Long-term Morbidity of Testicular Cancer Treatment

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KEYWORDS

• Testicular cancer • Survivorship • Long-term morbidity • Cardiovascular disease
• Second malignant neoplasms • Neurotoxicity • Hypogonadism • Nephrotoxicity

KEY POINTS

- Potentially long-term life-threatening complications, including second malignant neoplasms, cardiovascular disease, neurotoxicity and ototoxicity, pulmonary complications, hypogonadism, and nephrotoxicity have accompanied the remarkable successes of testicular cancer treatment.
- Testicular cancer survivors should follow applicable national guidelines for cancer screening and management of cardiovascular risk factors.
- Health care providers should capitalize on the time of testicular cancer diagnosis as a teachable moment to introduce and promote lifestyle changes in testicular cancer survivors, including smoking cessation, better nutrition, and participation in a regular exercise regimen.
- Testicular cancer is positioned to become a paradigm in survivorship research for adult-onset cancer and the most comprehensive multi-institutional study to date is currently underway to examine genetic variants associated with long-term toxicities of platinum-based chemotherapy in testicular cancer survivors.

INTRODUCTION

Testicular cancer (TC) is the most common cancer among men age 18 to 39 years.[1] Because of effective cisplatin-based chemotherapy introduced in the 1970s[2] it is also the most curable cancer, with the 10-year relative survival for all patients with TC approaching 95%.[3,4] The incidence of TC has increased steadily in the past 20 years in the United States,[5] likely attributable to genetic and environmental factors.[6] However, potentially life-threatening complications, including second malignant neoplasms (SMN), cardiovascular disease (CVD), neurotoxicity and ototoxicity, pulmonary complications, hypogonadism, and nephrotoxicity,[7–9] have accompanied these remarkable

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successes.[3,6] This article focuses on pathogenesis, risks, and management of late effects experienced by long-term TC survivors (TCS), which are defined as individuals who are disease free 5 years or more after primary treatment.[10]

SECOND MALIGNANT NEOPLASMS

Pathogenesis

SMNs can be classified according to their predominant causal factors, including syndromic, cancer treatment, and shared causal exposures.[11] Categories are not mutually exclusive, and reflect the joint contribution of lifestyle factors, genetic susceptibility, environmental exposures, and host effects, including gene-environment interactions (**Fig. 1**).[12] Age at exposure and attained age are risk modifiers for selected SMNs.[13]

Risks of Leukemia

Radiotherapy for TC is associated with an increased risk of leukemia.[14] An international population-based study of leukemia in 18,567 TCS (n = 36 cases, 106 matched controls) reported a significant 3-fold increased risk of leukemia after abdominal and pelvic radiotherapy (mean dose to active bone marrow = 10.9 Gy).[14] The median latency of the leukemias (22 of 36 occurred after radiotherapy alone) was 5.0 years, with 25% developing after 1 decade. However, the absolute risk of leukemia was low (9 excess cases per 10,000 patients per year followed for 15 years after 25 Gy of abdominal and pelvic radiation).[14]

Both cisplatin and etoposide are also associated with significant excesses of secondary leukemia.[14–17] The cumulative incidences of leukemia 5 years after receiving a cumulative etoposide dose of less than 2000 mg/m^2 and greater than or equal to 2000 mg/m^2 are approximately 0.5% and 2.0%, respectively.[17] In a multivariable model that adjusted for radiation dose, an international nested case-control study of leukemia[14] reported a significant dose-response relationship between increasing cumulative dose of cisplatin and leukemia (P_{trend} = .001). Although the excess risk was small (16 excess cases among 10,000 patients with TC at 15 years of follow-up), the estimated risk of leukemia after a cumulative cisplatin dose of 650 mg was increased about 3.2-fold.

Risks of Solid Cancers

The overall relative risk (RR) of second solid cancers in TCS compared with the general population is 1.4 to 1.9, with risks increasing 5 years after treatment (**Table 1**).[13,18,19] In an international population-based investigation of 40,576 TCS, patients with TC who survived at least 10 years (n = 20,984) had significantly increased risks of solid cancers associated with radiotherapy alone (RR = 2.0; 95% confidence interval [CI], 1.9–2.2), chemotherapy alone (RR = 1.8; 95% CI, 1.3–2.5), or both (RR = 2.9; 95% CI, 1.9–4.2).[13] In particular, significantly 1.5-fold to 4.0-fold increased risks for malignant melanoma and cancers of the lung, thyroid, esophagus, pleura, stomach, pancreas, colon, rectum, kidney, bladder, and connective tissue were reported.[13] Compared with population expected risks of 23%, the cumulative risks of solid cancer by 75 years of age among men diagnosed with seminomas or nonseminomas at 35 years of age were 36% and 31%, respectively. In particular, among patients given radiotherapy alone, the risks of SMN at sites included in standard infradiaphragmatic radiotherapy fields were significantly larger than risks at unexposed sites (RR = 2.7 vs 1.6; P<.05), and remained increased for more than 35 years.

Several studies reported significant dose-response relationships between radiotherapy and SMN risks in TCS.[19–22] In a case-control study of 5-year TCS (1959–1987),[22] TCS given radiotherapy had a 5.9-fold increased risk of stomach cancer compared with controls, and risk increased with increasing radiation dose to stomach (P_{trend}<.001). The odds ratios (OR) for developing gastric cancer at radiation doses to the stomach

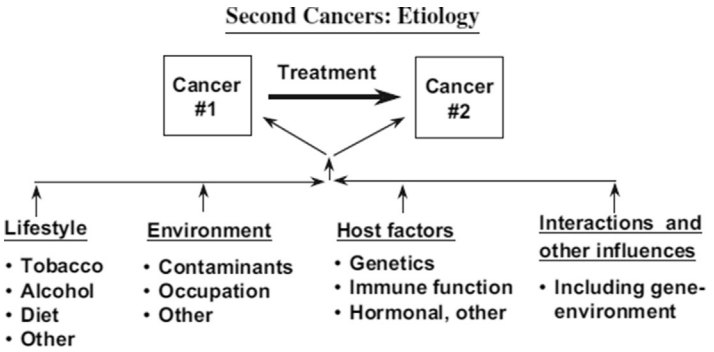

Fig. 1. Risk factors for second primary cancer (refer to text). Many influences, some of which are shown here, may contribute to the development of multiple primary cancers, including interactions between exposures. (*Adapted from* Travis LB. Therapy-associated solid tumors. Acta Oncol 2002;41(4):324; with permission.)

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