Testicular cancer survivorship: Long-term toxicity and management

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Table of contents

Introduction

Testicular cancer (TC) occurs most commonly in young men but, fortunately, is highly curable with surgery, chemotherapy, and/or radiation therapy.[1,2] Thus, testicular cancer survivors (TCS) may live for many decades, which increases their risk of developing long-term complications related to their initial cancer diagnosis and treatment. Long-term complications may increase mortality and morbidity and decrease quality of life (QoL) in TCS relative to similar aged men without cancer.[3] Therefore, a delicate balance must be struck between optimizing cure and minimizing complications.

The goals of this manuscript are to:

1. Educate urologists, oncologists, and primary care physicians, as well as TCS, about the potential long-term complications of surgery, chemotherapy, and radiation therapy.
2. Make recommendations for monitoring and managing these complications.

Unfortunately, for many long-term complications of TC treatment, there is limited evidence-based literature and, therefore, many of our recommendations are based on expert opinion and multidisciplinary input. The most important recommendation to decrease long-term complications is to ensure that all TC patients are treated appropriately at initial presentation to maximize cure rates and minimize overtreatment. For guidance on appropriate management, refer to the recently published Canadian Urological Association (CUA) testicular germ cell cancer consensus guideline.[4]

1. Chemotherapy

Chemotherapy is an integral component in the management of advanced TC and most often consists of bleomycin, etoposide, and cisplatin (BEP) but may also include ifosfamide, paclitaxel, or carboplatin.[1] For other cancers, strategies to minimize chemotherapy toxicity may include treatment delays or dose reductions; however, this is not an option in TC, as these maneuvers may impact cure rates.[5] Significant interindividual variability exists and increasingly we are learning of factors, including genomic markers, that may result in increased susceptibility to chemotherapy toxicities.[6] Long-term toxicities are described below.

Neurotoxicity

Peripheral neuropathy (PN) can occur in patients treated with cisplatin, carboplatin, or paclitaxel, primarily due to effects in the dorsal root ganglion, where platinum compounds accumulate and lead to cell death. This results in an axonal neuropathy of predominantly large myelinated sensory fibers.[7]

Patients often present with paresthesias and dysesthesias distally that, over time, advance proximally. An early sign of PN is decreased vibratory sensation in the toes and loss of deep tendon reflexes. Autonomic neuropathies can happen but are rare. PN can start during or after chemotherapy and can worsen for months following chemotherapy. Improvement can occur but may be incomplete.[7]

In one study of 739 TCS, objective evidence of PN was present in 21.7% who received chemotherapy vs. 9.1% who did not at a median of 11 years from initial treatment (range 3–19 years); however, subjectively, 12.5% of TCS who received chemotherapy vs. 5.5% who did not reported PN symptoms.[8] Higher long-term serum platinum levels are associated with more severe self-reported chemotherapy-induced neurotoxicity (PN, ototoxicity, and Raynaud's phenomenon) 5–20 years post-platinum-based chemotherapy.[9] Most reports show that cumulative doses >300 mg/m^2 of cisplatin increase PN risk, while almost all patients have evidence of PN after a cumulative dose >500–600 mg/m^2.[10]

In a study of 680 TCS, risk factors for PN include increased age, smoking, alcohol use, and hypertension. Pre-existing PN or predisposing conditions like diabetes mellitus also increase the risk of developing PN.[11]

Management recommendations

- No evidence-based preventative therapies for PN have been shown to be consistently beneficial in TCS treated with chemotherapy.[12]
- Treatment of PN primarily involves symptomatic management. Based on the American Society of Clinical Oncology (ASCO) guidelines, there are trials supporting the use of duloxetine. The use of gabapentin/pregabalin and cannabinoids is not recommended outside of clinical trials. There are small clinical trials demonstrating benefit of exercise, acupuncture, and electrocutaneous treatments; however, larger, definitive studies are needed to confirm efficacy and clarify risks.[12]
- Depending on the degree of motor impairment, physiotherapy and occupational therapy may be beneficial.[12]

Ototoxicity

Ototoxicity from cisplatin can cause both bilateral high-frequency sensorineural hearing loss and tinnitus. Several potential mechanisms exist, with the primary one being dose-dependent cochlear damage, especially to the outer hair cells. Release of proapoptotic factors and excess production of reactive oxygen species can trigger cell death of these hair cells.[13]

In a study of 488 TCS, patients were questioned and underwent formal audiometric analysis at a median of 4.25 years (range 1–30.3 years) post-chemotherapy. Self-reported hearing loss was noted in 30% and tinnitus in 40%. Objectively, hearing loss was found in 80%, with severe to profound loss in 18%.[14]

Factors that may influence ototoxicity include cumulative cisplatin dose (>400 mg/m^2) and older age at diagnosis.[15] The concurrent use of other ototoxins, noise exposure, hypertension, smoking, and pre-existing hearing loss are other factors that may influence chemotherapy-induced ototoxicity.[15,16] Examples of ototoxins include: aminoglycoside antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs), and salicylates (ASA).[17]

Management recommendations

- No evidence-based preventative therapies for ototoxicity have been shown to be consistently beneficial in TCS who receive chemotherapy.
- Patients should minimize noise exposure, wear hearing protection in noisy environments, avoid other ototoxic drugs, and minimize other potential factors that may influence hearing loss, such as hypertension and smoking exposure.
- Formal audiometric analysis should play a role in TCS who have had cisplatin or high-dose carboplatin given that testing detects more hearing loss than subjective symptoms. We recommend at least one analysis 4 –5 years post-platinum-based chemotherapy and followup based on that evaluation and symptoms.[14]
- Men who have moderate or moderately severe hearing loss (by American Speech-Hearing Association criteria) should have regularly scheduled audiological followup.
- Hearing aids are recommended for severe to profound hearing loss but are often not used for a number of reasons, including financial.[18]

- Management of tinnitus is difficult but may include cognitive behavioral therapy, acoustic stimulation, and educational counselling.[19]

Nephrotoxicity

Nephrotoxicity from cisplatin is due to tubular cell injury/death, inflammation, and damage to the renal vasculature. This results in a reduction of the glomerular filtration rate (GFR), which may be permanent, and associated with magnesium wasting.[20,21]

Renal dysfunction is directly correlated with cisplatin dose and use of concomitant nephrotoxic drugs (e.g., NSAIDs). High-dose chemotherapy, dose-intense cisplatin, and cumulative cisplatin dose are associated with a higher risk of developing nephrotoxicity.[20,21] In a study of 1206 TCS with a median followup of 15.2 years, renal function decline was 11.3%, 15.4%, and 25.9% after three, four, or ≥5 chemotherapy cycles, respectively. Pre-existing chronic kidney disease was associated with higher risk of nephrotoxicity but age at diagnosis and resection of residual disease were not. There was a significant, although incomplete, recovery of renal function at one, three, and five years followup post-chemotherapy.[22]

Cisplatin-induced nephrotoxicity could exacerbate long-term exposure to latent circulating serum platinum, which, in turn, may worsen other late effects of treatment.[23]

Management recommendations

- Intravenous hydration during chemotherapy administration for patients with TC significantly reduces the incidence of acute cisplatin renal complications and should be used routinely.[24]
- Studies have shown conflicting results regarding the benefit of mannitol-forced diuresis to prevent cisplatin-induced nephrotoxicity. In general, this is not recommended for low/intermediate doses of cisplatin (<100 mg/m^2), as it may result in dehydration. [24]
- During chemotherapy, avoidance of nephrotoxic drugs, monitoring and replacing magnesium, and maintaining adequate hydration status (e.g., optimizing anti-emetics and encouraging oral intake of fluids) are important.[25]
- Post-chemotherapy, TCS who develop renal impairment should continue to avoid nephrotoxic drugs. These patients also require monitoring of renal function and blood pressure, and referral to nephrology should be considered.[26]

Lung toxicity

Bleomycin pulmonary toxicity (BPT) consists of pneumonitis, which may progress to pulmonary fibrosis. It can occur during or after chemotherapy.[27] Bleomycin binds to deoxyribonucleic acid (DNA) resulting in single- and double-stranded breaks through free radical formation in the presence of iron and oxygen.[28,29] The symptoms are often subtle and include dry cough, dyspnea, and occasionally fever.[27] There is no gold-standard predictive test for clinically significant BPT.[28,30] Incidence estimates vary from 7–12%, with a risk of death of 0–1.5%.[27,28,30,31] High-resolution computed tomography (CT) scans may show bilateral consolidation, ground glass opacities, and alveolar and interstitial infiltrates.[32]

A Danish study demonstrated that during BEP chemotherapy, diffusing capacity for carbon monoxide (DLCO) decreased significantly but returned to baseline during followup. The 15-year cumulative risk for late pulmonary adverse affects (pulmonary fibrosis, pneumonia, obstructive disease, and pulmonary embolism) was not increased in BEP-treated patients compared to clinical stage I patients on surveillance. Only 1/565 patients died from BPT. Prolonged impaired pulmonary function was associated with pulmonary surgery, pulmonary embolism, and International Germ Cell Cancer Collaborative Group (IGCCCG) poor risk group.[31]

Other potential BPT risk factors are cisplatin dose and age; however, these are more controversial.[31,33] In a Norwegian study, both cumulative cisplatin dose >850 mg and age >40 years at diagnosis showed a higher risk of restrictive pulmonary disease (odds ratio [OR] 3.1 and 4.0, respectfully) after a median 11.2-year followup.[33] Bleomycin is primarily renally excreted and reduced renal function may play a role in increased toxicity.[28] In a series of 835 TCS, estimated GFR <80 ml/min and age >40 years were risk factors for BPT; [28] however, the above-mentioned Danish study did not show any correlation between age or cisplatin dose to BPT. Also, a study by Thomsen et al similarly did not show any association between age >40 years and BPT.[34] Therefore, age should be considered a relative risk factor and the decision to omit bleomycin should be made on a more comprehensive clinical evaluation of the patient.[27,28,31,33]

Although often quoted as a concern, there is little medical literature regarding the safety of exposure to high concentrations of oxygen post-bleomycin for anesthesia or scuba diving. In a retrospective study of 77 TCS undergoing major surgery, 25% had postoperative oxygen saturation problems consisting of prolonged intubation, pulmonary edema, dyspnea, tachypnea, or desaturation requiring diuresis. The authors concluded that intravenous fluid management was the most significant factor affecting postoperative pulmonary morbidity and perioperative oxygen restriction was not necessary in TCS.[35] There are no published reports of BPT associated with scuba diving. Van Hulst et al proposed an algorithm to assess for fitness of scuba diving, at least 6–12 months after completion of bleomycin treatment, consisting of history and physical, pulmonary function tests (PFTs), exercise test with arterial blood gases, and high-resolution CT scans.[36]

Management recommendations

- Primary prevention of bleomycin pulmonary toxicity should be considered by selecting chemotherapy regimens that omit bleomycin for TCS age >40 years, impaired kidney function, pre-existing lung disease, significant smoking history, and planned pulmonary surgery.[27,28,31,37]
- TCS should be educated to stop smoking during and post-chemotherapy.
- Clinicians and TCS should be vigilant in monitoring for symptoms of BPT during and shortly after completing chemotherapy. Bleomycin should be held when signs or symptoms of BPT develop, and the chemotherapy regimen should be re-evaluated.[37]
- There is no strong evidence suggesting that pre- or post-chemotherapy changes in PFTs or DCLO are predictive of BPT. PFTs, however, may be useful as a baseline pre-therapy or as an investigation in symptomatic patients.[37]
- TCS who require surgery in the future must inform their anesthetist that they have had prior bleomycin therapy.[27,31]
- If TCS plan to scuba dive, they should wait at least 6–12 months post-bleomycin treatment, seek medical advice prior, and may require assessment by a dive medicine specialist.[38,39]

Raynaud's phenomenon

Raynaud's phenomenon is a condition in which spasm of small arteries causes episodes of reduced blood flow, typically in the fingers, and less commonly the toes. Symptoms may consist of numbness, pain, and pallor, followed by a red flash. It can last minutes to hours and in severe cases, can lead to skin sores or gangrene. Raynaud's phenomenon is primarily a dose-dependent bleomycin toxicity and less frequently associated with cisplatin and vinca-alkaloids. Raynaud's phenomenon can occur in up to 30–40% of men receiving chemotherapy (OR 2.9 for four cycles BEP compared with no chemotherapy).[8,40-43] It can be chronic but is only persistently bothersome in about 10% of TCS.[8] Concurrent smoking may increase the risk of developing Raynaud's phenomenon in TCS.[40]

Management recommendations

- Avoiding triggers of Raynaud's phenomenon, such as cold and keeping hands warm, could minimize the phenomenon, although there is little evidence to support this.[41]
- TCS should be educated on smoking cessation to prevent Raynaud's phenomenon.
- For TSC with persistent and bothersome symptoms of Raynaud's phenomenon, clinicians should consider a referral to a rheumatologist for pharmacological management with vasodilators, such as calcium channel blockers, selective serotonin reuptake inhibitors, and angiotensin receptor blockers. [41]

Cognitive impairment

Cognitive impairment, including problems with memory, executive functioning, attention, and/or processing speed, have been reported in survivors with non-central nervous system cancers, primarily post-chemotherapy.[44] This toxicity is particularly concerning for TCS, as most are young and cognitive function is crucial for independent activities of daily living, employment, social life, and well-being for many years to come.[45] Studies have demonstrated cognitive impairment in TCS; however, there are conflicting results as to the contribution of chemotherapy vs. other TC treatments.

To determine the prevalence of cognitive impairment in TCS compared to normative data, 72 TCS (36 post-orchiectomy ± radiation therapy and 36 postorchiectomy + chemotherapy) were evaluated 2–7 years post-treatment with a battery of neuropsychological tests to assess multiple cognitive domains (attention and working memory, processing speed, verbal fluency, learning and memory, and executive function). Over 60% of the TCS were classified as having cognitive impairment, significantly exceeding the expected 25% of the normal population; however, no association was found between treatment modality and cognitive impairment.[46]

In contrast, a study by Stouten-Kemperman et al examined cognitive impairment in TCS using questionnaires, neurocognitive tests, and 3T magnetic resonance imaging (MRI) at an average of 14 years post-treatment. The 28 chemotherapy-treated TCS demonstrated significantly lower performance scores compared to the 23 surgery-only TCS. Further, a significantly higher percentage of memory complaints were reported in the chemotherapy group (35.7 vs. 4.3%). Although chemotherapy affected white matter microstructure on imaging, this was unrelated to cognitive performance.[47]

Similarly, Wefel et al performed longitudinal neuropsychological assessment to determine if adjuvant chemotherapy was associated with cognitive impairment in TCS with non-seminoma histology treated with orchiectomy and surveillance (14 patients), low-exposure chemotherapy (≤3 cycles) (25 patients), or high-exposure chemotherapy (≥4 cycles) (30 patients). Compared to the orchiectomy group, TCS treated with chemotherapy had higher rates of cognitive decline at 12 months (surveillance=0%, low-exposure=52%, high-exposure= 67%) in a dose-dependent manner. Younger age was associated with greater incidence of overall cognitive decline at 12 months.[48]

Management recommendations

- Early identification of cognitive issues for TCS is important through history and formal neurocognitive testing if required.
- Physical activity, exercise programs, and yoga, along with cognitive behavioral therapy can be helpful to manage cognitive impairment in some patients.[44,49-51]
- There is limited evidence to recommend pharmacological management of cognitive impairment for patients with TCS.[44,51]

Cardiovascular disease, coronary artery disease, and metabolic syndrome

Cardiovascular disease (CVD) includes thromboembolic events, stroke, peripheral atherosclerotic disease, and coronary artery disease. These are serious long-term toxicities in TCS that can occur several years after treatment of TC.[27]

Older studies show an increased risk of CVD in TCS after chemotherapy.[52-55] More recent research provides a more nuanced message. Surveillance, Epidemiology, and End Results (SEER) data for non-seminomatous germ cell tumor (NSGCT) patients identified a substantially increased risk in cardiovascular (CV) deaths within one year of commencing chemotherapy (hazard ratio [HR] 4.86 in multivariable analysis, with increasing age and distant disease as independent risk factors), without apparent increase beyond one year.[56] A large Danish study looking only at modern chemotherapy noted an increased risk of myocardial infarction and CV death in the first year after initiation of chemotherapy (HR 6.3 and 7.4, respectively), no increased risk of either from years 1–10 post-chemotherapy, and a modest increase of each beyond 10 years (HR 1.4 and 1.6, respectively).[57] This study also pointed to an increased risk of stroke (HR 6.0) and venous thromboembolism (HR 24.7) in year 1. In addition to increased risk of metabolic syndrome in chemotherapy patients, there is mounting evidence of early or accelerated vascular aging, leading to increased arterial stiffness, thought to be secondary to direct cisplatin-related vascular damage.[58] At present, there is no clear management strategy for decreasing the risk of chemotherapy-induced early vascular aging.[58]

Metabolic syndrome occurs in the general population and is a major risk factor for CVD. Metabolic syndrome is defined as having ≥3 risk factors: hypertension, abdominal obesity, hypertriglyceridemia, decreased high-density lipoprotein (HDL), elevated cholesterol, and insulin resistance.[59]

A European study compared 255 TCS treated with orchiectomy ± chemotherapy (mean 7.8 years post-cancer therapy) to 360 healthy men. TCS had an increased risk of metabolic syndrome (OR 1.9) compared to healthy controls, and this risk was even higher for the subgroup treated with BEP chemotherapy for disseminated disease (OR 2.2). There was no increase in 10-year CV risk.[59]

A study of 486 North American TCS treated with first-line platinum-based chemotherapy (median 4.7 years post-completion of treatment) were compared to age-matched controls to identify clinical and genetic risk factors for metabolic syndrome.[60] TCS had a higher prevalence of hypertension (43 vs. 31%), increased low-density lipoprotein (LDL) (18 vs. 9%), and total cholesterol (26% vs. 11%) but, surprisingly, lower rates of decreased HDL (24 vs. 34%) and abdominal obesity (28 vs. 40%). On multivariate analysis, increased age at evaluation, low serum testosterone level, and elevated sICAM-1 (an adhesion molecule that plays a role in the inflammatory process of atherosclerosis) level were associated with metabolic syndrome. No significant difference in prevalence of metabolic syndrome between TCS and controls (21 vs. 22%) was found; however, this may be because the metabolic syndrome criteria developed for the general population do not reflect the full spectrum of metabolic abnormalities seen in TCS. These metabolic abnormalities related to cancer treatment-induced metabolic syndrome require further characterization. It is hypothesized that the main causes for metabolic abnormalities in cancer treatment-induced metabolic syndrome are hypogonadism and chemotherapy as opposed to sedentary behavior as in traditional metabolic syndrome.[60]

Management recommendations

- TCS should be screened and managed for hypertension, abnormal lipids, and diabetes, and educated on the risk of developing metabolic syndrome.[59-62]
- A "heart healthy" lifestyle is recommended for TCS, including maintenance of ideal body weight, avoidance of tobacco, and participation in regular exercise.[27,59-62]
- Testosterone replacement should be considered for TCS with symptomatic hypogonadism (refer to "Testosterone deficiency" section below); however, future research is required to assess the CV benefits and risks.[59]

Second malignant neoplasms

Population-based studies from national registries have shown an increased risk of solid and hematological second malignant neoplasms (SMNs) in TCS post-chemotherapy.[63-67] The most recent National Cancer Institute study using SEER data assessed 6340 TCS initially treated with chemotherapy (1973–2014). Solid SMN risk was increased by 1.26 compared to the general population.[63] Thirty-year cumulative incidence of solid SMN after chemotherapy was 10.1%. There was a 2.7-fold risk of leukemia driven by a 7.0-fold risk of acute myeloid leukemia 1–10 years after TC diagnosis. On subgroup analysis stratified by the extent of disease, only patients with distant metastases demonstrated a statistically significant higher risk of developing a SMN (OR 1.43), likely reflective of higher

doses of chemotherapy (i.e., 3–4 cycles compared to 1–2).[63] Other studies have found a similar dose association.[64,66] A recent publication demonstrated that the most commonly associated solid SMNs in the cisplatin era were head and neck, esophagus, lung, and bladder cancers.[67]

Management recommendations

- TCS should be educated regarding the risk of developing a SMN and should participate in standard cancer screening programs.[62,63]
- TCS should be educated regarding lifestyle and behavior modifications to reduce the risk of SMN, including smoking cessation, reduction of alcohol intake, healthy diet, and increased physical activity.[62,63,65]

2. Radiotherapy

A wealth of data now demonstrates the potential risk of long-term adverse effects of radiotherapy in TCS, particularly for patients with seminoma, where its use has largely been confined. Secondary malignant neoplasms are an established late toxicity associated with radiotherapy, while CVD and gastrointestinal toxicity are viewed as somewhat more controversial. Some toxicities, such as CVD and SMNs may increase when TCS receive both chemotherapy and radiotherapy.

Cardiovascular disease

Data are conflicting but multiple studies do suggest that TCS treated with radiotherapy are at significant greater risk of CV morbidity and mortality.[54,68-70] Estimated standardized cardiac mortality ratio for patients >15 years after radiotherapy was 1.80 (95% confidence interval [CI] 1.01–2.98) in one study.[68] In another single-center study, the estimated risk-ratio was 2.4 (95% CI 1.04–5.45) in those treated with infra-diaphragmatic radiotherapy as compared to those managed by surveillance.[54]

Second malignant neoplasms

Data demonstrate that radiotherapy is associated with a risk of developing SMN more than 10–15 years post-treatment. SMNs after radiotherapy for stage I seminoma have been documented in a number of studies.[70-74] The largest study in TCS combined 14 population-based registries and included 10 534 seminoma TCS treated with radiotherapy.[75] Compared with matched cohorts from corresponding registries, the overall relative risk of a non-testicular SMN was 2.0 (95% CI 1.8–2.2). This translated into a 36% cumulative 40-year risk of SMN compared with 23% in the normal population for a 35-year-old male at time of radiotherapy.[75] Similarly, in a Dutch population-based study of more than 2700 TCS, the SMN risk estimate was a 2.6-fold increase after subdiaphragmatic radiotherapy compared to surgery alone.[61] A recent population-based cohort of 5707 TCS showed an increased standardized mortality ratio (SMR) of 1.59 (95% CI 1.34–1.89) from SMN after radiotherapy and SMR of 3.24 (95% CI 2.17–4.83) after radiotherapy and platinum-based chemotherapy treatment. Radiation was associated with excess second cancer mortality of head and neck, stomach, liver, pancreas, and bladder.[67]

Gastrointestinal toxicity

There may be an increased risk of long-term gastrointestinal toxicity, in particular peptic ulceration and chronic diarrhea, among TCS treated with radiation;[76] however, these data stem from a time period when older radiotherapy techniques with higher doses of radiation were more common. Severe morbidity and death associated with such toxicities are seldom seen and risk estimates rely on population-based studies. A recent study examined non-cancer deaths in TCS and found a statistically significant increased SMR of 2.46 (95% CI 1.59–3.82) from all digestive diseases among TCS who received radiotherapy alone.[67] As with most population-based studies, this finding was based on a small number of events in a large population at risk.

Management recommendations

- TCS treated with radiation should be educated regarding the risk of developing a secondary malignant neoplasm and should participation in standard cancer screening programs.[61-63]
- TCS should be educated regarding lifestyle and behavior modifications to reduce the risk of SMN, including smoking cessation, reduction of alcohol intake, healthy diet, and increased physical activity.[62,63,65]
- TCS should be screened and managed for hypertension, abnormal lipids, and diabetes.[62]

3. Surgery

Surgery for TC primarily involves orchiectomy and retroperitoneal lymph node dissection (RPLND). Long-term complications of orchiectomy are included below under "Testosterone deficiency and fertility."

Retroperitoneal lymph node dissection

The most common long-term complication of RPLND is disordered ejaculation related to damage to or resection of the post-ganglionic sympathetic fibers extending from L1 to L4 to the hypogastric plexus.[77,78] Modern nerve-sparing techniques have dramatically decreased the long-term rates of ejaculatory disorders;[79] however, the technical feasibility of these approaches may be compromised in the post-

chemotherapy setting due to either the desmoplastic reaction that occurs after chemotherapy or the specific location of any residual masses.[80]

Rates of antegrade ejaculation with a nerve-sparing approach are as high as 99% in the primary RPLND setting and 76% in the post-chemotherapy RPLND setting;[79,81-83] however, these rates can be highly variable and dependent on the volume and expertise in the centers at which the surgery is performed.[79,83,84]

The contemporary approach to RPLND is through a transperitoneal midline laparotomy extending from the xiphoid process to a few centimeters below the umbilicus. Extraperitoneal, laparoscopic and robotic RPLND approaches have been used in an attempt to decrease morbidity; however, their use has been limited within the Canadian healthcare system.[85] The transperitoneal midline approach does leave patients with a large midline laparotomy scar and risk of ventral hernia of 1–4%.[79,84]

Scarring within the abdomen can lead to entrapment of the bowels but long-term rates of small bowel obstruction are <2% and cases of ureteral obstruction due to retroperitoneal fibrosis have been reported rarely.[79,86]

Management recommendations

- Nerve-sparing techniques for RPLND should be employed when possible.
- TCS having undergone open RPLND should be aware of the possibility of ventral hernia and rare risk of bowel entrapment.[79,84,86]

4. Testosterone deficiency and fertility

Testosterone deficiency

There is limited data on baseline testosterone levels in men diagnosed with TC prior to receiving any treatment,[87] although some patients may have pre-existing testosterone deficiency (TD).[88] Following orchiectomy alone, most patients retain normal serum testosterone levels, with one large cohort study showing low testosterone (total testosterone <10 nmol/L) in 11% of patients on surveillance for a median of 11.4 years.[89]

Compared to patients treated with orchiectomy alone, a meta-analysis found that the ORs for developing TD were 1.8 for conventional chemotherapy, 3.1 for non-conventional chemotherapy (>4 cycles or the combination of chemotherapy and radiation), and 1.6 for infra-diaphragmatic radiotherapy with followup of two months to 12 years.[90] The rate of TD in patients treated with chemotherapy or radiation increases over time post-treatment, particularly in older patients and those receiving multimodal therapy.[91]

Clinical signs and symptoms of TD include decreased libido, energy level, muscle strength, bone density, and lean body mass, in addition to depressive symptoms, impaired cognitive function, abdominal obesity, and anemia.[92,93] TD has also been associated with metabolic syndrome and CVD.[91,92,94]

Management recommendations

- For TCS, the presence of one or more signs or symptoms of TD should prompt evaluation of morning serum testosterone levels.[95,96]
- Current guidelines recommend testosterone replacement therapy only for men who have both signs or symptoms of TD AND low serum testosterone levels. In patients with symptoms of TD *without* low serum testosterone levels, alternate causes for the symptoms should be investigated (mood disorders, CVD, other medical conditions, cancer recurrence). For TCS started on testosterone replacement therapy, followup should be done to assess biochemical and clinical response.[95,97]
- Exogenous testosterone administration is contraindicated in TCS seeking future fertility due to the negative impacts testosterone replacement therapy can have on sperm production.[96,98]
- In men with symptoms of TD who wish to preserve future fertility, a referral to fertility specialist should be made for consideration of fertility-preserving therapies, such as selective estrogen receptor modulators, aromatase inhibitors, and human chorionic gonadotropin hormone.[93,96]

Fertility

TCS may have impaired fertility even prior to initiation of any treatment, with up to 50% having abnormal semen parameters.[99-101] and up to 24% having azoospermia.[102] The impact of orchiectomy on semen parameters is not well-defined, with some studies demonstrating worse semen parameters or even azoospermia after surgery,[103] while others demonstrate improvement after unilateral orchiectomy in patients on surveillance protocols.[104]

RPLND is associated with reduced fertility rates, although these impacts can be largely mitigated with the use of modern surgical techniques, such as nerve-sparing surgery. The fertility rate of TCS undergoing nerve-sparing RPLND was 62% vs. 37% in TCS who had non-nerve-sparing RPLND.[105]

Chemotherapy can negatively affect semen quality, although the severity depends on the specific treatment regimen.[106] The impacts of chemotherapy are lower with carboplatin vs. cisplatin[102,106-108] and single-dose adjuvant chemotherapy regimens,[102,109] and higher with more treatment cycles, higher cumulative doses, and use of alkylating agents.[102,106,110,111] In patients treated with platinum-based chemotherapy, 20% develop azoospermia at one year, with recovery of some spermatogenesis in 48% and 80% of patients at two and five years, respectively.[106,108,111]

The negative impact of radiation on spermatogenesis is dose dependent. This impact is highest with direct testicular radiation[106] but is much lower for men receiving adjuvant retroperitoneal radiation with gonadal shielding.[106] Both chemotherapy and radiation are associated with an increased risk of sperm aneuploidy and sperm DNA fragmentation for up to 24 months.[102,112]

Management recommendations

- The risk of infertility and fertility preservation should be discussed with all patients with TC prior to any treatment.
- Fertility preservation should be offered to all men presenting with TC, including teenagers and younger men whose desire for future fertility may be years or decades to come.[102,106,113]
- Cryopreservation of sperm remains the mainstay of fertility preservation prior to chemotherapy, radiation, and RPLND. [102,106,113]
- A discussion of cryopreservation prior to orchiectomy is also recommended, even though there is no standard on the optimal timing.[102,106] Advantages of cryopreservation pre-orchiectomy are: 1) to capture sperm in the approximately 10% men that will become azoospermic following orchiectomy;[103] and 2) to identify men who are already azoospermic prior to orchiectomy so that they can be appropriately counselled and be offered the option of surgical sperm retrieval from the orchiectomy specimen at the time of surgery. In addition, they should be offered to repeat cryopreservation attempts following surgery, as a small percentage of man may show return of sperm to the ejaculate following orchiectomy. Disadvantages of offering cryopreservation pre- orchiectomy include cost, potential delay in scheduling surgery, and overtreatment, as most TCS will remain fertile following orchiectomy, particularly if they undergo surveillance only.
- TCS who remain azoospermic after chemotherapy or radiation should be referred to a fertility specialist for consultation. Microdissection testicular sperm extraction in men remaining azoospermic can have a sperm retrieval rate of approximately 50% and can be offered to men who have not had cryopreservation prior to cancer treatment.[102,106,114]
- TCS and their partners should be educated that despite the risk of infertility associated with cancer therapy, they could still remain fertile and should use contraception during and post-treatment if they wish to avoid pregnancy.
- While there is no proof of higher rates of birth defects in the offspring of men treated with chemotherapy or radiation, it is recommended that men delay use of their own sperm for 12–24 months after completing chemotherapy and/or radiation.[102] During that time period, they may pursue assisted reproductive technologies using cryopreserved sperm obtained pre-treatment.[106]

5. Psychosocial issues

Quality of life

Cross-sectional evaluations of TCS would indicate QoL to be similar to age-matched controls.[115,116] Nonetheless, unique changes to QoL may occur in this population of men and persist for many years. Lack of employment and disease comorbidities are strong determinants of TCS QoL.[117] A large review of the literature involving over 1400 TCS, managed with a variety of cancer therapies, detected a small but measurable difference compared to age-matched controls with respect to more bodily pain, less vitality, and poorer social functioning.[116] Accordingly, QoL scores do not seem to be affected by the choice of treatment but rather the presence of treatment side effects. Beyond this direct relationship between side effects and QoL, there is concern that current QoL assessments lack the sensitivity to capture the complexity of QoL sequelae experienced by TCS.[116,118,119] Most TCS are diagnosed and treated during a life stage critical to the development of their autonomy and self-concept;[120] however, most studies to date report on older TCS with few studies explicating the adolescent and young adult TCS experience.[121] Having a stronger understanding of how TC may impede optimal progression through this critical life stage is imperative to mitigating potential long-term negative QoL effects.

Management recommendations

- Regular and ongoing QoL assessment to monitor and respond to potential long-term impacts on QoL should be performed for TCS. The QoL instrument employed should minimally assess work/education, psychological, relationship, fatigue, sexual, body image, and fertility domains (e.g., European Organization for. Research and Treatment of Cancer Quality of Life Questionnaire-Testicular Cancer [EORTC QLQ-TC26]).[122]

Psychological distress

TCS report mild to moderate levels of psychological distress following diagnosis and into survivorship.[123-127] Compared to the general population, TCS exhibit increased severity, prevalence, and risk profile for anxiety and, potentially, depression.[123,126] Fear of recurrence is a prevalent and key feature of TCS psychological distress,[126,128,129] with upwards of 31% of TCS reporting moderate to high levels of fear of recurrence years after diagnosis and treatment.[129] At least one

unmet supportive care need is reported in 66% of TCS,[130] with increasing numbers of unmet needs associated with higher rates of anxiety, depression, and stress.

A recent population-based study revealed that use of mental health services by TCS is 25% higher than that of age-matched controls. The difference in mental health service use persisted over a median followup of 12 years.[131] Another population-based cohort of 5707 TCS showed an increased SMR of 1.65 (95% CI 1.01–2.69) from suicide in patients treated with platinum-based chemotherapy compared to the general population.[67] Similar to the QoL studies, there appears to be an association with previous treatment toxicities and anxiety, specifically the presence of physical symptoms.[123,132] Those with sexual problems, chronic fatigue, body image disturbances, and unmet supportive needs are also at risk for anxiety.[130,133-135] Although intervention research is scarce, the strongest evidence is associated with behavioral interventions, including those that target increasing physical activity.[136] Overall, patient engagement in psychosocial intervention is challenging in the TCS population, necessitating innovative models of care, such as virtual/digital care.[137-139]

Management recommendations

- For TCS, regular and ongoing distress screening should occur, combined with targeted assessment to ascertain the origin of distress (e.g., fear of recurrence, sexual health, body image) and to ensure appropriate referral for psychosocial intervention.

Fatigue

The prevalence of chronic fatigue is greater among TCS compared to the general population and is associated with a poorer QoL.[135,140] In followup studies, 16–17% of TCS reported fatigue at a median of 11–12 years after completion of primary treatment compared to 10% in the general population.[135,140] No relationship was found between chronic fatigue and treatment type or time since orchiectomy.[135,140] In a long-term study involving 812 TCS, chronic fatigue increased from 15% at survey I (1998–2002) to 27% at survey II (2007–2008). Analysis of survey II revealed that chronic fatigue was associated with higher levels of anxiety, depression, neurotoxicity, and lower levels of testosterone. Conversely, high levels of physical activity appeared to be protective.[141] Intervention studies support the role of physical activity in lessening chronic fatigue in affected cancer survivors and one study demonstrated the benefits of high-intensity physical training in TCS specifically.[142-145] Cognitive behavior therapy has also been found effective in decreasing fatigue severity and associated functional impairment and psychological distress.[146,147]

Management recommendations

- TCS should be screened for chronic fatigue.
- Interventions that promote physical activity and/or cognitive behavioral therapy should be offered for TCS experiencing chronic fatigue.

Sexual dysfunction and body image

TC treatment results in significant and persistent sexual dysfunction in 20–33% of TCS.[148,149] The sexual dysfunction is characterized by both physical and psychosocial sequelae negatively affecting patient QoL.[150,151] Physical sexual dysfunction includes delayed orgasm problems, ejaculatory failure, and erectile dysfunction.[148,151] Psychological sexual dysfunction comprises decreased sex drive, avoidance of sexual activity, reduced masculinity, lower sexual satisfaction, and increased sexual distress.[121,148,152] Studies of TCS have found up to 17% suffer from poor body image as a consequence of TC and its treatment, while up to one-third report feeling less attractive post-orchiectomy.[152,153] Poor body image is further associated with both reduced sexual enjoyment and erectile dysfunction.[152]

Specific to orchiectomy, satisfaction studies indicate that patients should be offered a testicular prosthesis.[154,155] The impact of TC treatment modalities on sexual function varies,[123,150,152,156,157] with a higher likelihood of erectile dysfunction associated with chemotherapy or radiotherapy.[121,158] Sexual medicine approaches to erectile dysfunction, including use of phosphodiesterase type 5 inhibitors, are likely to be effective in this population.[159] It is noteworthy that needs assessment research concludes that TCS lack information specific to their post-treatment impairment and how to access support services.[125,160,161]

Management recommendations

- Healthcare professionals should initiate discussion with TCS (and his partner, if coupled) describing the potential impact of TC treatment on sexual function.
- TCS should be screened for sexual dysfunction and have access to institution-based or community-based aftercare sexual healthcare services.

Relationships

Being in a relationship during a life-altering diagnosis may play a protective role and improve physical and emotional adjustment.[121,123,133,148,158] Partnered TCS report better sexual functioning, social support, and overall mental health compared to unpartnered TCS;[121,158] however, some couples' preexisting conflicts might worsen, which can lead to reduced relationship satisfaction.[158] Unpartnered TCS report higher levels of cancer-related stress, including concerns about how their diagnosis may affect future romantic relationships.[158,161]

Management recommendations

- Relationship status and quality should be assessed for TCS and, where appropriate, tailored counselling offered to patients/couples at risk for poor adjustment.

Return to work

Returning to work or school after the diagnosis and treatment of TC is an important milestone for TCS as they strive to get back to normal life[162,163] and can be important factors in the development of a sense of identity and in achieving independence.[164] TCS experiencing difficulties in return to work/school can suffer impairment in their early career trajectory and related financial burden.[165] Encouragingly, most TCS are able to return to work/school after cancer treatment;[164,166-170] however, there may be a need for a modified return to work/school schedule to allow for recovery from treatment side effects.[164] Occupational and educational support programs for return to work/school can be effective to help with re-entry and in negotiating appropriate accommodations.[171]

Management recommendations

- Screen for barriers to return to work/school early and identify TCS with a higher risk of lasting absence from work or school.
- Early referral to occupational and educational support programs should be initiated for those TCS at elevated risk

6. Cancer recurrence and contralateral testicular cancer

TCS require ongoing followup for relapse either as part of their primary surveillance or after completion of therapy. Monitoring consists of physical examination, history, imaging, and tumor markers. Several of the cooperative groups have published specific scheduled recommendations.[172,173] If TC does relapse, it usually occurs in the first few years after treatment; however, late recurrences may occur.

Patients with unilateral TC are at increased risk of developing a contralateral testicular primary. The incidence in TCS is approximately 15 times higher than the general population rates and the 20-year cumulative incidence rate of 2–5%.[174-176] Patients diagnosed with their first TC at a younger age (<25 years) are at highest risk.[175,176]

Management recommendations

- TCS should be monitored for relapse as per a standardized followup guidelines with appropriate physical examination, history, imaging, and tumor markers based on presentation and management of initial disease.
- TCS should be educated regarding the risk and patterns of potential cancer recurrence based on initial stage and management, as this knowledge may help with earlier identification of recurrence and compliance with followup, and facilitate coping with their fear of recurrence.
- TCS should be educated on the small but real risk of contralateral TC and encouraged to continue testicular self-examination.

Conclusions

Curative treatment for TC has led to long-term survival but may also result in long-term toxicities that could impact QoL and shorten life expectancy. Physicians must be aware of these treatment-associated toxicities and long-term complications and should be vigilant for common signs and symptoms during routine followup (Table 1). TCS must also be educated regarding potential treatment complications and be encouraged to participate and self-advocate during ongoing monitoring. Long-term toxicity management should be addressed by a multidisciplinary team that includes allied healthcare professionals.

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Table 1. Long-term toxicity management and education for patients

Toxicity	Management strategies for physicians	Education for the patient
Chemotherapy		
Neurotoxicity	– Physiotherapy and occupational therapy assessment – Duloxetine	– Notify your physician if you experience tingling, numbness, and/or pain in your hands and feet – Check your legs regularly for sores if you are experiencing numbness or tingling in your feet
Ototoxicity	– Minimize noise exposure and avoidance of ototoxic drugs – Audiology assessment for 4–5 yrs post-chemotherapy or if hearing impairment – Cognitive behavioral therapy, acoustic stimulation, and educational counselling for bothersome tinnitus	– Notify your physician if you notice a decrease in your hearing or ringing in your ears – Try to avoid and protect your ears from loud noises
Nephrotoxicity	– Avoid nephrotoxic drugs – Monitor renal function and blood pressure – Refer to nephrologist if concerns of decreased renal function and/or persistent hypertension	– Stay well-hydrated – Ensure that your kidney function and blood pressure are checked regularly by your physician
Cognitive impairment	– Encourage regular physical activity – Assess for cognitive impairment	– Notify your physician if you notice a change in your memory, speech, ability to concentrate, or any change in your thinking
Raynaud's phenomenon	– Smoking cessation should be encouraged – Consider referring to rheumatologist for pharmacological management with vasodilators for patients with persistent and/or bothersome symptoms	– Avoiding triggers, such as cold – Keep hands and feet warm – Notify your physician if exposure to cold causes your finger and toes to change colors (white, blue, red), particularly if these episodes are prolonged and include tingling, numbness, or pain. – Notify your physician if there are sores that do not heal on your fingers or toes
Chemotherapy and radiotherapy		
Secondary malignant neoplasm	– Cancer screening according to the Canadian Task Force on Preventive Health Care – Counsel regarding lifestyle modification: smoking cessation, alcohol reduction, optimal nutrition, regular physical activity, maintenance of ideal body weight Website information: *https://canadiantaskforce.ca/* *https://www.aafp.org/family-physician/patient-care/clinical-recommendations.html*	– Notify your physician if you lose weight unexpectedly, have new pain, tiredness, shortness of breath, or loss of energy – Lead a healthy lifestyle: exercise regularly, do not smoke, maintain a healthy body weight – Ask for a dietitian consultation if you have questions regarding your diet or weight control
Cardiovascular disease (CVD) and metabolic syndrome	– Educate patients on the risk and symptoms of CVD – Screening for hypertension, lipid profile, and diabetes (often at a younger age than recommended in the general population), and manage accordingly – Counsel regarding lifestyle modification: smoking cessation, alcohol reduction, optimal nutrition, regular physical activity, maintenance of ideal body weight Website information: *https://canadiantaskforce.ca/* *https://www.aafp.org/family-physician/patient-care/clinical-recommendations.html*	– Lead a healthy lifestyle: exercise regularly, do not smoke, maintain your body weight – Ensure your blood pressure, blood sugar, and cholesterol level are monitored regularly by your physician – Notify your physician if you have a new headache, frequent urination, or weakness – Ask for a dietitian consultation if you have questions regarding your diet or weight control
Surgery		
Retroperitoneal lymph node dissection	– Monitor for ventral hernia – Refer appropriately for ejaculation loss	– Notify your physician if you have changes or bulging in the surgery scar – Notify your physician if you no longer ejaculate

Table 1 (cont'd). Long-term toxicity management and education for patients

Toxicity	Management strategies for physicians	Education for the patient
Testosterone deficiency and fertility		
Testosterone deficiency	– Testosterone therapy should be prescribed if symptoms of testosterone deficiency and low serum testosterone levels *Do not use testosterone therapy in patients that seek future fertility. Refer those patients to reproductive specialist for fertility-preserving therapies	– Notify your physician if you have decreased sex drive, energy level, muscle strength, or muscle bulk – Notify your physician if you have low mood, depressive symptoms, changes in thinking (memory, concentration), and abdominal obesity
Fertility	– Refer to fertility expert regarding infertility risk and fertility preservation options if indicated – Recommend patient delay the use of their own sperm 12–24 months following treatment	– Notify your physician if you are having difficulties fathering a child
Psychosocial issues		
Quality of life Psychological distress	– Asses for psychosocial symptoms and distress – Ascertain the origin of distress (e.g., fear of recurrence, sexual health, body image, etc.) – Refer to the psychosocial team or other appropriate health care specialists if intervention is needed	– Notify your physician if you have feelings of distress, anxiety, low mood, depression, poor body image, fear of cancer returning, tiredness, problems with sleep, relationship difficulties, and difficulties with return to work or school – Ask your physician to refer you for psychological help, relationship counselling, or occupational support, if required – Refer to Testicular Cancer Canada at *www.testicularcancer.ngo* for information, peer-to-peer support – Consult your physician if you have sexual dysfunction issues, such as low sex drive, poor body image, erectile dysfunction, ejaculatory failure, delayed orgasm, or no orgasm – Ask your physician to refer you for sexual counselling if required
Fatigue	– Encourage regular physical activity – Refer to cognitive behavioral therapy if persistent and/or bothersome fatigue	
Relationship issues	– Assess relationship distress – Refer to counselling if indicated	
Return to work/school	– Assess for barriers to retºurn to work or school – Refer to occupational and educational support programs if indicated	
Sexual dysfunction	– Inform the patient and partner on the potential impact of the treatment on the sexual dysfunction – Refer to sexual healthcare services if indicated	
Cancer recurrence and metachronous contralateral testicular cancer		
Cancer recurrence	– Monitor for relapse according to accepted followup guidelines – Monitoring should include physical examination, history, imaging, and tumor markers based on presentation and management of initial disease *https://uroweb.org/guideline/testicular-cancer/* *https://www.nccn.org/guidelines/*	– Notify your physician if you lose weight unexpectedly, have new pain, tiredness, shortness of breath, loss of energy – Attend clinic appointments and complete blood work and imaging tests
Metachronous contralateral testicular cancer	– Monitor for contralateral testicular primaries during followup visit	– Do testicular self-examination regularly – Notify your physician if you are worried about a new mass on the remaining testicle

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