REVIEW

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Testis cancer: Rare, but curable with prompt referral

ABSTRACT

Testis cancer is rare and rapidly progressive but can almost always be cured. Early detection and prompt treatment by an experienced clinician are the cornerstones of successful management. A delay in diagnosis and inadequate or inappropriate treatment increase the risk of death. The author reviews risk factors, diagnostic features, and current treatment.

KEY POINTS

Consider testicular cancer in any adolescent, young adult, or middle-aged male with a testicular or retroperitoneal mass.

Testis cancer is exceedingly rare in African American men. It is more than four times more likely in white non-Hispanic Americans, and more than twice as likely in Hispanic, Asian, and Native Americans.

Educating adolescent males about testis cancer and alerting them to the need for urgent evaluation of any testicular nodules or enlargement or unexplained pain is prudent.

Risk factors include cryptorchidism, infertility, and a family history or personal history of testicular cancer.

Infertile or subfertile men may have an increased risk of testis cancer. This is not surprising in that most testis cancer patients have abnormal semen analysis results at the time of diagnosis.

TESTIS CANCER IS one of the greatest success stories of medical and surgical oncology: even patients with distant metastases can usually be cured with a combination of chemotherapy and resection.

However, because it is so rare, few urologists and oncologists have extensive experience treating these tumors. Once the diagnosis is made, referral to a center with special expertise is strongly encouraged, as studies have reported that such centers produce higher survival rates.

Although testis cancer accounts for only a small proportion of all cancers, it is the most common malignancy in young adult men and should be considered in any adolescent, young adult, or middle-aged male with a testicular or retroperitoneal mass. Risk factors include cryptorchidism (undescended testicles), infertility, and a family history or personal history of testicular cancer.

Roughly 2% to 3% of testis cancer patients go on to develop a contralateral testicular malignancy. Survivors also have an increased risk of infertility and hypogonadism, and, depending on which treatment they have received, they may have an increased risk of cardiovascular events and second non-germ-cell cancers.

INCIDENCE RATE RISING, DEATH RATE DECLINING

Testicular cancer is by far the most common malignancy in men aged 15 to 35 years and accounts for nearly 25% of all cancers diagnosed in that age range.[1,2] However, because of the high cure rate of this disease, it causes fewer than 5% of cancer deaths at those ages.[1]

Compared with other cancers across the life span, testis cancer is rare, with about 8,000 new cases and 400 deaths in 2006 in the United States. The incidence is increasing while the death rate is decreasing. The cause of the rise in incidence is unclear, but the declining death rate is attributed to the development of curative chemotherapy for advanced disease, improved treatment algorithms, earlier stage at presentation, and a growing proportion of seminomas to nonseminomas.[3] The US male lifetime risk of being diagnosed with testis cancer is 3 to 4 out of 1,000, while the lifetime risk of death from testis cancer is 0.02%, or 2 out of every 10,000 males.

Ethnicity and prevalence

Testis cancer is exceedingly rare in African American men: it is more than four times more likely in white non-Hispanic Americans, and more than twice as likely in Hispanic, Asian, and Native Americans.[1]

Ups and downs: What is responsible for the trends?

Even patients with distant metastases can usually be cured

The incidence of testicular cancer increased in the United States and worldwide between the years 1950 and 2000, but with substantial regional variation.[2] During that period, the US incidence of testicular cancer increased 168%, while the mortality rate declined 73% and the relative 5-year survival rate improved from 57% to 96%.[4] Between 1975 and 2000, the incidence increased 54%, to 5.7 cases per 100,000 cases per year. During the same period, the death rate declined by 71%. Most of this decrease occurred between 1975 and 1984, when cisplatin-based chemotherapy became widely used, but a slower downward trend in the death rate has continued.[4]

The rising incidence of testis cancer over the past half century would appear to indicate that environmental factors play a major role, but such factors have not been identified.

RISK FACTORS

The major risk factors for testis cancer include a personal history of testicular cancer, a family history of testicular cancer, cryptorchidism, and infertility or subfertility.

Personal or family history

Men who have had a diagnosis of testis cancer have about a 2% to 3% risk of developing a second cancer in the contralateral testis.[5,6]

Having a brother with testis cancer raises the risk about eightfold to 10-fold to an absolute risk of about 2%, whereas testis cancer in the father raises the son's risk fourfold.[7,8] This finding supports the hypothesis that the development of testis cancer is strongly influenced by maternal factors, but if this hypothesis is correct, the specific factors have not been identified.

Undescended testicle

The risk of testis cancer in men with cryptorchidism is estimated to be four times higher than in the general population, resulting in a roughly 1% lifetime risk.[9,10] Undescended testicles can often be brought into the scrotum through a surgical operation called orchiopexy. If the undescended testicle cannot be brought into the scrotum it should be resected. Prepubertal orchiopexy or resection (if orchiopexy is not possible) is strongly recommended in boys with cryptorchidism to facilitate detection of testis cancer (in addition to other benefits), but whether orchiopexy reduces the risk of testis cancer has not been definitely answered and remains controversial. Orchiopexy before the age of 12 to 15 months has been recommended, but such early intervention is advocated mainly due to concern about infertility.[11]

Abnormal results of semen analysis

Infertile or subfertile men may have an increased risk of being diagnosed with testis cancer.[12] This is not surprising in that most testis cancer patients have abnormal semen analysis results at the time of diagnosis. These abnormalities in semen analysis usually diminish after treatment of the cancer. It thus appears that testis cancer interferes with normal sperm development, but it is also possible that infertility is conducive to the development of testis cancer (perhaps due to elevated levels of serum gonadotropins) or that a common factor predisposes men to both infertility and testis cancer.

SOME BIOLOGIC FEATURES OF TESTICULAR TUMORS

Anatomic overview

The testes consist of coiled tubes called seminiferous tubules in which sperm are produced after puberty and which drain into a network of larger tubules referred to as the rete testis, located in the hilum of each testis. Sperm travel through the rete testis into the efferent ducts that connect to the epididymis, which in turn connects to the vas deferens. The rete testis is part of the testis, whereas the epididymis is not.

The testes are covered by a layer of fibrous connective tissue called the tunica albuginea, which in turn is covered by the tunica vaginalis, a serous membrane with visceral and parietal layers that is created when the prenatal testis descends from the abdomen into the scrotum. A hydrocele is a collection of fluid within the tunica vaginalis.

Testis cancers are almost always germ cell tumors. Lymphomas of the testis are much less common but can be confused with seminoma. Leydig cell and Sertoli cell carcinomas and carcinomas of the rete testis are extremely rare.

Germ cell tumors: Seminoma vs nonseminoma

Testicular germ cell tumors are cancers that consist of any combination of the following malignancies: seminoma, embryonal carcinoma, yolk sac tumors (also termed endodermal sinus tumors), choriocarcinoma, or teratoma. Most germ cell tumors contain a mixture of these different histologic types and are referred to as mixed germ cell tumors.

Germ cell tumors consisting of only seminoma are called seminomas or pure seminomas. All other germ cell tumors, including all mixed germ cell tumors, are considered nonseminomas. The presence of even a tiny proportion of embryonal carcinoma, yolk-sac tumor, choriocarcinoma, or teratoma makes a germ cell tumor a nonseminoma, even if the vast majority of the tumor consists of seminoma.

It is important to note that seminomas do not produce the tumor marker alpha-fetoprotein but that nonseminomas often do. Thus, an elevated serum level of alpha-fetoprotein indicates the presence of nonseminomatous elements even if histopathologic analysis shows only seminoma. Such tumors are treated as nonseminomas.

The importance of distinguishing pure seminoma from nonseminoma derives from differences in prognosis and treatment, with seminoma having a slightly better prognosis. Seminomas and nonseminomas are treated differently, so distinguishing pure seminoma from nonseminoma is critical.

In contrast, the specific histologic composition of a nonseminomatous germ cell tumor of the testis does not have a strong impact on treatment, and the impact on prognosis is not entirely clear.

Types of nonseminomas

Teratomas are tumors that consist of at least two of the three germinal layers (endoderm, ectoderm, and mesoderm). They appear to have a lower metastatic potential than other testicular germ cell tumors.

Embryonal carcinomas are very poorly differentiated cancers. They appear similar to early embryonic tissue and have high metastatic potential.

Yolk sac tumors, also called endodermal sinus tumors, derive their name from their similarity in appearance to the yolk sac. Yolk sac tumor elements predict a lower risk of relapse in men with stage I nonseminomas with normal serum tumor marker levels who are managed with surveillance. This finding is likely because yolk sac tumors almost always cause elevations in serum levels of alpha-fetoprotein. Micrometastatic tumors with yolk sac elements are thus more likely to be detected with serologic testing. In patients with nonseminomas with lymph node or visceral metastases, the presence of yolk sac tumor as a component of the cancer does not appear to affect the prognosis.

Choriocarcinoma is a highly aggressive cancer that, like the placenta, contains cytotrophoblasts and syncytiotrophoblasts. Unlike other germ cell tumors, choriocarcinoma is much more likely to spread hematogenously than lymphatically and is associated with metastases to unusual locations such as the brain and eye. Choriocarcinoma is associated with highly elevated serum levels of human chorionic gonadotropin (hCG).

Seminoma needs to be distinguished from nonseminoma, as the treatments differ

Tumor markers have several uses

Alpha-fetoprotein, the beta subunit of hCG, and, to a lesser extent, lactate dehydrogenase (LDH) all play a critical role as serum tumor markers in the management of testicular cancer.

Elevated levels of these tumor markers are usually the first sign of metastatic disease, and the degree of elevation carries important prognostic information that helps determine the duration of chemotherapy. Similarly, a sluggish rate of decline in the markers during chemotherapy signals disease that is resistant to chemotherapy. In addition, an elevated alpha-fetoprotein level usually rules out a diagnosis of pure seminoma. Serum tumor markers are thus used for diagnosis and staging, to monitor response to treatment, and to evaluate for relapse.

Alpha-fetoprotein and hCG are present only at extremely low levels in healthy men and are not thought to be of physiologic significance. Alpha-fetoprotein levels are elevated in fetuses, but although it is an albumin-like protein, its exact role in embryonic development remains unclear. It is elevated in hepatocellular carcinoma, gastric cancer, and several other non-germ-cell cancers. Levels of hCG are elevated in women after conception, and hCG serves to maintain pregnancy by sustaining progesterone production. In rare cases, hCG is elevated in gastrointestinal cancers.

Monitoring tumor markers is essential to testis cancer management

LDH catalyzes the interconversion of lactate and pyruvate. LDH elevations are nonspecific and can be seen in lymphoma, myocardial infarction, liver disease, and other conditions.

EARLY DETECTION IMPORTANT, DESPITE CHALLENGES

Obstacles to general screening

Testis cancer is rare, grows very rapidly, and almost always is detected by the patient himself at an early stage. It is cured more than 95% of the time, but early-stage disease carries a substantially better prognosis than advanced disease. Nevertheless, data on whether delays in diagnosis affect testis cancer outcomes are sparse and inconsistent.[13]

Special efforts at early detection are difficult to defend, primarily because tens of millions of men are at risk, yet fewer than 400 deaths occur annually. Also, we have no compelling evidence that efforts at early detection would save lives, and the US Preventive Health Services Task Force recommends against screening for testis cancer.[14]

Given these obstacles to early identification, educating adolescent males about testis cancer and alerting them to the need for urgent evaluation of any testicular nodules or enlargement or unexplained pain is prudent.

Pros and cons of promoting self-examination

Some recommend teaching how to perform a monthly self-examination, but whether such training increases the early detection of tumors remains unknown. While testicular palpation is part of a complete physical examination, few testis cancers are detected incidentally as part of a routine physical.

The appeal of teaching testicular self-examination is that it is easy to perform and alerts men to the importance of seeking medical attention should a testicle become indurated, enlarged, atrophied, nodular, or painful. Unlike breasts, which are difficult to examine skillfully, testicles do not change with a menstrual cycle, and they have a smooth and homogeneous texture. Moreover, testis cancers typically grow rapidly and are easily palpated.

The argument against promoting self-examination derives from the absence of evidence that self-examination leads to improved outcomes and from the risk that it may cause unnecessary anxiety, especially in light of how uncommon the disease is. An alternative to teaching self-examination is promoting awareness of testis cancer, so that men will seek medical evaluation for signs or symptoms of testis cancer.

Self-examination technique

Self-examination for testis cancer is best performed during or after a bath or shower, when the scrotum is relaxed and the testicles are more easily palpated. The standard procedure involves using both hands to examine one testicle at a time, holding the testis with the thumbs positioned superiorly and the index and middle fingers inferiorly. The testis should be rolled back and forth so that the entire sur-

face can be evaluated. Men should be alert for nodules, induration, tenderness, enlargement, and atrophy.

CLINICAL PRESENTATION AND DIAGNOSIS OF TESTICULAR CANCER

The textbook presentation of testis cancer is in a man who has noticed a painless testicular mass or nodule; however, up to half the time the mass or nodule is painful. Thus, while the absence of pain makes an infectious cause less likely, the presence of pain by no means excludes cancer.

Other presenting signs and symptoms may include gynecomastia, thromboembolic events, palpable supraclavicular adenopathy, and symptoms from metastatic disease, such as back pain from retroperitoneal lymphadenopathy.[15,16]

Patients with signs or symptoms of testis cancer should be referred to a urologist for evaluation.

The workup

The workup of a testicular mass includes trans-scrotal ultrasonography, which provides excellent imaging of the testes. Testicular symptoms thought to result from infection can be treated with a trial of antibiotics, but close follow-up is mandatory, given that testis cancer can be mistaken for an infectious process. Suspected testicular infections that fail to resolve with antibiotics should be further investigated with scrotal ultrasonography and tests for serum tumor markers.

Orchiectomy is the standard way to establish the diagnosis

The diagnosis of testis cancer is made histopathologically after surgical removal of the testicle. When ultrasonography identifies a likely cancer, serum tumor marker tests should be ordered, and inguinal (ie, radical) orchiectomy should be performed. Trans-scrotal testicular biopsy or fine-needle aspiration should not be performed because of concerns about seeding the needle track with cancer and disrupting normal lymphatic drainage patterns; much of the management of testis cancer depends on normal lymphatic drainage of the testes to the retroperitoneum. In contrast, the scrotal lymphatics drain to the inguinal lymph nodes.

Although data on outcomes after scrotal violation with the biopsy needle have not shown reduced survival rates, a higher local relapse rate has been confirmed.[17] Inguinal orchiectomy is thus the standard-of-care procedure for establishing a diagnosis of testis cancer.

STAGING

Testis cancer staging is relatively simple, but it is essential to keep in mind the key role of serum tumor markers in staging. Staging tests include post-orchiectomy measurement of serum tumor markers (alpha-fetoprotein, hCG, LDH) and computed tomography (CT) of the abdomen and pelvis. If these tests are normal, a chest radiograph should be obtained. On the other hand, patients with elevated tumor marker levels after orchiectomy or evidence of metastatic disease in the abdomen or pelvis should undergo chest CT.[18] Bone scans and brain imaging are not part of the routine management unless clinical signs or symptoms indicate metastases to those regions.

A 'best' approach to treating stage I testis cancer is yet to be defined

Testis cancer has three stages.[19] Stage I patients have no radiographic evidence of disease beyond the testis and spermatic cord. Stage II patients have disease that has spread to the retroperitoneum, the primary lymphatic drainage site of the testes. Stage III patients have disease that has spread more distantly, either to organs or to lymph nodes outside the retroperitoneum.

Patients with elevated tumor marker levels that do not return to normal after orchiectomy are generally considered at stage III regardless of radiographic findings. The degree of elevation carries strong prognostic implications, and patients with high elevations are treated with more aggressive chemotherapy.

However, all testis cancer patients—even those with widespread metastasis—have a substantial chance of being cured with modern treatment algorithms. Fortunately, most patients present early: 50% have stage I seminoma, roughly 10% have stage I nonseminomas, and about 25% and 15% have metastatic seminoma and nonseminoma, respectively.

TREATMENT OF STAGE I TUMORS

The treatment of stage I testicular germ cell tumors when serum tumor marker levels after orchiectomy are normal is the most controversial area of testis cancer management.

Currently, we have three therapeutic options for seminomas (surveillance, radiation, chemotherapy) and three options for nonseminomas (surveillance, retroperitoneal lymph node resection, chemotherapy), but different experts accept and reject different choices among these options.[20,21] Nonetheless, all three approaches for each disease result in disease-specific survival in the range of 98% to 100%, and there is no substantive evidence that one approach results in better long-term outcomes than another.

Regardless of whether the tumor is seminoma or nonseminoma, surveillance is a widely accepted approach to the management of stage I disease.[22] The rationale is that 80% of stage I seminoma patients and 70% of stage I nonseminoma patients are cured with orchiectomy alone. Those who have a relapse during close surveillance can almost always be cured, and the survival rates on surveillance are entirely comparable with the survival rates with active treatment.[23,24]

Testis cancer patients may be at higher risk of metabolic syndrome

The benefit of surveillance is that most men avoid any treatment and the associated side effects and complications. The downside of surveillance is that it requires frequent doctor visits and medical tests, which requires that the patient be compliant. Surveillance should be conducted by a physician with substantial experience treating testis cancer.

Alternatives to surveillance for seminoma are radiation therapy (20 to 26 Gy to either a paraaortic or paraaortic plus ipsilateral hemipelvis field) and chemotherapy (either one or two cycles of carboplatin). Each is highly effective, and each has its proponents and detractors. Chemotherapy is a newer approach, and some argue that the long-term evidence is insufficient to support its use, whereas radiation therapy has been associated with secondary cancers, leading some to question its use in a disease that is so rarely fatal.[25–27]

For stage I nonseminomas, the alternatives to surveillance are retroperitoneal lymph node dissection and BEP chemotherapy, which is two cycles of bleomycin (Blenoxane), etoposide (Toposar), and cisplatin (Platinol). It is important to note that chemotherapy for stage I disease is much more aggressive for nonseminomas than for seminomas, and that the rate of side effects and complications is therefore higher. The advantage of retroperitoneal lymph node dissection is that it provides more definitive pathologic staging and lowers the risk of relapse without exposing patients to potential long-term toxicity from chemotherapy.[28] The disadvantage is that after lymph node dissection patients may need chemotherapy anyway if metastatic disease is found during the operation, whereas those without lymph node metastases detected still have a 10% chance of relapse.

Proponents of chemotherapy cite the low (3%) rate of relapse after treatment, while detractors worry about late toxicity from chemotherapy and about late relapses in the retroperitoneum, which may harbor slowly progressive teratomatous elements that are refractory to chemotherapy.

So far no published randomized controlled trial has compared these approaches, except for a trial of radiation therapy vs chemotherapy for stage I seminoma, which showed equivalent disease control and survival with 4-year median follow-up.[29] If there is a best approach, it is yet to be defined. Particularly attractive would be a risk-adapted approach, such that low-risk patients were subject to surveillance and high-risk patients were actively treated, but current prognostic models have limited accuracy.[30,31]

TREATMENT OF STAGE II TUMORS

Treatment of stage II disease is far less controversial. For patients with small-volume retroperitoneal metastases and normal tumor marker levels, the current standard of care is retroperitoneal lymph node dissection for nonseminoma and radiation therapy for seminoma. For patients with larger-volume disease or elevated serum tumor markers or both, chemotherapy is recommended.[32,33]

Points of contention include the specific size criteria for choosing chemotherapy instead of surgery or radiation, and the rele-

vance of mildly elevated hCG or LDH in patients with seminoma. Patients with early stage II disease have a 5-year survival rate greater than 90%, while patients with advanced stage II disease have a prognosis similar to that for stage III patients.

TREATMENT OF STAGE III DISEASE

The management of testis cancer is best defined for stage III. Numerous randomized controlled trials have clearly established the preferred standard chemotherapeutic regimens.[34–41] Risk can be classified as good (with a 5-year survival rate of about 90%), intermediate (5-year survival rate about 75%), or poor (about 50%).[42] The adverse prognostic factors that decide risk classification for nonseminomas include highly elevated serum tumor markers, a primary mediastinal (as opposed to testicular or retroperitoneal) germ cell tumor, and metastases in any organ other than the lungs. All seminomas are considered low-risk unless there are nonpulmonary visceral metastases, in which case the cancer is considered intermediate-risk.

Patients with good-risk tumors receive either 9 weeks of BEP chemotherapy or 12 weeks of etoposide and cisplatin. Patients with intermediate-risk and poor-risk tumors receive 12 weeks of BEP. Patients who have a relapse after first-line chemotherapy can be cured with second-line therapy 25% to 45% of the time, though some patients who have a relapse may have a better prognosis.[43–47]

RESIDUAL DISEASE

One of the unusual aspects of the management of nonseminomatous germ cell tumors is the practice of resecting all residual masses at the conclusion of chemotherapy. Nonseminomas often have elements of teratoma that are resistant to chemotherapy but are amenable to resection. On average, residual masses contain teratoma about 40% of the time and viable cancer 10% to 15% of the time, while the rest are simply necrosis or fibrosis. An aggressive surgical approach after chemotherapy is the current standard of care, but it requires unusual surgical expertise and is best performed at a center of excellence in this area.[28] Resection of residual masses is performed more selectively with pure seminomas because they are more difficult to resect and are less likely to harbor residual neoplasm.[48,49]

COMPLICATIONS OF TREATMENT

Early side effects

Early side effects of chemotherapy with BEP or etoposide and cisplatin for testis cancer include pancytopenia, fatigue, nausea, vomiting, hearing loss, peripheral neuropathy, and reduced renal function. Bleomycin carries a small risk of potentially fatal pulmonary fibrosis.

With appropriate monitoring and precautions, the risk of major pulmonary complications has almost been eliminated (death rate < 0.2%) in patients receiving up to three cycles of BEP, but studies of patients receiving four cycles have reported pulmonary death in up to 2% of patients. Mild declines in pulmonary diffusion capacity are common after two or more cycles of BEP, but the clinical significance of this is unclear.

The major potential side effect early in chemotherapy is neutropenic sepsis, which causes death in 1% to 2% of patients receiving three or four cycles of BEP or etoposide-cisplatin.

Acute toxicity from radiation therapy includes fatigue, peptic ulcer disease, nausea, vomiting, diarrhea, and erythema.

Side effects that may occur later

Both chemotherapy and radiation therapy have been associated with adverse effects in the decades after treatment. Radiation therapy for seminoma has been linked to an increased risk of death from second cancers and from gastrointestinal and cardiovascular diseases, while chemotherapy has been linked to an increased risk of cardiovascular events, secondary cancers, and death from infectious diseases.[25,50–52]

It is worth noting that one recent study has drawn the link between cardiovascular events with chemotherapy and radiation therapy into doubt,[53] and more work is needed in this area.

Testis cancer patients appear to be at increased risk of metabolic syndrome,[54] so monitoring for cardiovascular risk factors such

Late complications of treatment include second cancers and gastrointestinal and cardiovascular disease

as hypertension and dyslipidemia would thus appear to be prudent. Hypogonadism in testis cancer patients may predispose to sexual dysfunction and depression.

Other late effects of chemotherapy include peripheral neuropathy, hearing loss, tinnitus, Raynaud phenomenon, and renal insufficiency. Infertility can result from chemotherapy, radiation, or retroperitoneal lymph node dissection, and patients should be encouraged to bank sperm before undergoing any of these three treatments. Nonetheless, most testis cancer patients are able to conceive children after treatment. Testis cancer survivors suffering from any of these late complications of treatment should be evaluated by a specialist in the relevant field or referred to a cancer survivorship clinic. ■

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