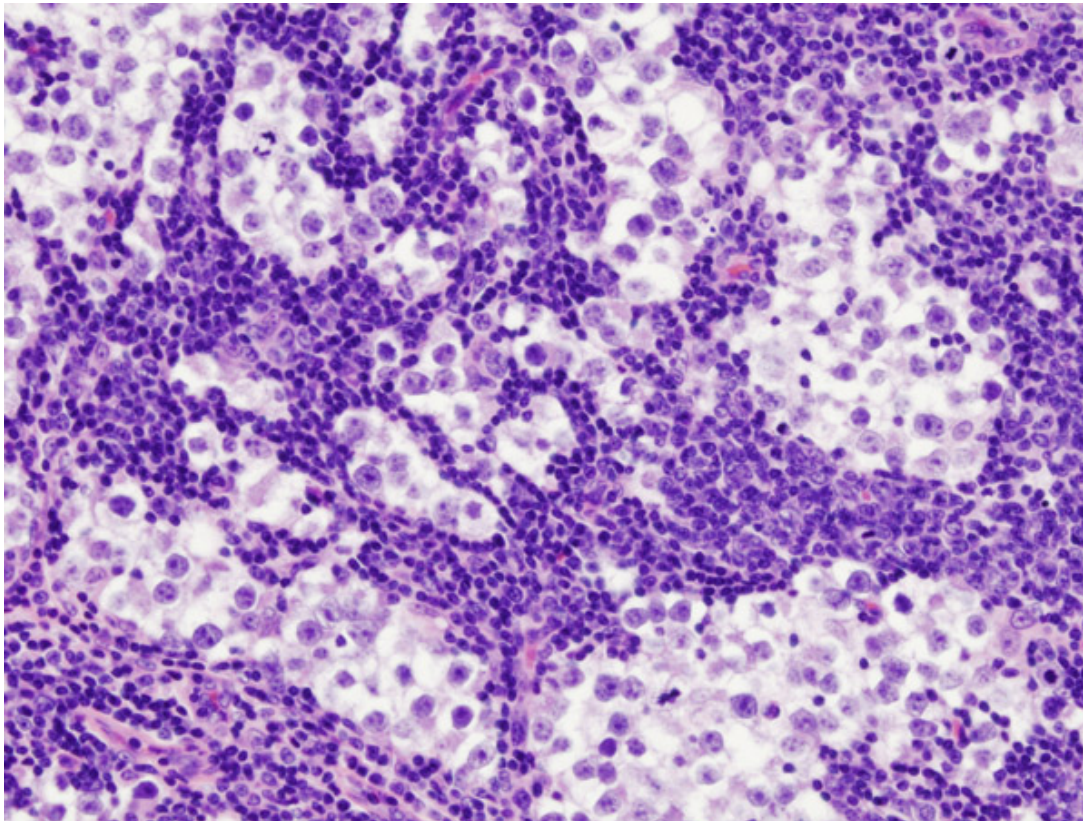


Testicular Cancer (Malignant Neoplasm of Testis) — Diagnosis and Treatment

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Testicular cancer is an uncommon malignancy. Most of the testicular cancers are of the germ cell tumor type and they can be classified into seminomas or nonseminomas. The most common presentation of testicular cancer is a painless testicular nodule. Alpha-fetoprotein can be elevated in nonseminomas, while beta-human chorionic gonadotropin is usually elevated in both seminomas and nonseminomas. Radical inguinal orchiectomy along with retroperitoneal lymph node dissection helps in confirming the diagnosis and can be curative in early stages of testicular seminomas.



Definition of Testicular Cancer

Testicular cancer is usually of the **germ-cell type** and is either **seminomas** or **nonseminomas**. Nonseminomas include tumors originating from embryonal cells, yolk sac, choriocarcinoma, or [teratomas](#).

Germ cell tumors	Morphology	Serum markers	Prognosis	Remarks
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Yolk sac (EST)	Schiller-Duval bodies	AFP	Aggressive	MC < 5 years boys
Choriocarcinoma	Trophoblastic cells	HCG	Aggressive	Hemorrhagic, hyperthyroidism
Teratoma	3 cell lines	The immature form is aggressive	N/A	Benign in children

These tumors secrete different hormones, such as **alpha-fetoprotein**, **lactate dehydrogenase**, and **beta-human chorionic gonadotropin**. These biomarkers can be used to diagnose a germ-cell tumor, monitor response to treatment, and determine prognosis.

Epidemiology of Testicular Cancer

The annual incidence of testicular cancer in the United States is 8,000-10,000 men. Approximately 95% of all testicular cancers are comprised of germ cell tumors, which are curable in most patients.

Testicular germ cell tumors are more common in men aged 15-34 years. Risk factors include a previous **history of a germ cell tumor**, a **family history of testicular cancer**, **cryptorchidism**, **Klinefelter syndrome**, and **testicular dysgenesis**.

Etiology of Testicular Cancer

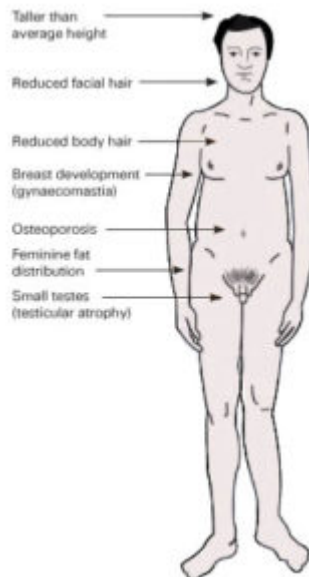


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Cryptorchidism, also known as undescended testes, is associated with an increased risk of testicular germ cell tumors. The relative risk of developing testicular cancer for patients with a previous history of cryptorchidism who were treated after the age of 13 years is estimated to be about 5.4.

Another common etiology of testicular cancer is a previous history of testicular cancer. These patients have a 500-fold higher risk of developing a testicular germ cell tumor in the contralateral side.

Genetics

Patients with Klinefelter syndrome (47XXY) have a high risk of developing germ cell tumors. A family history of Klinefelter syndrome increases the chance of having a germ cell tumor 6-10 fold. Patients with Down syndrome are also at risk. Risk is also increased with the following disease conditions:

- Mixed gonadal dysgenesis
- Cutaneous ichthyosis
- Androgen insensitivity syndrome
- Mullerian syndrome

Family History

A family history of testicular cancer also puts the patient at a significantly higher risk of developing testicular tumors. Incidence is low (only 2%) and is seen in first-line family members, emphasizing the importance of a genetic component in the condition.

Infertility

Patients with a history of male factor infertility have a three-fold higher risk of developing testicular cancer.

Environmental Factors

Exposure to **diethylstilbestrol** has been linked to cryptorchidism, which as we pointed above increases the risk of testicular cancer.

Activities that increase the temperature in the scrotal region, like horse riding, bike riding, and wearing tight clothing, increase the risk for testicular cancer. Local trauma may also increase the risk.

Pathophysiology of Testicular Cancer

The exact cause of testicular cancer is unknown. Genetic testing in sporadic cases of testicular cancer revealed a **common abnormality in chromosome 12p**, emphasizing this region's role in regulating germ cells. A family history of testicular cancer also puts the patient at an increased risk of developing a testicular germ cell tumor, further emphasizing the role of genetics.

One hypothesis states that **fetal gonocytes** should be present in the growing testis for germ cell tumors to occur. These gonocytes do not differentiate into **spermatogonia**, and they retain their ability to divide and grow. Eventually, during puberty, **gonadotropin stimulation** facilitates the invasive growth of these immature cells and tumor forms.

Another hypothesis states that these germ cell tumors are still not completely malignant, and a multistep process involving the **duplication of chromosome 12p** usually occurs, leading to **malignant transformation**. **Cyclin D2 gene**, which is located on chromosome 12p, is over-expressed in testicular cancer.

Clinical Presentation of Testicular Cancer

Most patients present to the clinic complaining of a **painless testicular nodule** or a **recent increase in the testis size**. Physical examination is essential to confirm the suspicion of a testicular tumor. The testicular mass should not be separable from the testis and should not be tender.



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Other patients might complain of a sensation of **heaviness** or a **dull ache**. Seminomas commonly **metastasize** through the lymphatic system; patients might present with signs of **disseminated disease** rather than a testicular mass. These patients may also present with a **supraclavicular mass** due to **supraclavicular lymph node metastasis**.

Germ cell tumors produce **beta-human chorionic gonadotropin** that can cause **gynecomastia** in 5% of the cases.

In a minority of patients, the presenting feature might be **scrotal erythema, pain, and swelling**. This picture might resemble that of **acute epididymitis**. These patients should take a full course of **antibiotics**; if the swelling is not resolved after that, they should undergo further workup to exclude possible testicular tumors.

Diagnostic Work-up for Testicular Cancer

Many disease conditions like hydrocele, epididymo-orchitis, varicocele, metastasis of tumors from other sites, hematoma, hernia, testicular torsion, syphilitic gumma, tuberculosis or other infections, spermatocele, and Non-Hodgkin's lymphoma may be confused with testicular cancer. **Laboratory investigations** and **imaging studies** can help diagnose testicular cancer, give prognostic figures, stage the disease, guide treatment, and monitor response to treatment.

Alpha-fetoprotein

Serum alpha-fetoprotein is higher in **nonseminomas** and in **hepatocellular carcinoma**. An elevated alpha-fetoprotein should be combined with **histologic confirmation** of a testicular nonseminoma to diagnose testicular cancer.

Beta-human chorionic gonadotropin

Beta-human chorionic gonadotropin secretion is linked to both types of germ cell tumors, testicular seminomas, and nonseminomas. Additionally, high levels of beta-human

chorionic gonadotropin can cause gynecomastia. Similar to alpha-fetoprotein, an elevated level alone is insufficient for diagnosing testicular cancer and should be combined with **histologic evidence** of a testicular tumor.

Lactate dehydrogenase (LDH)

LDH has an important prognostic role in testicular cancer but is not specific for testicular seminomas or nonseminomas. Its serum concentration **correlates with tumor size, growth, and dissemination**.

Imaging studies in testicular cancer

Ultrasonography is helpful for evaluating any **scrotal or testicular mass**. A **cystic lesion** on ultrasonography is unlikely to be malignant, while a **solid hypoechoic testicular lesion** is likely to be seminoma. Nonseminomas appear as **hyperechoic lesions with calcifications and cystic areas**.

Abdominal and pelvic computed tomography (CT) scans are helpful for staging the disease. A **chest x-ray** is also indicated because testicular cancer can **metastasize** early to the **lungs**. Abdominal and pelvic CT scans are usually indicated after confirming the testicular cancer diagnosis by histology.

Histologic examination in testicular cancer

Any patient with a testicular mass, suspicious ultrasonography, and an elevated alpha-fetoprotein or beta-human chorionic gonadotropin result should undergo a **radical inguinal orchiectomy with retroperitoneal lymph node dissection**.

This procedure has many advantages. It provides enough tissue to establish the testicular cancer diagnosis and controls local tumor growth. Even if the patient has disseminated disease, the testis should be removed because **chemotherapy** does not reach the testicles.

A histologic examination can reveal a pure seminoma or a nonseminoma. Most nonseminomas are, in fact, mixed seminomas with some seminoma component.

Treatment of Testicular Cancer

After performing a radical **inguinal orchiectomy**, it is essential to identify the type of the tumor and its stage to determine the primary treatment plan and follow-up treatment.

Stage I pure seminomas are usually cured after the first procedure, but such patients might also benefit from **radiotherapy or single-drug chemotherapy with carboplatin**. Recommended follow-up includes repeat history and physical examinations with a reassessment of beta-human chorionic gonadotropin, alpha-fetoprotein, and LDH levels.

Stage II disease indicates a **lymphatic spread of the seminoma**. These patients should undergo **radiotherapy after a radical inguinal orchiectomy**. The overall five-year survival for stage I and II disease is approximately 95%.

Patients with **pulmonary or nonpulmonary metastatic seminomas** are considered **stage III**. **Chemotherapy with BEB (Bleomycin, Etoposide, and Cisplatin) or Etoposide and cisplatin** alone, is indicated in all patients with stage III

disease.

After completing four cycles of treatment, a repeat **serum biomarkers assessment** and abdominopelvic **CT scan** are indicated. If no residual mass is identified, the patient should only undergo surveillance, as we discussed above. If a mass is identified, **second-line chemotherapy** is usually indicated. When serum biomarkers are abnormal but the CT scan is negative, **PET** is generally indicated.

Treatment for nonseminomas in the early stages is similar to that for seminomas. However, metastatic nonseminoma patients should undergo **adjuvant chemotherapy** to lower the risk of **tumor recurrence**.

Patients with advanced metastatic disease who do not go into full remission after primary chemotherapy should undergo **second-line chemotherapy**, including **high dose carboplatin and etoposide**, followed by **autologous stem cell transplantation**. Other second-line regimens for metastatic testicular cancer include **cisplatin**, **ifosfamide**, and paclitaxel.

Complications of Testicular Cancer

Complications arise due to drug toxicity during treatment and secondary metastases.

Prognosis of Testicular Cancer

Good prognosis criteria:

- Primary testicular or retroperitoneal lesion
- No nonpulmonary visceral metastases
- Low levels of tumor markers in serum

Intermediate prognosis criteria:

- Primary testicular or retroperitoneal lesion
- No nonpulmonary visceral metastases
- Intermediate levels of serum tumor markers

Poor prognosis criteria:

- Mediastinal primary
- Nonpulmonary visceral metastases
- High levels of serum tumor markers

References

Motzer RJ, Bolger GB, Boston B, et al (2012) Testicular cancer. Clinical practice guidelines in oncology. J Natl Compr Cancer Netw JNCCN 4:1038-1058.

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