The management of testis cancer

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Abstract

Testis cancer is the most common solid malignancy in young men and represents a clinically and pathologically diverse disease. Between 90% and 95% of tumours are germ cell tumours (GCTs) that are categorized into seminoma and non-seminomatous germ cell tumours (NGSCTs). Testis cancer typically presents as a painless testicular mass and must be investigated with ultrasound imaging and tumour marker assay before being treated urgently with radical inguinal orchidectomy if suspicion persists. Disease localized to the scrotum is curable with surgery alone in most cases, but high-risk features in clinical stage I disease predict failure in a significant proportion. Such cases need close surveillance or adjuvant intervention therapy following primary surgery. More advanced disease (clinical stage II or greater) requires treatment with combination platinum based chemotherapy, usually including bleomycin, etoposide and platinum (BEP). Post chemotherapy tumour masses are resected surgically when this is possible. Metastatic disease is sub-stratified into low-, intermediate- and high-risk categories based on the extent and location of metastases on cross-sectional imaging and on the level of specific tumour markers according to the International Germ Cell Cancer Collaborative Group (IGCCCG) criteria. This enables use of risk stratified treatment regimens tailored to individual patients according to their disease characteristics. Treatment outcome is excellent with 5-year overall survival rates of 97%, demonstrating that this cancer is a modern model for the curable neoplasm, although high-risk NSGCT has a significant mortality. The aim of reducing treatment related toxicity and improving outcomes in the high-risk metastatic group represent ongoing and significant challenges in the management of this condition.

Keywords Chemotherapy; germ-cell; non-seminoma; radical orchidectomy; RPLND; seminona; surveillance; testis; testis cancer

Overview

Testicular tumours may be benign or malignant: the latter present either with signs and symptoms of the primary tumour or with problems relating to metastatic spread. The 8th edition of the Union for International Cancer Control (UICC) TNM classification of testicular cancer is shown in Table 1.[1] These malignant tumours are relatively rare, representing approximately 1% of all male cancers and 5% of urological tumours with 3–10 new cases occurring per 100,000 males/per year in Western countries. However, the incidence of the disease is projected to rise in the UK to 10 cases/100,000 males by 2035.[2] Higher incidence rates are seen in developed countries compared to developing countries.

Germ-cell tumours (GCTs) comprise the majority in 90–95% of cases: approximately 90% are localized to the testis and 2–5% are extragonadal.[3] Most testicular tumours are unilateral, although 1–2% occur bilaterally, usually as a metachronous event. The different types of testicular tumour are set out in Box 1. This article will concentrate on the diagnosis and management of seminoma and non-seminomatous germ cell tumours (NGSCTs).

Testicular germ cell tumours demonstrate marked chemosensitivity particularly to cisplatin based chemotherapy regimens and this renders the disease curable in the majority of cases. However, preservation of reproductive function, quality of life and delayed treatment effects remain significant concerns. High-risk NSCGT is still lethal in approximately 50% of patients. Seminomas usually represent a less invasive form of disease that metastasizes late, usually to retroperitoneal lymph nodes. Approximately 80% of seminoma patients have stage I disease at diagnosis, 15% have stage II and <5% present with advanced disease. Pure seminomas have a peak incidence in the fourth decade and are normally radiosensitive. Non-seminomatous germ cell tumours have a peak incidence in the third decade.[3] They are less radiosensitive and more commonly spread via haematogeneous routes. Stage III metastasis occurs more commonly in these tumours.

Presentation and diagnosis

The most common presentation of testicular cancer is with a painless unilateral testicular mass (Figure 1). However a significant number of men present with pain and are misdiagnosed with epididymitis or orchitis, leading to a delay in essential treatment in up to 10% of cases. GCTs can also present with a secondary hydrocele or more rarely, a para-neoplastic syndrome. One example of this is hCG induced hyperthyroidism, seen in GCTs containing high levels of hCG. This can activate the TSH receptor as both TSH and hCG have similar alpha subunits.

An uncommon but well-recognized problem is the acute presentation with disseminated disease. *This is an oncological emergency* and urgent referral to an oncologist is required. Such cases need immediate chemotherapy without orchidectomy. Patients with disease of this type *must* be referred to a specialist oncology team within 24 hours of presentation.

Risk factors for testicular cancer include a previous or family history, with a higher risk if the affected male family member is a brother. The presence of germ cell neoplasia *in situ* (GCNIS) and testicular dysgenesis syndrome (cryptorchidism, hypospadias and impaired spermatogenesis) are additional risk factors. Examination should include inspection for the presence of bilateral testicular tumours, noting the size of the contralateral testicle. The abdomen and thorax should be examined for nodal or visceral disease and gynaecomastia (present in 7% of men and associated with elevated hCG levels). In men with an unexplained retroperitoneal, pulmonary/mediastinal or midline mass, testis cancer should always be considered as a primary cause.

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TNM classification for testicular cancer (UICC, 2017, 8th edn.)[1]

pT-Primary Tumour			
	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-Regional Lymph Nodes- 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 of 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 metastasis	
	M1b	Distant metastasis other than non-regional lymph nodes and lung	
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	$<1.5 \times$ N and	<5,000 and	<1,000
	S2	$1.5–10 \times$ N or	5,000–50,000 or	1,000–10,000
	S3	$>10 \times$ N or	>50,000 or	>10,000

N= upper limit of normal for LDH assay. LDH= lactate dehydrogenase; hCG=human chorionic gonadotrophin; AFP=alpha-fetoprotein.

Table 1

US scanning of the testis is the standard imaging modality, with a sensitivity of almost 100%. On occasion difficulty can arise differentiating between orchitis and tumour. In addition, small intratesticular lesions may produce considerable diagnostic uncertainty. Further imaging with contrast enhanced US or MRI can help clarify the diagnosis. MRI has a higher sensitively and specificity than US but its high cost limits its routine use. PET scanning is not recommended for the initial staging of testicular cancer but it can be used for assessment of residual metastatic masses post chemotherapy.[4]

Staging investigations include computed tomography (CT) of the thorax, abdomen and pelvis with IV and oral contrast. Cranial imaging should also be performed if there are neurological symptoms or if there is widespread metastatic disease with high marker levels.[4]

Where precise clinical diagnosis is impossible and a lesion is suspicious, biopsy or orchidectomy may be needed for definitive verification. In these circumstances, surgical exploration should *always* be through the groin: testis conservation should be attempted where possible. Percutaneous needle biopsy or

Testicular tumour types

2016 WHO Classification of tumours of the testis

Germ cell tumours derived from germ cell neoplasia in situ
- Germ cell neoplasia *in situ* (non-invasive germ cell neoplasia)
- Seminoma
- *Non-seminomatous germ cell tumours*
- Embryonal carcinoma
- Yolk sac tumour
- Choriocarcinoma
- Teratoma (postpubertal-type, teratoma with somatic-type malignancy)
- Mixed germ cell tumours

Germ cell tumours unrelated to germ cell neoplasia in situ
- Spermatocytic tumour
- Teratoma, prepubertal type

Sex cord stromal tumours
- Leydig cell tumours
- Sertoli tumours
- Granulosa cell tumours
- Fibroma/thecoma
- Mixed sex cord stromal tumour

Miscellaneous tumours
- Ovarian epithelial type tumours
- Lymphoma
- Myeloid sarcoma
- Adenoma/Adenocarcinoma

Box 1

Figure 1 The typical presentation of testis cancer is with a painless scrotal mass as seen in the right scrotum in this patient. Urgent diagnosis by ultrasound scanning is essential and blood must be drawn for assay of tumour markers before orchidectomy.

testicular biopsy via the scrotum is contraindicated for any suspected testicular tumour (scrotal violation). If this happens, additional subsequent treatment may be required, often involving local radiotherapy to the scrotal area. This carries the potential for immediate compromise of fertility and delayed impairment of endocrine function of the contralateral testicle.

It is inevitable that following surgery some lesions will ultimately prove to be benign: this should be explained to the patient preoperatively.

Serum tumour markers

These include beta human chorionic gonadotrophin, (β-hCG), α-fetoprotein (AFP) and lactate dehydrogenase (LDH). AFP is raised in the presence of embryonal and/or yolk sac elements and has a half-life of 5–7 days after treatment. β-hCG is raised in the presence of syncytiotrophoblastic elements and has a half-life of 24–36 hours. It is raised in all choriocarcinomas. Elevations of AFP are seen in 50%–70% of NSGCTs. AFP is not elevated in pure seminomas. Seminoma with elevated AFP is treated as a NSGCT.

β-hCG is raised in 40%–60% of men with NSGCTs and <30% of men with seminomas. LDH is a non-specific marker of tumour bulk but may be raised in 80% of patients with advanced disease.[3] Tumour markers are essential in the diagnosis and disease stratification for treatment in all patients with testicular cancer. New molecular markers are in development; there is evidence that micro-RNAs may be more accurate in detecting recurrent or residual disease. Further validation studies of these are required.[3]

Primary surgery

The standard treatment is radical inguinal orchidectomy. Prior to surgery each patient should be counselled regarding cryopreservation of semen and prosthesis insertion. Up to 50% of men will have evidence of impaired spermatogenesis and baseline sperm count and banking is recommended. Unilateral surgery may not necessarily have an impact on fertility but with bilateral tumours, or where subsequent adjuvant chemotherapy is required, fertility may be affected. Surgery involves a groin approach, opening the inguinal canal surgically and detaching the spermatic cord at the level of the internal inguinal ring before delivering the testis from the scrotum and removing the testis and cord en-bloc (Figure 2). If the patient wishes, a testicular prosthesis can be inserted at this time, although this should be avoided if the tumour is invading the scrotal wall or there is active infection. Debate about the suitability of testicular prosthesis insertion at the time of primary surgery has been resolved following a large UK study of testicular prosthetic implant at orchidectomy revealed an infection rate of only 0.4%. Synchronous prosthesis insertion can therefore be undertaken safely and should be offered during primary surgery.[5]

Testis-preserving surgery

This may be considered in specific circumstances, namely, when there is a high degree of confidence that a lesion is benign, when there are synchronous bilateral tumours, following development of a metachronous contralateral tumour, or in patients with a single testis and normal preoperative testosterone levels. Organ-sparing surgery can be performed when tumour volume is <30% of total testicular volume although it may be possible to undertake local excision of larger tumours in the polar areas.[3] Germ cell neoplasia *in situ* (GCNIS) is present in up to 80% of patients

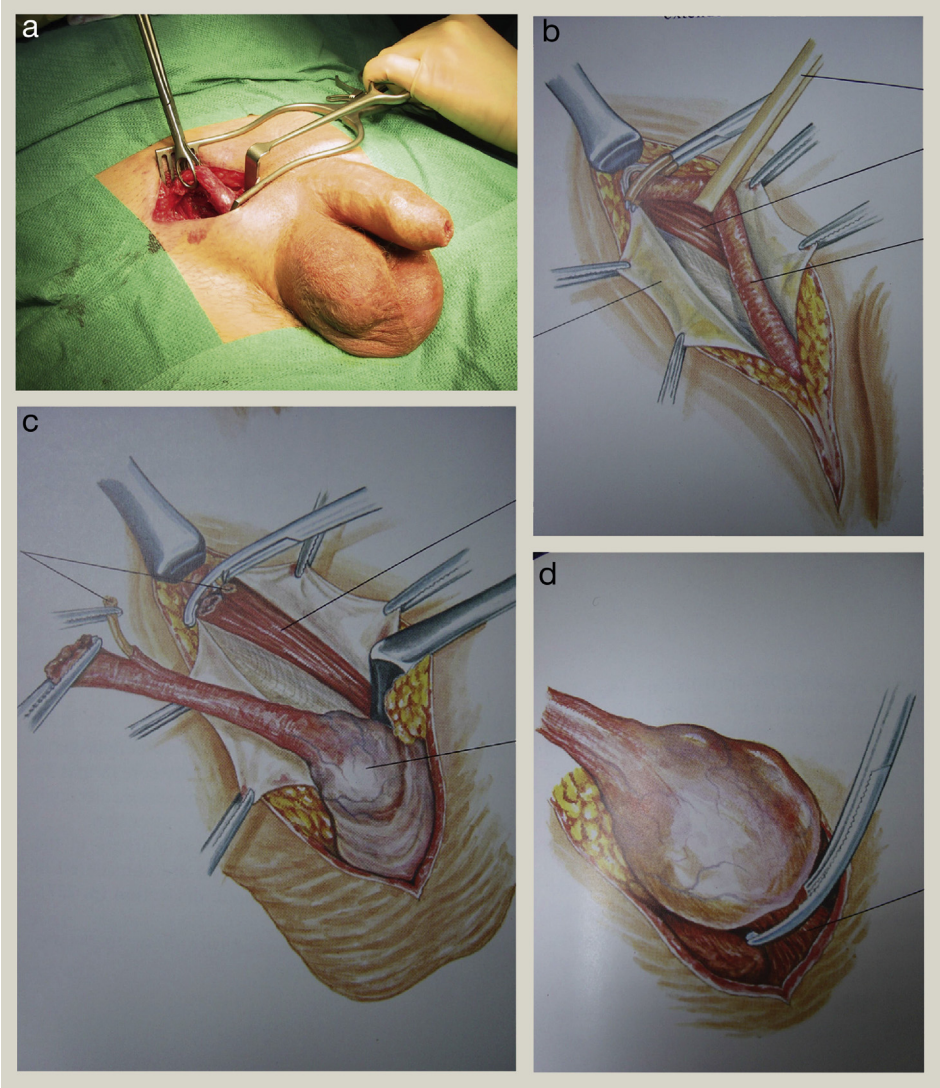


Figure 2 Radical orchidectomy. The spermatic cord is approached through the groin (**a**) by opening the inguinal canal (**b**). Once the cord is mobilized it is detached at the level of the internal inguinal ring (**c**) and delivered in to the groin. The testis is then detached from the inner scrotum by division of the gubernaculum (**d**).

undergoing testis preservation. Sperm storage issues should be discussed prior to surgery and the patient should be counselled about the long-term risks of tumour recurrence, long-term endocrine failure and the requirement for subsequent radiotherapy or completion orchidectomy if GCNIS is detected.

Contralateral testicular biopsy and GCNIS

Germ cell neoplasia *in situ* is present in 4–8% of men presenting with testicular cancer: the risk of a contralateral metachronous tumour is approximately 2.5%.[6] When present there is a higher chance of progression to invasive disease as it is a malignant precursor lesion in GCTs. GCNIS is now the WHO recommended term for all precursor lesions of invasive germ cell tumours.[7] This has previously been known as either carcinoma *in situ* or intratubular germ cell neoplasia, unclassified (IGCNU). Treatment by low-dose irradiation of the affected testis after preliminary storage of semen has been used previously but more recently, surveillance strategies using self-examination and interval US scanning have now been adopted almost universally. If low-dose radiotherapy has to be used, treatment comprises scrotal radiotherapy (16–20 Gy in fractions of 2 Gy).[3] The patient needs counselling that this will lead to irreversible infertility and that about 30% of men will develop Leydig cell insufficiency requiring testosterone replacement therapy.

In the case of primary orchidectomy, controversy surrounds the issue of whether synchronous contralateral testicular biopsies should be performed routinely, and because of this, the policy of contralateral biopsy at the time of primary surgery varies. High-risk cases can be identified, limiting contralateral sampling to those whose risk is greatest. Risk factors for contralateral GCNIS include cryptorchidism, younger age (<40 years), testicular microlithiasis, infertility and testicular atrophy (≤12 ml).[3,4] Two-site biopsy technique has been recommended with improved sensitivity of 18% compared to single-site biopsy.[4]

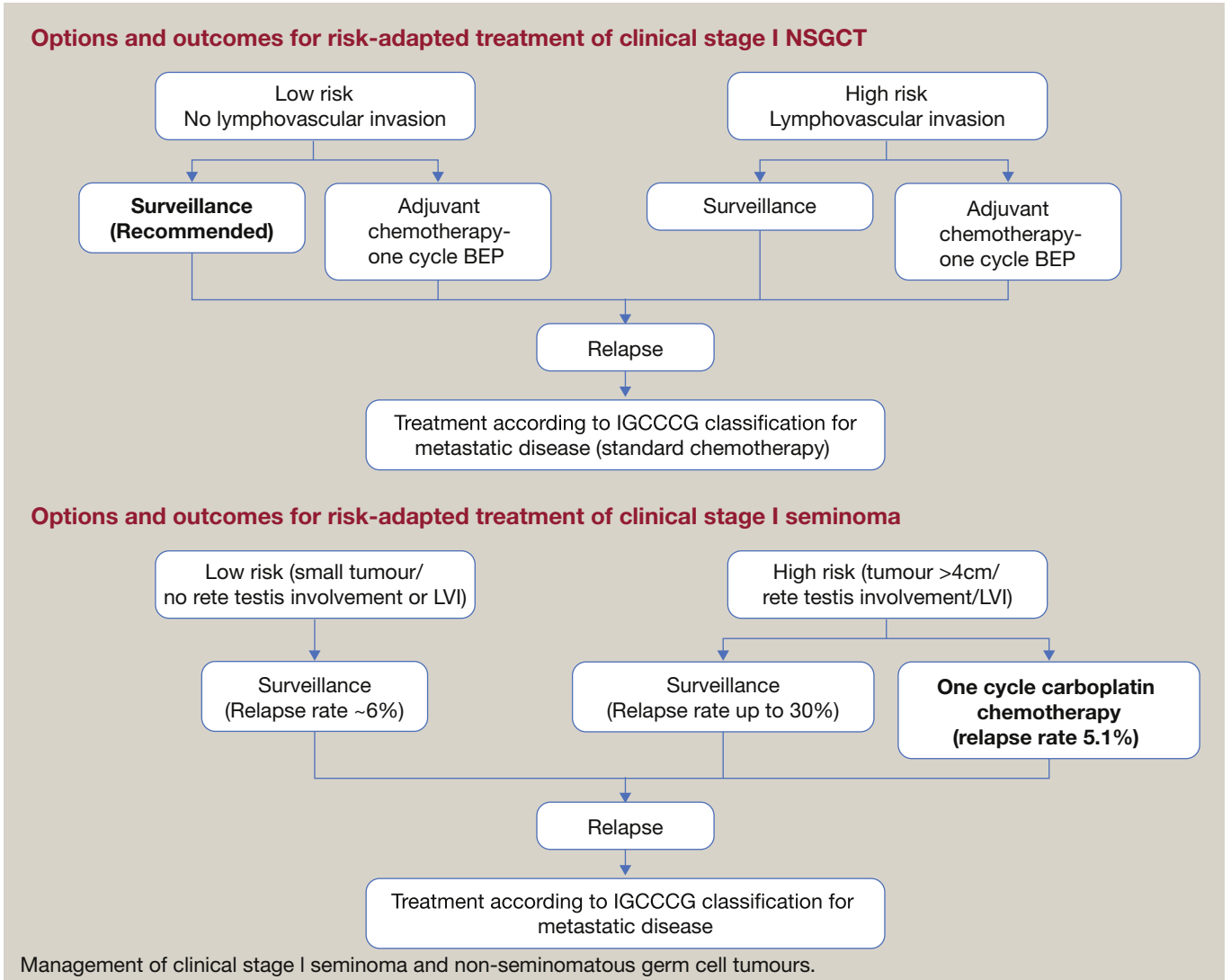
Post-orchidectomy management

Histological classification and clinical staging is undertaken after primary surgery and subsequent management is predicated on these results. The disease stage is classified into two basic groups: clinical stage I (low and high risk) or stage IIA/IIB/III. (Sub-categorized for the three International Germ Cell Collaborative Consensus Group [IGCCCG] types[8]). These sub-types are based on the findings of cross-sectional imaging and post-orchidectomy tumour marker levels.

Defined treatment schedules are followed according to specific protocols (Figure 3). Patients with clinical stage I (CSI) seminoma or NSGCT have traditionally been managed very differently. However in recent years there have been changes aligning the follow up of these two histological types. Surveillance is now the dominant option for both CSI seminoma and NSGCT in the absence of high-risk histological features. For seminoma, single dose carboplatin is also commonly used according to a dose schedule known as area the under curve 7 (AUC). Para-aortic radiotherapy should not now be used except in exceptional circumstances.

If the disease is stage II or more, the standard treatment for most tumours is by combination platinum based chemotherapy using bleomycin, etoposide and cisplatin (BEP) with subsequent surgical removal of post-chemotherapy residual masses. The combination of chemotherapy with post-chemotherapy resection of surgical masses is undertaken for most NSGCT, whereas chemotherapy is used alone for most seminomas, surgery being indicated only for highly selected cases.

Staging is by CT scanning of the chest, abdomen and pelvis and assay of tumour markers (Box 2). The first-order lymph nodes in the retroperitoneum are usually the initial site of metastatic spread although primary distal haematogenous dissemination can occur in up to 15% of men. CT scanning has its limitations: up to 30% of patients with negative CT scans will have microscopically positive lymph nodes detected subsequently at surgical staging. By contrast, up to 25% of patients may be radiologically over-staged, having abnormal nodes on CT staging which are subsequently shown to be negative following surgical exploration. MR imaging has been used in this scenario although it has not proved to be more effective or reliable than



Management of clinical stage I seminoma and non-seminomatous germ cell tumours.

Figure 3

Staging system

The two most commonly used staging systems worldwide are the Union for International Cancer Control (UICC) Eighth Edition (Europe) and the American Joint Committee on Cancer (AJCC) Eighth TNM Version.

The AJCC staging system subdivides seminomas into pT1a and 1b based on tumour size <3 cm or >3 cm.Rete testis invasion remains under T1 classification while hilar soft tissue and epididymal invasion have been reclassified as T2. This is considered to provide a better classification system.

Stage I encompassed all cases with no radiological evidence of disease outside the scrotum. Clinical stage I is sub-classified as follows:

Stage IA: Primary tumour limited to the testis. No vascular/lymphatic invasion (pT1)

Stage IB: Locally invasive Tumour. No evidence of metastases (pT2, 3 or 4: N0M0S0)

Stage IS: Marker elevation post orchidectomy (Any pT: N0M0S+). This is seen in approximately 5% of patients after orchidectomy.

Box 2

CT scanning. PET scanning has significant problems with false negativity and therefore has no role in primary tumour staging. In the case of seminoma, PET does have role in assessing the post-chemotherapy residual retroperitoneal mass; a negative scan in this circumstance has a very strong association with post-chemotherapy fibrosis in residual masses.

Management of clinical stage I disease (CSI)

CSI non-seminomatous germ cell tumour (NSGCT)

Risk Stratification: Approximately 30% of patients with NSGCT clinical stage I will have occult micrometastatic disease. There are a number of histopathological risk factors seen in the primary tumour which predict for occult metastatic disease in stage I, including lymphovascular invasion (LVI), the presence of embryonal carcinoma (undifferentiated cells) and the absence of yolk sac elements. A study by Kollmannsberger et al. found the presence of lymphovascular invasion (LVI) was associated with a 44% relapse rate compared to 14% without LVI.[9] LVI is an important validated risk factor and if present with embryonal carcinoma and rete testis invasion is associated with a relapse risk of 50% compared to a relapse rate of 12% without them.[10]

Active treatment schedules involve the use of low-dose adjuvant chemotherapy using one or two cycles of BEP but surveillance is used more commonly. Retroperitoneal lymph node dissection (RPLND) has largely been discontinued in this setting, although some centres in the USA still use this approach. It is rarely used elsewhere, apart from patients with a contraindication to adjuvant chemotherapy or where there are patient compliance issues.

Surveillance in clinical stage I NSGCT: With the use of risk stratification profiles based on histology and markers, it is possible to predict with accuracy of approximately 80% that low-risk cases will not relapse and furthermore, if they do, they can then undergo systemic treatment with chemotherapy with excellent results. Patients relapsing on surveillance are successfully treated with standard chemotherapy and have long-term cure rates of 98%, which is the same as that for primary surgery. In addition, >95% of patients who are going to relapse will do so within the first 2 years of diagnosis of their original cancer.[9] Prolonged and intensive follow up over many years is therefore not required although a degree of follow up is needed because of the risk of late relapse.

Adjuvant treatment for high-risk disease: Surveillance is now the standard of care in most high volume centres for low- and high-risk disease. More recently, some groups have advocated adjuvant chemotherapy using one or two cycles of BEP when high-risk features are present. Concerns about this approach are that 50% of cases who would not have relapsed are exposed to the significant long-term effects of platinum-based chemotherapy. Long-term studies have also shown that the survival of the 50% of high-risk patients who do relapse and require full-dose systemic treatment have an excellent long-term survival.[10]

In the presence of risk factors, 50% of patients surveilled with stage I NSGCTs will relapse. One cycle of adjuvant BEP chemotherapy will reduce the risk of relapse by over 90%, while two courses are even more effective. In 2015 the SWENOTECA group demonstrated that adjuvant treatment can safely be reduced to one cycle of BEP. A reduction in the relapse rate of 90–95% was seen with the benefit of reduced toxicity and decreased need for salvage therapy thus ensuring relapsing patients avoid overtreatment with salvage chemotherapy involving 3–4 cycles of BEP.[11] However, this adjuvant intervention with chemotherapy is associated with measurable short-term toxicity and in the long term, BEP is known to have adverse consequences. While there seems to be benefit for those who will definitely relapse, there is clear and potentially avoidable toxicity for those who would not.

CSI seminoma

Risk stratification: Compared to NSCGTs, seminomas demonstate a more favourable prognosis, they remain localized for longer and approximately 75–80% of patients have stage I disease at initial diagnosis. They tend to metastasize to the retroperitoneal lymph nodes initially with a lower rate of occult metastasis than NSGCTs. They are sensitive to radiotherapy and platinum-based chemotherapy. Adjuvant radiotherapy is no longer used in this setting due to the long-term risks associated with treatment. Single-cycle carboplatin chemotherapy is now recommended as the main intervention for high-risk clincal stage I disease as it has less neurotoxicity, ototoxicity and nephrotoxicity compared to cisplatin chemotherapy, although many clinicians are now adopting surveillance strategies on the basis that 85% of all clinical stage I seminomas will need no intervention at all in the long term. Only about 15% of patients with stage I will relapse without adjuvant therapy. Most recurrences are in the retroperitoneal lymph nodes and are salvageable with BEP. The relapse rate is higher in men with high-risk features (see below).

Surveillance in clinical stage I seminoma: Since 2007, strategies have emerged using a similar approach to those adopted for many years in stage I NSGCT. Observation of patients with clinical stage I seminoma has shown that about 16% are at risk for recurrent disease: the median time to relapse is 12–15

months with 96% of these occurring in the retroperitoneum or inguinal region.

Multivariate analyses of several retrospective observation studies have evaluated and concluded risk factors related to increased rates of disease recurrence. These include:

- Tumour size >4 cm
- Stromal invasion of the rete testis
- Lymphovascular Invasion (LVI)

Patients with these adverse factors have a higher risk of disease relapse. If both risk factors are present, patients undergoing surveillance have a 32% risk of relapse, decreasing to 16% if either risk factor is present and if both risk factors are absent the risk of relapse is only 12%.[12] Prospective studies using risk factors have now also been performed (e.g. by the Spanish Testicular Cancer Group). One-third of the patients in this group's study had neither of the above risk factors: they received surveillance only following orchidectomy. Only 6% of these patients relapsed after a median follow-up of 3 years. The remaining patients, with one or both risk factors, were treated with adjuvant carboplatin chemotherapy, and showed a relapse rate of 3.3%.[13] Studies of this type represent a significant way forward in targeting post-orchidectomy treatment for patients with clinical stage I seminoma who have a high risk of occult metastatic disease at the time of orchidectomy. Strategies to reduce immediate adjuvant treatment in as many patients as possible will confine treatment and treatment related risk to those who need intervention most. This approach has been used to show that if the risk of relapse in patients managed with surveillance is under 10%, the number of follow-up investigations can be reduced. It is, however, notable that in the early surveillance series, patients needed up to 20 CT scans as part of their surveillance protocol and relapses occurred after more than 5 years of follow-up. The TRISST study in the UK is currently evaluating whether a reduced CT schedule or MR surveillance can safely be used in patients with clinical stage I seminoma managed by surveillance.

Adjuvant low-dose chemotherapy: Studies using single agent chemotherapy with carboplatin as an alternative to radiotherapy in CSI seminoma have now shown that this therapeutic strategy is effective treatment for this type of disease. Pilot studies reported the relapse rate for patients treated with single dose carboplatin using dose schedule known as 'AUC7' was 4% (median follow-up of 51 months) and that 99% of patients remained disease free. These results were consolidated in the MRC TE19 study of carboplatin monotherapy versus adjuvant radiotherapy in clinical stage I seminoma. Results showed no statistical difference in recurrence rates. After a mean follow-up of >4 years the relapse rate with a single-cycle of carboplatin at 3 years was 5.2%.[14] For these reasons, single-cycle carboplatin is the first-line treatment for stage I seminoma with high-risk characteristics. It is however notable that a number of relapses occurred after more than two years follow up and further long-term analysis of data is required to assess the true long-term outcome, particularly relating to toxicity and other late sequelae such as the induction of a second malignancy, acquisition of drug resistance in recurrences, the effect on fertility and the impact on quality of life.

Longer-term data relating to the use of this regimen is now becoming available. This shows that there is a higher relapse rate in those patients with higher risk categories and the optimal treatment strategy for this patient group need further study.

Management of metastatic testis cancer – clinical stage II and III

Following initial orchidectomy, tumour markers should be monitored. These should normalize at a rate reflecting the half-life of AFP, hCG and LDH as previously discussed.

Rising tumour markers indicate metastatic disease and these need to be investigated with cross-sectioning imaging to establish the extent of disease. The presence of a contralateral testicular tumour must also be considered as a cause for elevated markers.

Primary combination chemotherapy

As with clinical stage I disease, the management of advanced disease is conducted according to risk stratified protocols. These are based on the collective outcome of >5000 patients with advanced disease, analysed by the International Germ Cell Consensus Collaborators Group and published in 1997 (Table 2).[8] These outcomes have been made possible since the introduction of cisplatin based chemotherapy regimens. Good prognosis patients have the potential for good outcome, with a cure rate of >90% and even intermediate risk patients have a long-term survival >75%. However, patients with high-risk characteristics have a much worse prognosis, with <50% surviving at 5 years.

Standard treatment for metastatic seminoma and NSGCT is with combination chemotherapy although there is still a role for radiotherapy in selected seminoma cases up to clinical Stage IIA (see below). For these patients, treatment involves radiation to the para-aortic region and ipsilateral iliac nodes at a dose of 30 Gy in 2 Gy fractions.[3] However, ongoing concern remains regarding the long-term morbidity associated with this treatment including secondary malignancies and cardiovascular events. Combination chemotherapy is also an option for this cohort with three cycles of BEP or four cycles of EP in older patients or those with pulmonary risk factors. Patients with stage IIB disease should be treated with either 3 cycles of BEP or four cycles of EP as shown by a meta-analysis looking at the efficacy and toxicity of both treatments. Radiotherapy was associated with a slightly improved outcome for stage IIA patients with no difference observed for stage IIB patients.[4] Seminoma with good prognosis is treated with three cycles or BEP or four cycles of EP; 4 x VIP (etoposide, ifosfamide, cisplatin) can be used for intermediate-risk patients if there is a contraindication to bleomycin.

For GCT patients with low volume stage IIA disease it is important that metastasis is confirmed by repeat CT imaging 8 –12 weeks following orchidectomy if the tumour markers are low as reactive para-aortic lymphadenopathy can be misleading. Patients with stage IIA NSGCT are treated with combination chemotherapy with cure rates of ~98%. Primary BEP/EP

IGCCCG Prognostic-based staging system for metastatic germ cell cancer[8]

Prognosis group	Seminoma	Non-seminoma
Good-prognosis group	Any primary site ***and*** no non-pulmonary visceral metastases ***and*** Normal AFP Any hCG Any LDH 90% of seminomas 5-year PFS 82% 5-year Survival 86%	Testis/retroperitoneal primary ***and*** no non-pulmonary visceral metastases ***and*** AFP <1000 ng/ml *and* hCG <5000 iu/l *and* LDH <1.5 × upper limit of normal 56% of non-seminomas 5-year PFS 89% 5-year survival 92%
Intermediate-prognosis group	Any primary site ***and*** non-pulmonary visceral metastases ***and*** Normal AFP Any hCG Any LDH 10% of seminomas 5-year PFS 67% 5-year Survival 72%	Testis/retroperitoneal primary ***and*** no non-pulmonary visceral metastases ***and*** AFP ≥1000–≤10,000 ng/ml *or* hCG ≥5000–≤50,000 iu/l *or* LDH ≥1.5–≤10 × upper limit of normal 28% of non-seminomas 5-year PFS 75% 5-year survival 80%
Poor-prognosis group	No patients classified as poor	Mediastinal primary ***or*** non-pulmonary visceral metastases ***or*** AFP>10,000 ng/ml *or* hCG >50,000 iu/l *or* LDH>10 × upper limit of normal 16% of non-seminomas 5-year PFS 41% 5-year survival 48%

Table 2

Good prognosis	BEP × 3 cycles or EP × 4 cycles (if contraindications to Bleomycin – advanced age, impaired renal function, significant lung disease or current smokers)
Intermediate prognosis	BEP × 4 cycles or VIP (if at risk of pulmonary toxicity)
Poor prognosis	BEP × 4 cycles or VIP (if at risk of pulmonary toxicity) NSGCT only

therapy is recommended for patients with stage IIB disease and normal tumour markers.

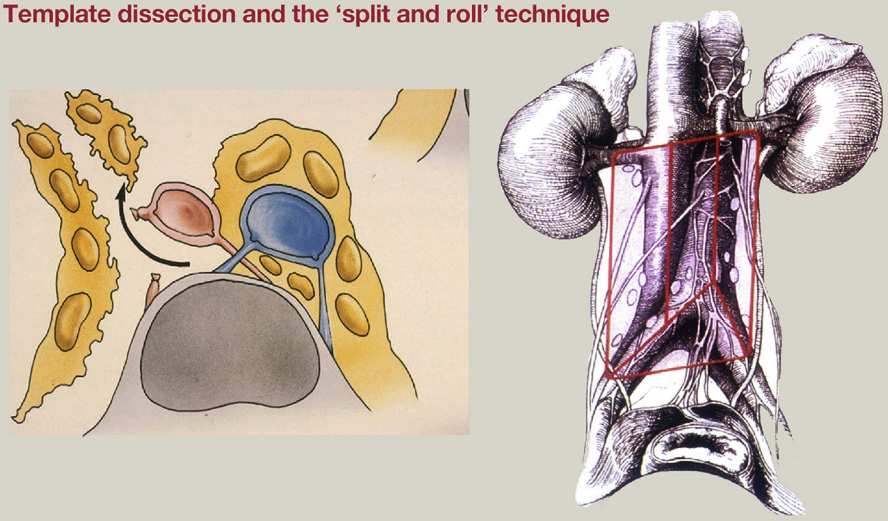
Assessment and treatment of all GCTs following primary orchidectomy should be in high-volume cancer centres with multidisciplinary surgical, non-surgical and nursing oncological teams specializing in the management of testis cancer. There is clear evidence that such centres have better outcomes than those dealing with low numbers of patients. It is also important to emphazise that patients with high-risk disease should be referred to a specialist centre immediately for evaluation and treatment without necessarily having an orchidectomy first.

There is variation in the chemotherapy dosage scheduling but most patients are treated with drugs given by centrally placed parenteral lines with added hydration, osmotic diuretics, antiemetics and antibiotics (usually for the first cycle). Growth factor support is not usually necessary, although it is used in some circumstances. Different combinations have been tried for good prognosis disease (e.g. the GETUG trial of three versus four cycles of BEP) but to date, none of these, including studies of taxanes, have shown superiority in outcome without adding significantly to the toxicity profile. In patients where there is concern about pulmonary function, bleomycin is used with caution or is omitted because of its known toxicity in inducing pulmonary fibrosis.

In intermediate and high-risk tumours attempts have been made to improve outcome in the primary setting by using different schedules and drug combinations and by increasing the dose of the drugs in 'high-dose' combinations. The augmented benefit of such toxic treatment regimens remains to be proven in adequately powered studies.

Late toxicity: Combination chemotherapy has resulted in dramatic improvements in the cure rates of testis cancer but there are long-term toxicities related to treatment. While these are relatively low in frequency, they can be significant and the long-term cardiovascular effects of platinum-based chemotherapy are only now beginning to emerge. They include a doubling of the rate of long-term risks of treatment-related malignancy, a

Template dissection and the 'split and roll' technique



Template dissection and the 'split and roll' technique. The lumbar branches of the aorta and IVC are ligated and divided, enabling rolling and lifting of the great vessels to give access to nodal/tumour tissue behind. Both templates remove all lymphatic tissue from the inter-aorto-caval space. The right template (right sided tumours) has a 'dog leg' configuration based on the IVC and proximal common iliac vessels, sparing the inferior mesenteric artery (IMA). The left template (left sided tumours) has a mirror image configuration sparing the IMA where possible. Salvage RPLND however, often involves ligation and division of the IMA and it is often not possible to use a template because of the extent of the mass.

Figure 4

Treatment options for advanced testis cancer

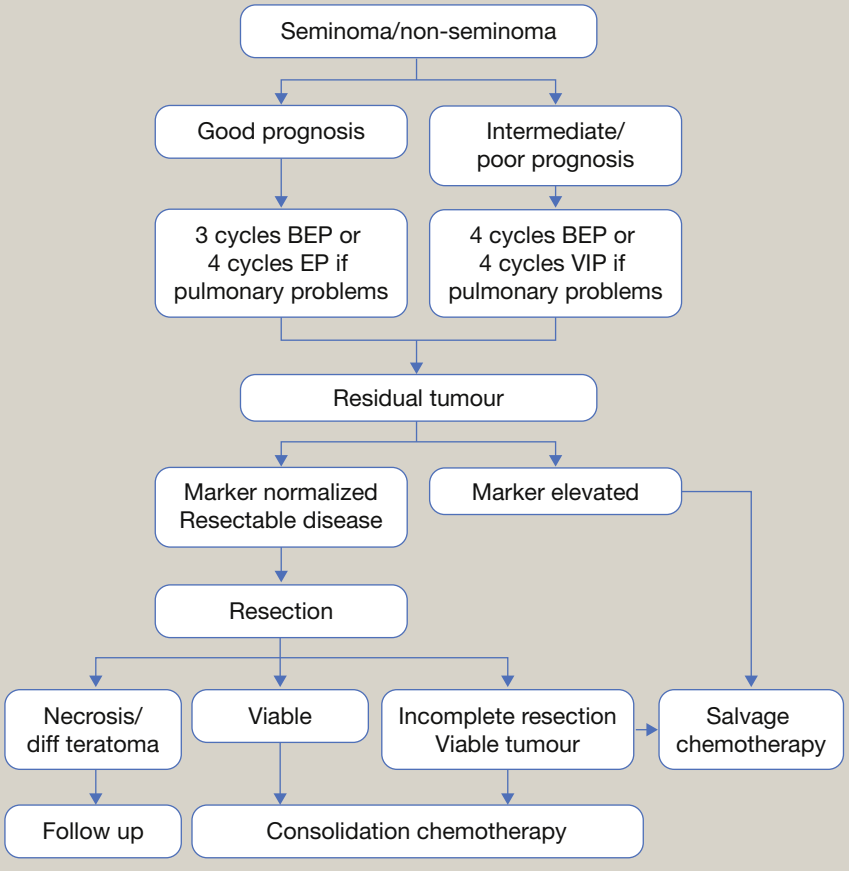


Figure 5

doubling of the long-term cardiovascular risk and additional effects on long-term testicular endocrine, reproductive and psychological function. These must be borne in mind when counselling patients and when planning their long-term survivorship.

Post-chemotherapy resection of residual masses: The rationale for surgical removal of post-chemotherapy residual masses is well established and a critical component of patient treatment. Most resections are required to remove retroperitoneal lymph nodes in a process known as retroperitoneal lymph node dissection (PC-RPLND). Lymph nodes which are persistently enlarged (>1 cm) following primary chemotherapy are removed routinely. This is undertaken because of the risk of persistent active disease, presence of mature teratoma (associated with development of the 'growing teratoma syndrome') and the potential for teratomatous or somatic de-differentiation, which can occur in up to one in five of residual masses if left unresected.

PC-RPLND is not usually indicated in seminoma, where the incidence of fibrosis is very high and the technical challenges are greater.

Resection is usually indicated in NSGCT for residual masses of 1 cm or more. Pathological analysis shows that the residual masses contain mature teratoma in 50%, necrotic fibrotic tissue in 40% and vital cancer in about 6–10%.[3] Resections in this setting are usually curative if all the residual disease is removed and the overall outcome is better if resection is undertaken early rather than when residual lesions show signs of progression. Imaging is usually undertaken 6–8 weeks after the last chemotherapy cycle and surgery is not usually undertaken if the tumour markers have not normalized. In these circumstances further chemotherapy is given before assessment of response and surgery if appropriate at that time. The surgery is technically challenging and should not be undertaken outside specialist centres. It involves full mobilization of the great vessels using the 'split and roll' technique (Figure 4) and resection of concomitant structures (kidney/bowel/vena caval resection/aortic replacement) are required in some circumstances. There is debate as to whether bilateral or template based PC-RPLND should be used. Bilateral procedures induce ejaculatory failure but there is a small risk of leaving vital disease using template methods in all cases. Large-scale data has now shown that template techniques are quite safe when used in selected cases (e.g. masses confined to the ipsilateral landing sites of up to 5 cm in diameter). Following resection the long-term outcome is good if all disease can be resected, but if there is residual vital disease left after surgery the long-term outcome is poor if there is residual vital tumour.

Salvage strategies: Salvage treatment is used for early (<2 years) or late (>2 years) relapse (Figure 5). Early relapse is usually due to platinum resistance, which may be complete at the outset or apparent after an initial response to primary treatment. In establishing a diagnosis of 'relapse' it is vital to be aware of the pitfalls which can mimic disease persistence or recurrence. These include the growing teratoma syndrome, whereby residual masses increase in size after chemotherapy because of cystic change and transformation from active to mature teratoma, false positive marker relapse, new pulmonary nodules arising secondary to bleomycin and elevations in tumour markers from a metachronous new primary testicular cancer. Approaches to treatment involve re-challenge with cisplatin-based chemotherapy, acceleration of cisplatin dose, use of newer drugs including combinations of ifosfamide, paclitaxel, gemcitabine and oxaliplatin, high-dose chemotherapy and 'desperation' surgery. There is evidence that high-dose regimens may confer a benefit of around 10% and that sequential HDC may be advantageous. However, these are toxic regimens and they carry a significant mortality of themselves. Salvage 'desperation' surgery is indicated but only in the very limited circumstances where there is a feasible chance of resecting all residual tumour tissue. Patients generally do not benefit from this type of extensive surgery if all disease cannot be removed.[15]

Late relapse (defined as relapse following complete remission with chemotherapy occurring 2 years or more after treatment) occurs in approximately 3% of all cases. This is often associated with 'somatic transformation'. This is the de-differentiation of the cancer cell type to a specific sub-type (most commonly adenocarcinoma or sarcoma). Treatment of this tumour type is with surgery to remove the mass en-bloc with affected structures if this is possible. If it is cure is possible in up to 50%. Treatment with chemo or radiotherapy is not effective in this type of relapse: tissue sampling with CT-guided biopsy may be very helpful in this setting.

Conclusion

Testis cancer is a rare tumour in general but it is the most common cancer in young men. With early diagnosis and appropriate treatment in expert centres the long-term results are excellent in good prognosis cases. In intermediate prognosis disease the majority of patients are cured long term but in poor prognosis testis cancer, mortality is still significant and new approaches are required. By comparison with the outcomes from recent history in this disease, the advances in the last 40 years of testis cancer treatment are a testimony to the benefits of collaborative translational science, clinical trial planning and risk adapted therapeutic approaches. ◆

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