

Testicular cancer: an overview of contemporary practice

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Testicular cancer is a common cancer in younger men. It can be successfully treated with surgery, radiotherapy and chemotherapy, but early diagnosis is key. In this article, the authors describe the diagnosis, pathology and management of the disease.

Testicular cancer (TC) accounts for 1–2% of male cancers and is the most common malignancy in men aged 20–34.¹ There are 2400 new cases and 60 deaths in the UK each year, with peak incidence in men aged 30–34. Rates of TC have risen by 11% over the last decade, but mortality has fallen due to the introduction of platinum-based chemotherapy in the 1980s. Overall survival is excellent, with a 98% 10-year survival rate (England and Wales in 2010–11). All men diagnosed with stage 1 disease will survive for five years or more, compared to 80% of those diagnosed with advanced disease.^{2,3}

A NEW LUMP IN THE TESTIS

TC will typically present as a hard, painless lump noticed on self-examination (Figure 1). The history should enquire about duration of the lump, pain, risk factors for TC and sexual activity. A systemic enquiry should ask about symptoms of fever, cough, weight loss and back or flank pain – suggesting metastatic disease. General examination should look for gynaeecomastia (present in 7%), supraclavicular lymphadenopathy



Figure 1. All patients with a suspicious lump on the testes should be referred for urgent specialist assessment (© Dr P. Marazzi/Science Photo Library)

and an abdominal mass. Scrotal examination should note the lump size, location, firmness, tenderness and transilluminability. A misconception is that pain excludes malignancy, which can lead to a misdiagnosis of epididymitis in 17–33% of cases.⁴ All patients with a suspicious lump should be referred urgently for specialist assessment.

RISK FACTORS

TC has high incidence in Scandinavia and Switzerland, intermediate incidence in the USA, Australia and the UK, and low incidence in Africa and Asia. In the USA, Caucasian men appear to be at higher risk than African-American men living in the same area.¹ A previous history of TC confers a 12-fold risk of developing disease in the contralateral testis, and history of TC in a first-degree relative confers a 12-fold

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risk.⁵ Maternal oestrogen exposure and greater adult height are also associated with increased risk.⁶

Testicular dysgenesis syndrome (TDS) is a developmental abnormality causing impaired spermatogenesis and infertility, associated with cryptorchidism, hypospadias and possibly inguinal hernias.⁷ The components of TDS are independent risk factors for the development of TC. Those with cryptorchidism who undergo orchidopexy before the age of 13 have a significantly reduced risk of developing TC.⁸ Research into genetic markers associated with TC is ongoing. An isochromosome of the short arm of chromosome 12 and alterations to the p53 locus have been identified as specific markers for TC.^{9,10}

Testicular microlithiasis is the presence of diffuse small calcifications within the testis diagnosed on ultrasound. It was once felt to be strongly associated with TC, but follow-up studies show men with testicular microlithiasis are not at increased risk of developing TC. Regular self-examination is recommended for all those with risk factors for TC.

INVESTIGATIONS AND STAGING

Serum tumour markers are alpha-fetoprotein (AFP), human chorionic gonadotrophin (hCG) and lactate dehydrogenase (LDH). Raised tumour markers are both diagnostic and prognostic, although normal levels do not exclude cancer. A diagnostic ultrasound scan is nearly 100% sensitive for diagnosing a testicular mass and should be performed even if TC is clinically obvious. All patients with TC undergo staging computerised tomography (CT) of the chest, abdomen and pelvis to assess for metastatic disease. Where there is clinical suspicion, magnetic resonance imaging (MRI) of the spine, CT of the head or a nuclear bone scan may be required to diagnose metastatic disease.

Staging of TC is with the tumour, node and metastases (TNM) staging system, with the

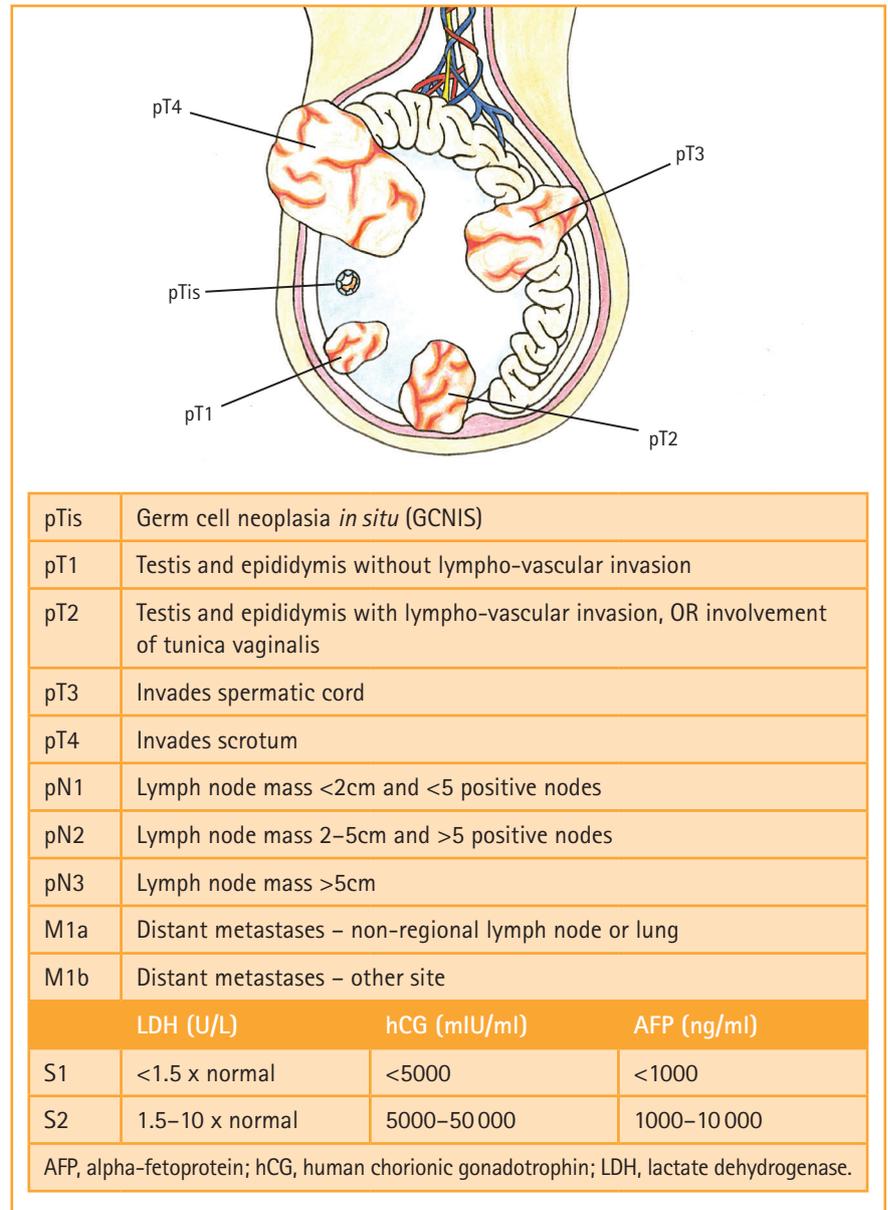


Figure 2. Diagram and summary of TNM staging for testicular cancer (drawing by Beth Goddard)

addition of the 'S' value, based on the nadir values of the tumour markers following orchidectomy (Figure 2).

There is currently no screening programme for TC, but numerous novel biomarkers are undergoing development as screening tools for those at high risk for TC. One such biomarker is the OCT 3/4 transcription factor, which can be detected in the semen. A critical amount of OCT 3/4 is required

to maintain stem cell self-replication, and altered levels have been shown to be associated with seminomas, embryonal carcinomas and germ cell neoplasia *in situ* (GCNIS).¹¹

MANAGEMENT

Initial management is urgent inguinal orchidectomy with division of the spermatic cord at the internal inguinal ring. Patients may occasionally present with respiratory

failure secondary to pulmonary metastases and require immediate life-saving chemotherapy, with orchidectomy delayed until clinical stabilisation. Those with raised tumour markers require careful monitoring post-orchidectomy. Failure of levels to fall at their expected half-life (hCG 2–3 days and AFP 5–7 days) suggests metastatic disease and conveys a worse prognosis. Those of a reproductive age group should be offered sperm banking and a fertility assessment, ideally prior to orchidectomy. All patients are offered a testicular prosthesis, either at the time of orchidectomy or following resolution of treatment.

Organ-sparing surgery is now a recommended treatment option for those with a solitary testis or bilateral tumours and reduces the morbidity associated with orchidectomy. Enucleation of the mass, followed by histopathological frozen section from the resection margins, can guide as to whether the lesion is benign or malignant and whether further resection or orchidectomy is necessary.^{3,12}

PATHOLOGY

Germ cell tumours (GCTs) account for 95% of TCs, half of which are seminomas; the other half are non-seminomatous germ cell tumours (NSGCTs). Seminomas tend to occur in a higher age group (peak age 30–45 years) than NSGCTs (peak age 20–35 years). NSGCTs predominate in infantile cases, while in men over 50 the main types of TC are lymphomas and spermatocytic seminomas.¹ Non-GCTs account for less than 5% of TC cases and include stromal-cell tumours such as Leydig cell and Sertoli cell tumours.⁵

GCNIS is a pre-invasive precursor to GCT and is present in the contralateral testis in up to 5% of those with TC. Untreated, 50% of cases will develop invasive cancer within five years.¹³ Current European guidelines suggest that men below 40 years who have risk factors for GCNIS (testicular volume <12ml, history of cryptorchidism or infertility) should have contralateral

Good prognosis group	
Non-seminoma	No non-pulmonary visceral metastases AFP <1000ng/ml, hCG <5000IU/L, LDH <1.5 x ULN
Seminoma	No non-pulmonary visceral metastases Normal AFP Any hCG or LDH
Intermediate prognosis group	
Non-seminoma	No non-pulmonary visceral metastases AFP 1000–10 000ng/ml or, hCG 5000–50 000IU/L or, LDH 1.5–10 x ULN
Seminoma	Non-pulmonary visceral metastases Normal AFP Any hCG or LDH
Poor prognosis group	
Non-seminoma	Mediastinal primary AFP <10 000ng/ml or, hCG >50 000IU/L or, LDH >10 x ULN
Seminoma	No patients classified as poor prognosis
AFP, alpha-fetoprotein; hCG, human chorionic gonadotrophin; LDH, lactate dehydrogenase; ULN, upper limit of normal.	

Table 1. Summary of International Germ Cell Collaborative Group (IGCCG) prognostic staging system for metastatic germ cell cancer

testis biopsy at the time of orchidectomy. If GCNIS is detected, local radiotherapy is recommended. Close ultrasound surveillance is an option for those who wish to delay treatment until they have completed their family.³

OVERVIEW OF SYSTEMIC THERAPIES

Treatment of TC following orchidectomy depends on the histology of the primary tumour and the presence of metastatic disease. Active surveillance is a treatment option for those with localised tumours and favourable histology. Five-year survival is 97–100% for stage 1 seminoma, but for NSGCTs 30% will ultimately develop metastatic disease and require salvage chemotherapy. Surveillance requires rigorous follow-up with serial CT scans

and clinical examination, so patients must be suitably reliable to attend their outpatient appointments. Primary adjuvant chemotherapy is given to those with localised tumours who do not wish to undergo surveillance or who have unfavourable histology (tumour >4cm, invasion of the rete testes, vascular invasion on histology or T2–T4 disease).³

For metastatic TC, treatment is defined according to the International Germ Cell Collaborative Group (IGCCG) prognostic staging tool (Table 1), which categorises patients into good, intermediate or poor prognosis for metastatic TC.

Seminoma is highly radiosensitive and chemotherapy was traditionally reserved

only for those with more advanced disease. However, modern studies show equivalent results with single dose carboplatin treatment for early metastatic seminoma and UK management has adapted accordingly. For metastatic NSGCTs, initial treatment is typically with three to four cycles of 'BEP' chemotherapy (bleomycin, etoposide, cisplatin).³

LYMPH NODE SURGERY FOR TESTICULAR CANCER

Retroperitoneal lymph node dissection (RPLND) is surgical resection of the retroperitoneal lymph nodes. In the UK, it is reserved almost exclusively for the removal of residual retroperitoneal NSGCT masses after chemotherapy. Traditional RPLND involves a laparotomy and resection of the retroperitoneal lymph nodes following standardised anatomical templates. More recently, laparoscopic RPLND and subsequently robot-assisted laparoscopic RPLND have been described. While robot-assisted RPLND remains in its infancy, early case series report similar cancer outcomes compared to the traditional open approach, with shorter length of stay in hospital, less blood loss and better maintenance of antegrade ejaculation post-procedure.¹⁴

CONCLUSION

TC is a common cancer in men in their 20s and 30s. If diagnosed early, survival is excellent. Treatment is with urgent inguinal orchidectomy, followed by a tailored oncological follow-up. Research is ongoing into improved surgical and oncological treatments to further improve the detection and management of TC.

Declaration of interests: none declared.

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