Chapter 44
What types of testicular tumors occur in men? How effective are existing therapeutic approaches and what is the prognosis?

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Introduction

Testicular tumor is a commonly used general term which covers a large variety of different neoplasia that occur in the testis, some malignant, some benign. In epidemiology, testicular cancer is practically synonymous with testicular germ cell tumors (TGCT), which constitute the vast majority of all cases. TGCTs are particularly fascinating because of their origin from germ cells, which have very different biologic features than other (somatic) cells in the body. Germ cells are the only cells in the body that can undergo two different types of cell division (mitosis and meiosis), which can cause problems during transition, and they are also known for propensity to undergo apoptosis, which renders them sensitive to cytotoxic treatment. TGCT is considered a developmental disease (Chapter 45). In contrast to other solid tissue cancers, TGCT is the most common cancer occurring in young men. The peak incidence is around 25-35 years of age, which coincides with the peak reproductive activity of most men, thus fertility issues, possible hypogonadism and sexual function are of particular importance for these patients. Thanks to the advancements of modern treatment, mortality is very low, and the survival rates exceed 95% in most countries.

Interestingly, the incidence of testicular cancer is variable in world populations, with the highest rates among white men of Northern European origin (age-standardized rate of 9-11 per 100,000), and the lowest (0.5 – 1 per 100,000) in men of African and East-Asian ancestry, in whom this cancer is a rare disease. Such a big difference in the incidence indicates that the risk of testicular cancer is strongly linked to the genetic variability. Even more fascinating is the fact that the incidence of testicular cancer in each population is not stable but has been changing markedly during the second half of

the twentieth century and the beginning of the twenty first century. Some populations with historically low incidence rates, for example, Finland and Hispanic populations of the America, including in the United States, experienced a rapid increase (doubling or tripling) during recent decades. By contrast, the rates in several European countries, including Denmark and Norway, previously known for the highest incidence of testicular cancer in the world, have been showing signs of levelling off. The reasons behind these rapidly changing incidence trends are not yet known but it is obvious that environmental or lifestyle factors are involved. For further information about these aspects and possible mechanisms see Chapter 45 which deals with the origin of germ cell tumors. The focus of this chapter is on the pathology of testicular tumors and clinical management, with emphasis on andrological aspects.

Main types of testicular tumors

The testicle is a complex organ and in addition to germ cells contains different cell types that can give rise to a tumor. The tumor types that originate from testis-specific somatic cells - Leydig cells or Sertoli cells - are grouped under the name of sex-cord-stromal tumors. Other cell types, for example, epithelium of rete testis can also grow into a malignant tumor. Finally, the testis is frequently a site of hematologic malignancies, such as lymphoma (mainly in older men) or acute leukemia (mainly in young boys). All these tumor types differ significantly from each other with regard to their histology, pathogenesis, typical age at presentation, incidence, clinical course, and prognosis. This huge variety of phenotypes has been a problem for generations of pathologists and clinicians. The World Health Organization (WHO) has been updating the classification of testicular tumors regularly. In 2016 the morphology-based division was replaced by a new classification, based on the biology and cell of origin of each tumor, and the latest edition in 2022 upheld the changes. A list of main types of testicular tumors, with currently accepted names, is presented in Table 1, and those most important clinically are briefly described in the next section.

Table 1. Main types of testicular tumors.

Testicular germ cell tumors (TGCT)

• **TGCT derived from germ cell neoplasia in situ (GCNIS)**
  ○ Preinvasive: GCNIS, gonadoblastoma
  ○ Seminoma (germinoma)
  ○ Nonseminoma
  - Embryonal carcinoma
  - Yolk sac tumor
  - Choriocarcinoma and other trophoblastic tumors
  - Teratoma
• **TGCT unrelated to GCNIS**
  ○ Childhood (pediatric) tumors
  - Teratoma, prepubertal type, incl. (epi)dermoid cysts
  - Yolk sac tumor, prepubertal type
  ○ Spermatocytic tumor

Sex cord-stromal tumors
• Leydig cell tumors • Sertoli cell tumors • Granulosa cell tumors • Other or unclassified sex cord-stromal tumors
Other tumors and malignancies

• Haematolymphoid tumors
  ○ Lymphoma
  ○ Leukemia
  ○ Myeloid sarcoma
• Tumors of collecting ducts and rete testis

Testicular germ cell tumors (TGCT)

The group of testicular tumors derived from germ cells (TGCT) is the largest and clinically most important. The TGCT are divided into two main types, depending on their association (or lack of thereof) with

a preinvasive lesion, called *germ cell neoplasia in situ* (GCNIS). The commonest tumors (approximately 95%) that occur in adolescents and young adults are derived from GCNIS. Roughly half of the cases are of the type called seminoma and the other half are nonseminomas. In individuals with disorders of sex differentiation (DSD, a rare complex condition), who have poorly developed gonads, the preinvasive lesion called *gonadoblastoma* can also occur.

It is important to emphasize that the GCNIS-derived TGCTs are associated with an impaired early development of the reproductive system and belong to the so-called testicular dysgenesis syndrome (TDS), along with other abnormalities, such as cryptorchidism (undescended testis), hypospadias and infertility with testicular atrophy (small testes). Hence attending physicians must be aware of this association and always exclude a possibility of testicular malignancy in patients with these disorders. If left untreated, patients with GCNIS will eventually develop invasive tumors, although it can take several years.

GCNIS is present inside seminiferous tubules in the place normally occupied by spermatogonia (Fig. 1). In the tubules with GCNIS, Sertoli cells are always present and occasionally normal germ cells and inflammatory cells can be seen. GCNIS cells, however, are different from normal adult spermatogonia, have larger nuclei and resemble immature fetal germ cells, called gonocytes. The two cell types express embryonic markers of pluripotency and antigens normally found in primordial but not in mature adult germ cells, e.g. OCT3/4, NANOG, AP-2 gamma (TFAP2C), placental-like alkaline phosphatase (PLAP), and podoplanin (D2-40) (Fig. 1). In addition to protein-coding genes, GCNIS and all GCNIS-derived tumors, except mature teratomas, have a high expression of embryonic-type micro-RNAs (miRNA), among which the miR-371-3 cluster is clinically most important.

Seminoma is a homogeneous tumor composed of gonocyte-resembling cells that express the same markers as GCNIS cells and can contain prominent immune cell infiltrates. By contrast, nonseminomas are morphologically very heterogenous and can contain one or more of the subtypes listed in Table 1; embryonal carcinoma, yolk sac tumor, choriocarcinoma and teratoma. Because of the high expression of the above-mentioned pluripotency factors, the early tumor cells can differentiate in any type of embryonic or extra-embryonic somatic tissues.

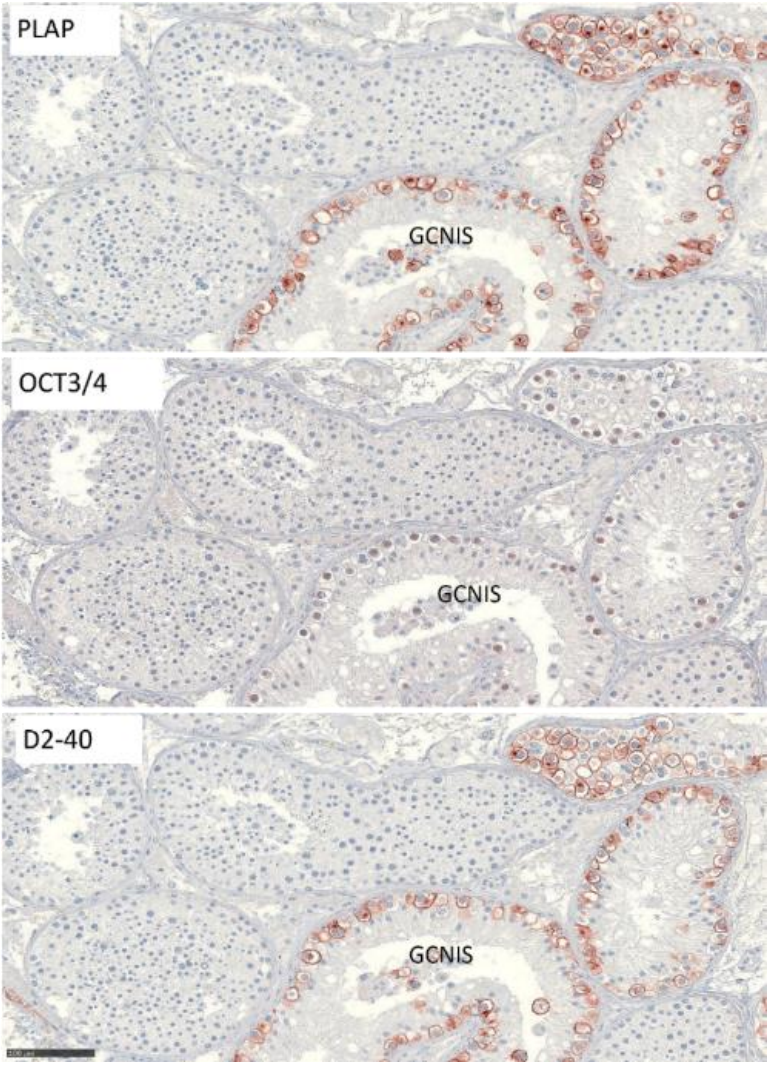

Figure 1. An example of testicular biopsy with germ cell neoplasia in situ (GCNIS). GCNIS cells are marked in several tubules by immunohistochemical (IHC) expression of PLAP (cytoplasmic), OCT3/4 (nuclear) and D2-40 (cytoplasmic). Other tubules (without IHC reaction) contain ongoing spermatogenesis, with all stages of germ cell maturation present. Scale bar equals100 μm. Reprinted from Rajpert-De Meyts et al. BJUI 2022, © The Authors.

TGCT can also occur in early childhood, typically at the age from birth to 4 years, but these tumors are rare and their incidence has not been increasing. The main types are yolk sac tumor, which has an aggressive clinical course, and mature teratoma, which is usually benign. Importantly, the childhood TGCTs are not associated with GCNIS and have different pathogeneses, which remain unknown.

A third, rare TGCT type is called *spermatocytic tumor* and occurs in relatively older men (median age at diagnosis 50-55 years). This tumor is derived from post-pubertal germ cells; spermatogonia or early spermatocytes, which can grow into a tumor as a result of genetic aberrations, with either gain-of-function mutations promoting spermatogonial proliferation or chromosomal errors blocking the progress of meiosis at the early stage and promoting polyploidy. Spermatocytic tumors have usually a benign clinical course and are treated by surgery alone.

Sex cord-stromal tumors

These tumors arise from testicular somatic cells and are much less common than germ cell tumors.

Leydig cell tumors account for approximately 3-5% of all testicular tumors, and only 1 in 10 is malignant. These tumors can occur in children and adults. The main patient groups that harbor Leydig cell tumors include boys with peripheral precocious puberty, men with unexplained infertility, gynecomastia or Klinefelter syndrome. Among genetic defects, activating mutations of the luteinizing hormone (LH) receptor have been best described. Leydig cell tumors are usually small, well demarcated and are detected by ultrasound examination.

Sertoli cell tumors are rare and can occur in children and adults, sometimes in patients with undescended testes and in men with Klinefelter syndrome. Two subtypes of these tumors, both with prominent calcifications, occur in association with Carney complex and Peutz-Jeghers syndrome; these are multiple neoplasia syndromes with a dominant inheritance characterized by non-endocrine and endocrine tumors, adrenocortical disease, skin hyperpigmentation and gynecomastia.

Diagnosis of testicular tumors

Diagnosis at the precursor stage of GCNIS is rare because this lesion is asymptomatic. GCNIS is usually an incidental finding in patients

from risk groups (see next section *Prevention*). Overt testicular tumors are often reported by the patients themselves, if large enough to be felt during self-examinations, or are found during andrological work-up that includes physical examination and scrotal imaging, usually by ultrasound. If a malignancy is suspected, blood tests must follow to measure biochemical markers secreted by germ cell tumors. Serum tumor markers include human chorionic gonadotropin (β-hCG) secreted by trophoblastic cells and choriocarcinoma, alpha fetoprotein (AFP) secreted by yolk sac tumors, and lactate dehydrogenase (LDH) produced by seminoma. These markers are raised in only 60% of patients with TGCTs. Recently, a new blood test has been developed – it is based on the detection of GCT-specific micro-RNAs (miR-371a-3p cluster). This test is sensitive and helps to diagnose practically all TGCTs, except mature teratomas. There are currently no blood tests to detect the sex cord-stromal tumors, except Leydig cell tumors, which usually secrete excessive amounts of steroid hormones, and can be manifested by peripheral precocious puberty in boys or gynecomastia in any age.

The final diagnosis of testicular tumors, including preinvasive lesions, must be confirmed by the histopathologic analysis of the excised tissue. Here, a panel of clinically useful immunohisto-chemical markers is very helpful. The similarity of GCNIS and seminoma to gonocytes is exploited by several markers not otherwise present in the adult testicle (Fig. 1). Recognition of different components of nonseminomas is essential, because these tumors have worse prognosis than pure seminoma. The immunohistochemical staining for the presence of AFP, HCG, or SOX2 can be helpful to reach correct diagnosis.

Prevention

Because of unknown etiology it is not yet possible to prevent testicular cancer in the general population, but the invasive cancer can be prevented in patients from high-risk groups by early diagnosis at the GCNIS stage. The main risk groups include DSD, history of cryptorchidism, poor semen quality or infertility, especially if there are signs of testicular dysgenesis, such as small testicular volume or microlithiasis (microcalcifications on ultrasound). GCNIS is present in the other testicle of about 5% of patients with unilateral TGCT, and its detection can significantly reduce the risk of metachronous bilateral cancer.

Currently, the diagnosis of GCNIS requires testicular biopsy, which in at-risk patients should be bilateral, while in patients with TGCT a contralateral testis biopsy can be performed at the time of orchiectomy for the primary tumor. The biopsies should be large enough and evaluated carefully, with obligatory immunohistochemical staining for at least one GCNIS marker to avoid overlooking the neoplastic cells (Fig. 1). Ongoing research efforts aim to develop a detection method less invasive than biopsy. GCNIS cells can be detected in semen by an immuno-cytological method, and the above-mentioned miRNA test in blood can detect about half of patients with GCNIS but further improvement of sensitivity is needed for routine use of these approaches.

Management, prognosis and late effects

Radical removal of the testis (orchiectomy) is the treatment of choice for malignant testicular cancer, including the vast majority of the TGCTs. Other tumors, for example small and well-demarcated Leydig cell tumors, which are often benign, can be treated more conservatively by testis-preserving surgery, when the surgeon carefully removes only the tumor tissue. In all young adults with testicular cancer, semen cryopreservation ought to be offered before surgery or any other treatment.

Patients with GCNIS alone can be treated by orchiectomy of the involved testicle or by low-dose radiotherapy in patients with bilateral GCNIS, which can eradicate the malignant cells while preserving Leydig cells and androgen production. All patients with malignant TGCT must be evaluated for a possible spread of malignancy, which would define their prognosis and treatment. Prognostic staging takes into account the levels of the above-mentioned circulating serum tumor markers, primary tumor type and size, and the presence of distant metastases. The patients are subsequently stratified to the good, intermediate, or poor prognosis groups.

The rates of survival in patients with testicular cancer are in general excellent, mainly because of good methods of diagnosis, surgical treatment, and the very efficient chemotherapy regimens based on cisplatin in combination with other cytotoxic drugs. For the US population (2008-2014), the 5-year relative survival rate was overall >95%, but as high as >99% if the tumor was detected in early localized stage. For disseminated testicular cancer, the survival rate drops to 70-75%, underlying the importance of early diagnosis. The greatest management challenges are in patients, who do not

respond to therapy and have recurrent tumors. The patients with poor prognosis (survival rates 50-60%) are treated in experienced oncology centers, with aggressive salvage regimens containing additional cytotoxic drugs. Patients treated with radio- or chemotherapy are at an increased risk of ototoxicity and hepatoxicity, peripheral neuropathy, cardiovascular disease, and second cancers.

Most testicular cancer survivors are young men and have several decades of life after treatment. Even though most of them will be declared 'cancer-free', they should be followed for many years, not only with regard to the possibility of a late relapse, but also the health issues caused by loss of one or both testes, which can contribute to numerous health problems and reduced life expectancy. The most common problems include infertility and testosterone deficiency, which in some patients occur even before the appearance of cancer, due to the frequent association of TGCT with a general impairment of testicular function. Other possible health problems are sexual dysfunction, psychological stress, metabolic syndrome, and osteoporosis later in life. Each patient ought to be cared for by a team of collaborating specialists, including an andrologist.

Suggested reading

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