Testicular cancer (TC) accounts for only 1 per cent of all male cancers.1,2 The current global incidence is 6.3 cases/100 000 per year, with the highest rate in Northern Europe (Norway 9.6/100 000 per year) and the lowest in Asia and Africa (0.2–1/100 000 per year), with a UK incidence of 6.4/100 000 per year.2 While the worldwide incidence has more than doubled in the past 40 years,3 the mortality rate is very low, with an overall cure rate of 90–95 per cent. The reasons for this increased incidence remain unclear, with possible causes including exposure to environmental contaminants, dietary habits and lifestyle factors.

Each year, approximately 2100 men are diagnosed with TC in the UK. Most survive because of the availability of effective treatment, with fewer than 70 deaths each year caused by disease.4 Testicular cancers are very sensitive to chemotherapy and radiotherapy and therefore, unlike other solid tumours, metastatic disease can be cured with chemotherapy.

HISTOPATHOLOGICAL CLASSIFICATION
Testicular cancer can be classified into two main categories: germ cell tumours (GCT), derived from testicular germ cells, and cord stromal tumours, derived from testicular mesenchymal cells. The latter are rare (5 per cent of all TCs) and include Leydig cell and Sertoli cell tumours. Other cancers that can present in the testes include lymphoma, carcinoid tumors and metastatic carcinoma.

Testicular GCTs account for 95 per cent of malignant TCs; in this article TC refers only to GCT. They are distributed between seminomas (Figure 1; no non-seminomatous elements present) and all other histological subtypes, which are grouped together and termed non-seminomatous GCTs. Forty per cent of TCs are pure seminomas and 55 per cent are non-seminomas. The average age at presentation for seminomas is 40 years (about 10–15 years older than
for non-seminomas). Non-seminomas may contain only one histological subtype, or more commonly they consist of a mixture of two or more subtypes. These include choriocarcinoma, embryonal carcinoma, yolk-sac tumour and teratoma, as well as different combinations of non-seminoma with seminoma (approximately 20 per cent of mixed GCTs).

Testicular cancers are thought to develop from a non-invasive lesion called carcinoma in situ, also called intratubular germ-cell neoplasia (ITGCN), whose malignant transformation is likely to be influenced by hormones at or after puberty.

**RISK FACTORS**

There are a number of known risk factors for TC, including cryptorchidism, positive family history, prior history of TC and HIV infection. Cryptorchidism, or undescended testicle, is associated with a 4.8-fold increased related risk of developing TC. However, a history of cryptorchidism is identified in only 10 per cent of TC. Other testicular abnormalities such as atrophy, hypospadias, inguinal hernia and infertility or subfertility are also known risk factors for developing TC.

Approximately 1–3 per cent of patients with TC have a positive family history. First-degree relatives of men with TC have a 3- to 10-fold increased risk of developing TC. Likewise, contralateral TC constitutes a 25-fold increased risk of TC. The incidence of contralateral TC is roughly 2.7 per cent, being slightly greater in seminomas. The relationship between testicular microlithiasis and TC is controversial and has not been demonstrated conclusively. However, a meta-analysis has shown that among patients with associated risk factors for TC, the presence of testicular microlithiasis may further increase the risk of developing TC.

**DIAGNOSIS OF TESTICULAR CANCER**

Diagnosis is based on history, examination, tumour markers, testicular ultrasound and staging CT scan. Definitive diagnosis comes from histological analysis of the testicular mass removed by orchidectomy or biopsy of metastatic disease.

**Clinical presentation**

The typical presentation is a unilateral testicular mass, which is usually painless, although 10–20 per cent of men report pain, testicular discomfort or ‘heaviness’. Frequently, patients present with testicular swelling suggestive of epididymitis or orchitis and are initially treated with antibiotics. Patients may present with a ‘smaller’ testicle when in fact it is the other testicle that is enlarged. Gynaecomastia is present in 7 per cent of patients because of the hormonal effects of β-human chorionic gonadotrophin (β-hCG), most commonly in non-seminoma, where levels of β-hCG are higher. Non-seminomas are usually more aggressive than seminomas.

In approximately 25 per cent of advanced TC, the first presentation is a result of metastatic disease (for example, back pain caused by retroperitoneal lymphadenopathy, dyspnoea caused by lung metastases or thoracic pain caused by mediastinal lymphadenopathy). The initial presentation may rarely be a result of systemic symptoms such as lethargy or anorexia.

In a minority of cases (5–10 per cent), GCT may originate extragonadally in the retroperitoneum or mediastinum without any evidence of a testicular primary. Interestingly, one-third of these patients have ITGCN in the testis and another third have scar tissue in the testis suggesting a regressed primary tumour or ‘burned-out tumour’. The remaining third have...
definitive primary extragonadal GCT. Very rarely, GCT may present as a primary intracranial tumour, usually in the pineal area, representing a specific entity that will not be reviewed here.

Testicular physical examination may reveal a solid testicular mass or a nodule. Occasionally, the whole testis may be swollen with no definitive palpable mass. Clinical examination should include inguinal and abdominal examination, particularly looking for paraaortic lymphadenopathy.

Serum tumour markers
Tumour markers for TC include alphafetoprotein (AFP), β-hCG and lactate dehydrogenase (LDH). AFP and β-hCG are relatively specific and sensitive markers, which have prognostic value and are useful tools in diagnosis and management. LDH is a less specific tumour marker that correlates with the burden of disease. Markers should be checked before orchidectomy and repeated after surgery, even when pre-orchidectomy levels are within normal range. Pre-orchidectomy markers are frequently increased (21 per cent in seminomas, 79 per cent in non-seminomas), although normal levels do not exclude TC. In localised disease, post-orchidectomy markers should be checked until they normalise, as persistently raised levels post-orchidectomy suggest the presence of metastatic disease.

β-hCG may be produced by both seminomas and non-seminomas, whereas AFP is only secreted by non-seminomas. Patients with raised AFP should be treated as having non-seminomas even if the histology shows pure seminoma.

Testicular imaging
Testicular ultrasound is the gold-standard imaging test for a testicular mass or swelling (see Figure 1). It is also useful for assessing the contralateral testis and for determining whether a testicular mass is intra- or extra-testicular. As it is an innocuous and inexpensive technique, it should be performed in all men with a testicular nodule. Testicular magnetic resonance is rarely used but may be useful when the location of a scrotal mass is uncertain or when ultrasound does not allow differentiation between a solid mass and an inflammatory or vascular abnormality.

Staging
A CT scan of chest, abdomen and pelvis is the gold standard for staging. Whenever possible, the CT scan should be performed with intravenous contrast to assess retroperitoneum and mediastinum and exclude pathological lymphadenopathy (Figure 2). Fluorodeoxyglucose–positron emission tomography (FDG-PET) has failed to show any benefit over CT scan for initial staging of TC. Overall, TC can be classified into three stages: stage I (disease confined to the testicle), stage II (presence of metastatic pelvic or retroperitoneal lymphadenopathies) and stage III (presence of metastatic supradiaphragmatic lymphadenopathies and/or visceral metastases). Stage II disease is further subdivided into IIA, IIB and IIE according to lymphadenopathy size (≤2cm, 2–5cm, >5cm, respectively).

Risk classification should be done according to the International Germ Cell Collaborative Group Prognostic Classification (Table 1), which is applicable only in the metastatic setting.

TREATMENT OF PRIMARY TUMOUR
Radical inguinal orchidectomy is the standard treatment for TCs. It is both a diagnostic and therapeutic procedure. In the metastatic setting, surgery of the
primary tumour should be performed before any systemic treatment, unless there is a significant burden of metastatic disease necessitating immediate systemic therapy.

Scrotal orchidectomy should be avoided if possible. Scrotal violation for biopsy or surgery increases the risk of local recurrence and may alter lymphatic spread, increasing the possibility of an inguinal relapse to the typical retroperitoneal recurrence. This is because the lymphatic drainage of the scrotum is to the inguinal lymph nodes, while lymph from the testicles drains to the paraortic lymph nodes.

SEMINOMA MANAGEMENT
Stage I seminoma
The treatment options post-orchidectomy for stage I seminoma are surveillance, adjuvant retroperitoneal radiotherapy or adjuvant chemotherapy (Figure 3). Risk factors for recurrence are tumour size ≥4cm and rete testis invasion. The rete testis is a network of tubules that participate in the transport of sperm. The five-year relapse rates are 12, 16 and 32 per cent in patients with zero, one and two risk factors, respectively. Adjuvant chemotherapy or radiotherapy are equally effective and reduce the relapse risk to around 5 per cent. We recommend surveillance for patients with no or one risk factor and adjuvant treatment or surveillance for those with two risk factors. In the UK, one cycle of adjuvant carboplatin has replaced radiotherapy for men receiving adjuvant treatment. However, since patients who relapse while on surveillance can still be cured with chemotherapy, the overall survival remains >99 per cent regardless of the chosen strategy. Therefore surveillance minimises overtreatment and is the preferred option for stage I seminoma.

Stage IIA/B seminoma
Retroperitoneal radiotherapy to paraortic and iliac fields has been considered the standard treatment for stage IIA/B seminomas, with an overall survival of 94 per cent. Several chemotherapy regimens have proven to be effective, but the most commonly used is the combination of bleomycin, etoposide and cisplatin (BEP).

Three courses of BEP is an alternative to radiotherapy with similar survival rate. Four cycles of EP is an acceptable alternative to three cycles of BEP.

Advanced seminoma (stage IIC and III)
BEP chemotherapy is the standard treatment for advanced seminoma: three cycles for good-prognosis patients and four cycles for intermediate-prognosis patients. Overall survival is 86 and 72 per cent for good-prognosis and intermediate-prognosis groups, respectively. In case of factors predisposing for bleomycin-induced lung toxicity (emphysema, severe smokers), four cycles of EP and four cycles of ifosfamide, etoposide and cisplatin (VIP) are recommended for good- and intermediate-prognosis patients, respectively.

NON-SEMINOMA MANAGEMENT
Stage I non-seminoma
The treatment options post-orchidectomy for stage I non-seminoma are surveillance, retroperitoneal lymph node dissection (RPLND) or adjuvant chemotherapy (Figure 4). Stage I non-seminoma patients...
are divided into low risk or high risk depending on the presence of vascular invasion (VI). The five-year relapse rate is 20 per cent for low-risk patients (VI negative) and 40–50 per cent for high-risk patients (VI positive), with 80 per cent of relapses occurring during the first year. We recommend surveillance for low-risk patients and two cycles of adjuvant BEP for high-risk patients. Adjuvant chemotherapy reduces the relapse risk to 2–3 per cent at the expense of a considerable number of patients being overtreated. Irrespective of the chosen strategy, overall survival is approximately 98 per cent.\textsuperscript{12,13}

RPLND is now rarely used for stage I disease and is usually restricted to cases where surveillance or adjuvant chemotherapy are not applicable or there are issues of diagnostic uncertainty.

**Advanced metastatic non-seminoma**

BEP chemotherapy is the standard treatment for advanced non-seminoma: three cycles for good-prognosis patients and four cycles for intermediate- and poor-prognosis patients. Overall survival is 92, 80 and 48 per cent for good-, intermediate- and poor-prognosis groups, respectively (see Figure 2). In patients at risk of bleomycin-induced lung toxicity, four cycles of EP and four cycles of VIP are recommended for good- and intermediate-/poor-prognosis patients, respectively.

**RESIDUAL DISEASE MANAGEMENT**

In case of normal tumour markers but persistent residual disease after first-line chemotherapy, further treatment management will depend on tumour type. In case of seminoma residual masses, a FDG-PET scan is recommended, as a positive uptake is a strong indicator of residual viable tumour and surgery should be considered. In case of non-seminoma, all sites of residual disease should be resected if technically feasible. FDG-PET has limited predictive value in the assessment of non-seminoma residual masses and therefore its use is not recommended. Patients with residual disease and elevated tumour markers should be treated with second-line salvage chemotherapy.

**SALVAGE TREATMENT FOR RELAPSED DISEASE**

Approximately 15 per cent of men with metastatic TC will relapse after first-line chemotherapy, of whom 30 per cent can be cured with salvage treatment.\textsuperscript{14} Standard salvage treatment is a conventional dose chemotherapy combination of cisplatin with chemotherapeutic agents that have not been used first line. Late relapses (defined as after two years) respond less well to chemotherapy. If technically feasible, radical surgical resection should be the first treatment option.

**ACUTE TOXICITY FROM CHEMOTHERAPY**

Chemotherapy toxicity can be divided into haematological and non-haematological toxicity. Neutropenia is the most common...
haematological toxicity and may develop in up to 38 per cent of patients on BEP.\textsuperscript{11} Anaemia and thrombocytopenia appear less frequently and rarely require transfusional support. Single-agent carboplatin is associated with a lower incidence of neutropenia than BEP, but has a higher proportion of thrombocytopenia.

Other acute toxicities include vomiting, diarrhoea, mucositis and alopecia, which are the most frequently experienced. Cisplatin-related non-haematological toxicities include sensory peripheral neuropathy caused by neurotoxicity, hearing loss caused by ototoxicity and electrolyte disturbances and nephrotoxicity. Neuro-, nephro- and ototoxicity may be permanent. Bleomycin may cause severe pulmonary toxicity, mainly pneumonitis and fibrosis, in up to 10 per cent of patients.\textsuperscript{15}

\section*{SURVIVORSHIP ISSUES}

The high cure rate of TC, which largely affects young men, means that long-term side-effects of treatment are important. These include infertility, secondary malignancies and cardiovascular disease. Compared to the general population, fertility rates in men treated for TC are 30 per cent lower, with a fatherhood rate of approximately 70 per cent within 15 years. It is therefore important that patients should be offered sperm storage before starting treatment.

Overall there is a two-fold increased risk of developing a secondary malignancy among patients treated with radiotherapy or chemotherapy for TC. Leukaemia, gastrointestinal cancers, genitourinary cancers, lung cancer and sarcoma are the most common secondary cancers seen.

Survivors of TC treated with chemotherapy or radiotherapy have a 20–30 per cent increased risk of developing metabolic syndrome (hypercholesterolaemia, hypertension, diabetes mellitus). Moreover, its onset usually occurs earlier than expected for the patient’s age, approximately four to five years after completing the treatment.

Finally, the risk of developing cardiovascular disease (such as congestive heart failure, myocardial infarction, cerebrovascular accident) is roughly doubled after treatment with chemotherapy and radiotherapy.\textsuperscript{16}

\textbf{Declaration of interests: none declared.}

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