Abstract

123. Gerl A, Clemm C, Lamerz R, Mann K, Wilmanns W. Prognostic implications of tumor marker analysis in non-seminomatous germ cell tumours with poor prognosis metastatic disease. Eur J Cancer 1993;29A:961-965. EBM IIa.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7684597&dopt=Abstract

124. Murphy BA, Motzer RJ, Mazumdar M, Vlamis V, Nisselbaum J, Bajorin D, Bosl GJ. Serum tumor markers decline is an early predictor of treatment outcome in germ cell tumor patients treated with cisplatin and ifosfamide salvage chemotherapy. Cancer 1994;73:2520-2526. EBM IIa.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7513603&dopt=Abstract

125. Andre F, Fizazi K, Culine S, Droz J, Taupin P, Lhomme C, Terrier-Lacombe M, Theodore C. The growing teratoma syndrome: results of therapy and long-term follow-up of 33 patients. Eur J Cancer 2000; 36:1389-1394. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10899652&dopt=Abstract

126. De Wit R, Collette L, Sylvester R, de Mulder PH, Sleyfer DT, ten Bokkel Huinink WW, Kaye SB, van Oosterom AT, Boven E, Stoter G. Serum alpha-fetoprotein surge after the initiation of chemotherapy for non-seminomatous testicular cancer has an adverse prognostic significance. Br J Cancer 1998;78:1350-1355. EBM IIb.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9823978&dopt=Abstract

127. Zon RT, Nichols C, Einhorn LH. Management strategies and outcomes of germ cell tumor patients with very high human chorionic gonadotropin levels. J Clin Oncol 1998;16:1294-1297. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9552028&dopt=Abstract

128. Fossa AD, Stenning SP, Gerl A, Horwich A, Clark PI, Wilkinson PM, Jones WG, Williams MV, Oliver RT, Newlands ES, Mead GM, Cullen MH, Kaye SB, Rustin GJ, Cook PA. Prognostic factors in patients progressing after cisplatin-based chemotherapy for malignant non-seminomatous germ cell tumours. Br J Cancer 1999;80:1392-1399. EBM IIb.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10424741&dopt=Abstract

129. Herr HW, Bosl G. Residual mass after chemotherapy for seminoma: changing concepts of management. J Urol 1987;137:1234-1235. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=2438431&dopt=Abstract

130. Loehrer PJ Sr, Birch R, Williams SD, Greco FA, Einhorn LH. Chemotherapy of metastatic seminoma: the SouthEastern Cancer Study Group Experience. J Clin Oncol 1997;15:1212-1220. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=2442317&dopt=Abstract

131. Motzer R, Bosl G, Heelan R, Fair W, Whitmore W, Sogani P, Herr H, Morse M. Residual mass: an indication for further therapy in patients with advanced seminoma following systemic chemotherapy. J Clin Oncol 1987;5:1064-1070. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=3598610&dopt=Abstract

132. Peckham MJ, Horwich A, Hendry WF. Advanced seminoma treatment with cisplatinum based combination chemotherapy or carboplatin (JM8). Br J Cancer 1985;52:7-13. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=3893507&dopt=Abstract

133. Duchesne GM, Stenning SP, Aass N, Mead GM, Fossa SD, Oliver RT, Horwich A, Read G, Roberts IT, Rustin G, Cullen MH, Kaye SB, Harland SJ, Cook PA. Radiotherapy after chemotherapy for metastatic seminoma - a diminishing role. Eur J Cancer 1997;33:829-835. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9291801&dopt=Abstract

134. Mosharafa AA, Foster RS, Leibovich BC, Bihrle R, Donahue JP. Is the post-chemotherapy resection of seminomatous elements associated with higher acute morbidity? J Urol 2002;167:172. Abstract 692. EBM III.

135. De Santis M, Becherer A, Bokemeyer C, Stoiber F, Oechsle K, Sellner F, Lang A, Kletter K, Dohmen BM, Dittrich C, Pont J. 2-18fluoro-deoxy-D-glucose positron emission tomography is a reliable predictor for viable tumor in postchemotherapy seminoma: an update of the prospective multicentric SEMPET trial. J Clin Oncol 2004; 22:1034-1039. EBM IIb.

136. Becherer A, Santis MD, Karanikas G, Szabo M, Bokemeyer C, Dohmen BM, Pont J, Dudczak R, Dittrich C, Kletter K. FDG PET is superior to CT in the prediction of viable tumour in post-chemotherapy seminoma residuals. Eur J Radiol 2005;54:284-288. EBM IIb.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15837411&query_hl=8

137. Fossa SD, Ous S, Lien HH, Stenwig AE. Post-chemotherapy lymph node histology in radiologically normal patients with metastatic nonseminomatous testicular cancer. J Urol 1989;141:557-559. EBM IIb.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=2918591&dopt=Abstract

138. Toner GC, Panicek DM, Heelan RT, Geller NL, Lin SY, Bajorin D, Motzer RJ, Scher HI, Herr HW, Morse MJ et al. Adjunctive surgery after chemotherapy for nonseminomatous germ cell tumors: recommendations for patient selection. J Clin Oncol 1990;8:1683-1694. EBM IIb.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=2170590&dopt=Abstract

139. Donohue JP, Rowland RG, Kopecky K, Steidle CP, Geier G, Ney KG, Einhorn L, Williams S, Loehrer P. Correlation of computerized tomographic changes and histological findings in 80 patients having radical retroperitoneal lymph node dissection after chemotherapy for testis cancer. J Urol 1987;137:1176-1179. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=3035236&dopt=Abstract

140. Richie JP. The surgical management of advanced abdominal disease. Semin Urol 1984;2:238-243.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=6505446&dopt=

141.   Stomper PC, Fung CY, Socinski MA, Jochelson MS, Garnick MB, Richie JP. Detection of
        retroperitoneal metastases in early-stage nonseminomatous testicular cancer: analysis of different CT
        criteria. Am J Roentgenol 1987;149:1187-1190. EBM III.
        http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=2825494&dopt=
        Abstract

142.   Aprikian AG, Herr HW, Bajorin DF, Bosl GJ. Resection of post-chemotherapy residual masses and
        limited retroperitoneal lymphadenectomy in patients with metastatic testicular nonseminomatous germ
        cell tumors. Cancer 1994;74:1329-1334. EBM IIa.
        http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8055456&dopt=
        Abstract

143.   Herr HW. Does necrosis on frozen-section analysis of a mass after chemotherapy justify a limited
        retroperitoneal resection in patients with advanced testis cancer? Br J Urol 1997;80:653-657. EBM IIa.
        http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9352708&dopt=
        Abstract

144.   Hendry WF, A'Hern RP, Hetherington JW, Peckham MJ, Dearnaley DP, Horwich A. Para-aortic
        lymphadenectomy after chemotherapy for metastatic non-seminomatous germ cell tumors: prognostic
        value and therapeutic benefit. Br J Urol 1993;71:208-213.
        http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8384914&dopt=
        Abstract

145.   Wood DP, Herr HW, Heller G, Vlamis V, Sogani PC, Motzer RJ, Fair WR, Bosl GJ. Distribution of
        retroperitoneal metastases after chemotherapy in patients with nonseminomatous germ cell tumors.
        J Urol 1992;148:1812-1815. EBM IIb.
        http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1331547&dopt=
        Abstract

146.   Baniel J, Foster RS, Rowland RG, Bihrle R, Donohue JP. Complications of post-chemotherapy
        retroperitoneal lymph node dissection. J Urol 1995;153:976-980. EBM III.
        http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7853586&dopt=
        Abstract

147.   Hartmann JT, Schmoll HJ, Kuczyk MA, Candelaria M, Bokemeyer C. Post-chemotherapy resection of
        residual masses from metastatic non-seminomatous germ cell tumors. Ann Oncol 1997;8:531-538.
        EBM III.
        http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9261521&dopt=
        Abstract

148.   Rabbani F, Goldenberg SL, Gleave ME, Paterson RF, Murray N, Sullivan LD. Retroperitoneal
        lymphadenectomy for post-chemotherapy residual masses: is a modified dissection and resection of
        the residual mass sufficient? Br J Urol 1998;81:295-300. EBM III.
        http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9488075&dopt=
        Abstract

149.   Tekgul S, Özen HA, Celebi I, Ozgu I, Ergen A, Demircin M, Remzi D. Postchemotherapeutic surgery for
        metastatic testicular germ cell tumors: results of extended primary chemotherapy and limited surgery.
        Urology 1994;43:349-354. EBM III.
        http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8134989&dopt=
        Abstract

150.   Steyerberg EW, Keizer HJ, Fossa SD, Sleijfer DT, Toner GC, Schraffordt Koops H, Mulders PF,
        Messemer JE, Ney K, Donohue JP et al. Prediction of residual retroperitoneal mass histology after
        chemotherapy for metastatic nonseminomatous germ cell tumor: multivariate analysis of individual
        patient data from six study groups. J Clin Oncol 1995;13:1177-1187. EBM IIb.
        http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7537801&dopt=
        Abstract

151.   Hartmann JT, Candelaria M, Kuczyk MA, Schmoll HJ, Bokemeyer C. Comparison of histological
        results from the resection of residual masses at different sites after chemotherapy for metastatic non-
        seminomatous germ cell tumours. Eur J Cancer 1997;33:843-847. EBM III.
        http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9291803&dopt=
        Abstract

152.   Stenning SP, Parkinson MC, Fisher C, Mead GN, Cook PA, Fossa SD, Horwich A, Jones WG,
        Newlands ES, Oliver RT, Stenwig AE, Wilkinson PM. Post-chemotherapy residual masses in germ cell
        tumor patients: content, clinical features and prognosis. Medical Research Council Testicular Tumour
        Working Party. Cancer 1998;83:1409-1419. EBM III.
        http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9762943&dopt=
        Abstract

153. Albers P, Weissbach L, Krege S, Kliesch S, Hartmann M, Heidenreich A, Walz P, Kuczyk M, Fimmers R. Prediction of necrosis after chemotherapy of advanced germ cell tumors: results of a prospective multicenter trial of the German Testicular Germ Cell Group. J Urol 2004;171:1835-1838. EBM IIb.

154. Hendry WF, Norman AR, Dearnaley DP, Fisher C, Nicholls J, Huddart RA, Horwich A. Metastatic nonseminomatous germ cell tumors of the testis: results of elective and salvage surgery for patients with residual retroperitoneal masses. Cancer 2002;94:1668-1676. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11920527&dopt=Abstract

155. Sheinfeld J. The role of adjunctive post-chemotherapy surgery for nonseminomatous germ-cell tumors: current concepts and controversies. Sem Urol Oncol 2002;20:262-271. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12489059&dopt=Abstract

156. Foster RS, Donohue JP. Can retroperitoneal lymphadenectomy be omitted in some patients after chemotherapy? Urol Clin North Am 1998;25:479-484. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9728217&dopt=Abstract

157. Steyerberg EW, Kaiser HJ, Habbema JD. Prediction models of the histology of residual masses after chemotherapy for metastatic testicular cancer. ReHiT Study Group. Int J Cancer 1999;83:856-859. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10597211&dopt=Abstract

158. Vergouwe Y, Steyerberg EW, De Wit R, Roberts JT, Keizer HJ, Collette L, Stenning SP, Habbema JD. External validity of a prediction rule for residual mass histology in testicular cancer: an evaluation for good prognosis patients. Br J Cancer 2003;88:843-847. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12644820&dopt=Abstract

159. Fizazi K, Tjulandin S, Salvioni R, Germa-Lluch JR, Bouzy J, Ragan D, Bokemeyer C, Gerl A, Flechon A, de Bono JS, Stenning S, Horwich A, Pont J, Albers P, De Giorgi U, Bower M, Bulanov A, Pizzocaro G, Aparicio J, Nichols CR, Theodore C, Hartmann JT, Schmoll HJ, Kaye SB, Culine S, Droz JP, Mahe C. Viable malignant cells after primary chemotherapy for disseminated nonseminomatous germ cell tumors: prognostic factors and role of postsurgery chemotherapy - results from an international study group. J Clin Oncol 2001;19:2647-2657. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11352956&dopt=Abstract

160. Miller KD, Loehrer PJ, Gonin R, Einhorn LH. Salvage chemotherapy with vinblastine, ifosfamide and cisplatin in recurrent seminoma. J Clin Oncol 1997;15:1427-1431. EBM IIb.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9193335&dopt=Abstract

161. Loehrer PJ, Gonin R, Nichols CR, Weathers T, Einhorn LH. Vinblastine plus ifosfamide plus cisplatin as initial salvage therapy in recurrent germ cell tumor. J Clin Oncol 1998;16:2500-2504. EBM IIb.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9667270&dopt=Abstract

162. Beyer J, Rick O, Siegert W, Bokemeyer C. Salvage chemotherapy in relapsed germ cell tumors. World J Urol 2001;19:90-93. EBM IIb.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11374323&dopt=Abstract

163. Schmoll HJ, Beyer J. Prognostic factors in metastatic germ cell tumors. Semin Oncol 1998;25:174-185. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9562450&dopt=Abstract

164. Beyer J, Stenning S, Gerl A, Fossa S, Siegert W. High-dose versus conventional-dose chemotherapy as a first-salvage treatment in patients with non-seminomatous germ-cell tumors: a matched pair analysis. Ann Oncol 2002;13:599-605. EBM IIb.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12056711&dopt=Abstract

165. Bhatia S, Abonour R, Porcu P, Seshadri R, Nichols CR, Cornetta K, Einhorn LH. High-dose chemo-therapy as inital salvage chemotherapy in patients with relapsed testicular cancer. J Clin Oncol 2000;18:3346-3351. EBM IIb.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11013274&dopt=Abstract

166. Rosti G, Pico JL, Wandt H et al. High-dose chemotherapy (HDC) in the salvage treatment of patients failing first-line platinum chemotherapy for advanced germ cell tumors (GCT): first results of a prospective randomised trial of the European Group for Blood and Marrow Transplantation (EBMT): IT-94 study. Proc ASCO 2002;21:180a. Abstract 716. EBM Ib.

167. Motzer JR, Sheinfeld J, Mazumdar M, Bains M, Mariani T, Bacik J, Bajorin D, Bosl GJ. Paclitaxel, ifosfamide, and cisplatin second-line therapy for patients with relapsed testicular germ cell cancer. J Clin Oncol 2000;18:2413-2418. EBM IIb.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10856101&dopt=Abstract

168. Bokemeyer C, Gerl A, Schoffski P, Harstrick A, Niederle N, Beyer J, Casper J, Schmoll HJ, Kanz L. Gemcitabine in patients with relapse or cisplatin refractory testicular cancer. J Clin Oncol 1999;17:512-516. EBM IIa.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10080593&dopt=Abstract

169. Kollmannsberger C, Beyer J, Liersch R, Schoeffski P, Metzner B, Hartmann JT, Rick O, Stengele K, Hohloch K, Spott C, Kanz L, Bokemeyer C. Combination chemotherapy with gemcitabine plus oxaliplatin in patients with intensively pretreated or refractory germ cell cancer: a study of the German Testicular Cancer Study Group. J Clin Oncol 2004;22:108-114. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14701772&query_hl=47

170. Fox EP, Weathers TS, Williams SD, Loehrer PJ, Ulbright TM, Donohue JP, Einhorn LH. Outcome analysis for patients with persistent nonteratomatous germ cell tumor in postchemotherapy retroperitoneal lymph node dissections. J Clin Oncol 1993;11:1294-1299. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8391067&dopt=Abstract

171. Gerl A, Clemm C, Schmeller N, Dienemann H, Lamerz R, Kriegmair M, Wilmanns W. Outcome analysis after post-chemotherapy surgery in patients with non-seminomatous germ cell tumors. Ann Oncol 1995;6:483-488. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7545430&dopt=Abstract

172. Hollender A, Stenwig EA, Ous S, Fossa SD. Survival of patients with viable malignant non-seminomatous germ cell tumor persistent after cisplatin-based induction chemotherapy. Eur Urol 1997;31:141-147. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9076455&dopt=Abstract

173. Pizzocaro G, Nicolai N, Milani A. Is further chemotherapy necessary in radically resected residual cancer in non-seminomatous germ cell tumors (NSGCT) of the testis following induction chemotherapy? Proc ASCO 1998;17:309a. Abstract 1191.

174. Coogan CL, Foster RS, Rowland RG, Bihrle R, Smith ER Jr, Einhorn LH, Roth BJ, Donohue JP. Post-chemotherapy retroperitoneal lymph node dissection is effective therapy in selected patients with elevated tumor markers after primary chemotherapy alone. Urology 1997;50:957-962. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9426730&dopt=Abstract

175. Eastham JA, Wilson TG, Russell C, Ahlering TE, Skinner DG. Surgical resection in patients with nonseminomatous germ cell tumor who fail to normalize serum tumor markers after chemotherapy. Urology 1994;43:74-80. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7506856&dopt=Abstract

176. Kisbenedek L, Bodrogi I, Szeldeli P, Baki M, Tenke P, Horti J. Results of salvage retroperitoneal lymphadenectomy (RLA) in the treatment of patients with nonseminomatous germ cell tumors remaining marker positive after inductive chemotherapy. Int Urol Nephrol 1995;27:325-329. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7591598&dopt=Abstract

177. Murphy BR, Breeden ES, Donohue JP, Messemer J, Walsh W, Roth BJ, Einhorn LH. Surgical salvage of chemorefractory germ cell tumors. J Clin Oncol 1993;11:324-329. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8381163&dopt=Abstract

178. Ravi R, Ong J, Oliver RT, Badenoch DF, Fowler CG, Hendry WF. Surgery as salvage therapy in chemotherapy-resistant nonseminomatous germ cell tumors. Br J Urol 1998;81:884-888. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9666776&dopt=Abstract

179. Albers P. Ganz A, Hanning E, Miersch WD, Muller SC. Salvage surgery of chemorefractory germ cell tumors with elevated tumor markers. J Urol 2000;164:381-384. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10893590&dopt=Abstract

180. Fossa SD, Bokemeyer C, Gerl A, Culine S, Jones WG, Mead GM, Germa-Luch JR, Pont J, Schmoll HJ, Tjulandin S. Treatment outcome of patients with brain metastases from malignant germ cell tumors. Cancer 1999;85:988-997. EBM IIa.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10091779&dopt=Abstract

181. Bokemeyer C, Nowak P, Haupt A, Metzner B, Kohne H, Hartmann JT, Kanz L, Schmoll HJ. Treatment of brain metastases in patients with testicular cancer. J Clin Oncol 1997;15:1449-1454. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9193339&dopt=Abstract

182. Hartmann JT, Bamberg M, Albers P et al. Multidiciplinary treatment and prognosis of patients with central nervous metastases (CNS) from testicular germ cell tumor (GCT) origin. Proc ASCO 2003;22:400. Abstract 1607. EBM III.

183. Edelman MJ, Meyers FJ, Siegel D. The utility of follow-up testing after curative cancer therapy. JGIM 1997;12:318-331.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9159703&dopt=Abstract

184. Gerl A, Clemm C, Schmeller N, Hentrich M, Lamerz R, Wilmanns W. Late relapse of germ cell tumors after cisplatin-based chemotherapy. Ann Oncol 1997;8:41-47. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9093706&dopt=Abstract

185. Baniel J, Foster RS, Einhorn LH, Donohue JP. Late relapse of clinical stage I testicular cancer. J Urol 1995;154:1370-1372. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7658541&dopt=Abstract

186. George DW, Foster RS, Hromas RA, Robertson KA, Vance GH, Ulbright TM, Gobbett TA, Heiber DJ, Heerema NA, Ramsey HC, Thurston VC, Jung SH, Shen J, Finch DE, Kelley MR, Einhorn LH. Update on late relapse of germ cell tumor: a clinical and molecular analysis. J Clin Oncol 2003;21:113-122. EBM III.

187. Dieckmann KP, Albers P, Classen J, De Wit M, Pichlmeier U, Rick O, Müllerleile U, Kuczyk M. Late relapse of testicular germ cell neoplasms: a descriptive analysis of 122 cases. J Urol 2005;173:824-829.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15711278&query_hl=52

188. Gietema JA, Meinardi MT, Sleifer DT, Hoekstra HJ, van der Graaf WT. Routine chest X-rays have no additional value in the detection of relapse during routine follow-up of patients treated with chemotherapy for disseminated non-seminomatous testicular cancer. Ann Oncol 2002;13:1616-1620. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12377651&dopt=Abstract

189. McCaffrey JA, Bajorin DF, Motzer RJ. Risk assessment for metastatic testis cancer. Urol Clin North Am 1998;25:389-395.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9728209&dopt=Abstract

190. Rabbani F, Sheinfeld J, Farivar-Mohseni H, Leon A, Rentzepis MJ, Reuter VE, Herr HW, McCaffrey JA, Motzer RJ, Bajorin DF, Bosl GJ. Low-volume nodal metastases detected at retroperitoneal lymphadenectomy for testicular cancer: pattern and prognostic factors for relapse. J Clin Oncol 2001;19:2020-2025. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11283135&query_hl=12

191. Travis LB, Fossa SD, Schonfeld SJ, McMaster ML, Lynch CF, Storm H, Hall P, Holowaty E, Andersen A, Pukkala E, Andersson M, Kaijser M, Gospodarowicz M, Joensuu T, Cohen RJ, Boice JD Jr, Dores GM, Gilbert ES. Second cancers among 40,576 testicular cancer patients: focus on long-term survivors. J Natl Cancer Inst. 2005 21;97:1354-65.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16174857&query_hl=4&itool=pubmed_docsum

192. Lashley DB, Lowe BA. A rational approach to managing stage I nonseminomatous germ cell cancer. Urol Clin North Am 1998;25:405-423.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9728211&dopt=Abstract&itool=iconabstr

193. Baniel J, Donohue JP. Cost and risk benefit considerations in low stage (I and II) nonseminomatous testicular tumors. AUA Update Series 1997;26:50-55.

194. Tjan-Heijnen VCG, Oosterhof GON, de Wit R, de Mulder PHM. Treatment of germ cell tumours: state of the art. Eur J Surg Oncol 1997;23:110-117.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9158183&dopt=Abstract

195. Donohue JP, Thornhill JA, Foster RS, Rowland RG, Bihrle R. Primary retroperitoneal lymph node dissection in clinical stage A non-seminomatous germ cell testis cancer: review of the Indiana University Experience 1965-1989. Br J Urol 1993;71:326-335. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8386580&dopt=Abstract

196. Klepp O, Flodgren P, Maartman-Moe H, Lindholm CE, Unsgaard B, Teigum H, Fossa SD, Paus E. Early clinical stages (CS1, CS1Mk+ and CS2A) of non-seminomatous testis cancer. Value of pre- and postorchiectomy serum tumor marker information in prediction of retroperitoneal lymph node metastases. Swedish-Norwegian Testicular Cancer Project (SWENOTECA). Ann Oncol 1990; 1:281-288. EBM IIb.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1702312&dopt=Abstract

197. Schmoll HJ, Weissbach L. [Diagnostics and therapy of testicular tumours], Interdisziplinäre Konsensus-Konferenz, Halle (Saale), 1996. [German] EBM IIa-IIb-III.

198. Warde P, Jewett MAS. Surveillance for stage I testicular seminoma. Is it a good option? Urol Clin North Am 1998;25:425-433.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9728212&dopt=Abstract&itool=iconabstr

199. Buchholz TA, Walden TL, Prestidge BR. Cost-effectiveness of post-treatment surveillance after radiation therapy for early stage seminoma. Cancer 1998;82:1126-1133. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9506359&dopt=Abstract

200. Tana S, Cerrotta A, Gardani G, Palazzi M, Pizzocaro G. Post surgical policy in stage I testicular seminoma: cost and benefit of prophylactic irradiation in a long-term experience. Tumori 1997; 83:918-921. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9526584&dopt=Abstract

201. Jones WG, Fossa SD, Mead GM, Roberts JT, Sokal M, Naylor S, Tenning SP. A randomised trial of two radiotherapy schedules in the adjuvant treatment of stage I seminoma (MRC TE 18). Eur J Cancer 2001;37(Suppl 6):S157. Abstract 572. EBM Ib.

202. Sultanem K, Souhami L, Benk V, Bahary JP, Roman T, Shenouda G, Freeman C. Para-aortic irradiation only appears to be adequate treatment for patients with stage I seminoma of the testis. Int J Radiat Oncol Biol Phys 1998;40:455-459. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9457835&dopt=Abstract

203. Kiricuta IC, Sauer J, Bohndorf W. Omission of the pelvic irradiation in stage I testicular seminoma: a study of postorchiectomy paraaortic radiotherapy. Int J Radiat Oncol Biol Phys 1996;35:293-298. EBM IIb.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8635936&dopt=Abstract

204. Warde P, Gospodarowicz MK, Panzarella T, Catton CN, Sturgeon JF, Moore M, Goodman P, Jewett MA. Stage I testicular seminoma: results of adjuvant irradiation and surveillance. J Clin Oncol 1995;13:2255-2262. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7666083&dopt=Abstract

205. Fossa SD, Aass N, Kaalhus O. Radiotherapy for testicular seminoma stage I: treatment results and long-term post-irradiation morbidity in 365 patients. Int J Radiat Oncol Biol Phys 1989;16:383-388. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=2921142&dopt=Abstract

206. Stein ME, Leviov M, Drumea K, Moshkovitz B, Nativ O, Milstein D, Sabo E, Kuten A. Radiation-induced tumors in irradiated stage I testicular seminoma: results of a 25-year follow-up (1968-1993). J Surg Oncol 1998;67:38-40. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9457255&dopt=Abstract

207. Akimoto T, Takahashi I, Takahashi M, Yamakawa M, Hayakawa K, Mitsuhashi N, Niibe H. Long-term outcome of postorchiectomy radiation therapy for stage I and II testicular seminoma. Anticancer Res 1997;17:3781-3785. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9427780&dopt=Abstract

208. Von der Maase H, Specht L, Jacobsen GK, Jakobsen A, Madsen EL, Pedersen M, Rorth M, Schultz H. Surveillance following orchidectomy for stage I seminoma of the testis. Eur J Cancer 1993;14:1931-1934. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8280484&dopt=Abstract

209. Horwich A, Alsanjari N, A'Hern, Nicholls J, Dearnaley DP, Fisher C. Surveillance following orchidectomy for stage I testicular seminoma. Br J Cancer 1992;65:775-778. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1586607&dopt=Abstract

210. Germá Lluch JR, Climent MA, Villavicencio H, Gomez de Segura G, Blanco R, Mercedes A, de Andres L, Sole Balcells FJ. Treatment of stage I testicular tumors. Br J Urol 1993;71:473-477. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8499994&dopt=Abstract

211. Warde P, Gospodarowicz MK, Goodman PJ, Sturgeon JF, Jewett MA, Catton CN, Richmond H, Thomas GM, Duncan W, Munro AJ. Results of a policy of surveillance in stage I testicular seminoma. Int J Radiat Oncol Biol Phys 1993;27:11-15. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8365931&dopt=Abstract

212. Allhoff EP, Liedke S, de Riese W, Stief C, Schneider B. Stage I seminoma of the testis: adjuvant radiotherapy or surveillance? Br J Urol 1991;68:190-194. EBM IIb.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1715798&dopt=Abstract

213. Bukowski RM. Management of advanced and extragonadal germ-cell tumors. Urol Clin North Am 1993;20:153-160.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8381995&dopt=Abstract

214. Frohlich MW, Small EJ. Stage II nonseminomatous testis cancer: the roles of primary and adjuvant chemotherapy. Urol Clin North Am 1998;25:451-459.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9728214&dopt=Abstract

215. Fair W, Dalbagni G, Machele Donat S, Theodorescu D. Evaluation and follow-up of patients with urologic cancer. AUA Office of Education Publications 9958 PG, 1999.

216. Pizzocaro G. Non-seminomatous germ-cell tumors (NSGCT) of the testis: diagnosis and management, stage by stage. Eur Urol Update Series 1997;6:139-145.

217. Sheinfeld J, Bajorin DF, Solomon M. Management of postchemotherapy residual masses in advanced germ cell tumors. Urol Clin North Am 1997;3:18-23.

218. Little JS, Foster RS, Ulbright TM, Donohue JP. Unusual neoplasms detected in testis cancer patients undergoing postchemotherapy retroperitoneal lymphadenectomy. J Urol 1994;152:1144-1149. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8072083&dopt=Abstract

219. Aas N, Kaasa S, Lund E, Kaalhus O, Heier MS, Fossa SD. Long-term somatic side-effects and morbidity in testicular cancer patients. Br J Cancer 1990;61:151-155. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=2297486&dopt=Abstract

220. Donohue JP, Thornhill JA, Foster RS, Bihrle R, Rowland RG, Einhorn LH. The role of retroperitoneal lymphadenectomy in clinical stage B testis cancer: the Indiana University Experience (1965 to 1989). J Urol 1995;153:85-89. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7966799&dopt=Abstract

221. Motzer RJ, Sheinfeld J, Mazumdar M, Bajorin DF, Bosl GJ, Herr H, Lyn P, Vlamis V. Etoposide and cisplatin adjuvant therapy for patients with pathological stage II germ cell tumors. J Clin Oncol 1995; 13:2700-2704. EBM IIb.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7595727&dopt=Abstract

222. Hermans BP, Sweeney CJ, Foster RS, Einhorn LE, Donohue JP. Risk of systemic metastases in clinical stage nonseminoma germ cell testis tumor managed by retroperitoneal lymph node dissection. J Urol 2000;163:1721-1724. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10799168&dopt=Abstract

223. Hartlapp JH, Weissbach L, Bussar-Maatz R. Adjuvant chemotherapy in nonseminomatous testicular tumor stage II. Int J Androl 1987;10:277-284.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=2438221&dopt=Abstract

224. Logothetis CJ, Swanson DA, Dexeus F, Chong C, Ogden S, Ayala AG, von Eschenbach AC, Johnson DE, Samuels ML. Primary chemotherapy for clinical stage II nonseminomatous germ cell tumors of the testis: a follow-up of 50 patients. J Clin Oncol 1987;5:906-911. EBM IIb.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=2438389&dopt=Abstract

225. Fossa SD, Borge L, Aass N, Johannessen NB, Stenwig AE, Kaalhus O. The treatment of advanced metastatic seminoma: experience in 55 cases. J Clin Oncol 1987;5:1071-1077. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=2439660&dopt=Abstract

226. Rathmell AJ, Brand IR, Carey BM, Jones WG. Early detection of relapse after treatment for metastatic germ cell tumour of the testis: an exercise in medical audit. Clin Oncol (R Coll Radiol) 1993;5:34-38. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7678749&dopt=Abstract

9.2 Non-germ cell tumours

1. Cheville JC, Sebo TJ, Lager DJ, Bostwick DG, Farrow GM. Leydig cell tumour of the testis: a clinicopathologic, DNA content, and MIB-1 comparison of nonmetastasizing and metastasizing tumours. Am J Surg Pathol 1998;22:1361-1367. EBM IIA.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=9808128

2. Kim I, Young RH, Scully RE. Leydig cell tumours of the testis. A clinicopathological analysis of 40 cases and review of the literature. Am J Surg Pathol 1985;9:177-192. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=3993830&query_hl=87&itool=pubmed_docsum

3. Matveev BP, Gurarii LL. [Leydig-cell tumours of the testis.] Urol Nefrol (Mosk) 1997:34-36. [Russian] EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=9381620

4. Young RH, Koelliker DD, Scully RE. Sertoli cell tumours of the testis, not otherwise specified: a clinicopathologic analysis of 60 cases. Am J Surg Pathol 1998;22:709-721. EMB III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=9630178

5. Proppe KH, Scully RE. Large-cell calcifying Sertoli cell tumour of the testis. Am J Clin Pathol 1980;74:607-619. EMB III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=7446466

6.   Zukerberg LR, Young RH, Scully RE. Sclerosing Sertoli cell tumour of the testis. A report of 10 cases. Am J Surg Pathol 1991;15:829-834. EMB III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=1719830

7.   WHO histological classification of testis tumours. In: JN Eble, G Sauter, JI Epstein, IA Sesterhenn, editors. *Pathology & genetics. Tumours of the urinary system and male genital organs.* IARC Press: Lyon, 2004, p 218, 250-262. EBM III.

8.   Ulbright TM, Amin MB, Young RH. Tumours of the testis, adnexia, spermatic cord and scrotum. AFIP 1999. EBM III.

9.   McCluggage WG, Shanks JH, Arthur K, Banerjee SS. Cellular proliferation and nuclear ploidy assessments augment established prognostic factors in predicting malignancy in testicular Leydig cell tumours. Histopathology 1998;33:361-368. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=9822927

10. Mineur P, de Cooman S, Hustin J, Verhoeven G, de Hertogh E. Feminizing testicular Leydig cell tumour: hormonal profile before and after unilateral orchidectomy. J Clin Endocrinol Metab 1987;64:686-691. EBM IIB,
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=3818898

11. Reznik Y, Rieu M, Kuhn JM, Mandard JC, Bottet P, Lemonnier D, Bekka S, Mahoudeau J. Luteinizing hormone regulation by sex steroids in men with germinal and Leydig cell tumours. Clin Endocrinol (Oxf) 1993;38:487-493. EBM IIB.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=8392454

12. Bercovici JP, Nahoul K, Tater D, Charles JF, Scholler R. Hormonal profile of Leydig cell tumours with gynecomastia. J Clin Endocrinol Metab 1984;59:625-630. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=6434575

13. Haas GP, Pittaluga S, Gomella L, Travis WD, Sherins RJ, Doppman JL, Linehan WL, Robertson C. Clinical occult Leydig cell tumour presenting with gynecomastia. J Urol 1989;142:1325-1327. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=2810523

14. Ruthgers JL, Young RH, Scully RE. The testicular "tumour" of the adrenogenital syndrome. A report of six cases and review of the literature on testicular masses in patients with adrenocortical disorders. Am J Surg Pathol 1988;12:503-513. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=3291624

15. Maizlin ZV, Belenky A, Kunichezky M, Sandbank J, Strauss S. Leydig cell tumours of the testis: gray scale and color Doppler sonographic appearance. J Ultrasound Med 2004;23:959-964. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15292565

16. Ponce de Leon Roca J, Algaba Arrea F, Bassas Arnau L, Villavicencio Mavrich H. [Leydig-cell tumours of the testis.] Arch Esp Urol 2000; 53:453-458. [Spanish] EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11002512

17. Wegner HE, Dieckmann KP, Herbst H, Andresen R, Miller K. Leydig cell tumour - comparison of results of radical and testis sparing surgery in a single center. Urol Int 1997;59:170-173. EBM IIB.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=9428434

18. Mosharafa AA, Foster RS, Bihrle R, Koch MO, Ulbright TM, Einhorn LH, Donohue JP. Does retroperitoneal lymph node dissection have a curative role for patients with sex cord-stromal testicular tumours? Cancer 2003;98:753-757. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12910519

19. Giglio M, Medica M, De Rose AF, Germinale F, Ravetti JL, Carmignani G. Testicular Sertoli cell tumours and relative sub-types. Analysis of clinical and prognostic features. Urol Int 2003;70:205-210. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12660458

20. Jacobsen GK. Malignant Sertoli cell tumours of the testis. J Urol Pathol 1993;1:233-255. EBM III.

21. Kratzer SS, Ulbright TM, Talerman A, Srigley JR, Roth LM, Wahle GR, Moussa M, Stephens JK, Millos A, Young RH. Large cell calcifying Sertoli cell tumour of the testis: contrasting features of six malignant and six benign tumours and a review of the literature. Am J Surg Pathol 1997;21:1271-1280. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=9351565

22. Henley JD, Young RH, Ulbright TM. Malignant Sertoli cell tumours of the testis: a study of 13 examples of a neoplasm frequently misinterpreted as seminoma. Am J Surg Pathol 2002;26:541-550. EBM III.

23. Plata C, Algaba F, Andujar M, Nistal M, Stocks P, Martinez JL, Nogales FF. Large cell calcifying Sertoli cell tumour of the testis. Histopathology 1995;26:255-259. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=7541015

24. Anderson GA. Sclerosing Sertoli cell tumour of the testis: a distinct histological subtype. J Urol 1995;154:1756-1758. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=7563340

25. Grabrilove JL, Freiberg EK, Leiter E, Nicolis GL. Feminizing and non-feminizing Sertoli cell tumour. J Urol 1980;124:757-767.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=7003168

26. Gierke CL, King BF, Bostwick DG, Choyke PL, Hattery RR. Large-cell calcifying Sertoli cell tumour of the testis: appearance at sonography. AJR Am J Roentgenol 1994;163:373-375. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=8037034

27. Chang B, Borer JG, Tan PE, Diamond DA. Large-cell calcifying Sertoli cell tumour of the testis: case report and review of the literature. Urology 1998;52:520-522. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=9730477

28. Washecka R, Dresner MI, Honda SA. Testicular tumours in Carney's complex. J Urol 2002;167:1299-1302. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11832717

29. Young S, Gooneratne S, Straus FH, Zeller WP, Bulun SE, Rosenthal IM. Feminizing Sertoli cell tumours in boys with Peutz-Jeghers syndrome. Am J Surg Pathol 1995;19:50-58. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=7802138

30. Kaplan GW, Cromie WJ, Kelalis PP, Silber I, Tank ES Jr. Gonadal stromal tumours: a report of the prepuberal testicular tumours registry. J Urol 1986;136:300-302. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=3723681

31. Al-Bozom IA, El-Faqih SR, Hassan SH, El-Tiraifi AE, Talic RF. Granulosa cell tumour of the adult type. A case report and review of the literature of a very rare testicular tumour. Arch Pathol Lab Med 2000;124:1525-1528. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11035589

32. Perito PE, Ciancio G, Civantos F, Politano VA. Sertoli-Leydig cell testicular tumour. Case report and review of sex cord/gonadal stromal tumour histogenesis. J Urol 1992;148:883-885. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=1512847

33. Scully RE. Gonadoblastoma. A review of 74 cases. Cancer 1970;25:1340-1356. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=4193741

34. Ulbright TM, Srigley JR, Reuter VE, Wojno K, Roth LM, Young RH. Sex-cord-stromal tumours of the testis with entrapped germ cells: a lesion mimicking unclassified mixed germ cell sex cord-stromal tumours. Am J Surg Pathol 2000;24:535-542. EBM III.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10757400

10. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive for the most common abbreviations.

AFP	alpha-fetoprotein
β-hCG	beta-human chorionic gonadotrophin
CNS	central nervous system
CT	computed tomography
EBM	evidence-based medicine
EGCCCG	European Germ Cell Cancer Collaborative Group
EORTC	European Organization for Research and Treatment of Cancer
FDG-PET	fluorodeoxyglucose-positronemission tomography
FSH	follicle-stimulating hormone
G-CSF	granulocyte - colony stimulating factor
GI	gastrointestinal
HPF	high-power field
IGCCCG	International Germ Cell Cancer Collaborative Group
LDH	lactate dehydrogenase
LH	luteinizing hormone
MRC	Medical Research Council
MRI	magnetic resonance imaging
NSE	neuro-specific enolase
NSGCT	non-seminomatous germ cell tumour
PA	para-aortic
PEB	cisplatin, etoposide, bleomycin
PEI/VIP	cisplatin, etoposide, ifosfamide
PET	positron emission tomography
PFS	progression-free survival
PLAP	placental alkaline phosphatase
PVB	cisplatin, vinblastine, bleomycin
RPLND	retroperitoneal lymph node dissection
TIN	intratubular germ cell neoplasia
TNM	Tumour Node Metastasis
UICC	International Union Against Cancer
ULN	upper limit of normal range
VelP	vinblastine, ifosfamide and cisplatin
VIP/PEI	cisplatin, etoposide, ifosfamide
WW	watchful waiting