Ministry of Defence

Synopsis of Causation

Cancer of the Testis

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Disclaimer

This synopsis has been completed by medical practitioners. It is based on a literature search at the standard of a textbook of medicine and generalist review articles. It is not intended to be a meta-analysis of the literature on the condition specified.

Every effort has been taken to ensure that the information contained in the synopsis is accurate and consistent with current knowledge and practice and to do this the synopsis has been subject to an external validation process by consultants in a relevant specialty nominated by the Royal Society of Medicine.

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1. Definition

1.1. Cancers of the testis are malignant tumours affecting the male gonads. Two main classification systems are in use: the World Health Organisation (WHO) classification and the British Testicular Tumour Panel and Registry (BTTPR) classification;[1] pathology reports may use both classifications side by side.

1.2. Broadly, however, there are two main types of testicular cancer: **seminomas**, and **teratomas** (in the WHO classification) or non-seminomatous germ-cell tumours (in the BTTPR classification).

1.3. The non-seminomatous germ-cell tumours or teratomas are subdivided into further categories, such as mature teratomas, embryonal carcinomas with teratoma, embryonal carcinoma, yolk-sac tumour and choriocarcinoma (in the WHO classification) and differentiated teratoma, intermediate malignant teratoma, undifferentiated yolk-sac tumour and malignant trophoblastic teratoma (in the BTTPR classification).[2]

1.4. Both classifications include a third category, the **spermatocytic seminoma**.

2. Clinical features

2.1. Testicular cancer accounts for about 1% of all neoplasms in males and is the most common malignancy in men aged between 20 and 40 years.[3] The peak prevalence is 25–35 years.[3] There are smaller peaks in boys aged under 10 years and in elderly men.[4] About 1900 new cases are diagnosed each year in the UK.

2.2. Seminomas and non-seminomatous germ cell tumours or teratomas each account for about 50% of testicular tumours.[2]

2.3. The most typical presentation is of a painless testicular lump, which may be noticed either by the patient or by his partner. Testicular enlargement, a feeling of firmness, an ache or discomfort, or asymmetry between the testes are other presentations of localised disease.[3]

2.4. Presentation of disseminated disease depends on the site of metastases; for example, spread to the para-aortic lymph nodes may cause back pain, and spread to the lungs may cause shortness of breath or haemoptysis.

2.5. Bilateral tumours are not uncommon, with between 2% and 4% of patients having either cancer or intratubular germ cell neoplasia, a precursor of cancer, in both testicles at the time of presentation.[5,6] Bilateral tumour is associated with infertility.[3]

2.6. Spermatocytic seminomas are relatively rare, accounting for less than 5% of all testicular tumours, and they are most commonly seen in older men.[6] These tumours are often asymptomatic and may grow to a very large size before being detected.

2.7. Yolk sac tumours are the most common type of testicular tumour in children.[6]

3. Aetiology

3.1. **Risk factors for testicular cancer.** A number of risk factors for testicular cancer have been identified, but the overall aetiopathogenesis remains unclear.

3.2. **Racial and geographical factors.** The incidence of testicular germ cell tumours has risen steadily throughout the 20th century, and increases of 15–20% over some 5-year periods have been reported.[3] The incidence of testicular germ cell tumours shows a marked racial and geographical variation, with the highest incidence being seen in white men in northern Europe.[3] Furthermore, a wide geographical variation exists between the countries of northern Europe and in one large study the highest and the lowest age-standardised incidence rates were 15.2 in Denmark and 2.1 in Lithuania.[7] These and other epidemiological findings suggest that there is both a genetic and an environmental component in the aetiology of testicular germ cell tumours.

3.2.1. **Genetic factors.** Overall, a positive family history in patients with testicular cancer is relatively unusual, being found in about 2% of patients. However, brothers of men with testicular cancer have been reported to be up to 10 times more likely to be affected themselves.[3]

3.2.2. Almost all testicular germ cell tumours have an abnormality in the short arm of chromosome 12. In up to 80% this takes the form of duplication of the short arm; in the other affected cases, parts of the short arm of chromosome 12 are overexpressed.

3.2.3. The relationship between abnormalities in chromosome 12 and the development of testicular germ cell tumours is not clear. However, some cases of intratubular germ cell neoplasia are not associated with chromosome 12 abnormalities, which suggests that the abnormality might be related to progression of the tumour rather than its genesis.[8]

3.2.4. Recently, a mutation in chromosome Xq27 has been identified as being associated with a familial risk of testicular cancer;[9] this association appears to be particularly strong when one or more of the family members has had bilateral testicular cancer.

3.2.5. The relative risk of developing a second testicular cancer has been put at 25.[10] One study has found that the risk of a patient with a positive family history developing a second tumour is substantially higher (at 9.8%) than the risk of a patient with no family history developing a second tumour (at 2.8%).[11]

3.3. **Prenatal or early childhood influences.** The age distribution, with the peak prevalence in men aged 25–35 years, suggests that an initiating event may occur prenatally or in childhood and that the tumour may often start to develop in adolescence.[3]

3.3.1. **Maternal smoking** One group of workers found a clear correlation between the increase in incidence of the disease and the increase in smoking by women and suggest that there may be a link between maternal smoking and testicular cancer.[12] The hypothesis awaits further investigation.

3.3.2. **Cryptorchidism.** Undescended or maldescended testes is a strong risk factor for developing testicular cancer. A relative risk of 3.8 or more has been demonstrated in cryptorchidism if orchidectomy is not performed;[13] orchidectomy before the age of 10 years removed the increased risk.

3.3.3. **Low birth weight.** Low birth weight has been shown to be associated with an increased risk of non-seminomatous testicular cancer, with a relative risk of 2.6.[14] On the other hand, there may be no association between low birth weight and seminomatous testicular cancer.[12]

3.3.4. **Infantile hernia.** The presence of infantile hernia has been shown to be associated with an increased risk of testicular cancer, with a relative risk of 1.9.[11]

3.3.5. What is not so clear is whether these features are a direct cause of testicular cancer or whether they themselves derive from environmental or genetic factors that are directly related to increased risk of testicular cancer.[3] Familial cases of maldescended testes are more likely to carry a genetic mutation in the Xq17 region.[8]

3.4. **Early age at puberty** The rapid growth of the testes during puberty may represent a period of vulnerability to carcinogenic exposures and early age at puberty has been associated with an increased risk of testicular cancer.[15,16]

3.5. **Adult height.** Height, but not weight, appears to be positively correlated with a risk of testicular cancer.[17] This concept proposes a modulating effect by high dietary intake during childhood and it is postulated that, since adult height is partly related to energy intake during early life, the pathogenesis of these tumours might be promoted by childhood nutrition. This theory is supported by experience in Japan,[18] where the intake of high-protein animal foods, especially milk, increased dramatically after World War 2, an increase that was mirrored by an increase in the incidence and mortality rates of testicular cancer. A recent Swedish case-control study appears to support an association between adult height and testicular cancer [19] and a similar finding has been reported by Norwegian workers[20] who also found an inverse relationship with body mass index (BMI).

3.6. **Environmental factors** A number of environmental factors have been proposed as possible risk factors. These include residential exposure to overhead high-voltage lines, a hypothesis which has not been supported by a recent study.[21] Occupational factors associated with fire-fighting, maintenance work in pulp mills and exposure to synthetically-produced endocrine-disruptors have all been postulated as risk factors for testicular cancer but there is as yet no firm scientific evidence to support these links.

3.7. There is no evidence that either vasectomy or trauma is associated with an increased risk of testicular cancer.

4. Prognosis

4.1. Testicular cancer is potentially highly curable and in seminoma in particular, localised disease is associated with a survival rate of almost 100%. Most cases of disseminated disease are also curable with appropriate chemotherapy.

4.2. In metastatic disease, most centres rely upon platinum-based chemotherapy. However, surgical treatment continues to play an important part in the management of more advanced disease, and retroperitoneal lymph node dissection in conjunction with chemotherapy has enabled a high cure rate to be achieved (80%-95%).

5. Summary

5.1. Testicular tumours are not common, accounting for about 1% of all neoplasms in males, but they are the most common malignancy in young men.

5.2. They are classified at present by two separate systems, and pathology reports may use both systems side by side.

5.3. The most usual presentation is with a painless testicular lump or other local symptoms, although disseminated disease can present with clinical features referable to the area of metastasis.

5.4. A number of risk factors have been identified, but the overall relationship between these risk factors and the genesis of testicular cancers is not yet clear.

5.5. There are marked racial and geographical variations in the incidence of testicular cancer. The highest incidence is in white men in northern Europe, the figures rising steadily throughout the 20th century. These factors suggest that both genetic and environmental factors are likely to play a part.

5.6. There is clearly a genetic component in the aetiology of testicular tumour, with an increased risk in people with an affected family member and identified chromosomal abnormalities associated with the development of disease.

5.7. Cryptorchidism, low birth weight and infantile hernia are all associated with increased risk, although it is not clear whether these factors increase the risk *per se* or whether they in turn derive from other environmental or genetic factors.

5.8. Adult height is associated with an increased risk, suggesting that energy intake during early life may be a background risk.

5.9. There is no evidence that vasectomy or trauma is associated with an increased risk of testicular cancer.

5.10. Cure rates are very high. Localised testicular cancer is associated with a survival rate of almost 100% and even in metastatic disease a survival rate of 80%-95% is possible.

6. Related Synopses

7. Glossary

cryptorchidism	Failure of one or both testicles to descend into the scrotum.
haemoptysis	Coughing up blood or bloodstained sputum.
metastasise	Process whereby a malignant tumour spreads to a distant site in the body.
mutation	A permanent change in genetic material that can be transmitted to future generations.
orchidectomy	Surgical removal of one or both testes.

8. References

[1] Management of adult testicular germ cell tumours. SIGN publication number 28. Edinburgh: Scottish Intercollegiate Guidelines Network (SIGN); 2000; (http://www.sign.ac.uk/pdf/sign28.pdf; accessed 17 August 2005).
[2] Jones RH, Vasey PA. Part I: testicular cancer - management of early disease. Lancet Oncol 2003;4:730-7.
[3] Dearnaley DP, Huddart RA, Horwich A. Managing testicular cancer. Br Med J 2001;322:1583-8.
[4] Kundra V. Testicular cancer. Semin Roentgenol 2004;39:437-50.
[5] Harland SJ, Cook PA, Fossa S, et al. Intratubular germ cell neoplasia of the contralateral testis in testicular cancer. Defining a high-risk group. J Urol 1998;160:1353-7.
[6] Small. EJ, Garcia JA, Torti F. Testicular cancer. In: Abeloff MD, Armitage JO, Niederhuber JE, Kastan MB, McKenna GW, editors. Clinical Oncology. 3rd ed. Philadelphia: Elsevier; 2004. p. 2175-216.
[7] Richiardi L, Bellocco R, Adami H-O et al. Testicular cancer incidence in eight Northern European countries: secular and recent trends. Cancer Epidemiol Biomarkers Prev 2004;13:2157-2166.
[8] Summersgill B, Osin P. Lu YJ, Huddart R, Shipley J. Chromosomal imbalances associated with carcinoma in situ and associated testicular germ cell tumours of adolescents and adults. Br J Cancer 2001;85:213-20.
[9] Rapley E, Crockford G, Teare D, Briggs P, Seal S, Barfoot R, et al. Localization to Xq27 of a susceptibility gene for testicular germ-cell tumours. Nat Genet 2000;24:197-200.
[10] Lutke Holzik MF, Rapley EA, Hoekstra HJ, Sleijfer DT, Nolte IM, Sijmons RH. Genetic predisposition to testicular germ-cell tumours. Lancet Oncol 2004;5:363-71.
[11] Heimdal K, Olsson H, Tretli S, Flodgren P, Borresen AL, Fossa SD. Familial testicular cancer in Norway and southern Sweden. Br J Cancer 1996;73:964-69.
[12] Pettersson A, Kaijser M, Richiardi L. Women smoking and testicular cancer: one epidemic causing another? Int J Cancer 2004;109(6):941-4.
[13] United Kingdom Testicular Cancer Study Group. The aetiology of testicular cancer: association with congenital abnormalities, age at puberty, infertility and exercise. Br Med J 1994;308:1393-9.
[14] Akre O, Ekbom A, Hsieh CC, Trichopoulos D, Adami HO. Testicular nonseminoma and seminoma in relation to perinatal characteristics. J Natl Cancer Inst 1996;88:883-9.
[15] Weir HK, Kreiger N, Marrett LD. Age at puberty and risk of testicular germ cell cancer. Cancer Causes Control 1998;9:253-258.
[16] United Kingdom Testicular Cancer Study Group. Aetiology of testicular cancer: association with congenital abnormalities, age at puberty, infertility, and exercise. Br Med J 1994;308:1393-1399.
[17] Dieckmann KP, Pichlmeier U. Is risk of testicular cancer related to body size? Eur Urol 2002;42:564-9.
[18] Ganmaa D, Li XM, Qin LQ, et al. The experience of Japan as a clue to the etiology of testicular and prostatic cancers. Med Hypotheses 2003;60:724-30.
[19] Richiardi L, Askling J, Granath F, Akre O. Body size at birth and adulthood and the risk for germ-cell testicular cancer. Cancer Epidemiol Biomarkers Prev 2003;(12):669-673.
[20]Akre O, Ekbom A, Sparen P, Tretli S. Body size and testicular cancer. J Natl Cancer Inst 2000;92(13):1093-1096.
[21] Baumgardt-Elms C, Schumann M, Ahrens W, et al. Residential exposure to overhead high-voltage lines and the risk of testicular cancer: results of a population-based case-control study in Hamburg (Germany). Int Arch Occup Environ Health 2005:78(1);20-6.