ELSEVIER

CrossMark

Urologic Oncology: Seminars and Original Investigations 33 (2015) 392–398

UROLOGIC ONCOLOGY

Seminar article

Secondary malignant neoplasms in testicular cancer survivors

Stephanie A. Curreri, M.P.H.[a,*], Chunkit Fung, M.D.[b], Clair J. Beard, M.D.[a]

[a] *Dana-Farber Cancer Institute, Brigham and Women's Hospital, Harvard Medical School, Boston, MA*
[b] *University of Rochester Medical Center, Rochester, NY*

Received 19 February 2015; received in revised form 28 April 2015; accepted 1 May 2015

Abstract

Background: Testicular cancer is the most common cancer among men aged 15 to 40 years, and the incidence of testicular cancer is steadily increasing. Despite successful treatment outcomes and the rate of survival at 5 to 10 years being 95%, survivors can experience late effects of both their cancer and the treatment they received, including secondary malignant neoplasms (SMNs). We discuss the development of non–germ cell SMNs that develop after diagnosis and treatment of testicular cancer and their effect on mortality.

Results: Patients diagnosed with testicular cancer frequently choose postoperative surveillance if they are diagnosed with clinical stage I disease. These patients may experience an increased risk for developing SMNs following radiation exposure from diagnostic imaging. Similarly, radiotherapy for testicular cancer is associated with increased risks of developing both solid tumors and leukemia. Studies have reported that patients exposed to higher doses of radiation have an increased risk of developing SMNs when compared with patients who received lower doses of radiation. Patients treated with chemotherapy also experience an increased risk of developing SMNs following testicular cancer, though the risk following chemotherapy and radiation therapy combined is not well described. A large population-based study concluded that the rate ratios for both cancer-specific and all-cause mortality for SMNs among testicular cancer survivors were not significantly different from those of matched first cancers.

Conclusions: Although it is known that patients who receive adjuvant chemotherapy or radiotherapy or who undergo routine diagnostic or follow-up imaging for a primary testicular cancer are at an increased risk for developing SMNs, the extent of this risk is largely unknown. It is critically important that research be conducted to determine this risk and its contributing factors as accurately as possible.

Keywords: Testicular cancer; Radiation therapy; Chemotherapy; Diagnostic imaging; Second cancer

Introduction

Testicular cancer is the most common cancer among men aged 15 to 40 years. For unclear reasons, the incidence of testicular cancer is steadily increasing and has doubled in North America and many European countries over the past 20 years. Contemporary data on survival reveal that 95% of patients with testicular cancer survive for more than 5 to 10 years and go on to live for decades, given their young age at diagnosis. Over time, however, survivors may develop serious treatment- and cancer-related late effects such as cardiovascular disease and secondary malignant neoplasms (SMNs). All available data suggest that these life-threatening illnesses occur more often in testicular cancer survivors than in the general population. Large studies taken from national and international databases suggest that over time, some patients who are cured of testicular cancer have an increased risk of mortality when compared with age- and gender-matched controls. The authors reviewed these studies and others describing the risk of developing SMNs in testicular cancer survivors based on search criteria including testicular cancer histologies and treatment regimens. This article focuses on the development of non–germ cell SMNs that develop in the decades following the diagnosis and treatment of testicular cancer and its effect on mortality.

Orchiectomy and surveillance

With the exception of patients who present with very advanced disease necessitating urgent therapy, the diagnosis of testicular cancer is made following a radical inguinal

* Corresponding author. Tel.: +1-973-632-6260.
E-mail address: scurreri@lroc.harvard.edu (S.A. Curreri).

http://dx.doi.org/10.1016/j.urolonc.2015.05.002
1078-1439/

orchiectomy, which completely removes the cancerous testicle. Patients with clinical stage I disease (CS I), defined as no disease beyond the testicle at the time of diagnosis, frequently select active surveillance after orchiectomy as their treatment strategy. With active surveillance, no adjuvant therapy is given, and patients are monitored by physical examination, tumor markers, and imaging studies for a period, usually 5 years, after diagnosis. Unless a patient develops recurrent testicular cancer, no treatment beyond orchiectomy is administered. As most relapses in patients with CS I disease are in retroperitoneal nodes and are asymptomatic, surveillance protocols rely heavily on retroperitoneal imaging. Although a few testicular cancer surveillance strategies use ultrasound imaging of the retroperitoneum, most patients undergo episodic abdominopelvic computerized tomography (APCT) and chest x-rays. In the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines In Oncology (NCCN Guidelines) [1], the number of recommended CT scans in asymptomatic patients ranges from 5 to 8 depending on the histology of the primary tumor and the risk of recurrence following orchiectomy, which is approximately 15% for patients with CS I seminomatous tumors, 10% for patients with CS I low-risk nonseminomatous tumors, and up to 50% for those with high-risk CS I nonseminomatous tumors. Both chest x-rays and APCT scans expose patients to ionizing radiation, although the exposure is much lower with a chest x-ray (0.02 mSv) than with an APCT scan or a chest CT scan (10 mSv) [2]. Ionizing radiation is a known carcinogen. The exact risk of developing a radiation-induced malignancy after low-dose exposure, such as a chest x-ray, is controversial. However, concerns have been raised regarding obtaining repeated APCT scans taken in this young patient population [3,4]. Brenner et al. estimated that approximately 1.5% of all cancers in the United States could be attributed to the radiation from diagnostic CT scans [2]. Although concerning, this number should be put into perspective. A second modeling study suggested that the lifetime attributable risk of mortality from cancer for an individual is extremely small (0.02%) following an abdominal CT taken at 35 years of age [3].

A modeling study looking at the risk of developing a radiation-induced SMN after CT scans was reported in 2009 by Tarin et al. [2]. Using sets of normalized dose data for different normal soft tissues provided by the National Radiological Protection Board following a typical APCT scan, the authors estimated a 1 in 52 (1.9%) lifetime cancer risk for an 18-year-old patient and a 1 in 63 (1.2%) risk for a 40-year-old patient after 13 to 16 scans. These rates increased with the addition of a chest CT scan to 2.6% and 1.8%, respectively. It is well established that beyond very low doses of ionizing radiation, the risk of developing a secondary cancer increases linearly as the dose of ionizing radiation increases. Furthermore, young patients are considered more at risk, as they have longer to live and more time to develop a radiation-induced malignancy. This study did not consider lifestyle factors associated with an increased risk developing of cancer, such as tobacco use. A study performed by Chamie et al. [5] retrospectively compared the risk of developing an SMN for patients who underwent a retroperitoneal lymph node dissection with that of those who did not, based on the assumption that most patients in the first group underwent surveillance only. With a median follow-up time of 15 years, an increased rate of developing SMNs was identified only in patients older than 45 years at the time of SMN diagnosis who did not undergo retroperitoneal lymph node dissection, but this study did not look at other risk factors for development of SMNs, such as positive family history or tobacco use. In a study of 2,569 testicular cancer survivors managed with surveillance, at a median follow-up time of 11 years, the hazard ratio for developing SMNs per 10 mSv increase was 0.99 (95% CI: 0.95–1.04) [4]. The median number of CT scans in this cohort was 10, with a median radiation dose of 110 mSv. However, as the authors pointed out, longer follow-up may be necessary to detect any increased risk of developing SMNs.

Although the risk of developing an SMN may be small after diagnostic exposure to radiation, most authors agree that the possible risks should be minimized. To do so, the NCCN Guidelines for active surveillance in testicular cancer have been changed to minimize the number of APCT scans undertaken per patient [1]. Furthermore, low-dose CT scans have been tested and found to be readable and useful for surveillance, further decreasing the exposure and potential risk. In a study of 100 patients with testicular cancer undergoing CT-based surveillance, low- and standard-dose CT scans were taken for each patient [6]. The authors reported that the low-dose CT provided a diagnostically acceptable image for 99% of patients and achieved a 55% reduction in ionizing radiation dose. Low-dose CT scan has become the standard of care in many institutions, and its use is encouraged by most testicular cancer specialists. An obvious question is whether magnetic resonance imaging (MRI) could be substituted for CT-based imaging, as MRI is unassociated with ionizing radiation and the risk of an induced malignancy. Unfortunately, MRI of the retroperitoneum requires special breath-holding and sequencing techniques that are not widely available, and it is not recommended outside centers of excellence. A British randomized trial comparing CT-based surveillance with MR-based surveillance recently reached its enrollment goals, but it will be several years before the results of this study are known [7].

Radiation therapy

One of the earliest reports of an increased risk of developing SMNs following therapeutic radiation for testicular cancer dates back to 1984. Hay et al. [8] reported on the outcomes of 897 patients with testicular cancer who received radiotherapy between 1950 and 1969. With a mean follow-up of 15 years, the observed incidence of SMNs was