

Long-Term Medical Care of Testicular Cancer Survivors

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Testicular cancer is the most common solid tumor diagnosed in men 20 to 35 years of age. Because of highly effective treatments that may include surgery, chemotherapy, and radiation therapy, most patients become long-term survivors. Health-related issues that confront testicular cancer survivors include the late medical effects of chemotherapy, the late relapse of disease, the development of second cancers, the effect of the disease and treatment on

fertility, and the psychosocial consequences. This case-based discussion focuses on the primary care physician's evaluation and management of a long-term survivor of testicular cancer who was previously treated with surgery and chemotherapy.

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A 30-year-old man presents to a general internist for evaluation. The patient states that he received curative therapy for testicular cancer at age 18. He has no other significant medical problems. He smokes one pack of cigarettes daily and drinks alcohol socially. He is married, has no children, and works as a computer programmer. He had been closely followed by his oncologist until age 24, but because of a work-related move has had no follow-up for 6 years.

WHAT DOES THE PRIMARY CARE PHYSICIAN NEED TO KNOW ABOUT THE PATIENT'S HISTORY RELATING TO TESTICULAR CANCER?

Testicular cancer is the most common solid tumor in men 20 to 35 years of age, with approximately 6900 cases diagnosed annually in the United States (1, 2). It has been described as "a model for a curable neoplasm" (3). Most patients will be cured and become long-term survivors. Many will be seen throughout their lives by primary care physicians.

The primary care physician should ask the patient about risk factors for testicular cancer, such as cryptorchidism or family history. Information on the histologic characteristics of the tumor (for example, seminoma or nonseminomatous germ-cell tumor) must also be obtained. Knowing the cancer stage at presentation is also important because prognosis and treatment are based on stage at presentation and histologic findings.

Testicular cancer may be localized (stage I) or metastatic. Testicular cancer spreads via the lymphatic system to the retroperitoneal lymph nodes (stage II). Blood-borne metastases may involve the lung and, less commonly, the liver, skeleton, and brain (stage III). Patients with metastatic disease are further classified as

good risk, intermediate risk, or poor risk on the basis of defined prognostic criteria (4).

The patient had a left testicular mass at 18 years of age. Serum tumor marker assays demonstrated an α -fetoprotein level of 265 $\mu\text{g}/\text{mL}$ and a human chorionic gonadotropin level of 120 IU/L. Left inguinal orchiectomy was performed. Results of pathologic testing showed a nonseminomatous germ-cell tumor. Computed tomography of the abdomen and pelvis revealed a 4-cm retroperitoneal mass. Chest radiography revealed no abnormalities. Chemotherapy consisting of three cycles of bleomycin, etoposide, and cisplatin was given. After chemotherapy, results of tumor marker assays and computed tomography were normal. The patient has been in continuous remission since the end of treatment.

WHICH THERAPIES ARE USED FOR TESTICULAR CANCER?

Radical orchiectomy is done to diagnose and treat testicular cancer. Retroperitoneal lymph node dissection results in staging and treatment in some patients with stage I and stage II nonseminomatous germ-cell tumors. Para-aortic radiation therapy may be used for seminomas, both as adjuvant therapy for stage I disease and as definitive treatment for nonbulky stage II disease. Cisplatin-based chemotherapy regimens are given to patients with metastatic disease. Other agents commonly used include etoposide and bleomycin. The risk classification system described earlier (4) determines the choice of regimen and the number of chemotherapy cycles administered. Selected patients may require postchemotherapy surgery for residual disease.

WHICH LATE TOXICITIES ARE ASSOCIATED WITH CHEMOTHERAPY FOR TESTICULAR CANCER?

For many patients with testicular cancer, cisplatin-based chemotherapy is critical for cure. However, this

Table 1. Screening and Intervention for Potential Late Effects of Cisplatin-Based Chemotherapy in Testicular Cancer Survivors

Late Effect	Screening Approach	Intervention
Vascular		
Raynaud phenomenon	History	Behavior modification
Hyperlipidemia	Lipid profile	Diet, exercise, and medication
Hypertension	Blood pressure	Diet, exercise, and medication
Renal		
Impaired glomerular filtration rate	Serum creatinine level	Treat hypertension; avoid nephrotoxins
Hypomagnesemia	Serum magnesium level	Supplemental magnesium
Increased plasma renin and aldosterone levels	Blood pressure	Diet, exercise, and medication
Otologic		
Tinnitus and hearing loss	History; audiogram if otologic effect suspected	Avoid noise; refer to specialist
Neurologic		
Peripheral neuropathy	History; neurologic examination	Behavior modification; avoid neuropathic agents
Reproductive		
Impaired spermatogenesis	Semen analysis	Pretreatment sperm banking; in vivo or in vitro fertilization; testicular sperm extraction

therapy may be associated with long-term consequences that may affect several organ systems (Table 1) (5–11). A recent study showed that circulating plasma levels of cisplatin may be detectable for up to 20 years after treatment (12). The development of late consequences related to cisplatin-based chemotherapy is not specific to patients with testicular cancer but must be considered because of the high proportion of these patients who will become long-term survivors.

Chemotherapy for testicular cancer is associated with vascular toxicity. The reported incidence of Raynaud phenomenon in patients with testicular cancer treated with cisplatin-based chemotherapy ranges from 10% to 49% (6, 8, 9, 13). Bleomycin is largely responsible for these symptoms. In up to half of patients, symptoms will gradually resolve. Serious vascular complications, including myocardial infarction, stroke, and thromboembolic disease, have been reported in men with testicular cancer treated with cisplatin-based chemotherapy (14–16).

In a study of patients with testicular cancer who were treated with surgery or with surgery and cisplatin-based chemotherapy, Nichols and colleagues (17) reported no increased risk for cardiovascular events in the chemotherapy group at a median follow-up of 5 years. More recently, Meinardi and coworkers (18) demonstrated an observed-to-expected ratio of cardiovascular events of 7.1 (95% CI, 1.9 to 18.3) for patients with testicular cancer who were age 50 years or younger, had received chemotherapy, and were in remission for 10 or

more years compared with a general male population. The potential increased risk for cardiovascular events can be explained, in part, by studies that demonstrated the development of hypertension and hyperlipidemia after chemotherapy in these patients (9, 18–21). Increased risk could also be related to cisplatin-mediated vascular endothelial injury (11). Additional studies are needed to define the actual risk, if any, for early cardiovascular events in long-term survivors of testicular cancer who received chemotherapy. We recommend that the primary care physician be attentive to identifying and treating modifiable cardiovascular risk factors, including tobacco use, hypertension, and hyperlipidemia, in these patients.

Some degree of nephrotoxicity occurs in all patients who receive cisplatin (5–7, 9–11, 22, 23). The decrease in glomerular filtration rate may not improve over time (5–7, 9, 22, 23). Although this decreased glomerular filtration rate may not have immediate clinical relevance, its potential effect on long-term renal function and associated conditions is not clear (18). Cisplatin also results in hypomagnesemia and increased plasma renin and aldosterone levels (9, 24, 25), which may contribute to cardiovascular toxicity. We recommend that primary care physicians monitor magnesium levels because chronic magnesium wasting can occur for many years in some patients.

Tinnitus and high-frequency hearing loss (4 to 8 MHz) are persistent problems in approximately 20% of patients treated with cisplatin-based chemotherapy for

testicular cancer (7, 9, 26). Possible risk factors for ototoxicity include cumulative cisplatin dose, history of noise exposure, and preexisting hearing loss (26).

Peripheral neuropathy, typically sensory, may occur after cisplatin-based chemotherapy. Most of the reported cases of substantial neurotoxicity have resulted from the cisplatin, vinblastine, and bleomycin regimen, which currently is not standard therapy (27). Substituting etoposide for vinblastine has dramatically decreased the incidence of neuropathy (28).

Acute pulmonary toxicity secondary to bleomycin is a rare but well-known complication (29). Cigarette smoking has been identified as a risk factor for bleomycin-induced pulmonary toxicity (6, 11, 30). Long-term pulmonary function is preserved in most testicular cancer survivors, even if bleomycin was administered (31).

IF CHEMOTHERAPY-RELATED LATE TOXICITY IS IDENTIFIED, WHICH INTERVENTIONS SHOULD BE CONSIDERED?

Interventions should be based on the seriousness of the late effects. If the patient reports the Raynaud phenomenon or paresthesia, the physician can encourage the patient to modify any behavior that worsens the symptoms. Hypertension and lipid abnormalities can be addressed with dietary modification, exercise, and medications, as indicated. Renal function may be preserved over the long term by controlling hypertension and diabetes, if they are present, and by avoiding unnecessary exposure to nephrotoxic agents. Although the effect of ongoing smoking on pulmonary function in the bleomycin-exposed lung has not been defined, the cardiovascular and carcinogenic effects of smoking are well known. Patients should be strongly encouraged to stop smoking and offered the opportunity to participate in smoking cessation programs. The physician should ask about noise exposure in the workplace to potentially limit additional hearing loss. Patients in whom cisplatin-induced ototoxicity is suspected should be referred for audiologic examination; most, however, will not need corrective hearing devices (26).

The patient admits that his digits become discolored and uncomfortable when exposed to severe cold. Although mild, these symptoms are annoying. He has a dry cough that he attributes to smoking, but no dyspnea. He reports no hearing loss or tinnitus. The primary care physician counsels

the patient on ways to avoid cold exposure, strongly recommends discontinuing tobacco use, and refers the patient to a smoking cessation program.

The physician then begins to examine the patient.

WHICH ASPECTS OF PHYSICAL EXAMINATION ARE IMPORTANT FOR TESTICULAR CANCER SURVIVORS?

The physician caring for the testicular cancer survivor should perform a complete physical examination annually. Weight and blood pressure should be recorded. The skin should be examined for pigmented lesions because patients with testicular cancer appear to have an increased risk for dysplastic nevi (32, 33). The lymph node examination is important because recurrence can sometimes be detected in the neck. The remaining testicle should be examined because of the increased risk for developing a second germ-cell tumor (34, 35).

ARE LABORATORY TESTS INDICATED?

We recommend performing serum tumor marker assays (α -fetoprotein and human chorionic gonadotropin) and chest radiography annually to monitor for disease recurrence. For patients who received chemotherapy, renal function should be assessed at baseline by measuring serum creatinine and magnesium concentrations. In addition, we recommend that all patients, starting 2 years from the end of chemotherapy, have a baseline lipid analysis with subsequent testing as indicated.

On physical examination, the patient's blood pressure is 135/90 mm Hg and his heart rate is 72 beats/min. A skin examination reveals scattered nevi across the trunk, one of which is 6 mm in diameter with irregular borders. The remainder of the physical examination is normal. The remaining testicle is normal.

The patient is especially concerned about the risk for developing cancer later in life. He asks the physician for comprehensive cancer screening and for measures he can take to prevent the development of another cancer.

WHAT ARE THE RISKS FOR LATE RELAPSE OF TESTICULAR CANCER AND FOR SECOND TESTICULAR CANCER?

For patients with testicular cancer, most recurrences occur within 2 years of the end of treatment. However, late recurrence of testicular cancer may occur in both

early- and advanced-stage disease (36–38). The incidence of late relapse is approximately 2% to 3%. The most common sites of late recurrence are the retroperitoneum and chest. Late recurrences are primarily managed with surgery because they are often refractory to chemotherapy. Because of the possibility of late recurrence, patients with testicular cancer need lifelong monitoring.

Three percent to 4% of patients with a history of testicular cancer will develop a second testicular cancer, and the increased risk levels off 15 to 20 years after the initial diagnosis (34–35). This observation may, in part, result from an increased incidence of carcinoma in situ in the contralateral testis, a known precursor to germ-cell tumors (39). Chemotherapy may decrease the risk for or postpone the development of carcinoma in situ and subsequent testicular cancer (40). Patients who undergo a second orchiectomy will require long-term testosterone replacement therapy. The identification of bilateral testicular cancer may signify a genetic susceptibility to the disease. Recently, genetic linkage analysis of families with multiple cases of testicular cancer (including bilateral cancer) has led to identification of a testicular cancer susceptibility gene locus that is mapped to chromosome Xq27 (41).

HOW SHOULD THE PHYSICIAN LOOK FOR RECURRENT TESTICULAR CANCER?

The physician overseeing the long-term care of testicular cancer survivors should annually perform a complete physical examination that includes careful assessment of the remaining testicle. As noted previously, annual studies, including serum tumor marker assays and chest radiography, should be performed to screen for disease recurrence. Additional radiologic studies, such as testicular ultrasonography or computed tomography of the retroperitoneum, should be performed if recurrent disease is suspected.

ARE PATIENTS WHO SURVIVE TESTICULAR CANCER AT SUBSEQUENT RISK FOR DEVELOPING OTHER CANCERS?

Patients cured of testicular cancer have been shown to be at risk for the development of cancer later in life. In an analysis of 16 population-based cancer registries in North America and Europe, which included 28 843 patients treated for germ-cell tumors

between 1935 and 1993, the observed-to-expected ratio of second cancers in this population compared to the general population was 1.43 (CI, 1.36 to 1.51) (42). These second cancers included both radiation-induced solid tumors and chemotherapy-induced leukemia. Many patients treated in this series received outdated treatments that were probably more carcinogenic than are current treatments. In patients with testicular cancer treated more recently, the risk for a second cancer may be substantially lower.

For testicular cancer survivors who have received radiation therapy, the overall risk for developing a secondary solid tumor is approximately two to three times greater than that of like-aged persons in the general population. The risk for developing a secondary solid tumor increases in proportion to the duration of follow up. Solid tumors that have been identified include sarcomas and cancers of the gastrointestinal and genitourinary tract (42–46). Acute myelogenous leukemia with specific abnormalities in chromosome 11q23 may occur 2 to 3 years after treatment with etoposide (45–49). The risk for leukemia appears to be cumulative and dose-dependent. At standard doses of etoposide (≤ 2 g/m², the total cumulative dose for up to four cycles of either the bleomycin, etoposide, and cisplatin or the etoposide and cisplatin regimen), the overall incidence of leukemia is expected to be very low ($<0.5\%$). However, at higher doses of etoposide (>2 g/m²), the 5-year incidence increases to about 2% (46, 47).

An association has been reported between testicular cancer and dysplastic nevi (32, 33). Dysplastic nevi may be precursors to melanoma. One study demonstrated that 37% of patients with germ-cell tumors had multiple, atypical nevi as compared with 15% of healthy controls (33). An increased incidence of melanoma has also been reported in survivors of germ-cell tumors (42, 50). It is not known whether these patients have an inherent increased risk for dysplastic nevi or whether treatment plays a role. We recommend that patients with testicular cancer who have atypical nevi be referred to a dermatologist for careful skin assessment and surveillance.

WHAT CAN PATIENTS DO TO DECREASE THE RISK FOR SECOND CANCERS?

It is not known whether second cancers can be prevented in testicular cancer survivors. However, certain

measures may be helpful. Patients should be instructed and encouraged to self-examine the remaining testicle and skin regularly. In addition, patients should be vigorously encouraged to refrain from or discontinue smoking. Limiting sun exposure and using sunscreens should also be encouraged. Finally, early detection of common types of cancer, such as colorectal and prostate cancer, should be addressed at the appropriate age.

The patient mentions that he and his wife have been trying to have a child, but his wife has not yet become pregnant. The patient reports that he banked his sperm before receiving chemotherapy. He notes that his erectile and ejaculatory functions are normal.

WHAT IS THE LIKELIHOOD THAT THE PATIENT HAS DECREASED FERTILITY?

In newly diagnosed patients, decreased spermatogenesis and increased levels of follicle-stimulating hormone may be observed before orchiectomy (51, 52). Approximately one third of patients who have undergone orchiectomy have severe oligospermia or azoospermia (53). Cisplatin-based chemotherapy also substantially impairs spermatogenesis (54–58). The probability for recovery of spermatogenesis after chemotherapy depends on the age of the patient, the severity of pretreatment oligospermia, and the cumulative dose of chemotherapy received (54, 59). Some patients with oligospermia can still father children (57). Chemotherapy may also result in Leydig-cell dysfunction, which increases luteinizing hormone levels. Serum testosterone levels remain in the normal range in most patients (60–63). Patients who undergo retroperitoneal lymph node dissection may develop dry ejaculation. The introduction of nerve-sparing surgery has preserved normal ejaculation in most men who undergo this procedure (64–66).

ARE THERE INTERVENTIONS TO IMPROVE FERTILITY IN PATIENTS TREATED FOR TESTICULAR CANCER?

Patients with testicular cancer who will have retroperitoneal lymph node dissection or chemotherapy should be encouraged to bank sperm before having these treatments (67). If fertility is an important concern, infertile testicular cancer survivors should be referred to a center specializing in assisted reproductive technologies. In vitro and in vivo fertilization using banked sperm is usually successful. Recent technical advances, such as intracytoplasmic sperm injection, offer survivors additional hope of paternity. Finally,

sperm have been successfully extracted from testicular tissue in patients with chemotherapy-related, nonobstructive azoospermia (67, 68).

The patient's affect seems flat. He states that he is pleased with his marriage but worries about whether he and his wife will ever be able to have children.

ARE CERTAIN MENTAL HEALTH PROBLEMS PREVALENT IN TESTICULAR CANCER SURVIVORS? IS FORMAL PSYCHOLOGICAL TESTING INDICATED?

Studies have demonstrated that fewer than 10% of testicular cancer survivors are affected by long-term psychosocial consequences (69–74). In one study, the health-related quality of life in long-term testicular cancer survivors was reported to be as good as or even better than that of men in the general population (69). Studies have demonstrated that sexual function and fertility are important predictors of psychosocial outcome (74–77). Testicular cancer survivors may report concerns about sexuality, such as decreased libido, diminished orgasm intensity, and erectile or ejaculatory impairment (75–82). Potential sexual problems should be discussed with patients before commencing cancer treatment and at follow-up visits (83, 84). Because the minority of testicular cancer survivors suffer long-term psychological distress, we do not advocate formal psychological evaluation and testing unless psychosocial concerns are suspected.

The patient asks whether he should see an oncologist at this point. He also wonders how frequently he should see his primary care physician for follow-up.

HOW OFTEN SHOULD THE PRIMARY CARE PHYSICIAN SEE THE PATIENT FOR ROUTINE FOLLOW-UP? WHICH TESTS SHOULD BE DONE AT THESE VISITS? WHEN SHOULD THE PATIENT BE REFERRED TO A CANCER SPECIALIST?

At the end of treatment, most patients with testicular cancer begin a follow-up schedule with a cancer specialist to monitor for disease recurrence. Visits are usually more frequent during the first 2 years after treatment and become less frequent between years 3 and 5. After year 5, patients should be seen annually by a cancer specialist for detection of late recurrence. We also recommend that testicular cancer survivors who are more than 2 years from the

Table 2. Recommendations for the Annual Medical Evaluation of Testicular Cancer Survivors*

Recommendation	Rationale (Reference)
Complete history with special attention to Tobacco use Sunscreen use Fertility assessment Psychosocial and sexuality status Cardiovascular risk factors associated with cisplatin-based chemotherapy Late effects of cisplatin-based chemotherapy	Cardiovascular and carcinogenic risks Increased risk for dysplastic nevi (32, 33) Potential for subfertility associated with the disease and treatment Interrelationship between sexuality and psychosocial status (74–77) Postchemotherapy hypertension and hyperlipidemia (9, 18–21) Impact on multiple organ systems
Complete physical examination, including Blood pressure Skin examination Testis examination	Postchemotherapy hypertension (9, 18, 19) Increased risk for dysplastic nevi (32, 33) 3%–4% risk for secondary germ-cell tumor (34, 35)
Laboratory monitoring Serum tumor marker assays Serum creatinine and magnesium associated with cisplatin-based chemotherapy Lipid profile associated with cisplatin-based chemotherapy	2%–3% risk for late relapse (36–38) Decreased glomerular filtration rate and hypomagnesemia (5–7, 9, 22–25) Postchemotherapy hyperlipidemia (9, 18–21)
Radiologic studies Chest radiography	2%–3% risk for late relapse (36–38)

* These recommendations are the opinions of the authors and have not undergone consensus review or prospective validation.

completion of treatment have annual comprehensive medical evaluations. Either a primary care physician with knowledge of testicular cancer and treatment sequelae or a cancer specialist with expertise in general medicine should perform this medical evaluation. The visit should center on an assessment of the patient’s overall health status, with special focus on the potential late consequences of testicular cancer and its treatment. Our recommendations for the annual medical evaluation of testicular cancer survivors are summarized in Table 2. Primary care physicians should refer patients to a cancer specialist if disease recurrence is suspected. With careful attention to the medical and psychosocial issues that confront testicular cancer survivors, informed primary care physicians can have an important effect on the long-term well-being of these patients.

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