

Diagnosis and Treatment of Testicular Cancer

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Testicular cancer is the most common malignancy in men 20 to 35 years of age and has an annual incidence of four per 100,000. If diagnosed early, the cure rate is nearly 99 percent. Risk factors for testicular cancer include cryptorchidism (i.e., undescended testicles), family history, infertility, tobacco use, and white race. Routine self-examination and physician screening have not been shown to improve outcomes, and the U.S. Preventive Services Task Force and American Cancer Society do not recommend them in asymptomatic men. Patients presenting with a painless testicular mass, scrotal heaviness, a dull ache, or acute pain should receive a thorough examination. Testicular masses should be examined with scrotal ultrasonography. If ultrasonography shows an intratesticular mass, the patient should be referred to a urologist for definitive diagnosis, orchiectomy, and further evaluation with abdominal computed tomography and chest radiography. The family physician's role after diagnosis of testicular cancer includes encouraging the patient to bank sperm because of possible infertility and evaluating for recurrence and future complications, especially cardiovascular disease. (*Am Fam Physician*. 2008;77(4):469-474, 475-476. Copyright © 2008 American Academy of Family Physicians.)

► **Patient information:** A handout on testicular cancer, written by the author of this article, is provided on page 475.

Testicular cancer accounts for 1 to 2 percent of all neoplasms in men.¹ It is the most common malignancy in otherwise healthy men 20 to 35 years of age and has an annual incidence of approximately four per 100,000.² The incidence of testicular cancer has doubled over the past 40 years and continues to rise, particularly in white men.³ Family physicians should understand risk factors for testicular cancer, how to diagnose the condition, and their role in the care of these patients.

Risk Factors

Risk factors for testicular cancer include cryptorchidism (i.e., undescended testicles), family history, infertility, tobacco use, and white race. Cryptorchidism is an important risk factor; 10 percent of patients with testicular cancer have a history of this condition.⁴ A large cohort study found that cryptorchidism repair before puberty is associated with a twofold increase in the risk of testicular cancer; delaying repair until after 12 years of age increases the risk fivefold.⁵ There is also a genetic link associated with testicular cancer. Having a brother with testicular cancer increases a man's risk six- to 10-fold.⁶ This genetic link is one possible reason why one group (white men) are more likely than another (black men) to develop testicular

cancer.⁷ Research is ongoing to identify a connection between testicular cancer and the gene testicular germ cell tumor 1 on chromosome Xq27.⁸

Studies have found that testicular cancer is associated with infertility or abnormal semen characteristics.^{9,10} It is not clear whether this association is causal or if it is the result of cancer-related morbidity or selection bias in men presenting with infertility.^{9,10} Men exposed to the synthetic estrogen diethylstilbestrol in utero are at increased risk of testicular cancer¹¹; however, diethylstilbestrol has been removed from the market.

Although a number of studies have examined the effect of maternal smoking during pregnancy, they have had conflicting results showing increased, decreased, and no risk.¹²⁻¹⁴ However, a personal smoking history is associated with increased risk of testicular cancer. One study showed a statistically significant twofold increase in testicular cancer risk in smokers with at least a 12-pack-year history.¹⁵ The study found no change in testicular cancer risk after smoking cessation and no difference in risk between former and current smokers. Although it has been suggested, there is no clear or consistent evidence of an association between diet or trauma and testicular cancer.

SORT: KEY RECOMMENDATIONS FOR PRACTICE

| <i>Clinical recommendations</i> | <i>Evidence rating</i> | <i>References</i> |
|--|------------------------|-------------------|
| Routine physician screening and monthly self-examinations to detect testicular cancer are not recommended in asymptomatic patients. | B | 17, 18 |
| Scrotal ultrasonography should be the first diagnostic test in patients with a testicular mass. | C | 1 |
| An intratesticular mass should be considered testicular cancer until proved otherwise. | C | 1 |
| After definitive treatment for testicular cancer, the primary care physician should monitor the patient for recurrence, infertility, second malignancy, and cardiac disease. | C | 30, 32, 37 |
| Because of the risk of infertility, patients should be encouraged to bank sperm, if possible, before undergoing treatment for testicular cancer. | C | 29, 35, 36 |

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, see page 410 or <http://www.aafp.org/afpsort.xml>.

Screening

Although routine screening and monthly self-examination in young men have been recommended, studies have not shown that they improve outcomes.¹⁶ Testicular cancer is rare, but treatment is highly effective even when the diagnosis is made incidentally through examination or because of symptoms. Therefore, the U.S. Preventive Services Task Force recommends against routine screening and self-examination in low- and high-risk asymptomatic men.¹⁷ The American Cancer Society also does not recommend routine self-examination in men without risk factors.¹⁸ However, both groups emphasize the importance of careful evaluation in patients with suggestive signs and symptoms to avoid delayed diagnosis or misdiagnosis.

Diagnosis

HISTORY AND PHYSICAL EXAMINATION

Testicular cancer typically presents as a painless mass in the testis, although many patients have diffuse pain, swelling, or hardness in the scrotum.¹ *Table 1* presents the signs and symptoms of testicular cancer.^{1,19}

Testicular changes are usually found during self-examination, after testicular trauma, or by a sex partner. Patients with these changes are often treated for presumed epididymitis, but do not respond to antibiotic treatment. Patients should return for a follow-up appointment to determine if antibiotic treatment was effective and whether testicular findings have resolved. If the examination is too painful for the patient, ultrasonography may be obtained during antibiotic treatment.

Patients with symptoms of metastatic disease (about 5 percent of patients with testicular cancer) may present with a neck mass, abdominal mass, lumbar back pain, cough, hemoptysis, dyspnea, or gastrointestinal symptoms. Approximately 10 percent of men with testicular cancer have gynecomastia from tumors that secrete beta subunit of human chorionic gonadotropin (β -hCG).¹⁹

Normally, testes are homogenous, freely movable, and separate from the epididymis. To perform a self-examination, the patient places the thumb on top and the index and middle fingers underneath the testicle, then rolls the testicle several times between the thumb and fingers, feeling for lumps, hardness, or swelling. The testicle should be egg-shaped and smooth in texture, with the epididymis located posterior to the testicle. In most patients, one testicle is larger and hangs lower than the other.

If patients choose to perform them, self-examinations should occur about the same time every month while

Table 1. Signs and Symptoms of Testicular Cancer

| | |
|---------------------------------------|---|
| Discomfort | Metastases* |
| Acute pain in the testicle or scrotum | Gastrointestinal symptoms |
| Dull ache in the scrotum or abdomen | Gynecomastia |
| Scrotal heaviness | Lumbar back pain |
| Mass effect | Neck mass |
| Firmness of the testicle | Respiratory symptoms (e.g., cough, hemoptysis, dyspnea) |
| Infertility | |
| Intratesticular mass | |
| Painless swelling and redness | |

*—About 5 percent of patients with testicular cancer have symptoms of metastases.

Information from references 1 and 19.

Table 2. Definitions of TNMS Classifications for Testicular Cancer Staging

Tis: Carcinoma in situ
TX: Primary tumor cannot be assessed
T0: No evidence of primary tumor
T1: Tumor has not spread beyond testicles, blood vessels, lymphatic vessels, or tunica vaginalis
T2: Tumor has spread to blood vessels, lymphatic vessels, or tunica vaginalis
T3: Tumor invades the spermatic cord
T4: Tumor invades the scrotum
NX: Regional lymph nodes cannot be assessed
N0: No metastasis to regional lymph nodes
N1: Lymph node mass 2 cm or less across; five or fewer nodes positive
N2: Lymph node mass between 3 and 5 cm across or metastasis to five or more lymph nodes, none more than 5 cm across
N3: Metastasis to at least one lymph node with the mass more than 5 cm across
MX: Distant metastasis cannot be assessed
M0: No distant metastasis (i.e., no spread to nonregional lymph nodes or other organs such as the lungs)
M1: Distant metastasis is present
M1a: Metastasis to distant lymph nodes or lung
M1b: Metastasis to organs such as the liver, brain, or bones
SX: Marker studies not performed
S0: Normal LDH, β -hCG, and alpha-fetoprotein levels
S1: LDH level < 1.5 times the upper limit of normal; β -hCG level < 5,000 mIU per mL (5,000 IU per L); alpha-fetoprotein level < 1,000 ng per mL (1,000 mcg per L)
S2: LDH level 1.5 to 10 times the upper limit of normal; β -hCG level of 5,000 to 50,000 mIU per mL (5,000 to 50,000 IU per L); alpha-fetoprotein level of 1,000 to 10,000 ng per mL (1,000 to 10,000 mcg per L)
S3: LDH level > 10 times the upper limit of normal; β -hCG level > 50,000 mIU per mL (50,000 IU per L); alpha-fetoprotein level > 10,000 ng per mL (10,000 mcg per L)

NOTE: See Table 3 for testicular cancer staging based on TNMS classifications.

TNMS = primary tumor, regional nodes, metastasis, serum tumor markers; LDH = lactate dehydrogenase; β -hCG = beta human chorionic gonadotropin.

Information from reference 20.

the patient is standing. Any changes or abnormalities should be reported to the patient's primary care physician. In addition to testicular cancer, potential causes of a scrotal mass include epididymal mass, epididymitis, hydrocele, swelling of the testicular appendix, and varicocele.

Abnormal testicular findings include a firm, hard, or fixed mass. When a mass is found, transillumination can further define it. A malignant mass is solid, and the light will not pass through it, whereas a fluid-filled mass, such

Table 3. Cancer Stage Based on TNMS Classifications

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as a hydrocele, will transilluminate. However, results of transillumination do not preclude the need for scrotal ultrasonography. The physical examination also should include palpation to detect evidence of lymphadenopathy, especially inguinal.

DIAGNOSTIC TESTS

Patients with a testicular mass initially should receive scrotal ultrasonography,¹ which will determine whether the mass is intra- or extratesticular. Intratesticular masses are presumed to be testicular cancer until proved otherwise.¹

STAGING AND FURTHER TESTING

Testicular cancer is categorized using the TNMS (primary tumor, regional nodes, metastasis, serum tumor markers) staging system (Tables 2 and 3) created by the American Joint Committee on Cancer.²⁰ Staging is determined based on how much the primary tumor

Table 4. Treatment Options for the Stages of Testicular Cancer

| Stage | Seminoma | Nonseminoma |
|-------|--|--|
| I | Usually radiation, although observation and limited chemotherapy are also options | Retroperitoneal lymph node dissection or observation with monthly follow-up IB: Consider two cycles of chemotherapy IS: Full-dose chemotherapy if serum tumor marker levels do not rapidly decrease after surgery |
| II | IIA: Radiation of the regional lymph nodes IIB or IIC: Three cycles of three-drug chemotherapy | IIA: Retroperitoneal lymph node dissection followed by observation with monthly follow-up and frequent laboratory testing or two cycles of two-drug chemotherapy IIB or IIC: Three or four cycles of three-drug chemotherapy followed by retroperitoneal lymph node dissection if computed tomography still shows lymph nodes High serum tumor marker levels: chemotherapy followed by lymph node dissection |
| III | Three-drug chemotherapy; if there is no response, consider clinical trials of other chemotherapy drug combinations Brain metastasis is present: Treat with radiation of the brain or surgical removal | Three-drug chemotherapy; surgical removal of persistent tumors High serum tumor-marker levels: These patients often do not respond to usual chemotherapy; therefore, more aggressive clinical trials may be considered |

NOTE: Two-drug chemotherapy usually includes cisplatin (Platinol AQ) and etoposide (Vepesid); three-drug chemotherapy usually includes cisplatin, etoposide, and bleomycin (Blenoxane).

Information from reference 24.

has spread to the tissues surrounding the testicle, on the extent of spread to regional lymph nodes, on metastasis to other organs, and on serum levels of proteins produced by certain types of testicular cancer (i.e., serum tumor markers).

Serum tumor markers are usually obtained before orchiectomy and include alpha fetoprotein, β -hCG, and lactate dehydrogenase.^{21,22} In early stages of cancer, levels of these proteins tend to be in the normal range. As nonseminoma tumors progress, they elevate alpha-fetoprotein and β -hCG levels. Seminoma tumors do not increase alpha-fetoprotein levels and occasionally increase β -hCG levels. Lactate dehydrogenase levels are often elevated in widespread, metastatic testicular cancer.

After testicular cancer is diagnosed, the patient should receive computed tomography (CT) of the abdomen and pelvis to detect metastasis to the retroperitoneal lymph nodes and chest radiography. CT or chest radiography should be performed in patients with suspected mediastinal, hilar, or lung parenchymal disease.²³ Patients with neurologic symptoms should receive CT or magnetic resonance imaging of the brain.

Treatment

The primary treatment for testicular tumors is radical inguinal orchiectomy, which includes removal of the testicle and spermatic cord. After orchiectomy, further treatment is determined by microscopic diagnosis

(seminoma versus nonseminoma tumor) and staging. This article discusses treatment of germ cell tumors.

Treatment options after orchiectomy include observation, dissection of the retroperitoneal lymph node, radiation, and chemotherapy.²⁴ Observation is an option in patients with stage I seminomas and includes frequent (probably monthly) follow-up and laboratory testing. Observation is not a good treatment option without significant patient commitment.

Treatment options for specific stages of disease are summarized in *Table 4*.²⁴ As therapy progresses, further treatment decisions are based on response to therapy and changes in serum tumor markers.

Prognosis

The survival rate after treatment of testicular cancer is very good, and death rates decreased by 50 percent from 1980 to 2000.²⁵ For early cancer without metastases, the cure rate is about 99 percent.²⁶ In patients with metastasis to retroperitoneal lymph nodes, the five-year, relapse-free survival rate is 91 to 96 percent.²⁷ In patients with advanced metastatic cancer, the 10-year survival rate is 66 to 94 percent depending on extent of disease.²⁸

Follow-up

The next step for the primary care physician is posttreatment follow-up, which includes discussions about future fertility, risk of recurrence, and treatment complications (*Table 5*^{6,29-33}).

Table 5. Possible Complications of Testicular Cancer Treatment

| |
|--|
| Chemotherapy-specific complications |
| Azoospermia |
| Lung disease (with bleomycin [Blenoxane] use) |
| Neuropathy (with etoposide [Vepesid] use) |
| Renal or otologic injury (with cisplatin [Platinol AQ] use) |
| Increased risk of cardiovascular disease |
| Infertility |
| Recurrence |
| Cardiac mortality after radiation |
| Second malignancy (e.g., leukemia) after radiation or chemotherapy |

Information from references 6 and 29 through 33.

FUTURE FERTILITY

As many as 60 percent of patients with testicular cancer are subfertile at the time of diagnosis, although this may improve after orchiectomy.^{9,10,34} The treatment for testicular cancer also may affect fertility. Chemotherapy has a toxic effect on the germ cells, which can cause an increase in follicle-stimulating and luteinizing hormone levels and a decrease in testosterone levels. In one study of 272 patients treated for testicular cancer, 13 percent of patients developed hypogonadism requiring testosterone supplementation.³⁴

Azoospermia is a common adverse effect of chemotherapy, although many patients recover over time.²⁹ Retroperitoneal lymph node dissection could cause nerve damage leading to ejaculatory disorders or failed emission. A Norwegian study found a 30 percent lower fertility rate in patients treated for testicular cancer.³⁵ Because of the risk of infertility, patients with testicular cancer should be encouraged to bank sperm before treatment.^{29,35,36}

RECURRENCE

Patients with a history of testicular cancer have an increased risk of cancer in the contralateral testicle. In a study of nearly 30,000 patients with previous testicular cancer, the overall risk of new testicular cancer was 12-fold greater than in the general population.³⁶ This risk of new testicular cancer was significantly greater within five years of initial diagnosis and then gradually decreased. The risk of developing contralateral testicular cancer over 15 years was 1.9 percent. There was no significant change in testicular cancer risk based on initial treatment. The 10-year survival rate of patients with recurrent testicular cancer was 93 percent, and the development of recurrent testicular cancer did not increase the mortality risk.³⁶ Patients with testicular cancer should see their primary care physicians annually for at least 10 years

after treatment because this is the most common time for recurrence.

SECOND MALIGNANCY

A possible complication of testicular cancer treatment is a second malignancy. The most common type is leukemia, which can be a complication of radiation or chemotherapy.^{31,37}

Bone marrow exposure to radiation can cause acute myelogenous or lymphocytic leukemia. However, the risk of leukemia in patients treated for testicular cancer has decreased because of the lower doses and narrowed field used in current radiation treatment and because of the discontinuation of preventive radiation treatment to the mediastinum. The chemotherapy drugs etoposide (Vepesid) and cisplatin (Platinol AQ) slightly increase the risk of leukemia. The risk is greatest 5 to 10 years posttreatment. Radiation of lymph nodes in the abdomen and chest increase the risk of stomach cancer. However, the risk of a second malignancy in patients treated for testicular cancer is less than one third of that in patients treated for Hodgkin's disease.^{31,37}

CARDIOVASCULAR RISK

Multiple studies show increased risk of cardiovascular disease after treatment for testicular cancer. One study of British patients treated between 1982 and 1992 found an increased risk of a cardiac event after treatment (relative risk [RR] = 2.7 with radiation; RR = 2.6 with chemotherapy). Most of the cardiac events involved angina or myocardial infarction with no increase in mortality.³⁰ A study of 87 Dutch patients treated with chemotherapy at least 10 years earlier found that 6 percent of patients had cardiovascular disease compared with an expected rate of about 1 percent in persons of similar age in the general population.³² A much larger Norwegian study of nearly 4,000 patients found only a slight increase in the risk of cardiovascular disease after cancer treatment (RR = 1.0; 95% confidence interval [CI], 1.0 to 1.5) and found no significant increase in the risk of myocardial infarction (RR = 1.1; 95% CI, 0.9 to 1.4).³³

The cause of increased cardiovascular risk is uncertain. Chemotherapy does not appear to be the only cause because the risk also increases with radiation treatment. No genetic link has been found. One theory is that there is a hormonal relationship, although this is unproved. Because of the increased cardiovascular risk, primary care physicians should be especially cognizant of possible cardiac disease in patients with a history of testicular cancer treatment and should help patients address modifiable risk factors for cardiovascular disease.

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