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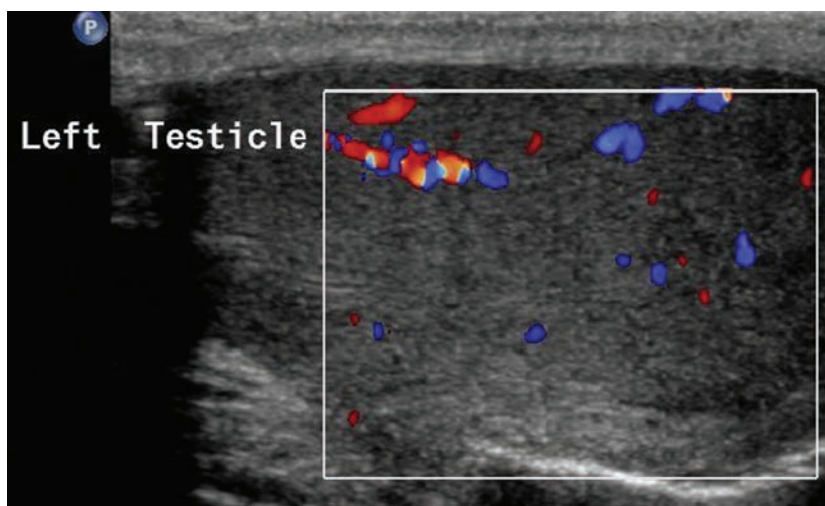
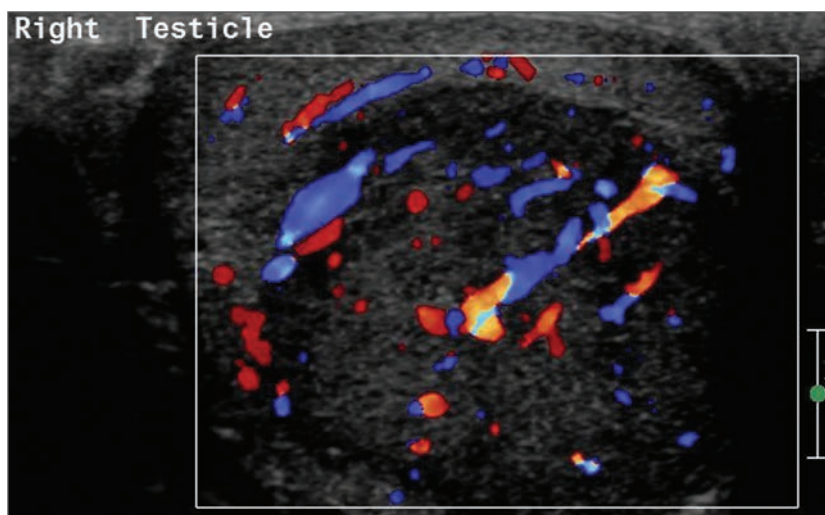


FIGURE 1
Doppler ultrasound image of the testes showing a heterogeneous round mass in the inferior aspect of the right testicle with associated hypervascularity corresponding to a seminoma. The left testicle is normal



IN THE UK, TESTICULAR CANCER ACCOUNTS FOR ONLY 1% OF ALL MALIGNANCIES IN MALES.¹

It is, however, the most frequently occurring solid tumour in men between the ages of 15 and 34 years.² In recent decades, the incidence of testicular cancer has increased and the lifetime risk for a man in the UK is now one in 190.¹ This article will refer only to testicular germ cell tumours (GCTs), these account for 95% of testicular cancer seen in young men.

Testicular GCTs are classified into two main types: pure seminomas and non-seminomas (also called

non-seminomatous germ cell tumours (NSGCTs). They are managed in different ways and have different prognoses.

NSGCTs include histological subtypes such as embryonal carcinoma, choriocarcinoma, yolk sac tumour and teratoma. Mixed GCTs are common and contain two or more of these subtypes. NSGCTs are more clinically aggressive than seminomas so those patients who have both seminoma and non-seminoma components are managed according to NSGCT guidelines.

Nowadays, testicular tumours have excellent cure rates, even in patients

How should patients be investigated?

What are the treatment approaches?

What are the long-term health consequences?

with metastases, as they are extremely sensitive to chemotherapy and radiotherapy. Five-year survival, which effectively represents long-term disease specific survival because it does not fall much beyond this point, is now 97.2%.³

Early diagnosis is, however, very important as treatment is more successful, less intensive and long-term health consequences can be minimised.

PRESENTATION

Testicular cancer usually presents with a unilateral painless lump in the body of the testis. Occasionally, patients »

complain of a dull ache or heaviness in the scrotum. The swelling may suddenly increase in size or become painful and can mimic epididymo-orchitis or cause a hydrocoele.

Much less commonly, testicular cancer presents with symptoms from metastases. Pain in the back, groin and lower abdomen can be caused by retroperitoneal lymphadenopathy. Cough, breathlessness and difficulty in swallowing can be caused by lung metastases.

Some testicular GCTs produce human chorionic gonadotrophin (HCG) which can cause gynecomastia and breast tenderness. In < 5% cases, germ cell tumours may originate extra-gonadally in the retroperitoneum or mediastinum with no evidence of a testicular primary.

SELF-EXAMINATION

Early diagnosis of testicular cancer is very important. It is recommended that men, particularly those with risk factors, see below, undertake monthly testicular self-examination. Men should be taught that the best time to check their testicles is during, or right after, a warm bath or shower when the scrotal skin is relaxed. A normal testicle should feel firm and smooth, but not hard.⁴

In a study of 740 unselected men attending a genitourinary medicine clinic, 79.2% had previously carried out testicular self-examination. The most common reason stated for not performing testicular self-examination was: 'I don't really know what to look for.' Men previously taught testicular self-examination were 11.5 times more likely to examine their testicles than those who had not been taught.⁵

RISK FACTORS

Unilateral cryptorchidism is associated with an increased risk of testicular cancer in both testes, even after orchidopexy, but is more common on the ipsilateral side with a relative risk of 6.33.⁶ In addition, having a contralateral testicular cancer increases the risk of developing a metachronous tumour (i.e. another primary testicular cancer occurring at a different time), by about 12 fold.⁷

The incidence of GCTs varies greatly worldwide. The highest rates of testicular cancer are reported in industrialised countries, particularly Western and Northern Europe and New Zealand/Australia. It is more common in white men than

Afro-Caribbean or Asian men.

For example, Western Europe reports age standardised rates (ASRs) of 7.8 per 100,000, while West Africa reports ASRs of 0.2 per 100,000.¹

Additionally, the risk of testicular cancer is higher in males with testicular atrophy or dysgenesis. The risk is 59% higher in subfertile men (without cryptorchidism)⁸ and up to 79% higher in males with HIV infection.⁹ Around 1-3% of patients have a positive family history of testicular cancer.¹⁰

EXAMINATION AND INVESTIGATIONS

The diagnosis of testicular cancer is suspected on physical examination when a solid testicular mass or nodule may be palpated. General physical examination should also be carried out to rule out an abdominal mass or lymphadenopathy.

NICE guidelines state that any patient with a swelling or mass in the body of the testis should be referred urgently for further investigation.¹¹ They also state that an urgent ultrasound should be considered in men with a scrotal mass that does not transilluminate and/or when the body of the testis cannot be distinguished. Patients with suspected testicular cancer should be referred to a urologist under the two week suspected cancer referral pathway.

Tumour markers for testicular cancer include alpha-fetoprotein (AFP), β HCG and lactate dehydrogenase (LDH). Patients with NSGCTs may have an elevated AFP and β HCG but about a third are negative for markers.¹² AFP is not secreted by pure seminomas and only 10-20% of patients with a pure seminoma have elevated serum β HCG. If AFP is significantly elevated in a tumour diagnosed as a seminoma based on histology, it is reclassified as NSGCT.¹³

Serum LDH may be raised in all germ cell tumours and can correlate

with burden of disease but it is much less specific than AFP and β HCG. As these tumour markers are not recommended for screening or diagnosis in testicular cancer, their role in primary care is limited.

CONFIRMING DIAGNOSIS

Bilateral scrotal ultrasound, which has a sensitivity of almost 100% in diagnosing testicular cancer, should be performed to confirm the diagnosis, see figure 1, p19. Histological analysis of the testicular mass occurs only after it has been removed by inguinal orchidectomy. A biopsy through the scrotum and scrotal orchidectomies are avoided as they carry an increased risk of local recurrence and inguinal node metastases.²

TREATMENT

Treatment options for men with testicular cancer include surgery, chemotherapy, radiotherapy, or a combination of the above, depending on the histology, presence of tumour markers and radiological staging.

Orchidectomy is the first step in treating testicular cancer. Serum tumour markers should be measured before orchidectomy and five to seven days later. Staging, see table 1 below, is usually undertaken after orchidectomy and helps determine prognosis and treatment. It requires a CT of the thorax, abdomen and pelvis but additional imaging may be performed depending on the patient's symptoms. More than 70% of patients are diagnosed with stage I disease at presentation.¹⁴

Raised serum tumour marker levels should fall after orchidectomy so patients with clinical stage I disease whose tumour marker levels fail to normalise after orchidectomy are presumed to have metastatic disease, even if their CT scan appears normal. These patients are categorised as clinical stage IS and should be treated with chemotherapy.²

Risk categories for patients with

Table 1

Stages of testicular cancer

Stage	
I	Disease confined to the testicle
II	Metastatic pelvic or retroperitoneal lymphadenopathy
IIA	Lymphadenopathy $\leq$ 2 cm
IIB	Lymphadenopathy 2-5 cm
IIC	Lymphadenopathy > 5 cm
III	Metastatic supradiaphragmatic lymphadenopathies and/or visceral metastases

metastatic germ cell tumours post-orchidectomy have been established by the International Germ Cell Cancer Collaborative Group for seminoma and non-seminoma based on clinically independent prognostic features, see table 2, below.¹⁵

Seminoma

An algorithm for the management of seminomas is shown in figure 2, below.

The recommended management post-orchidectomy for stage I seminoma is surveillance.

One cycle of adjuvant carboplatin chemotherapy may be advised if risk factors for recurrence are present.¹⁴

A recent study identified predictive factors for relapse including:

- Invasion of blood or lymphatic vessels
- Tumour size > 4 cm
- Serum HCG > 200IU/L¹⁶

Adjuvant carboplatin reduces the relapse rate from 15-20% to around 5%. Patients who relapse while on surveillance are very likely to be cured by chemotherapy, with an overall cancer specific survival rate > 99%.¹⁷

Metastatic seminoma

The standard treatment for stage IIA/B seminoma is retroperitoneal radiotherapy but this area has



FIGURE 2
Treatment
algorithm for
seminomas

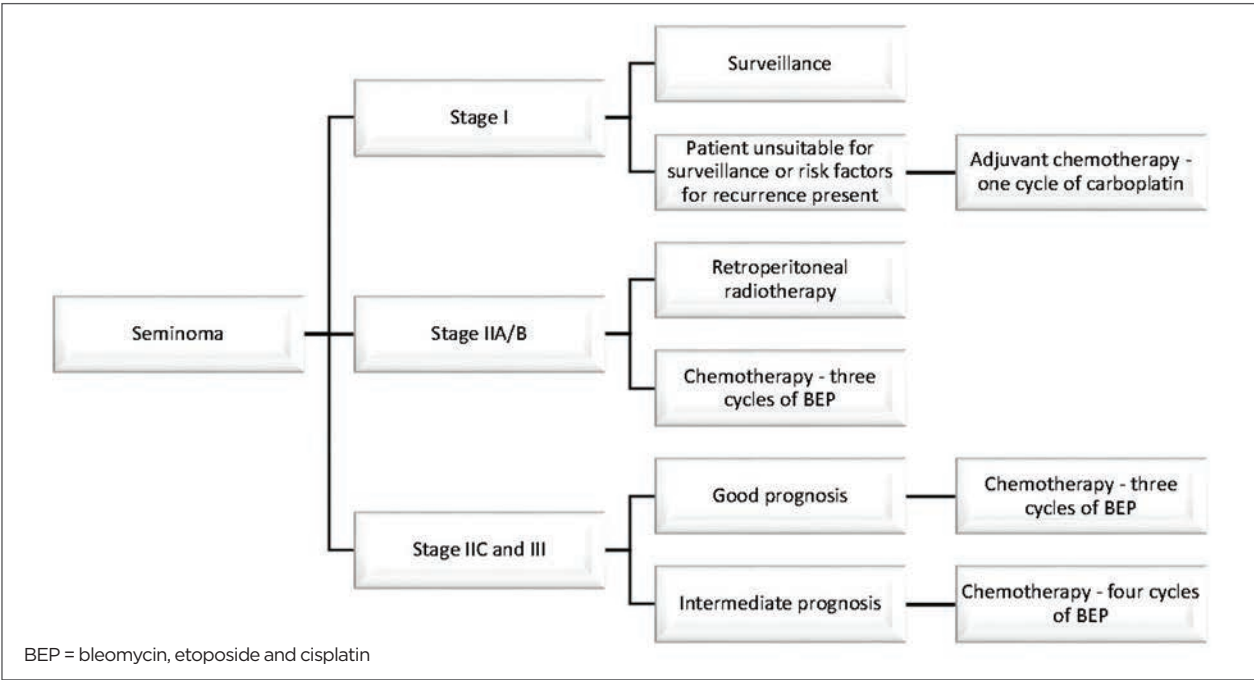


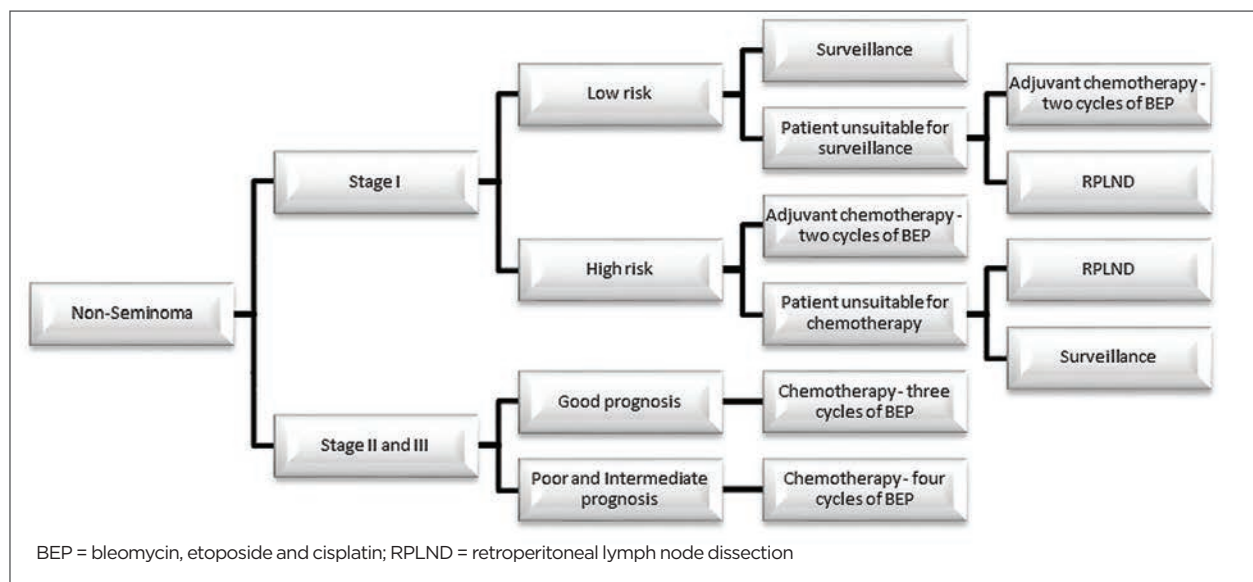
Table 2

International Germ Cell Cancer Collaborative Group prognostic classification of metastatic germ cell tumours¹⁴

	Good prognosis	Intermediate prognosis	Poor prognosis
Seminoma	Any primary site	Any primary site	No patients are classified as poor prognosis
	No non-pulmonary visceral metastases	No non-pulmonary visceral metastases	
	Normal AFP Any βHCG Any LDH	Normal AFP Any βHCG Any LDH	
	90% of seminomas	10% of seminomas	
Non-seminoma	Testes/retroperitoneal primary	Testes/retroperitoneal primary	Mediastinal primary or non-pulmonary visceral metastases
	No non-pulmonary visceral metastases	No non-pulmonary visceral metastases	
	AFP < 1,000 IU/L βHCG < 5,000 IU/L LDH < 1.5 X ULN	AFP 1,000-10,000 IU/L βHCG 5,000- 50,000 IU/L LDH 1.5-10 X ULN	Or any of: AFP > 10,000 IU/L βHCG > 50,000 IU/L LDH > 10 X ULN
	56% of non-seminomas	28% of non-seminomas	16% of non-seminomas

AFP = alpha-fetoprotein; βHCG = beta human chorionic gonadotrophin; LDH = lactate dehydrogenase; ULN = upper limit of normal

FIGURE 3
Treatment
algorithm for
non-seminomas



become controversial and concerns exist about its efficacy and the risk of radiotherapy-related induction of secondary cancers. Chemotherapy is an alternative to radiotherapy and a recent study has suggested that it may be associated with a lower relapse rate.¹⁸ The most commonly used regimen is three cycles of bleomycin, etoposide and cisplatin (BEP).

For advanced seminomas (IIC and III), the standard treatment is chemotherapy. Three cycles of BEP are given for patients in the good prognosis group and four cycles for those in the intermediate prognosis group.¹⁴

Non-seminoma

An algorithm for the management of non-seminomas is shown in figure 3, above.

Stage I NSGCT patients are divided into low or high risk depending on the presence of vascular invasion. The five-year relapse rate is 20% for low-risk patients and 40-50% for high-risk patients.

For low-risk patients, surveillance is recommended unless the patient is unwilling or unsuitable, in which case, adjuvant chemotherapy or nerve sparing retroperitoneal lymph node dissection are treatment options. Adjuvant chemotherapy with two cycles of BEP should be recommended for high-risk patients.¹⁴

Metastatic non-seminoma

The primary treatment of choice in metastatic NSGCT is BEP chemotherapy, three cycles for patients in the good prognosis group and four cycles for those in the intermediate or poor prognosis groups.¹⁴ Overall survival in the good, intermediate and poor prognosis groups is 94%, 83% and 71%, respectively.¹⁹ Figure 4, below, shows CT scans in a 51-year-old man before and after successful treatment with chemotherapy for metastatic NSGCT.

All patients are placed on a long-term follow-up schedule after

treatment which aims to detect relapse and to monitor the contralateral testis as well as monitoring the side effects of treatment, see below.

MONITORING SURVIVORS

Testicular cancer is a curable cancer predominantly affecting young men, so the need to identify and manage long-term health consequences in survivors is very important.

Some patients become hypogonadal after orchidectomy and require testosterone replacement.

Others will experience chronic side effects from chemotherapy which may be permanent. These include hearing loss, peripheral neuropathy, Reynaud's phenomenon, renal impairment and ototoxicity (hearing loss and tinnitus). In most patients, there is recovery of spermatogenesis two years after completion of chemotherapy²⁰ but in all patients, sperm banking should be offered before chemotherapy. Bleomycin may cause lung toxicity because it has the

FIGURE 4
CT scans in a
51-year-old man
with metastatic
non-seminomatous
germ cell tumour:
(a) left, shows a left
para-aortic nodal
mass at presentation;
(b) right, shows a
complete response
of the para-aortic
lymphadenopathy
after four cycles of
bleomycin,
etoposide and
cisplatin
chemotherapy



key points

SELECTED BY

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Testicular cancer accounts for 1% of all malignancies in males.

It is the most frequently occurring solid tumour in men between the ages of 15 and 34 years. Testicular germ cell tumours are classified into two main types: pure seminomas and non-seminomas which are also called non-seminomatous germ cell tumours (NSGCTs). NSGCTs are more clinically aggressive than seminomas so those patients who have both seminoma and non-seminoma components are managed according to NSGCT guidelines.

Testicular tumours have excellent cure rates, even in those with metastases, as they are extremely sensitive to chemotherapy and radiotherapy. Early diagnosis is, however, very important as treatment is more successful and less intensive, and long-term health consequences can be minimised.

It is recommended that men, particularly those with risk factors, undertake monthly testicular self-examination. Men should be taught that the best time to check their testicles is during, or right after, a warm bath or shower when the scrotal skin is relaxed. A normal testicle should feel firm and smooth, but not hard.

Unilateral cryptorchidism is associated with an increased risk of testicular cancer in both testes, even after orchidoplexy. The risk of testicular cancer is higher in males with testicular atrophy or dysgenesis and the highest rates are reported in industrialised countries, particularly Western and Northern Europe and New Zealand/Australia.

Treatment options for men with testicular cancer include surgery, chemotherapy, radiotherapy, or a combination of the above, depending on the histology, presence of tumour markers and radiological staging. Raised levels of tumour markers should fall after orchidectomy. Patients with clinical stage I disease in whom serum tumour marker levels fail to normalise after orchidectomy are presumed to have metastatic disease, even if their CT scan appears normal.

Some patients become hypogonadal after orchidectomy and require testosterone replacement. Others will experience chronic side effects from chemotherapy which may be permanent. These include hearing loss, peripheral neuropathy, Reynaud's phenomenon, renal impairment and ototoxicity (hearing loss and tinnitus). In most patients, there is recovery of spermatogenesis two years after completion of chemotherapy but in all patients, sperm banking should be offered before chemotherapy.

The risk of developing a secondary malignancy is increased in patients treated for testicular cancer. Men who have been treated with infradiaphragmatic radiotherapy or chemotherapy also have an increased incidence of cardiovascular disease and metabolic syndrome. Patients should be screened for cardiovascular risk factors, given healthy lifestyle advice and advised not to smoke.

potential to cause pulmonary fibrosis.

The risk of developing a secondary malignancy is increased in patients treated for testicular cancer. In a study of 40,576 testicular cancer survivors, those who survived at least ten years had significantly increased risks of secondary solid cancers. This risk was associated with the following treatment modalities:

- Radiotherapy alone, relative risk (RR) 2.0 (95% CI:1.9-2.2)

- Chemotherapy alone, RR 1.8 (95% CI:1.3-2.5)

- Radiotherapy + chemotherapy, RR 2.9 (95% CI:1.9-4.2)²¹

Men who have been treated for testicular cancer with infradiaphragmatic radiotherapy or chemotherapy also have an increased incidence of cardiovascular disease and metabolic syndrome.²² Patients should be screened for cardiovascular risk factors, given advice on healthy lifestyle choices and advised not to smoke.

A large study in Norway found significantly increased levels of anxiety which was associated with younger age, peripheral neuropathy, fear of relapse, economic concerns, alcohol abuse, sexual difficulties, and a history of treatment for mental health problems in long-term survivors of testicular cancer, compared with men in the general population.²³

Chemotherapy has revolutionised the treatment of testicular cancer and is one of the great success stories of modern oncology. Early diagnosis remains important to maximise cure rates and reduce the need for intensive treatment. GPs can help to educate young male patients about the risk and how to perform self-examination.

Early referral to a urologist, if a tumour is suspected, can result in early diagnosis, more effective and less intensive treatment with fewer long-term health consequences.

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Useful information

For patients

Cancer Research UK

www.cancerresearchuk.org

Macmillan Cancer Support

www.macmillan.org.uk

For healthcare professionals

European Association of Urology

www.uroweb.org/guidelines

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