

Regular review

Managing testicular cancer

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Germ cell tumours of the testis are the commonest malignancy in men aged 20-40 years. Considerable therapeutic improvements in management—based on the cancer's responsiveness to chemotherapy that contains platinum—mean that over 95% of these patients can now expect to be cured.

Methods

Much of the clinical management discussed in this review is based on the guidelines of the UK's Clinical Oncology Information Network, which were developed with the Scottish Intercollegiate Guidelines Network.¹ These were based on a systematic review of clinical data including prospective phase III randomised trials performed internationally. The sections that discuss causes, follow up, and future developments reflect our research interests and personal experience.

Incidence and aetiology

Testicular germ cell tumours

Testicular germ cell tumours are uncommon cancers; they account for around 1% of all cancers in males. About 1400 new cases are diagnosed in the United Kingdom each year. Germ cell tumours have a unique epidemiological profile for a solid tumour. Their peak incidence occurs among men aged 25-35 years, and there is a distinctive geographical and racial variation. The highest incidence is among white men in northern Europe.

These factors suggest that both genetic and environmental factors are important in the development of testicular germ cell tumours. The age distribution at onset suggests that an initiating event occurs prenatally and that the tumour develops from adolescence. The overall incidence of testicular germ cell tumours has been steadily rising throughout the 20th century, with an increase of 15-20% being seen in successive five year periods.² This increase might be the result of endogenous or environmental estrogenic compounds that affect the embryonic testis and increase the risk of testicular cancer³; these compounds might also be the cause of the decline in sperm counts and increased incidence of testicular maldescent seen over the same period. This suggestion however remains to be proven and other lifestyle changes could also have a role.

Summary points

Testicular cancer is the most common cancer in younger men

The incidence has been increasing by 15-20% in successive five year periods

Clinical trials organised by the UK's Medical Research Council and other international groups have defined modern clinical practice

Cure rates of >95% can be achieved

Advanced and recurrent cancers should be treated by multidisciplinary teams in specialist centres

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BMJ 2001;322:1583-8

Although testicular cancer has a genetic component, the overall incidence of a positive family history in testicular cancer is low (2%); however, siblings of men with testicular cancer are 6-10 times more likely to develop the disease. A mutation in chromosome Xq27 has recently been associated with this familial risk, especially when one or more of the affected men have bilateral testicular cancer.⁴

A number of other risk factors have been identified as predisposing men to testicular cancer. The most important of these is testicular maldescent. In a case-control study in the United Kingdom maldescent was associated with a relative risk of ≥ 3.8 if orchiectomy was not performed.⁵ Other abnormalities such as infantile hernia—which had a relative risk of 1.9 in the same study—and low birth weight—a relative risk of 2.6⁶—have also been linked to testicular cancer. Whether testicular maldescent and testicular abnormalities directly cause testicular cancers or share similar environmental or genetic factors, or both, remains uncertain. Families in which maldescent occurs are more likely to carry a mutation in the Xq27 region.

Little is known about the gene or genes that cause testicular germ cell tumours although amplification of a region on the short arm of chromosome 12 is seen in virtually all cases. In about 80% of men this is in the form of isochromosome 12p (that is, duplication of the short arm of chromosome 12), while the remainder

have an amplification of a section of the short arm of chromosome 12 that is translocated onto other chromosomes. This suggests that genes in this region play a part in the development of testicular germ cell tumours. The relation between these changes and testicular germ cell tumours is unclear, but the absence of these changes in some cases of intratubular germ cell neoplasia (see below) suggests that amplification of this chromosome may be related to the progression of the disease rather than initiation.⁷

Intratubular germ cell neoplasia

The precursor of testicular germ cell tumours is intratubular germ cell neoplasia. It is found adjacent to most testicular germ cell tumours and also in the contralateral testis of 2.5-5% of patients with germ cell tumours. Contralateral intratubular germ cell neoplasia is more common in younger patients and in those with atrophic testes; it is associated with infertility.⁸ In about 50% of men with intratubular germ cell neoplasia the neoplasm will progress to invasive cancer within five years. Low doses of radiotherapy, but not chemotherapy, reliably destroy intratubular germ cell neoplasia. Controversy exists over whether biopsy of the contralateral testicle should be undertaken in all men presenting with testicular cancer or whether biopsy should be reserved for men at high risk.

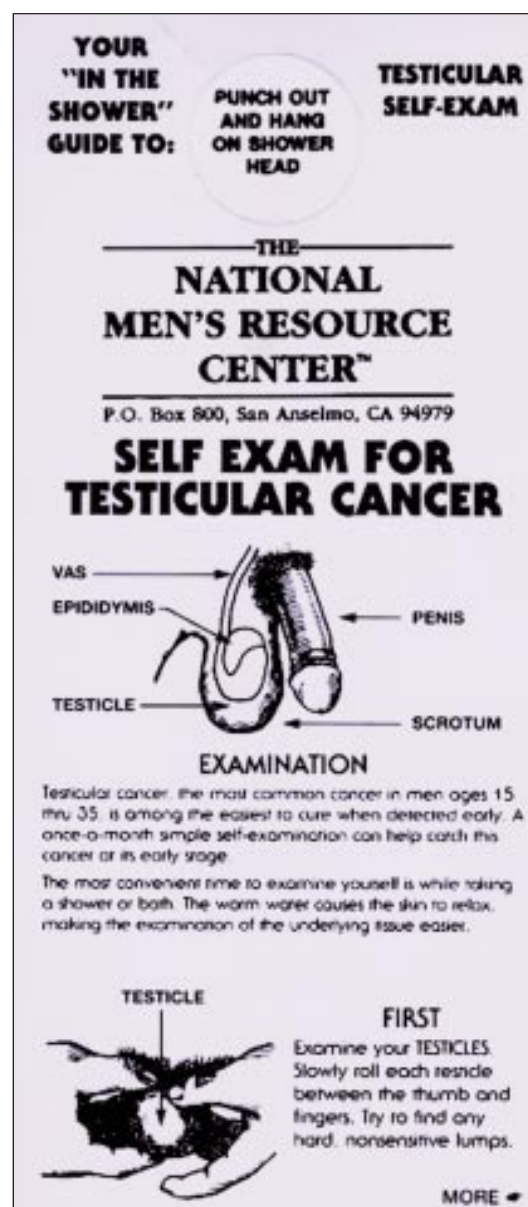
Pathology

The histopathology of testicular cancers is complex, and assessment should be made by a skilled pathologist. The most important discrimination is between seminomas, which account for about 50% of the total, and teratomas or non-seminomatous germ cell tumours, although mixed tumours can occur and account for about 10% of the total. Features such as vascular invasion should be specified.¹

Presentation and referral

Typically the man or his partner finds a painless lump in the testicle. Enlargement of the testicle, firmness, aching, discomfort, or asymmetry within the testis can also occur. Less commonly men with metastases to the para-aortic lymph nodes may present with back pain, and men with pulmonary metastases may present with breathlessness or haemoptysis. Men presenting with a swelling in the scrotum should be examined carefully and an attempt should be made to distinguish between lumps arising from the body of the testis and other intrascrotal swellings. Abnormal masses in the epididymis are common but unlikely to be testicular tumours. Ultrasound scanning helps distinguish between masses in the body of the testis and other intrascrotal swellings and should be done within two weeks of presentation if there is clinical uncertainty. Patients with possible epidymo-orchitis or orchitis that has not resolved within two weeks should be referred for urgent urological assessment and seen by a specialist within two weeks of referral.¹

Some evidence suggests that delays in presentation are more of a problem than delays in making referrals, and public awareness campaigns may therefore be helpful.⁹ Although there is no evidence to recommend routine testicular self examination, men should be



Self examination guide courtesy of the National Men's Resource Center

aware of the existence of testicular cancer and the early symptoms, particularly if there is a family history of maldescent or testicular cancer.

Diagnosis, treatment, and staging

For most men diagnosis will be made after an urgent inguinal orchiectomy. All patients should be advised that prostheses are available. In men with obvious metastatic disease, the diagnosis can be confirmed by the presence of raised serum concentrations of α foeto-protein or human chorionic gonadotrophin. In many men with advanced metastatic disease concentrations of human chorionic gonadotrophin often result in a positive pregnancy test; this can be used as a readily available and rapid diagnostic test. Knowledge of the histopathological tumour type, size, and relevant prognostic factors, such as the presence of vascular invasion (in non-seminomatous germ cell tumours) or involve-

ment of the rete testis (in seminomas) may help subsequent management decisions. Concentrations of α fetoprotein are raised in 50-60% of cases of non-seminomatous germ cell tumours (but not in pure seminomas), and human chorionic gonadotrophin is raised in 30-35% of non-seminomatous germ cell tumours and 10-25% of seminomas.

Measuring the concentrations of these tumour markers is invaluable in making the diagnosis, determining the prognosis (when used with lactate dehydrogenase), assessing response to treatment, and in following up patients. Concentrations of these markers should be evaluated before an orchiectomy and repeated after surgery until the pattern of a fall in concentrations or normalisation is clear. Urgent staging, including radiography of the chest and computed tomography of the chest, abdomen, and pelvis, should be arranged but should not delay referral to appropriate oncology services.

The first site in the lymphatic system that testicular germ cell tumours metastasise to is the para-aortic lymph nodes; this is because the testis originate in the abdomen. Haematogenous spread is more common in non-seminomatous germ cell tumours and metastases are most likely to occur in the lungs, liver, and brain. The Royal Marsden staging system is widely used internationally and quantifies the size of the tumour and the sites of metastatic disease (box).¹⁰ Men with stage I disease have no clinical or radiological evidence of metastases; involvement of the infradiaphragmatic or supradiaphragmatic lymph nodes occurs in stages II and III; and more distant metastases to the lung, liver, brain, or bone, are seen in stage IV.

The effects on fertility and the possibility of storing sperm should be discussed with all men before chemotherapy or radiotherapy. Sperm should be stored in a facility that has been appropriately licensed; in the United Kingdom this would be at a facility licensed by the Human Fertilisation and Embryology Authority.

Managing stage I disease

Non-seminomatous testicular germ cell tumours

A series of trials in the United Kingdom over the past 20 years has defined two primary strategies for patients with non-seminomatous testicular germ cell tumours. The first is a strict surveillance protocol that reserves chemotherapy for the 30% of men who develop metastases.¹¹ The second is immediate

Royal Marsden Hospital staging system for testicular cancer¹⁰

Stage	Details
I	No evidence of metastasis
IM	Rising concentrations of serum markers with no other evidence of metastasis
II	Abdominal node metastasis
A	≤2 cm in diameter
B	2-5 cm in diameter
C	≥5 cm in diameter
III	Supradiaphragmatic nodal metastasis
M	Mediastinal
N	Supraclavicular, cervical, or axillary
O	No abdominal node metastasis
ABC	Node stage as defined in stage II
IV	Extralympathic metastasis
Lung	
L1	≤3 metastases
L2	≥3 metastases, all ≤2 cm in diameter
L3	≥3 metastases, one or more of which are ≥2 cm in diameter
H + , Br + , Bo +	Liver, brain, or bone metastases

treatment with two courses of adjuvant chemotherapy (box).¹² Overall survival is nearly 100% with either approach. Vascular invasion, which is present in about 50% of primary tumours, is used to stratify men into high risk groups (vascular invasion has occurred) and low risk groups (vascular invasion has not occurred). About 50% of men at high risk will have a recurrence if surveillance is used compared with 15% of men at low risk. About 98-99% of men at high risk will remain free from recurrence after two courses of adjuvant chemotherapy containing cisplatin.¹² Surveillance and salvage treatment are preferred for patients at low risk. Surveillance involves monthly chest radiography and monitoring of serum concentrations of α fetoprotein or human chorionic gonadotrophin in the first year of follow up; the frequency of the use of computed tomography is currently being examined in a trial (box).

Seminomas

About 75% of men with seminomas have stage I disease.² Standard treatment is adjuvant radiotherapy to the para-aortic area at a dose of 30 Gy in 15 fractions delivered over three weeks. Only 2-3% of men

Standard management of testicular cancer in the United Kingdom

Non-seminomatous germ cell tumours (teratomas)

Stage I

Low risk (no vascular invasion)—Surveillance only

High risk (vascular invasion)—Adjuvant chemotherapy or surveillance

Metastatic

Good prognosis—Three courses of chemotherapy with bleomycin, etoposide, and cisplatin

Intermediate prognosis—Four courses of chemotherapy with bleomycin, etoposide, and cisplatin

Poor prognosis—Four to six courses of chemotherapy with bleomycin, etoposide, and cisplatin and referral to specialist oncology centre

Seminomas

Stage I—Adjuvant para-aortic radiotherapy (30 Gy over three weeks)

Metastatic

Good prognosis

Stage IIA-B—Para-aortic and ipsilateral pelvic radiotherapy (30-35 Gy over 3-3½ weeks)

Stage IIC-IV—Three courses of chemotherapy with bleomycin, etoposide, and cisplatin

Intermediate prognosis—Four courses of chemotherapy with bleomycin, etoposide, and cisplatin

Poor prognosis—No patients classed as having a poor prognosis

Trials organised by the UK's Medical Research Council and the European Organization for Research and Treatment of Cancer*

TER 2—Trial examining the risk of testis cancer in families with bilateral germ cell malignancy. This is being run in conjunction with the German Association of Urologic Oncology and is also using Danish and Swedish cancer registries

TE 08—Randomised trial of use of different schedules of computed tomography in surveillance of patients with stage I non-seminomatous germ cell tumours

TE 19—Randomised trial comparing carboplatin with radiotherapy in patients with stage I seminomas

TE 20-TIP—Phase II trial of paclitaxel, ifosfamide, and cisplatin in patients who have had a relapse after treatment with bleomycin, etoposide, and cisplatin

TE 21—Phase III trial comparing standard chemotherapy (bleomycin, etoposide, and cisplatin) with paclitaxel and bleomycin, etoposide, and cisplatin in patients who have an intermediate prognosis for metastatic germ cell cancers

EORTC 30974—Phase III trial comparing standard chemotherapy (bleomycin, etoposide, and cisplatin) with high dose cisplatin, ifosfamide, and etoposide in patients who have a poor prognosis for metastatic germ cell cancers

*Additional information about the trials can be found at www.ctu.mrc.ac.uk/ukcccr

develop a recurrence,¹³ and the cure rate after salvage treatment approaches 100%. Phase III trials organised by the UK's Medical Research Council (MRC) and the European Organization for Research and Treatment of Cancer have shown that this approach gives similar results to the more extensive radiotherapy previously used, which included both para-aortic and ipsilateral pelvic nodal areas. Trials are currently assessing whether the dose of radiation can be reduced to 20 Gy and the effectiveness of single agent carboplatin chemotherapy (box).

Although 80% of men are cured by orchiectomy alone, surveillance is regarded as an investigational approach. This is because conventional treatment has a high success rate and follow up is more difficult in men with seminomas than in men with teratomas because the concentrations of tumour markers are considerably less reliable in detecting recurrence. Additionally, recurrences may appear years after orchiectomy. However, the use of testicular size (≥ 4 cm) and involvement of the rete testis as prognostic factors¹⁴ together with concerns over the long term toxicity of treatment (see below) may lead to a re-evaluation of surveillance as a treatment strategy.

After orchiectomy patients need full and clear discussions of these alternative ways of managing either stage I seminoma or non-seminomatous germ cell tumours to help guide them in their choice of active treatment or surveillance.

Treating metastatic disease

An international collaboration organised through the MRC's trials office collated data on 5202 patients with metastatic non-seminomatous tumours and 660 patients with metastatic seminomas who had been treated with chemotherapy containing cisplatin.¹⁵ Data were analysed using multivariate analysis of risk groups defined by the tumour markers human chorionic gonadotrophin, α fetoprotein, and lactate

dehydrogenase, and the pattern of disease spread. The results offer a benchmark for practice (box).

Non-seminomatous germ cell tumours

Since the introduction of cisplatin and etoposide the standard treatment for all patients regardless of risk has been four courses of chemotherapy with bleomycin, etoposide, and cisplatin.^{16–18} Other drugs have been shown to be either more toxic—for example, ifosfamide¹⁹—or less active—for example, carboplatin.²⁰ Despite the risk of pulmonary toxicity bleomycin remains an essential component of treatment.²¹ A recent trial studied chemotherapy in patients with good prognosis and found that three courses of chemotherapy with bleomycin, etoposide, and cisplatin were as effective as four and that the drugs could be given over three days rather than five.²² For patients with higher risk disease four courses of this regimen remains the standard, but individual centres have had apparently better results using more intensive schedules.^{23–24} Studies are under way that incorporate new agents such as paclitaxel, “dose intense” schedules using weekly treatment, and high dose treatment with stem cell rescue for patients with features that suggest a poor prognosis.

Surgery after chemotherapy

About one third of patients with stage II–IV disease, as classed by the Royal Marsden criteria, have residual para-aortic masses after treatment. About 10% of these masses have active undifferentiated malignant elements. The remainder contain differentiated teratoma or necrotic and fibrotic tissue. Differentiated teratoma is unstable, and its presence is probably responsible for the late pattern of relapse: relapses may occur more than five years after treatment. Resection of all residual masses is recommended and should be undertaken by a specialist urological surgeon working in conjunction with the oncology team. Resection of residual pulmonary, mediastinal, and lymph node masses at other sites may also be required.

Seminomas

Patients with seminomas most commonly present with para-aortic lymph node metastases, but metastases to the lung, bone, and liver are also seen. In stage IIA and stage IIB disease radiotherapy alone is acceptable, and the 20% risk of subsequent relapse may be reduced by treatment with a single course of carboplatin.²⁵ For bulkier or more extensive disease combination chemotherapy with the bleomycin, etoposide, and cisplatin regimen used for non-seminomatous germ cell tumours is standard. Single agent chemotherapy using carboplatin remains a reasonable option if patients have significant comorbid disease.²⁶

Treating persistent or recurrent disease

Although 85% of men with metastatic disease will be cured with a combination of chemotherapy and surgery, treating those for whom treatment has failed poses a major challenge. Approaches that combine intensive chemotherapy, surgical resection, and, occasionally, radiotherapy are required; high dose chemotherapy with stem cell support is usually considered.^{27–28} About 30% of men will be cured by this regimen. Trials are under way to test the use of high dose chemotherapy and paclitaxel (box). In the United

Prognosis of metastatic germ cell cancers¹⁵**Non-seminomatous germ cell tumours (teratomas)**

Good prognosis—About 56% of patients; five year survival is 92%

- Primary site is testis or retroperitoneal area, and
- No non-pulmonary visceral metastases, and
- Low serum concentrations of α fetoprotein, human chorionic gonadotrophin, or lactate dehydrogenase

Intermediate prognosis—About 28% of patients; five year survival is 80%

- Primary site is the testis or retroperitoneal area, and
- No non-pulmonary visceral metastases, and
- Intermediate concentrations of the tumour markers

Poor prognosis—About 16% of patients; five year survival is 48%

- Primary site is the mediastinum, or
- Non-pulmonary visceral metastases, or
- High concentrations of the tumour markers

Seminomas

Good prognosis—About 90% of patients; five year survival is 86%

- Any primary site, and
- No non-pulmonary visceral metastases, and
- Any tumour marker with normal α fetoprotein

Intermediate prognosis—About 10% of patients; five year survival is 72%

- Any primary site, and
- Non-pulmonary visceral metastases, and
- Any tumour marker with normal α fetoprotein

Poor prognosis—No patients are classed as having a poor prognosis

Kingdom, these patients should be referred to supra-regional specialist centres for management.

Follow up

The aim of follow up care is to detect a relapse at a stage where salvage treatment has the best chance of being effective, to monitor and treat toxicity related to therapy, to detect contralateral cancers, and to offer support and counselling particularly about issues such as employment and fertility. Suggestions for clinical, biochemical, and radiological follow up have been made,¹ but the optimum timing of clinical and radiological follow up is under investigation. Our own institutional review suggests that it may be reasonable to discharge patients with seminomas (all stages) and stage I non-seminomatous germ cell tumours five years after treatment. Metastatic non-seminomatous germ cell tumours seem to have a continuing annual relapse rate of 1-2% even after 10 years; this suggests that longer term follow up might be indicated. Our preference is to undertake follow up at a cancer centre because of the advantages in maintaining detailed databases and allowing audit of biochemical and radiological tests, but this approach may not be practical or desirable in other locations. As data on long term toxicity develop there may be an increasing role for family practitioners in monitoring these patients.

Treatment toxicity

Chemotherapy with cisplatin causes significant side effects both in the short term and the long term. Acute side effects include nausea and vomiting, alopecia, fatigue (either due to anaemia or a direct effect of treatment), neutropenia, and sepsis. A particular complication of chemotherapy for testicular cancer is lung toxicity, which is associated with bleomycin; in most studies 0.5-1% of patients developed fatal pneumonitis.^{21 22} Risk factors for fatal pneumonitis include being older than 40 years, being a smoker, having a history of pulmonary disease, and having impaired renal function. Bleomycin may also be largely responsible for changes in skin pigmentation and nails as well as the long term risk of developing Raynaud's syndrome. Cisplatin may cause damage to both the

peripheral and auditory sensory nerves. This resolves in most patients over 6-12 months, but long term studies suggest that persistent damage occurs in a proportion of patients.²⁹ About 1-2% of patients are at risk of developing avascular necrosis of the hip 2-3 years after treatment, and this may be the result of the combination of chemotherapy and high dose steroids used as antiemetics with these regimens.³⁰

Chemotherapy frequently causes azoospermia. In 70-80% of patients it is reversible and many patients go on to have children. A proportion of patients, however, become infertile after treatment, and the risk increases with the dose of cisplatin and the use of alkylating agents.³¹

Other concerns relate to the increased risk of second malignancies that occurs after treatment with radiotherapy or chemotherapy and the possible increase in cardiovascular events in long term survivors of treatment.^{29 32 33} These effects need further study but the role of surveillance in managing patients with early disease may need to be re-examined.

Social and psychosocial aspects of treatment

Testicular tumours often occur at a time when good health is taken for granted. In addition to the toxicity of treatment, considerable psychological distress may arise from the lack of confidence engendered by the disease with regard to health, fertility, and body image; there may also be concerns about finances and employment, and occasionally patients' personalities change as do their professional relationships. Complete and comprehensible information should be available to allay uncertainties about treatment and prognosis, and good communication must be maintained between the specialist team and the general practitioner and any other community services that are involved. Additional routine formal counselling or psychosocial therapy is not helpful,³⁴ although such support should be available if specifically indicated.

Future developments

Collaborative and multicentre clinical trials have led to significant improvements in the management of testicular cancer; these improvements have been incor-

Additional educational resources

Horwich A, ed. *Testicular Cancer—Investigation and Management*. 2nd ed. London: Chapman and Hall, 1996

Clinical Oncology Information Network (COIN). *Guidelines on the management of adult testicular germ cell tumours*. Available at www.rcr.ac.uk/testicular.htm

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porated into treatment guidelines.¹ The optimum treatment for metastatic non-seminomatous germ cell tumours in patients with a good prognosis has been defined but the treatment of patients with poor prognosis and recurrent disease still needs improvement. The exploration of new, more intensive treatments is justified for these patients. In men with stage I disease attention is likely to focus on minimising treatment and reducing the long term risks of treatment. Surveillance may become more appropriate, especially if staging accuracy improves, for example, through the use of functional imaging, such as positron emission tomography.³⁵

In the more distant future improved understanding of the biology and the genetics of germ cell tumours may lead to new therapeutic targets and approaches. Great strides have been made in treating germ cell tumours over the past 20 years, but it is likely that further advances will occur in smaller steps that aim to maximise cure and minimise toxicity. Public education and awareness must also be priorities to help patients avoid unnecessary delays in presentation which may have an impact on survival.

Contributors: This paper was jointly written by DPD, RAH, and AH.

Funding: DPD is funded by the Bob Champion Cancer Trust. The Academic Unit of Clinical Oncology at the Institute of Cancer Research is supported by a programme grant from the Cancer Research Campaign.

Competing interests: None declared.

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