

What types of testicular cancers occur in men? What is their prognosis? How effective are existing therapeutic approaches?

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Germ cell tumors

Testicular cancer has been increasing in incidence all over the world and is now the most common malignancy among young men. The vast majority of these tumors are germ cell tumors. They are believed to originate from primordial germ cells or gonocytes, which fail to differentiate to spermatogonia in fetal life. However, these precursor cells, which persist during childhood do not develop into invasive cancer until after puberty. The peak incidence occurs around age 20-40 and these tumors are very rare in old men. Germ cell neoplasia can be non-invasive for many years as a preinvasive *carcinoma in situ (CIS)* pattern, where the normal germ cells of the seminiferous epithelium are replaced by a row of carcinoma in situ germ cells (Fig 1).

Such tubules may occupy from a few to almost 100 percent of the seminiferous tubules. In these tubules with CIS, Sertoli cells are always present although there are rarely any normal germ cells. Recent research has shown that CIS cells express stem cell markers, e.g. Oct-4, NANOG, AP-2 gamma and C-Kit. It is thought that patients with untreated CIS will eventually develop invasive tumors, either seminomas or non-seminomas. It should be noted that seminomas are in fact gonocytomas (not “semen” tumors, as the name may suggest). Four subtypes of non-seminomas exist, namely embryonal carcinomas, terato-carcinomas, choriocarcinomas and yolk sac tumors. In many cases elements of seminomas and non-seminomas may co-exist in the same testis.

The main reason for dividing the germ cell tumors into these categories is that prognosis and treatment for seminomas and non-seminomas are different. Prior to the introduction of cis-platinum based chemotherapy that was introduced in the 1980s, seminomas had a rather good prognosis, while non-seminomas were associated with a higher mortality rate, particularly if they had metastasised at the time of the initial presentation.

Diagnosis

The diagnosis of a testicular tumor must be based on taking a careful history. In most cases the patients present with a testicular mass with minimal

discomfort. Previous history of cryptorchidism may be elicited. Physical examination on careful palpation of both testes generally reveals a hard nodule. Further clinical evaluation may include testicular sonogram and measurement of serum tumor markers, including human chorionic gonadotropin (elevated in cases of choriocarcinoma) and alpha-foetoprotein (elevated in yolk-sac tumor). Unfortunately the diagnosis of testis cancer may be delayed due to the patient's unawareness of the signs of tumor or the doctor's misclassification of the tumor as an infection of the epididymis.

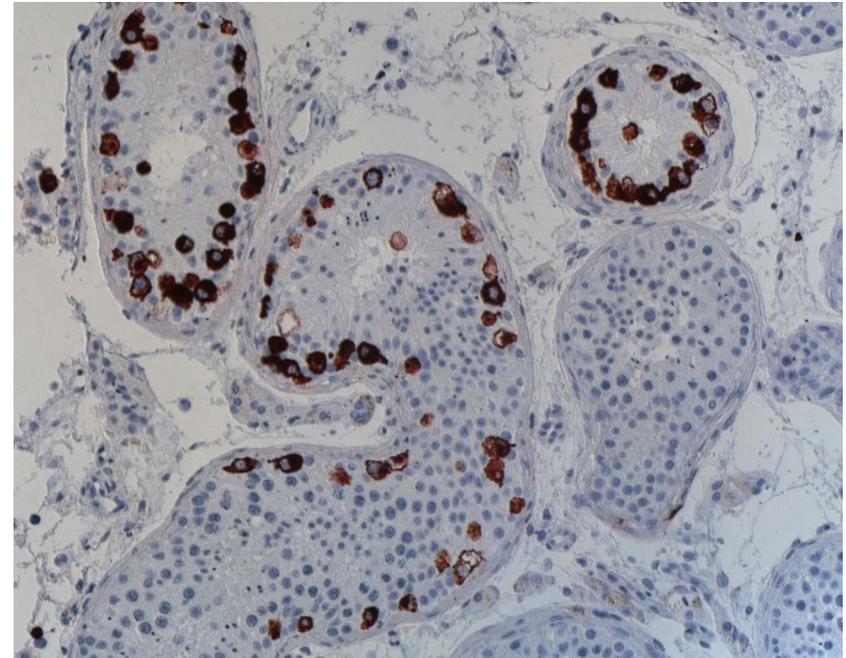


FIG. 1. Testicular biopsy showing several tubules with carcinoma in situ cells (the brown-red stained cells along the basal membrane). Placental like alkaline phosphatase (PLAP) immunostaining. The two upper tubules contain CIS cells and Sertoli cells and no normal germ cells, while the lower CIS tubule also contain normal germ cells. Note - for comparison - the tubule to the lower right with normal spermatogenesis.

Treatment and prognosis

The initial management of testicular germ cell tumors includes radical orchiectomy and tumor staging using computer-tomogram (CT) to evaluate for metastasis to the mediastinum of the chest and retroperitoneum.

In the absence of signs of metastases and depending on the histology of the testis tumor and the levels of serum tumor markers, it is adequate for the patients to have frequent follow-up visits and regular imaging procedures. In cases with more aggressive types of tumor, as suggested by the histological subtypes, elevated tumor markers or the presence of metastasis, combination chemotherapy and/or radiation therapy may be needed. Additional surgery to remove and evaluate the metastatic tumor tissues may be needed to evaluate its nature, as it can be different from the original tumor in the testis. Pure seminomatous metastases are generally very sensitive to radiation therapy. In cases where both seminomas and non-seminomatous tumor tissues are present in the same patient, the treatment strategy is directed towards the non-seminomatous tissue, that require a more aggressive form of therapy such as cis-platinum based combination chemotherapy. With the advances in diagnosis and treatment option, the prognosis of testis cancer has improved dramatically in the past decade with a five-year survival rate of 90-95% with a good quality of life.

Most cases of testicular germ cell cancer are unilateral, but the contralateral testis carries an increased risk of developing a second germ cell tumor, which may present months or years after the initial presentation. The increased risks of testis cancer in the contralateral testis is not due to metastasis from the original tumor, but to the presence of carcinoma in situ, found in 5% of the contralateral testis at the time of initial diagnosis. Therefore some oncologists advocate routine biopsy of the contralateral testis at the time of the primary orchiectomy. If the neoplasia is detected at this preinvasive stage, adjuvant treatment with 16-20 Gy of radiation therapy to the contralateral testis may avoid the need of a second orchiectomy in future and preserve some testicular function for the patient.

Risk factors

Generally, men with testicular germ cell cancer are less fertile than men in the general population, even before they develop their tumors. Testis cancer is also associated with a history of undescended testis and hypospadias. The concept of testicular dysgenesis syndrome ties together many of the related conditions, with germ cell cancer being the more severe one. Besides CIS lesions, dysgenetic testes may contain Sertoli-cell-only tubules, undifferentiated tubules, Leydig cell clumps and microliths. Because of the risks of infertility, we recommend that patients with a testicular tumor should be advised on sperm cryopreservation to preserve their fertility, particularly prior aggressive cancer treatment (Chapter 14).

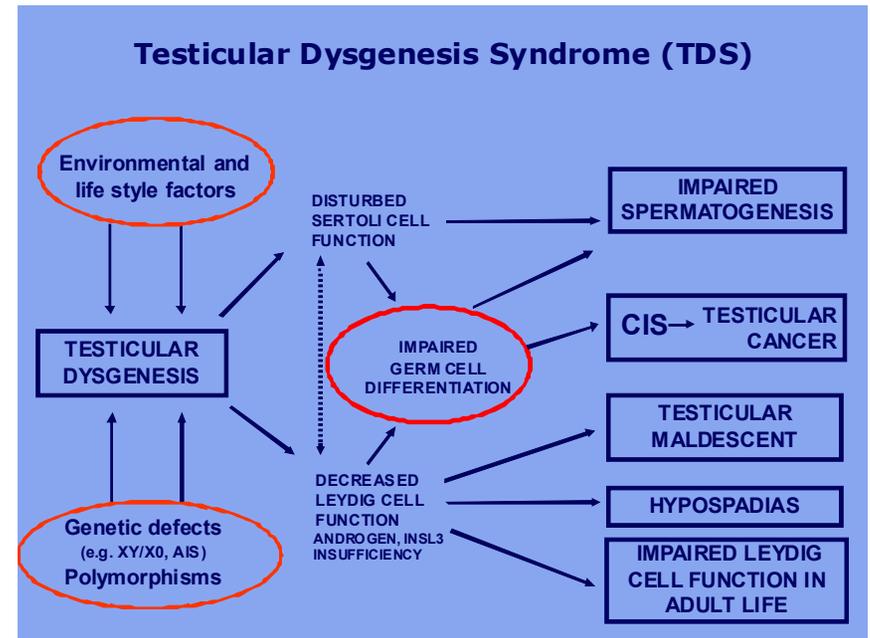


FIG. 2. Pathogenesis of testicular dysgenesis syndrome. Note that both genetic and environmental factors may contribute to testicular dysgenesis(modified from(9))

Other tumors of the testis

Rarely, germ cell tumors may occur in neonates and infants. Such tumors have different origins and pathogenesis than the germ cell tumors described above and are more frequently benign than those seen in young adults. Men above age 60 may harbour a special germ cell tumor called spermatocytic seminoma. In contrast to classical seminoma which occurs in younger men, spermatocytic seminoma have completely different pathogenesis. They are not biologically linked in any way. Spermatocytic seminoma is derived from spermatogenic cells, rather than from gonocytes as in the classical seminoma. Furthermore, the natural history of classical seminoma is more aggressive with higher metastatic risks than spermatocytic seminoma.

Somatic cells of the testis, including Sertoli cells and Leydig cells very rarely develop tumors, with most being benign in nature. Leydig cell tumor may often result in elevated production of testosterone which may be

converted into estrogens through peripheral aromatization and thereby causing gynecomastia. Finally lymphoma and leukemias may infiltrate the testes and falsely simulate a gonadal tumor. Thus clinician managing testis tumor should be familiar with the various clinical presentations.

Suggested reading

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