Testicular cancer is an uncommon malignancy. Most of 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 are either seminomas or nonseminomas. Nonseminomas include tumors originating from embryonal cells, yolk sac, choriocarcinoma or teratomas.

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

Epidemiology of Testicular Cancer

The annual incidence of testicular cancer is estimated to be about 8,000 in the United States. Germ cell tumors compromise 95% of all testicular cancers and fortunately they can be cured in most patients.

Testicular germ cell tumors are more common in men aged 15 to 34 years. Several risk factors have been linked to testicular cancer, which include a previous history of a germ cell tumor, family history of testicular cancer, cryptorchidism, Klinefelter syndrome and testicular dysgenesis.

Etiology of Testicular Cancer

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

Another common etiology of testicular cancer is previous history of testicular cancer. The risk of developing a testicular germ cell tumor in the contralateral side is increased by 500 fold.

Klinefelter syndrome and family history of testicular cancer also puts the patient at a significantly high risk of developing testicular tumors emphasizing the importance of a genetic component in the condition.
Exposure to diethylstilbestrol has been linked to cryptorchidism, which as we pointed above increases the risk of testicular cancer.

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 the important role of this region for the regulation of germ cells. 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.

For germ cell tumors to occur in the testis, it is hypothesized that fetal gonocytes should be first present in the growing testis. 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 a tumor forms.

It is also hypothesized that these germ cell tumors are still not completely malignant and a multistep process that involves the duplication of chromosome 12p usually occurs, which leads to malignant transformation. Cyclin D2 gene, which is located on chromosome 12p, has been found to be 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.

Other patients might complain of heaviness or a dull ache. Seminomas commonly metastasize through the lymphatic system and patients might present with signs of disseminated disease rather than a testicular mass. A supraclavicular mass due to supraclavicular lymph node metastasis can be identified in such patients.

Germ cell tumors produce beta-human chorionic gonadotropin which 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 undergo a full course of antibiotics and if the swelling is not resolved after that, they should undergo further workup to exclude possible testicular tumor.

**Diagnostic Work-up for Testicular Cancer**

Several **laboratory investigations** and **imaging studies** can help establish the diagnosis of testicular cancer, give prognostic figures, stage the disease, guide treatment and monitor response to treatment.

**Alpha-fetoprotein**

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

**Beta-human chorionic gonadotropin**

Beta-human chorionic gonadotropin secretion is known to be 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 not sufficient to diagnose 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 the tumor size, growth and dissemination.**

**Imaging studies in testicular cancer**

**Ultrasonography** is helpful in the evaluation of any **scrotal or testicular mass**. A **cystic lesion** on ultrasonography is unlikely to be malignant while **solid hypoechoic testicular lesions** are likely to be seminomas. Nonseminomas appear as **hyperechoic lesions with calcifications and cystic areas.**

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

**Histologic examination in testicular cancer**

Any patient with a testicular mass, a 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 diagnosis of testicular cancer, controls the local growth of the tumor, and even if the patient has disseminated disease, the testis should be removed sooner or later because **chemotherapy** does not reach the testicles.

**Histologic examination** can reveal a pure seminoma, or a nonseminoma. The majority
of 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**. Surveillance is recommended after the radical inguinal orchiectomy and is done by repeated history and physical examinations, and reassessment of beta-human chorionic gonadotropin, alpha fetoprotein, and LDH levels.

**Stage II disease** indicates **lymphatic spread of the seminoma**. These patients should undergo **radiotherapy** after the **radical inguinal orchiectomy**. Overall survival for stage I and II disease is estimated to be approximately 99%.

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

After completing four cycles of treatment, a repeat **serum biomarkers assessment** and **Abdomino-pelvic CT scan** is 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 usually indicated.

Treatment for nonseminomas in early stages is similar to seminomas. Patients with lymphatic spread of nonseminomas, however, should undergo **adjuvant chemotherapy** to lower the risk of **tumor recurrence**.

**Second line chemotherapy** for those who do not go into full remission after primary chemotherapy for advanced metastatic disease include **high dose carboplatin and etoposide** that is followed by **autologous stem cell transplantation**. Other second line regimens for metastatic testicular cancer include **cisplatin, ifosfamide** and **paclitaxel**.

**References**


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