Testis cancer
assessment and management

The improved survival rate of patients with testis cancer should be regarded as one of the successes of modern oncology; however, this cancer still claims lives and creates a major psychological burden for affected men and their families.

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Testicular cancers are relatively uncommon, although not rare, malignancies accounting for about 1 to 2% of all cancers in men. *Urology News Online* estimated that a GP in the UK sees on average one case of testicular cancer every 21.4 years in practice. However, in Australia, testicular cancer is one of the most common forms of cancer in men aged 15 to 45 years, with an age-standardised rate in 1998 of 5.3 per 100,000 men, and a lifetime risk of about 1 in 250 of being diagnosed with the disease.

The median age at diagnosis is 33 years, with a peak age range of 15 to 45 years of age. The disease is responsible for roughly 10% of all cancer deaths in men aged between 15 and 35 years of age.

The incidence of testicular cancer has been increasing at a rate of 2.5% annually for many years, due to unknown factors. It is also subject to geographical variations in incidence, being most common in Northern European and Scandinavian countries, intermediate in the UK, Australia and the USA, and lowest in Asia and Africa.

Most testis cancers in young adults are of the germ cell variety, with the peak incidence of non-seminomatous germ cell tumours (NSGCTs) being in those aged 25 to 29 years of age and seminomatous germ cell tumours in those aged 35 to 39 years of age. Beyond the age of 65 years, most malignancies are of a non-germ cell type, most typically lymphoma.

Aetiology

Risk factors associated with testis cancer are listed in the Table. The most documented risk factor is cryptorchidism; about 10% of men with testis cancer have a history of this condition. Research has shown that a man with a history of cryptorchidism has a four to five times increased risk of developing testis cancer than a man with a normally descended testis. Those children with cryptorchidism whose testes descend spontaneously or who have early orchidopexy

IN SUMMARY

- **Patients with testis cancer usually present with a painless, hard, swollen mass in the testis.**
- **Initial investigations comprise testicular ultrasonography and assessment of the tumour markers beta-human chorionic gonadotropin and alpha-fetoprotein.**
- **Once testis cancer has been diagnosed patients should be referred to a urologist for staging investigations and surgical orchidectomy.**
- **After orchidectomy, patients with stage 1 non-seminomatous tumours usually undergo surveillance, while those with stage 1 seminomas usually undergo adjuvant radiotherapy.**
- **The use of cisplatin has revolutionised the treatment of metastatic testis cancer.**
- **Survival rates for patients with early disease approach 100% and for those with advanced disease range from 70 to 95%.**

MedicineToday **PATIENT HANDOUT**

Testicular self-examination

Testicular cancer has a very good cure rate if it is found and treated early. It is important that young men check their testes each month for any lumps or swellings, and if they are concerned, they should see their doctor straight away.

- A testicular self-examination is a quick and simple process that may be easier after a warm bath or shower when the skin of the scrotum is relaxed.
- It is important that both testes are checked, one at a time.
- Using the palm of your hand, support your scrotum. Try to become familiar with the texture and size of each testis. If there is any change to how it feels normally, see your local doctor.
- Gently roll one testis between your thumb and fingers to feel for any lumps or swellings in or on the surface of the testis. Repeat with the other testis. The testes should feel firm and the surface smooth.
- Using your thumb and fingers, feel along the epididymis at the back of the testis. The epididymis is a soft, highly coiled tube that carries sperm from the testis to the vas deferens. Check for any swelling in this area.
- Even if you have had testicular cancer, or are being treated, it is still important to perform a testicular self-examination because there is about a 5% chance of testicular cancer developing in the other testis.

NOTE: It is normal for one testis to be slightly bigger than the other.

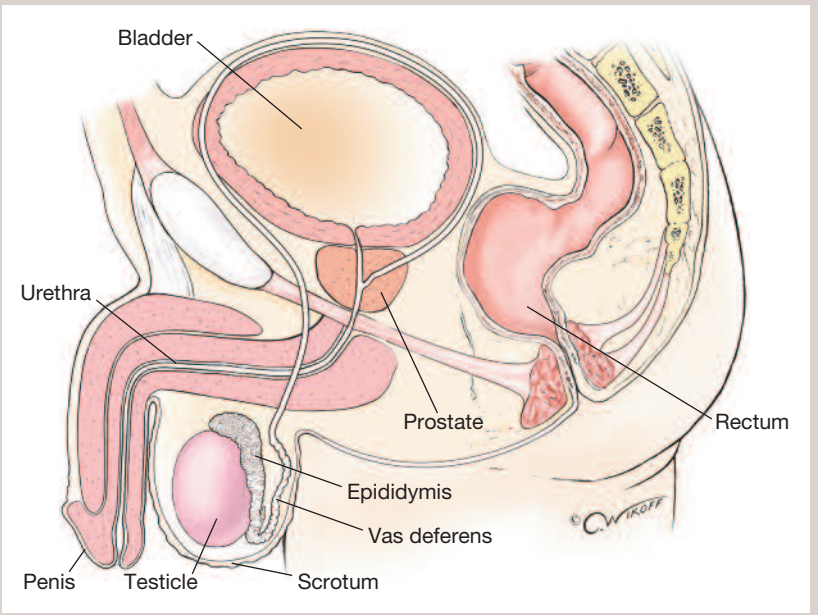

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Figure A. The male reproductive system.

Table. Testis cancer: main risk factors

- Cryptorchidism
- History of contralateral testis cancer
- Subfertility
- Low birth weight
- Infantile hernia
- Family history

usually have rates of testis cancer comparable to that of the general population. The risk of testis cancer is higher in men with abdominal rather than inguinal maldescent cryptorchidism, and in those with bilateral rather than unilateral cryptorchidism.

Presentation and assessment

Characteristically patients with testis cancer present with a painless, hard, swollen mass within the testis. A smaller percentage of patients complain of pain secondary to haemorrhage within the tumour. While there is no solid evidence base that testicular self-examinations will necessarily reduce testicular cancer mortality, it is certainly reasonable to educate young men about the anatomy of their genitalia so that they can be more aware when a testicular lump occurs and attend their GP. A guide regarding testicular self-examination is provided in the patient handout on this page.

At presentation patients should be assessed for metastatic disease, looking particularly for a history of abdominal or back pain (consider retroperitoneal lymphadenopathy), or haemoptysis or dyspnoea (consider lung metastases).

Examination should assess both testes (Figure 1), the presence or absence of abdominal or supraclavicular lymphadenopathy, and other signs, such as gynaecomastia and galactorrhoea (which could signify a high beta-human chorionic gonadotropin [βhCG] level associated with choriocarcinoma).

Initial investigations

In general practice the initial investigations should comprise testicular ultrasonography (Figures 2a and b) and assessment of testis tumour markers – namely, βhCG and alpha-fetoprotein (AFP). These markers are not always elevated in patients with testis cancer, but if they are, they provide a useful indication postoperatively of the success of disease eradication and a guide to tumour pathology. Notably:

- AFP is never elevated in patients with seminomas
- exceptionally high AFP levels usually signify a yolk sac tumour
- exceptionally high βhCG levels are indicative of choriocarcinoma
- lower levels of AFP and βhCG tend to signify a NSGCT.

The extent of marker elevation is also prognostic. Levels of βhCG exceeding 50,000 IU and AFP levels exceeding 10,000 IU usually signify poor prognosis, high-risk disease, based on the International Germ Cell Cancer Consensus Prognostic Classification.

Staging investigations and pathological assessment

Once testis cancer has been diagnosed, patients should be referred to a urologist, who will consider staging investigations – that is, CT of the chest, abdomen and pelvis.

Surgical exploration and orchidectomy provide a specimen for formal pathological diagnosis, as well as definitive treatment in many men. The lesion is removed via an inguinal incision to allow control of cord structures before the tumour is handled, thus avoiding possible spread (Figures 3a and b).

Before surgery some consideration should be given to whether the patient wishes to have a testicular prosthesis inserted for cosmetic and psychological reasons. Organ sparing surgery should only ever be considered in patients with a solitary testis and normal testosterone levels, and is often followed by adjuvant radiotherapy.

Pathologically, roughly 40% of all cancers are seminomas, 35% NSGCTs, 15% mixed germ cell tumours, 5% non-germ cell tumours (e.g. Sertoli cell tumours and Leydig cell tumours) and 5% secondary tumours such as lymphomas. The management of this latter group of tumours is beyond the scope of this article and not discussed further.

Seminomas are usually firm, grey-to-white and homogeneous (Figure 4a). Histologically the tumour is generally made of large clear cells arranged into broad sheets, separated in part by connective tissue septa (Figure 4b). Fifteen per cent of seminomas contain syncytiotrophoblastic cells and, therefore, may stain positively for βhCG.

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Figure 1. On examination, a testicular cancer does not exhibit brilliant transillumination (in contrast to a fluid filled swelling).

NSGCTs comprise a constellation of different germ cell tumours including embryonal carcinomas, yolk sac tumours, choriocarcinomas, and malignant teratomas. About 50 to 60% of patients with these tumours present with elevated markers.

The discovery of a preinvasive stage of testis cancer was made in 1972 and named carcinoma *in situ* (CIS); more recently it has been called intratubular germ cell neoplasia. Originally it was found adjacent to testis tumours; now it has been identified in the contralateral testis of men with testis tumours. Present experience indicates the need to look for this, particularly in infertile men with atrophic contralateral testes, those with low sperm counts and those with a

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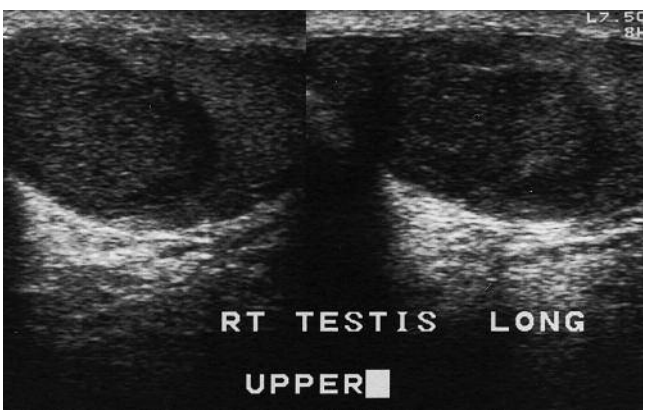

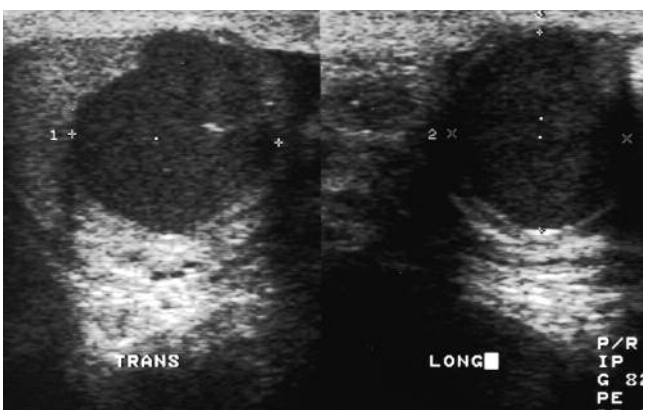

Figures 2a and b. Ultrasound scans showing a well-defined hypoechoic solid mass arising within and expanding the testis. These are virtually always testicular tumours.

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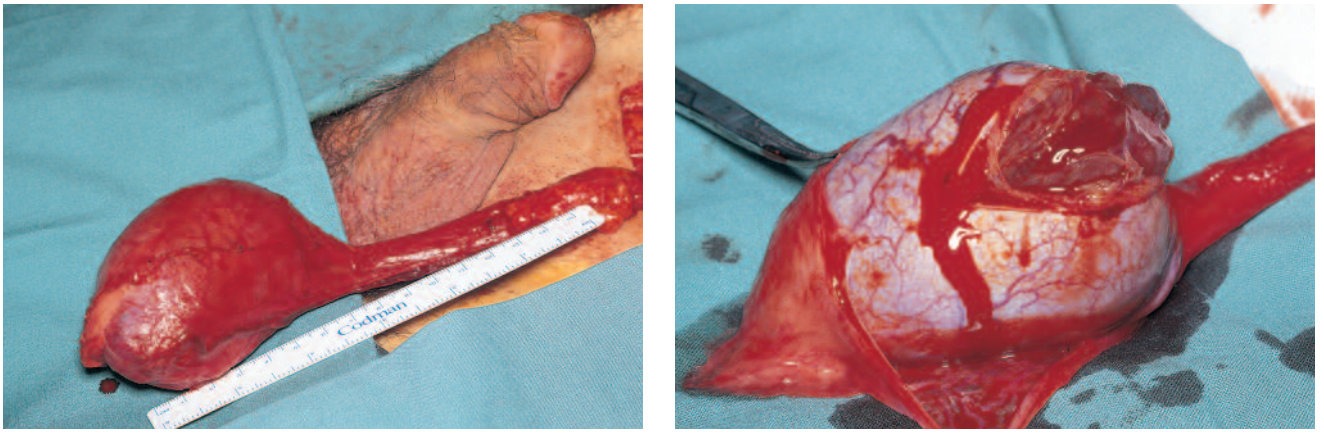

Figures 3a and b. Surgical orchidectomy. a (left). The inguinal surgical approach showing the mobilised testis and cord with intact coverings. b (right). The incised specimen showing a solid intratesticular lesion.

history of testis maldescent.

The risk of development of invasive malignancy in men with intratubular germ cell neoplasia is 50% over five years. If diagnosed, intratubular germ cell neoplasia can be managed expectantly with observation and regular ultrasonography, prophylactic excision with hormone replacement or radiotherapy.

Management of early stage testis cancer

A clinical stage 1 cancer is one that is confined to the testis with no evidence of spread radiologically or serologically (markers should fall postoperatively to normal according to half-life characteristics – the half-life of βhCG is 24 to 36 hours and AFP, four to five days).

NSGCTs

Roughly 70% of all patients with stage 1 NSGCTs do not relapse after orchidectomy; of the 30% who do, this usually manifests in the first one to two years postoperatively. More than 85% of patients will have a relapse in the retroperitoneal lymph nodes, with a smaller number relapsing in the lung fields, locally in the scrotum, or in the brain, liver or bones. The risk of spread and relapse in NSGCTs can be predicted by the presence of vascular or lymphatic involvement in the primary tumour as well as by the presence of embryonal carcinoma.

In Australia the most common approach to treating patients with stage 1 NSGCTs is surveillance to prevent overtreatment in those who were never destined to relapse. Of those who do relapse, cure rates should exceed 95%, indicating the effectiveness of chemotherapy in patients with metastatic testis cancer.

Surveillance includes regular examinations every one to two months for two years, with tumour marker assessment and alternating chest x-rays with CT scans of the chest, abdomen and pelvis. This surveillance should be continued with decreasing frequency over years three to five. A compliant patient, who understands the consequences of not adhering to the strict follow up regimen, is required for successful surveillance.

Adjuvant chemotherapy is occasionally given to patients with high-risk stage 1

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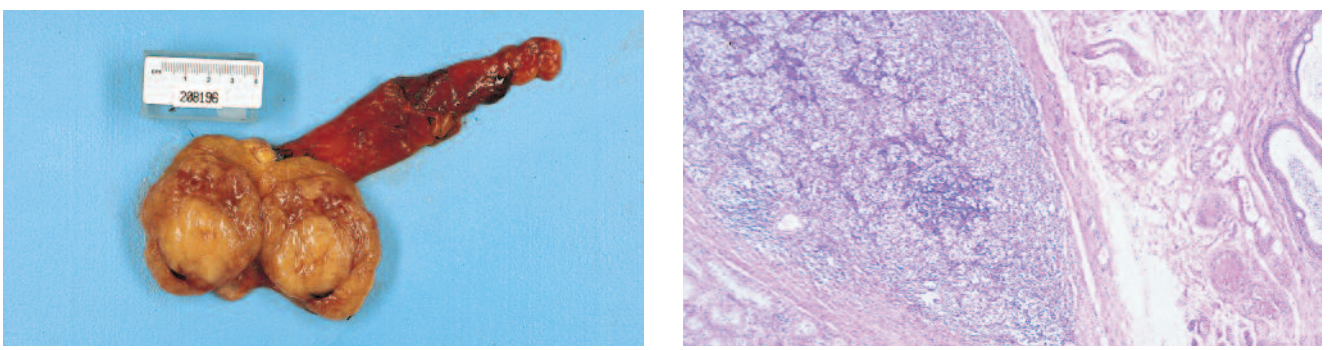

Figures 4a and b. Seminoma. a (left). Seminomas typically have a homogenous, slightly lobulated appearance. b (right). Seminoma histology showing sheets of cells with delicate cytoplasm and large round nuclei.

cancer who exhibit features suggesting a higher risk of relapse, as described above. This is controversial, however, because even those with the worst prognostic features have relapse rates no greater than 50%, and adjuvant treatment exposes 50% of patients to unnecessary therapy. Overall, adjuvant chemotherapy reduces the risk of recurrence in this higher risk group from 50% to 10%.

In the USA and some parts of Europe the standard treatment of patients with stage 1 NSGCTs is a retroperitoneal lymph node dissection, hence potentially curing those patients destined to have a relapse only in the retroperitoneal nodes. Although enormous advances have been made in the surgical technique, complications such as loss of antegrade ejaculation and chylous ascites can occur.

Seminomas

Fifteen per cent of patients with stage 1 seminomas will relapse in the retroperitoneum after orchidectomy; however, these cells are usually radiosensitive and adjuvant radiotherapy to the retroperitoneal lymph nodes results in cure rates in excess of 98%. Other approaches studied include surveillance and adjuvant chemotherapy with carboplatin (Carboplatin Injection); however, low to medium dose radiotherapy to the retroperitoneal nodes remains the standard of care. Between 0.3 and 5% of patients relapse after radiotherapy; they can usually be cured with combination chemotherapy.

Management of advanced testis cancer

The use of cisplatin (Cisplatin Injection) has revolutionised the treatment of metastatic testis cancer in large numbers of patients. Currently the most efficacious combination uses three (for patients with good prognosis) or four (for those with poor prognosis) cycles of BEP – that is, cisplatin with bleomycin (Blenamax, Blenoxane, Bleomycin Sulfate) and etoposide (Etopophos, Etoposide Injection).

For patients with NSGCTs, residual masses following chemotherapy, especially if associated with normalised tumour markers, require surgical excision. (These masses may represent viable cancer, mature teratoma or fibrosis.) This surgery is complex and should be done in specialised centres. Salvage retroperitoneal lymph node dissection can be associated with the need for en bloc nephrectomy, placement of aortic graft, duodenal resections, etc. In patients with relapse beyond the retroperitoneum, surgical excision of residual disease may require thoracotomy or craniotomy. As such, it is perhaps not surprising that studies have demonstrated superior outcome in higher volume, specialised centres.

In patients with residual cancer in the postchemotherapy mass, reinfusion of haemopoietic stem cells has allowed the use of higher doses of chemotherapy, usually using a combination of carboplatin, with etoposide and either cyclophosphamide (Cycloblastin, Endoxan) or ifosfamide (Holoxan). Durable remissions in 40 to 50% of patients have been demonstrated. This aggressive regimen is also being examined as possible initial inductive chemotherapy in those presenting with poor prognostic metastatic disease at diagnosis.

As late relapse can occur at any time, patients should receive annual follow up beyond 10 years. The risk of late relapse in those with high-risk disease who have been treated with chemotherapy is 2 to 4%. In patients presenting with a late relapse, the tumour exhibits different cell biology and is often resistant to chemotherapy, and the prognosis is poor, with survival rates in the order of 30%. Often the only prospect of prolonged survival rests with a complete surgical resection, highlighting the need for close and continuous follow up through the years.

Conclusion

Despite the advances in treatment, testis cancer still claims lives and always creates a major psychological burden for affected young men and their families.

The importance of appropriate counselling cannot be overemphasised, both regarding the patient's own prognosis and the potential side effects of therapy. These discussions are required particularly in the area of fertility and the effects of treatments (both chemotherapy and radiotherapy) on sperm counts. Pretreatment sperm storage and cryopreservation should always be recommended.

Testis cancer management should be regarded as one of the major successes of modern oncology, with survival rates for patients with early disease approaching 100% and for those with advanced disease ranging from 70 to 95%, depending on risk stratification at diagnosis. The management of patients with this disease highlights the effectiveness of a co-ordinated, multidisciplinary approach to cancer, and the role of major specialised cancer centres. MT

Further reading

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DECLARATION OF INTEREST: None.