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CLINICAL REVIEW

Testicular germ cell tumours

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Testicular germ cell cancer affects mainly young men, with 85% presenting between 15 and 44 years of age. The incidence of this disease is increasing—the lifetime risk for a man is now about one in 200 in the United Kingdom.[1] Presentation is usually with a painless lump. If the tumour is diagnosed early, more than 95% of men are cured and treatment can be less intensive. Recent management changes include avoidance of radiotherapy, although cured patients still have increased risk of cardiac problems and second cancers. Some patients also experience chronic side effects of chemotherapy, such as neuropathy, hearing loss, renal impairment, and borderline hypogonadism. This article will review how testicular cancer presents, how it is diagnosed, and what treatments are available, including recent management changes to minimise toxicity.

What kinds of cancer arise in the testis?

This review covers germ cell cancers, which make up almost all testicular cancers seen in young men. Germ cell tumours are classified as pure seminomas or non-seminomas, which include variants such as embryonal carcinoma, teratocarcinoma, yolk sac tumour, choriocarcinoma, and teratoma. Tumours may contain one or more of these elements; those with both seminoma and non-seminoma components are managed as non-seminomas. Spermatocytic seminoma tends to occur in older men and is rarely, if ever, malignant.

In older patients, primary lymphomas of the testis become more common; a study from the Danish population based non-Hodgkin's lymphoma registry found that the median age at presentation was 71 years.[2] Tumours arising from endocrine structures, such as Leydig cell tumours or Sertoli cell tumours, can occur at various ages but are uncommon and usually benign. Rare tumours arising in paratesticular structures include rhabdomyosarcomas in children and liposarcomas in older men.

How does testicular germ cell cancer present?

More than 95% of these cancers present with a lump in the body of the testis.[3] The lump is usually painless but may cause episodic pains, possibly due to haemorrhage, and occasionally may mimic epididymo-orchitis or cause a hydrocele. Rarely, these cancers present with symptoms from metastases, such as backache from enlarging abdominal lymph nodes or chest symptoms from lung metastases such as cough, pain, or haemoptysis. Human chorionic gonadotrophin (HCG) production by the tumour can cause nipple tenderness and gynaecomastia. Less than 5% of germ cell tumours arise from an extragonadal primary site, such as the retroperitoneum or mediastinum.[4] Germ cell cancers are more common in men who have had a germ cell cancer of the contralateral testis, men with a first degree relative who has had testicular germ cell cancer, and those with a history of testicular maldescent.[5]

The testicular lump is usually noticed by the patient. Because of the lack of pain, medical consultation is often delayed, typically for several months.[6] Delay can influence the stage of the cancer and survival in men with non-seminomas. The diagnosis is suspected on physical examination of the testis when a discrete lump is palpable within the body of the testis. Differential diagnoses include cysts and inflammatory swellings of the epididymis, which may be tender and separable from the body of the testis. Analysis of 1017 patients seen at a rapid access testicular clinic included 203 referred because of "testicular lump" and 41 referred using a two week wait proforma because of suspected cancer. Eleven radical orchidectomies were performed and 10 of these men had malignant disease.[7]

How should a testicular lump be investigated?

National Institute for Health and Care Excellence (NICE) guidelines recommend that any patient with a swelling or mass in the body of the testis should be referred urgently for investigation. Consider urgent ultrasound in men with a scrotal mass that does not transilluminate or when the body of the testis cannot be palpated, such as when there is a reactive hydrocele. Suspected tumours can be confirmed by scrotal ultrasound (fig 1⇓), which is the modality of choice for evaluating scrotal

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Summary points

- Testicular germ cell cancers occur mainly in young men
- Presentation is usually painless and the diagnosis can be confirmed by ultrasound
- Inguinal orchidectomy may be sufficient treatment in those with no evidence of metastases
- These tumours are sensitive to chemotherapy and radiotherapy, and even men with metastases are usually cured
- Men cured of metastatic disease have an increased risk of cardiac events and of second non-germ cell cancers

Methods

We searched our personal archives of references relating to the epidemiology, diagnosis, and management of testicular germ cell cancers as well as the Cochrane Database for reviews or meta-analyses. We also reviewed guideline publications from the European Society of Medical Oncology and the European Germ Cell Cancer Collaborative Group.

disease and has a sensitivity of almost 100% in diagnosing testicular cancer.[8]

Tumour markers, such as HCG or α fetoprotein, are often detectable on blood tests. The combination of a testicular lump and an increased concentration of HCG or α fetoprotein indicates a germ cell tumour. However, α fetoprotein is not increased in seminomas and HCG is raised in less than a quarter of cases[9]; in addition, about a third of non-seminomas are marker negative.[9] Because normal marker levels do not exclude testicular cancer and these markers are raised in other cancers and some benign conditions, they are not clinically useful in community practice.

How is the diagnosis of testicular cancer confirmed?

Testicular cancer is diagnosed on the basis of the results from the above tests. The diagnosis is not confirmed by a biopsy, and standard initial management is orchidectomy in continuity with the spermatic cord, performed with an inguinal approach. It is a day case procedure performed under general anaesthesia. Normal testosterone concentrations are usually maintained by the contralateral testis. Partial orchidectomy may be considered in a patient with only one testis or in the rare circumstance of bilateral tumours at presentation.

What needs to be discussed before orchidectomy?

In the context of a normal contralateral testis, a unilateral orchidectomy should not cause infertility or abnormally low testosterone concentrations. If there is particular concern, and especially if chemotherapy may be needed, men can be referred for sperm cryopreservation. Testosterone concentrations can be monitored after orchidectomy and replacement testosterone products, such as three monthly depot testosterone undecanoate, can be prescribed.

Scottish Intercollegiate Guidelines Network (SIGN) guidelines suggest that a prosthesis should be offered.[10] A retrospective questionnaire review of 424 men post-orchidectomy included 71 who had received a prosthesis[11]; about 70% were satisfied, but 30% were unhappy about the shape or size of the implant and 25% were unhappy with the position or weight. Of those who had not been offered an implant, 64% said they would have accepted one, but two thirds of them did not feel this wish was strong enough to merit a second surgical intervention.

How is testicular cancer staged?

Staging is undertaken after orchidectomy and requires a computed tomogram of the thorax, abdomen, and pelvis (fig 2⇓) and repeat tumour markers (table 1⇓).[9] Raised markers should fall after orchidectomy—HCG and α fetoprotein have half lives of less than two days and about five days, respectively. Persisting or rising concentrations indicate metastasis even if a computed tomogram is normal. A positive positron emission tomography scan or retroperitoneal node biopsy can clarify equivocal lymph nodes, although these are not part of standard staging.

Germ cell cancers are now being diagnosed at an earlier stage and about 75% of patients present without evidence of metastases—that is, at stage I.[12] The first site of metastasis is typically the para-aortic lymph nodes. Tumour staging influences prognosis and treatment. Seminomas rarely present with metastasis beyond the retroperitoneal lymph nodes, whereas lung metastases are seen in about 15% of non-seminomas at presentation, and less commonly liver and brain metastases are found.

Who needs adjuvant treatment?

The risk in stage I patients is that they may harbour microscopic metastases. There are two main strategies to manage this risk—adjuvant chemotherapy or surveillance (reserving treatment for relapse).[13 14]

Non-seminoma

In a minority of centres in some countries a staging lymph node dissection is considered, but it has the perceived disadvantage of being major surgery followed by the need for surveillance or adjuvant chemotherapy. A prospective randomised trial compared retroperitoneal node dissection with adjuvant chemotherapy in 382 patients and found recurrence rates within two years of 1% and 8%, respectively.[15]

With stage I non-seminoma, an overview analysis of multiple surveillance studies found an overall relapse risk of about 30% or 50% in men with lymphovascular invasion.[16] Relapse can be treated successfully by chemotherapy, with cure rates close to 100%.[17] Surveillance avoids unnecessary treatment in the 70% of men who will not need it, but it must be continued for five years, which some men find stressful. Others do not adhere to the surveillance protocol, risking recurrence with advanced disease.

An argument for the alternative strategy of adjuvant chemotherapy is that less chemotherapy is needed in the adjuvant setting than when patients relapse. A multicentre prospective Medical Research Council study established the

A patient's perspective

I discovered a swelling in my right testicle after falling on a rugby ball, and although I thought it was unlikely to be testicular cancer, I visited my general practitioner and was sent for an ultrasound. I had an orchidectomy as a day case and had no serious discomfort. Histological analysis showed that the testicle was cancerous.

I was sent to a specialist hospital for further treatment. This involved having a positron emission tomography scan, which I was worried about. Thankfully the results came back quickly and showed that I was fit and well. However, I was asked if I wanted chemotherapy as a precaution. After further discussion, I decided to have my abdominal lymph nodes removed to identify any secondary tumours. Although a major operation, I was in hospital for only five days and recovered quickly.

I received chemotherapy over the next three months and was fine until the third course, which took about four weeks to get over. I am now in remission and feeling fine, a bit achy with some loss of feeling in my toes. The tinnitus I was warned about was well managed by spreading the chemotherapy and doesn't cause any real problems. I feel "lucky" to have had this form of cancer—from the outset the doctors were confident of cure, which gave me confidence. After my first surveillance check all seems well thanks to the care and professionalism of the team who looked after me and the fantastic support of my family.

efficacy of two cycles of bleomycin, etoposide, cisplatinum in the adjuvant setting, with a relapse risk of less than 2%.[13] However, recent studies suggest that a single cycle may be equally effective. A large prospective randomised German multicentre trial reported a relapse risk of only 1% after one cycle of bleomycin, etoposide, cisplatinum.[18]

Seminoma

Several large prospective cohort studies in men with stage I seminoma show that the relapse rate on surveillance is about 18%,[19] higher in larger tumours. Seminomas are more indolent than non-seminomas, and radiological surveillance must continue for more than five years. The Royal Marsden Hospital surveillance regimen (fig 3⇓) includes three monthly outpatient visits for the first two years after orchidectomy, four monthly visits in the third year, and six monthly visits until five years. However, as for non-seminoma tumours, there are concerns that those who relapse require more anticancer treatment than with the adjuvant approach.

An alternative adjuvant strategy for stage I seminoma has also been investigated—a single dose of the low toxicity drug carboplatin, to which seminomas are particularly sensitive. Carboplatin at the moderate dose needed does not cause alopecia, nephrotoxocity, neuropathy, or hearing loss. Follow-up from a large randomised trial showed that the relapse-free rate at five years was 94.7% with carboplatin compared with 96% for adjuvant radiotherapy.[20] Thus, patients with stage I seminoma can be advised that surveillance is associated with a relapse risk of one in six compared with one in 25 after a single cycle of carboplatin. Agreed guidelines, such as those from the European Society of Medical Oncology or SIGN, recommend that management choice is based on discussion of these issues between the clinician and patient with both surveillance and adjuvant therapy curing about 99%. Many centres use a risk based approach, with adjuvant chemotherapy reserved for those with highest risk, such as those with larger tumours. The Spanish Germ Cell Group evaluated such an approach in a prospective multicentre study and found a recurrence rate of 7% in low risk patients on surveillance compared with 1% in high risk patients after adjuvant carboplatin.[21]

Reducing radiation

Until recently, standard adjuvant treatment for stage I testicular seminoma comprised abdominal radiotherapy, which achieved cure in 95% of men. Worries about the carcinogenic effects of radiation led to prospective multicentre trials that evaluated the impact of reducing the dose of radiation and the extent of the radiation field.[22] These established the efficacy of only 20 Gy in 10 fractions over two weeks, confined to a field that included the para-aortic nodes but spared the pelvic organs.[23 24]

What problems are associated with surveillance?

Failure to adhere to rigorous surveillance protocols may result in recurrence with advanced stage disease. A prospective UK study of 184 men who completed a range of questionnaires initially, and whose clinic attendance was subsequently analysed,[25] found no significant differences between attenders and non-attenders in most psychosocial and medical variables. However, a highly significant association was seen between non-attendance and a patient's perception of an unsatisfactory affective relationship with his clinician (P=0.005; hazard ratio 3.1, 95% confidence interval 1.4 to 6.6). This was shown by the level of agreement with statements in the medical interview satisfaction scale such as "The doctors are people I would trust with my life."

How effective is chemotherapy in metastatic disease?

More than 80% of men with metastatic germ cell cancer are cured.[26] This is due to exquisite sensitivity to cisplatinum based combination chemotherapy. The standard regimen for metastatic disease is three or four cycles of cisplatinum, etoposide, and bleomycin repeated every 21 days. If scans show any residual masses, surgery is considered. The high dose of cisplatinum requires intensive saline hydration to prevent nephrotoxicity. Previously this involved inpatient care for three to five days. Nowadays, in suitable patients, administration is on an outpatient basis with hydration supplemented orally.

Using a database of more than 5800 patients, relapse rates of 18-33% and 11-59% were found in seminoma and non-seminoma, respectively, after initial chemotherapy.[26] An international prognostic classification based on this information is now used to guide the intensity of chemotherapy for patients with metastatic disease. Prognostic groupings are based on serum concentrations of the tumour markers, α fetoprotein, HCG, and lactate dehydrogenase, as well as the presence of non-pulmonary visceral metastases or a mediastinal primary. Patients are classified into good, intermediate, and poor prognostic groups (table 2⇓) and 48-99% can expect to survive. Patients who do not respond to first line chemotherapy may still be cured, so overall survival is higher than progression-free survival.

What if there are residual masses after chemotherapy?

Residual masses after chemotherapy for non-seminoma may consist of necrotic or fibrotic tissue, but may also contain residual active cancer cells or teratoma (differentiated). Removal is recommended, because current imaging modalities cannot

reliably differentiate between these diseases. Teratoma is chemoresistant and resection prevents growth and risk of carcinomatous or sarcomatous transformation. The operation—generally referred to as a retroperitoneal lymph node dissection—requires a laparotomy, is a complex procedure, and patients must be referred to a specialist centre. A specific complication of this operation is retrograde (or dry) ejaculation. This can sometimes be avoided by a nerve sparing procedure. The operation can be performed in selected cases by laparoscopic or robotic surgery, but not when major vascular structures (such as the aorta, vena cava, and renal vessels) are involved. Residual masses at sites other than the abdominal lymph nodes (such as the chest) require similar management.

In seminoma, surgery is not usually recommended for residual masses, which are usually benign and associated with a dense fibrotic process obscuring anatomical planes.

How are patients who do not respond to initial chemotherapy treated?

Second line chemotherapy, often with surgery, can salvage about half of recurrences.[27] The chance of cure depends on the extent of disease at relapse and initial sensitivity of the disease. A recent multivariate analysis identified five prognostic groups with a chance of cure, varying from less than 10% to over 70%.[28] Relapses are challenging, requiring referral to specialist centres. Salvage chemotherapy usually involves further cisplatin, so the risk of chronic toxicities is high. The usefulness of high dose chemotherapy with autologous stem cell support is the subject of much debate and controversy. It has not yet been established in a prospective randomised trial, but pilot and retrospective studies have reported promising results.[29] Recent studies have shown that a small number of patients relapse late (defined as after two years, but sometimes after 10 years or more).[30] These relapses tend to be chemoresistant and surgical resection is recommended as primary treatment.

What are the side effects of combination chemotherapy?

Side effects depend on the choice of anticancer drug and total dose. For the standard germ cell regimen of bleomycin, etoposide, and cisplatinum, the side effects include nausea and vomiting, alopecia, fatigue, rashes and skin pigmentation, and neutropenia and thrombocytopenia. Gastrointestinal side effects are less problematic since the development of neurokinin antagonists (such as aprepitant) and serotonin antagonists, usually given together with steroids.[31]

Bleomycin may cause pneumonitis in some patients (during or within a few months of completing chemotherapy), so chest symptoms require urgent specialist assessment.[32] This drug can also affect the vasculature and lead to Raynaud's phenomenon.[33]

Cisplatinum can cause a peripheral neuropathy and ototoxicity, characteristically a loss of high tone sensitivity, both of which can persist and require specialist referral. Standard chemotherapy causes azoospermia, although men treated with no more than four cycles usually recover spermatogenesis,[34] and as a precaution men can be offered sperm cryopreservation before chemotherapy. An analysis of 170 patients who were re-assessed at least one year after chemotherapy showed that of 89 patients whose pre-chemotherapy sperm counts were normal, the post-chemotherapy count was normal in 64%, reduced in 16%, and zero in 20%. There was clear evidence for continued recovery beyond one year; the probability of spermatogenesis increased to 48% by two years and 80% by five.[34]

These concerns have led to studies aimed at maintaining cure rate with less toxicity.[35] A large prospective trial showed that for metastatic disease with a good prognosis, three cycles of bleomycin, etoposide, and cisplatinum are as effective as four.[36] For men who present with advanced disease and a poor prognosis, more intensive chemotherapy schedules have been evaluated,[37 38] although high dose treatments have not been proved to be beneficial.[39]

What are the long term health consequences in testicular cancer survivors?

Most survivors of testicular cancer regain a normal quality of life. A proportion of patients become hypogonadal after orchidectomy,[40] and this is likely to affect quality of life.[41] Testosterone concentrations clearly below the normal range should be treated, but the benefit of correcting borderline low values (7-12 nmol/L; 1 nmol/L=28.82 ng/dL) is uncertain and the subject of a current UK trial (TRYMS). Fertility may be reduced after chemotherapy, with risk depending on dose and type of chemotherapy.[34] Peripheral neuropathy, Raynaud's phenomenon, and hearing loss as a result of chemotherapy may persist for years.[33]

The risk of developing a second (non-germ cell) cancer is doubled in those who were treated in the past with standard chemotherapy regimens or radiotherapy.[42] For those who had radiotherapy the risk is to organs in the radiation field. After chemotherapy the risk includes leukaemias, lung cancer, and melanoma.[43] There is also an increased risk of cardiac events. A cohort study of UK survivors found a relative risk of cardiovascular disease of 2.6 after chemotherapy and 2.4 after radiotherapy.[44] The cause of this increase is not clear, but an increased rate of metabolic syndrome has been noted after treatment.

The increased risk of cardiovascular disease and a second cancer is similar to the risk seen from long term smoking. More comprehensive studies of the health of survivors of testicular cancer are needed.[45] Patients should be counselled with respect to lifestyle, strongly advised not to smoke, and screened for other cardiac risk factors.

A review of reports on problems encountered by survivors of testicular cancer found overall quality of life scores similar to those in the general population, but that anxiety associated with fear of recurrence, economic worries, alcohol misuse, and sexual difficulties were more common in survivors.[46]

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Tips for non-specialists

Refer patients with testicular lumps to a urologist under the two week suspected cancer referral pathway

Patients may present with gynaecomastia owing to the production of human chorionic gonadotrophin, or with backache or chest symptoms from metastases

Assessment of a germ cell cancer includes histological review; computed tomography of the thorax, abdomen, and pelvis; and monitoring of serum tumour markers

Cure rates are more than 90% even in those with metastases, but treatment can be less intensive when disease is diagnosed at an earlier stage

Ongoing research

Germ cell cancers are more common in first degree relatives of affected men and genetic studies are trying to identify predisposing genes

Because surveillance for stage I seminoma seems to be a safe and practicable option, an ongoing Medical Research Council (MRC) trial, TRISST, is investigating the optimal radiological techniques and schedule

There is limited evidence that a single cycle of bleomycin, etoposide, and cisplatinum is sufficient in the adjuvant setting to prevent recurrence in stage I non-seminoma, and further supportive evidence will come from the current MRC prospective 111 trial

The risks of cardiac events and second cancers were increased in patients given curative treatment before 1990, and we need to determine whether newer chemotherapy and radiotherapy regimens have reduced these risks. We also need a better understanding of the mechanisms underlying these toxicities

Additional educational resources

Resources for healthcare professionals

European Association of Urology Guidelines. Testicular cancer. 2012 edition. www.uroweb.org/guidelines/online-guidelines/

Beyer J, Albers P, Altena R, Aparicio J, Bokemeyer C, Busch J, et al. Maintaining success, reducing treatment burden, focusing on survivorship: highlights from the third European consensus conference on diagnosis and treatment of germ-cell cancer. *Ann Oncol* 2013;24:878-88

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Resources for patients

The following websites all provide patient information resources:

Cancer Research UK (www.cancerresearchuk.org/cancer-help/type/testicular-cancer/)

Macmillan Cancer Support (www.macmillan.org.uk)

Healthtalk online (www.healthtalkonline.org/cancer/testicular_cancer)

Everyman (www.everyman-campaign.org/)

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Tables

Table 1| Staging classification[10]

Stage	Characteristics
Stage I	No disease outside testis
Stage IM	No disease found outside testis but rising post-orchidectomy tumour markers
Stage II	Infradiaphragmatic nodes
Stage III	Supradiaphragmatic nodes
Stage IV	Extranodal metastases

The American Joint Committee on Cancer staging system, commonly used internationally, includes both supradiaphragmatic node metastasis and extranodal metastases as stage III and has no stage IV.

Table 2| **Cure rates in testicular germ cell cancers**

Type of disease	Seminoma	Non-seminoma
Stage	99%	99%
Metastatic:		
Good	86%	92%
Intermediate	72%	80%
Poor	—	48%

Figures

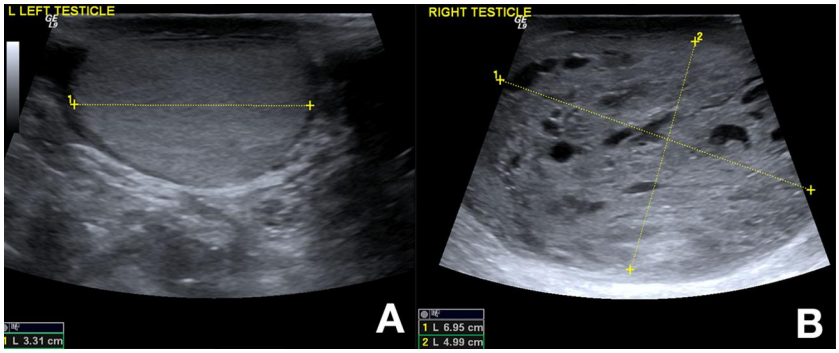

Fig 1 Testicular ultrasound scan of patient with normal left testis (A) and a germ cell tumour in the right testis (B)

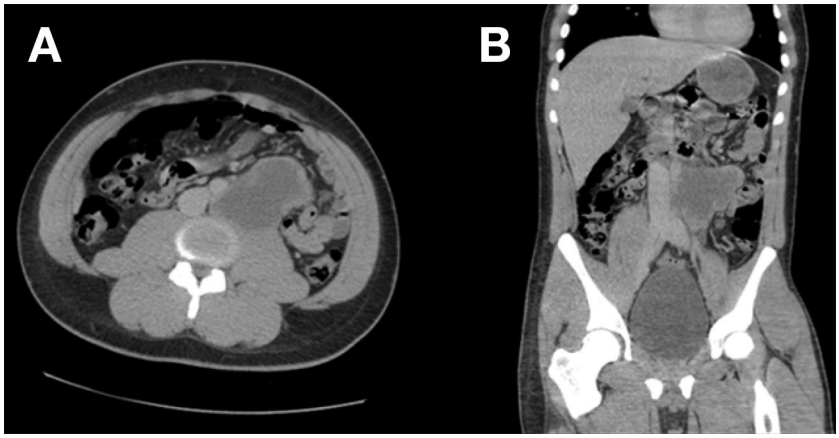

Fig 2 Axial (A) and coronal (B) computed tomograms showing a left sided retroperitoneal metastasis, which was causing backache

Month	Clinical	Markers	Chest radiography	CT abdomen
3	○	○		
6	○	○	○	○
9	○	○		
12	○	○	○	○
15	○	○		
18	○	○	○	○
21	○	○		
24	○	○	○	○
28	○	○		
32	○	○		
36	○	○	○	○
42	○	○		
48	○	○	○	○
54	○	○		
60	○	○	○	○
72	○	○		
84	○	○		
96	○	○		
108	○	○		
120	○	○		

Fig 3 Surveillance follow-up schedule after orchidectomy for seminoma. Computed tomography (CT) scans should be of the abdomen only unless the pelvis at risk. Markers: α fetoprotein, β human chorionic gonadotrophin, lactate dehydrogenase