Testicular Cancer Survivorship

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ABSTRACT

Testicular cancer (TC) is the most common cancer among men aged 18 to 39 years. It is highly curable, with a 10-year relative survival approaching 95% due to effective cisplatin-based chemotherapy. Given the increasing incidence of TC and improved survival, TC survivors (TCS) now account for approximately 4% of all US male cancer survivors. They have also become a valuable cohort for adult-onset cancer survivorship research, given their prolonged survival. Commensurately, long-term treatment-related complications have emerged as important survivorship issues. These late effects include life-threatening conditions, such as second malignant neoplasms and cardiovascular disease. Moreover, TCS can also experience hearing loss, tinnitus, neurotoxicity, nephrotoxicity, pulmonary toxicity, hypogonadism, infertility, anxiety, depression, cognitive impairment, and chronic cancer-related fatigue. Characterization of the number and severity of long-term adverse health outcomes among TCS remains critical to develop risk-stratified, evidence-based follow-up guidelines and to inform the development of preventive measures and interventions. In addition, an improved understanding of the long-term effects of TC treatment on mortality due to non-cancer causes and second malignant neoplasms remains paramount. Future research should focus on the continued development of large, well-characterized clinical cohorts of TCS for lifelong follow-up. These systematic, comprehensive approaches can provide the needed infrastructure for further investigation of long-term latency patterns of various medical and psychosocial morbidities and for more in-depth studies investigating associated etiopathogenetic pathways. Studies examining premature physiologic aging may also serve as new frontiers in TC survivorship research.

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Although the incidence of testicular cancer (TC) continues to increase globally,¹ TC mortality has declined,¹ attributable in large part to cisplatin-based chemotherapy.² Due to the 10-year relative survival rate approaching 95%,³ treatment-related complications, including second malignant neoplasms (SMNs), cardiovascular disease (CVD), ototoxicity, neurotoxicity, nephrotoxicity, pulmonary toxicity, hypogonadism, infertility, anxiety, depression, cognitive impairment, and chronic cancer-related fatigue, have emerged as critical survivorship issues in this young cohort of survivors.⁴ Platinum agents bind to and damage DNA, producing partly reactive platinum in the serum and platinum–DNA adducts in human organs, detectable up to 20 years after chemotherapy,⁵ and may contribute in part to several toxicities. This article reviews each of these toxicities, with recommended management detailed in supplemental eTable 1, available with this article at JNCCN.org.^{6–13}

Overview of TC Management

Approximately 70% of patients with stage I non-seminoma and 80% to 85% with stage I seminoma are cured with orchiectomy alone and 97% to 99% of those who experience relapse are ultimately cured with chemotherapy; thus, surveillance has emerged as an attractive management strategy for stage I TC.¹⁴ For stage I nonseminoma, adjuvant chemotherapy with 1 cycle of bleomycin/etoposide/cisplatin (BEPX1) and retroperitoneal lymph node dissection (RPLND) are other options, whereas adjuvant chemotherapy with 1 cycle of carboplatin and adjuvant radiotherapy (RT; 20 Gy) to the para-aortic lymph nodes are other options for stage I seminoma. Reductions in both RT fields (to include ipsilateral para-aortic lymphatics vs ipsilateral iliac and para-aortic lymphatics)¹⁵ and doses (20 vs 30 Gy)¹⁶ were adopted after randomized trials in stage I seminoma showed that these modifications caused no differences in 2-year TC relapse rates (3.0% vs 2.3%, respectively). For stage IIA and IIB seminoma, an RT dose of 30 to 35 Gy may be administered to the infradiaphragmatic area, which extends from the para-aortic region to the proximal

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ipsilateral iliac lymph nodes. For selected patients with stage IIB or IIC seminoma, EPX4 or BEPX3 are other options.¹⁴ Patients with good-risk metastatic TC according to the International Germ Cell Cancer Collaborative Group (IGCCCG) typically receive BEPX3 or EPX4, whereas those with intermediate- or high-risk disease receive BEPX4 or etoposide/ifosfamide/cisplatin (VIPX4).¹⁴ Approximately 20% of patients with TC in the United States require salvage therapy.¹⁷

Second Malignant Neoplasms

RT for TC is associated with significant risks of leukemia¹⁸ and solid cancers.^{19–22} In an international population-based study of 18,576 TCS,¹⁸ abdominal and pelvic RT were associated with a significant 3-fold risk of leukemia (n=22; median latency, 5 years). In another international population-based investigation of 40,576 10-year TCS,²⁰ SMN risks in locations typically within infradiaphragmatic RT fields were significantly higher (relative risk [RR], 2.7; n=212) compared with unexposed sites (RR, 1.6), and remained elevated for >35 years. Another analytic study²² of 5-year TCS (1959–1987; stage I/II and III/IV disease: 95.7% and 4.3%, respectively) reported a significant 5.9-fold risk of stomach cancer (n=87), with >20-fold risks ($P_{\text{trend}} < .001$) associated with gastric radiation doses of ≥ 50 Gy (8 cases vs 6 controls) vs <10 Gy (15 cases vs 49 controls). A multicenter hospital-based study by Groot et al²¹ reported that the hazard ratio (HR) of an infradiaphragmatic SMN increased by 8% per Gy of radiation dose administered ($P < .001$) compared with TCS who received no para-aortic RT. Groot et al²¹ reported that TCS had a lower risk of SMN after para-aortic radiation than after dog-leg radiation in a multivariable Cox analysis; however, this same study²¹ did not show a decline in solid SMN risk in patients treated in 1996 through 2007 compared with those treated in earlier decades, likely attributable to the relatively small number of patients with nonseminoma TC in the former period given high-dose RT, which is no longer used as primary treatment of nonseminoma.

Both cisplatin¹⁸ and etoposide²³ are associated with elevated risks of secondary leukemia in TCS. Alkylating agent-induced leukemia develops 5 to 8 years after therapy, usually preceded by myelodysplastic syndromes (MDS) with a karyotype involving long-arm deletions or monosomy of chromosomes 5 and 7. Topoisomerase II inhibitor-induced leukemia has a median onset of 2 to 3 years, usually presents without preceding MDS, and is often characterized by balanced translocations involving the *MLL* (11q23), *RARA* (17q21), and *RUNX1* (21q22) loci.²⁴ A series of >18,000 TCS (mean follow-up, 10.2 years) reported a significant dose-response relationship between cumulative cisplatin dose and leukemia risk

after adjusting for RT dose ($P_{\text{trend}} = .001$).¹⁸ A cumulative cisplatin dose of 650 mg was associated with a significant 3.2-fold risk of leukemia (n=16 excess leukemias), with larger doses (1,000 mg) associated with significant 6-fold risks. In a separate study,²³ the 5-year cumulative incidence of leukemia after cumulative etoposide doses of <2,000 and $\geq 2,000$ mg/m² was 0.5% and 2.0%, respectively. A Danish nationwide cohort study²⁵ of 5,190 men with TC (1984–2007) reported a significant 6.3-fold risk of myeloid leukemia after BEP ($P < .001$) compared with age-matched population-based controls (n=6 myeloid leukemia for the entire cohort).

Although most series^{20,26–28} of second solid cancers focused on TCS before the adoption of cisplatin-based chemotherapy, 3 recent studies^{21,25,29} reported significant associations of SMN risk in TCS given modern cisplatin-based chemotherapy. A US population-based investigation²⁹ of >12,000 TCS treated with cisplatin-based chemotherapy (1980–2008) reported an overall 1.4-fold significant risk of solid cancer (n=111) compared with surgery-only patients, with significant risks of kidney (standardized incidence ratio [SIR], 3.4; n=13), thyroid (SIR, 4.4; n=11) and soft tissue cancers (SIR, 7.5; n=10). In a subsequent Danish population-based study²⁵ of 5,190 TCS (1984–2007; median follow-up, 14.4 years), SMN risk after BEP was 1.7-fold higher (95% CI, 1.4–2.0) compared with surveillance, with a 20-year cumulative SMN incidence of 7.6% after BEP and a 1.6-fold significant excess mortality due to SMN. Similarly, a multicenter hospital-based Dutch investigation²¹ (median follow-up, 14.1 years) reported that TCS given cisplatin-based chemotherapy had a significant 2.4-fold risk of second solid cancers (n=151) compared with those not treated with chemotherapy. The same study²¹ reported significant linear dose-dependent increases in the risk of gastrointestinal cancers by 53% with each additional 100 mg/m² of platinum-containing chemotherapy ($P_{\text{trend}} < .001$), providing evidence of a potential dose-dependent relationship between platinum-based chemotherapy and solid tumors. The risk of gastrointestinal SMN was increased by 3.6-fold (n=21) and 5.0-fold (n=16) after 400 to 499 and ≥ 500 mg/m² of platinum-containing chemotherapy, respectively.

Cardiovascular Disease

Incidence

Compared with the general population or TCS under surveillance, those administered chemotherapy showed significantly increased RR for CVD, ranging from 1.4 to 7.1.^{26,30–32} The incidence of angina, myocardial infarction (MI), or sudden cardiac death was 7% in a British investigation³¹ of 390 TCS given chemotherapy in 1982 through 1992 (median follow-up, 9.7 years). The age-adjusted RR of

CVD was significantly increased by 2.6-fold when compared with TCS who had surgery alone. A Norwegian study³⁰ of 990 5-year survivors of TC (median follow-up, 19 years) reported that TCS treated with RT, chemotherapy, and combined RT/chemotherapy had significantly increased prevalence for antihypertensive medication use compared with age-matched male controls in the general population. Compared with controls, the odds ratio (OR) of diabetes was significantly higher in the RT (OR, 2.3) and RT/chemotherapy (OR, 3.9) groups.³⁰ Compared with surgery only, age-adjusted Cox regression analyses showed significant risks of atherosclerotic disease after RT (HR, 2.3), chemotherapy (HR, 2.6), and RT/chemotherapy (HR, 4.8) ($P_{\text{trend}}=.02$).³⁰ Furthermore, the risk of coronary artery disease was significantly increased 5.7-fold compared with surgery only, and MI risk was significantly increased 3.1-fold compared with age-matched male controls.³⁰ A multi-institution investigation³³ of 787 TCS (median age, 37.3 years; median follow-up, 4.2 years) showed no significant differences in Framingham Risk Score, reflecting similar CVD risks between EPX4, BEPX3, and BEPX4 in multivariable analysis, but TCS with lower levels of education and physical activity had significantly higher Framingham Risk Scores.

Three hypotheses have been proposed to elucidate the pathophysiology of CVD among TCS administered cisplatin-based chemotherapy.^{34,35} The direct vascular damage hypothesis postulates that cisplatin-based chemotherapy directly damages the vascular endothelium.³⁴ The indirect hypothesis proposes that cisplatin-based chemotherapy causes increased prevalence of CVD risk factors, resulting in CVD.³⁴ A multiple-hit hypothesis suggests that both chemotherapy-induced damage to vascular endothelium and chemotherapy-related increases in CVD risk factors may contribute to elevated CVD risks in TCS.³⁵ A multi-institutional study of 1,214 TCS after cisplatin-based chemotherapy reported that 26% and 3.9% of TCS have obesity, with respective body mass indexes of 30 to 39 and ≥ 40 kg/m², which is a significant CVD risk factor.³⁶

Mortality

TCS may have increased CVD mortality due to cancer treatments.³⁷ An international population-based investigation (1943–2002) reported a significant 1.6-fold risk of mortality due to circulatory disease (median follow-up, 10 years) among TCS who received chemotherapy after 1975.³⁷ Compared with TCS with primary testicular germ cell tumor (GCT), a SEER population-based study³⁸ showed that TCS with mediastinal or nonmediastinal extragonadal GCT had 4.5- and 2.8-fold significant risks of CVD mortality, respectively, likely attributable to increased numbers of chemotherapy cycles required for treatment. In contrast, another population-based study³⁹ of 15,006 TCS managed initially with chemotherapy or

surgery alone without RT (1980–2010) reported that significant CVD mortality after chemotherapy was confined to the first year after TC diagnosis (HR, 4.86); distant disease ($P<.05$) and older age at diagnosis ($P<.01$) were independent risk factors.

Raynaud Phenomenon

Raynaud phenomenon (RP) is primarily a clinical manifestation of bleomycin-associated vascular damage,^{8,40} although cisplatin is another chemotherapeutic agent that may contribute to RP.⁴¹ Approximately 18.7% to 39.0% of TCS develop RP within 4 to 12 months of chemotherapy, respectively, with a quarter of them experiencing symptoms up to 20 years.^{40,41} A multi-institutional investigation³⁶ of 1,214 TCS reported that 15.6%, 8.7%, and 9.1% experienced grade 1, 2, and 3 RP, respectively.

Ototoxicity

Cisplatin causes hearing loss, predominantly in the high frequency range, and tinnitus by damaging the outer hair cells of the cochlea.^{42,43} Almost 1 in 5 (18%) North American TCS reported severe to profound hearing loss as defined by the American Speech-Language-Hearing Association criteria in a multi-institutional study⁴² (median follow-up, 4.3 years). Supplemental eFigure 1 shows the severity of American Speech-Language-Hearing Association–defined hearing loss according to cumulative cisplatin dose. Increasing cumulative cisplatin dose was directly associated with hearing loss at 4, 6, 8, 10, and 12 kHz (P_{trend} for each $<.05$), with each 100 mg/m² increase in cumulative cisplatin dose resulting in a 3.2-dB impairment in age-adjusted overall hearing threshold (4–12 kHz; $P<.001$).⁴² Tinnitus (40% of TCS) was correlated with reduced hearing at each frequency ($P<.001$).⁴² Similarly, Boke-meyer et al⁴³ showed that 20% of TCS self-reported symptomatic ototoxicity after cisplatin-based chemotherapy, including tinnitus (59%), hearing loss (18%), or both (23%). Half of TCS who received >400 mg/m² of cumulative cisplatin dose self-reported tinnitus and hearing loss compared with one-fifth of those given ≤ 400 mg/m².⁴³ A Norwegian study⁴⁴ ($n=292$ cisplatin-treated TCS during 1980–1994) reported that increasing quartiles of residual serum platinum levels were directly associated with tinnitus ($P<.001$) and hearing impairment ($P=.04$). Other independent risk factors for ototoxicity included older age, a history of noise exposure, hypertension, impaired baseline hearing, and decreased baseline renal function.^{42,43}

Several prior investigations have identified significant associations of various single nucleotide polymorphisms (SNPs) with platinum-related ototoxicity, including megalin (rs2075252), *COMT* (rs9332377), *TPMT* (rs12201199), and *ACYP2* (rs1872328), as reviewed by

Wheeler et al.⁴⁵ Recently, *WFS1* (rs62283056)⁴⁵ was found to be associated with cisplatin-induced hearing loss in TCS. A variant near *OTOS* has been associated with cisplatin-induced tinnitus (rs7606353).⁴⁶

Neurotoxicity

Approximately 20% to 40% of TCS report peripheral neuropathy after cisplatin-based chemotherapy,^{41,47} with incidence directly related to cumulative cisplatin dose^{41,48} and possibly residual serum platinum levels.⁴⁴ A population-based investigation⁴¹ of Norwegian TCS (median time after TC treatment, 11 years) reported that 46%, 28%, and 10% of TCS experienced paresthesia after ≥ 5 cycles of cisplatin-based chemotherapy, 1 to 4 cycles of chemotherapy, and orchiectomy alone, respectively. Compared with TCS who had orchiectomy alone, those who received 1 to 4 cycles and ≥ 5 cycles of cisplatin-based chemotherapy had significant 2.0- and 3.9-fold risks of paresthesias of the hands, respectively, and significant 2.2- and 3.1-fold risks of paresthesias of the feet, respectively.⁴¹ RPLND was not an independent risk factor for peripheral neuropathy, but TCS who underwent RT had significant 1.5-fold risk for symptomatic paresthesias of the feet.⁴¹ Similarly, a population-based study⁴⁸ of Canadian TCS found a significant dose-response effect of chemotherapy on health system visits for neurotoxicity, as measured from 2 years before to 2 years after orchiectomy. Among TCS given 4, 3, and 1 to 2 cycles of chemotherapy, the proportion of patients with healthcare visits for neurotoxicity before and after treatment were as follows: 17% before vs 37% after; 17% before vs 28% after; and <13% before vs 20% after, respectively ($P=.013$).⁴⁸

Prior studies reported that certain germline SNPs of glutathione *S*-transferase (*GST*) *P1*⁴⁹ and *RPRD1B*⁵⁰ are associated with cisplatin-induced peripheral neuropathy in TCS. The *GSTP1*-GG genotype conferred a significantly lower risk of paresthesia in the fingers (OR, 0.46) and toes (OR, 0.42) than the *GSTP1*-AA and *GSTP1*-AG genotypes. A genome-wide analysis among TCS reported that lower expression levels of *RPRD1B* were significantly associated with cisplatin-induced peripheral neuropathy.⁵⁰ Expression or knockdown defects of *RPRD1B* disrupt DNA repair mechanisms critical for repairing cisplatin-induced damage.⁵¹

Nephrotoxicity

Cisplatin causes primarily proximal and distal renal tubular dysfunction, leading to acute and chronic nephrotoxicity.⁵² Two investigations^{53,54} reported a persistently decreased glomerular filtration rate (GFR) in TCS for years after the end of treatment compared with baseline renal function. More than 10 years after RT (n=18 TCS) or cisplatin-based chemotherapy (n=53 TCS), a Norwegian study⁵³ reported that GFRs decreased by 8% and 14%, respectively. Both older age at treatment

and higher cumulative cisplatin doses were associated with long-term impairment of renal function.⁵³ A Danish investigation⁵⁴ of 1,206 TC patients treated with BEP reported that GFRs in TCS with normal GFRs before treatment decreased by 11.3%, 15.4%, and 25.9% after 3, 4, and ≥ 5 cycles of BEP, but showed a significant, though incomplete rebound at 1-, 3-, and 5-year follow-up. The GFRs at 5-year follow-up for the 3 chemotherapy groups were approximately 94%, 89%, and 78% of the baseline GFRs, respectively. Treatment-related nephrotoxicity among long-term TCS may contribute in part to increases in incident CVD, including hypertension and MI.^{30,31} Renal function before and after cisplatin-based chemotherapy is an important determinant of long-term exposure to circulating serum platinum, which may be associated in part with several long-term effects of TC treatment.⁵⁵

Pulmonary Toxicity

Recent series^{56,57} reported no bleomycin-related deaths, likely attributable to bleomycin discontinuation at the earliest sign of pulmonary toxicity. Risk factors for late bleomycin-associated pulmonary toxicity include pulmonary surgery, tobacco use ≥ 20 pack years, and cumulative cisplatin dose >850 mg.⁵⁸ A Danish study⁵⁹ of 565 TCS given BEP (median follow-up, 16.1 years; 1984–2007) reported that the cumulative risk of all pulmonary disease was comparable to that of TCS with stage I disease who remained on surveillance, including pulmonary fibrosis (0.4% vs 0.2%), pulmonary embolism (0% vs 0.3%), pneumonia (2.6% vs 3.3%), obstructive disease (3.3% vs 2.8%), and pneumothorax (0.3% vs 0.4%).⁵⁹ Factors that negatively influenced pulmonary function test results included pulmonary surgery, pulmonary embolism, IGCCCG poor-risk TC, and smoking.⁵⁹

A Dutch study⁶⁰ suggests that the *HFE* gene, which is involved in iron metabolism and homeostasis, may be involved in bleomycin-induced pulmonary toxicity. Among 369 TCS given bleomycin and cisplatin (1978–2006), patients who were heterozygous and homozygous for the *H63D* variant of *HFE* had a higher frequency of bleomycin-induced toxicity (21% and 50%, respectively) compared with those with wild-type *HFE* (11%) ($P=.012$).⁶⁰ A prior Dutch investigation⁶¹ found no significant association of bleomycin-induced pneumonitis or changes in pulmonary function tests with the genetic polymorphism in *BLMH* (1450A>G) that encodes bleomycin hydrolase, which inactivates bleomycin.⁶²

Hypogonadism

Hypogonadism is directly associated with increased risks of metabolic syndrome, CVD risk factors, and CVD^{63–66} and may also contribute to depression, loss of energy, fertility problems, decreased sexual function, osteoporosis, and muscle weakness.^{67–73}

Table 1. Self-Reported AHOs

	n (%)	Treatment Regimen		
		EPX4 n (%)	BEPX3 n (%)	BEPX4 n (%)
Patients, N	952	294	364	170
Total number of AHOs				
Median (range)	2 (0–11)	2 (0–9)	2 (0–11)	2 (0–10)
0	194 (20.4)	64 (21.8)	83 (22.8)	25 (14.7)
1	209 (21.9)	68 (23.1)	71 (19.5)	42 (24.7)
2	191 (20.1)	61 (20.8)	82 (22.5)	27 (15.9)
3	143 (15.0)	48 (16.3)	48 (13.2)	25 (14.7)
4	96 (10.1)	28 (9.5)	38 (10.4)	18 (10.6)
≥5	119 (12.5)	25 (8.5)	42 (11.5)	33 (19.4)
Type of AHO ^a				
Tinnitus				
Yes	353 (37.1)	104 (35.4)	130 (35.7)	65 (38.2)
No ^b	599 (62.9)	190 (64.6)	234 (64.3)	105 (61.8)
Hearing impairment ^c				
Yes	300 (31.5)	95 (32.3)	109 (30.0)	56 (33.0)
No	652 (68.5)	199 (67.7)	255 (70.0)	114 (67.0)
Peripheral neuropathy ^d				
Yes	257 (27.0)	86 (29.2)	78 (21.4)	54 (31.8)
No	695 (73.0)	208 (70.8)	286 (78.6)	116 (68.2)
Peripheral neuropathy plus tinnitus and/or hearing issue				
Yes	156 (16.4)	49 (16.7)	48 (13.2)	31 (18.2)
No	796 (83.6)	245 (83.3)	316 (86.8)	139 (81.8)
Hypertension and on prescription medication				
Yes	110 (11.6)	35 (11.9)	45 (12.4)	15 (8.8)
No ^e	842 (88.4)	259 (88.1)	319 (87.6)	155 (91.2)
Hypercholesterolemia and on prescription medication				
Yes	100 (10.5)	32 (10.9)	31 (8.5)	20 (11.8)
No ^f	852 (89.5)	262 (89.1)	333 (91.5)	150 (88.2)
Cardiovascular disease ^g				
Yes	14 (1.5)	4 (1.4)	4 (1.1)	2 (1.2)
No ^h	938 (98.5)	290 (98.6)	360 (98.9)	168 (98.8)
Raynaud phenomenon				
Yes	178 (18.7)	34 (11.6)	78 (21.4)	49 (28.8)
No ⁱ	774 (81.3)	260 (88.4)	286 (78.6)	121 (71.2)
Peripheral vascular disease				
Yes	29 (3.0)	5 (1.7)	8 (2.2)	10 (5.9)
No ^j	923 (97.0)	289 (98.3)	356 (97.8)	160 (94.1)
Thromboembolic disease ^k				
Yes	5 (0.5)	0	0	4 (2.4)
No	947 (99.5)	294 (100)	364 (100)	166 (97.6)

(continued on next page)

Table 1. Self-Reported AHOs (cont.)

	n (%)	Treatment Regimen		
		EPX4 n (%)	BEPX3 n (%)	BEPX4 n (%)
Type of AHO (cont.)				
Renal disease				
Yes	25 (2.6)	7 (2.4)	6 (1.6)	7 (4.1)
No ^d	927 (97.4)	287 (97.6)	358 (98.4)	163 (95.9)
Diabetes and on prescription medication ^m				
Yes	30 (3.1)	9 (3.1)	10 (2.7)	3 (1.8)
No	922 (96.9)	285 (96.9)	354 (97.3)	167 (98.2)
Benign thyroid disease				
Yes	23 (2.4)	6 (2.0)	9 (2.5)	5 (2.9)
No ⁿ	929 (97.6)	288 (98.0)	355 (97.5)	165 (97.1)
Problems with balance/vertigo/dizziness ^o				
Yes	89 (9.3)	26 (8.8)	37 (10.2)	16 (9.4)
No	863 (90.7)	268 (91.2)	327 (89.8)	154 (90.6)
Hypogonadism with testosterone therapy ^p				
Yes	93 (9.9)	25 (8.6)	37 (10.3)	16 (9.5)
No	851 (90.1)	267 (91.4)	323 (89.7)	152 (90.5)
Erectile dysfunction				
Yes	115 (12.1)	28 (9.5)	39 (10.7)	34 (20.0)
No ^q	837 (87.9)	266 (90.5)	325 (89.3)	136 (80.0)
Psychotropic prescription medication for anxiety and/or depression ^r				
Yes	99 (10.4)	34 (11.6)	27 (7.4)	20 (11.8)
No	853 (89.6)	260 (88.4)	337 (92.6)	150 (88.2)

Abbreviations: AHO, adverse health outcome; BEP, bleomycin/etoposide/cisplatin; CAD, coronary artery disease; DVT, deep vein thrombosis; EP, etoposide/cisplatin; SCIN, Scale for Chemotherapy-Induced Long-Term Neurotoxicity.

^aP values were derived from the chi-square test comparing the proportions of AHOs reported by testicular cancer survivors in the EPX4 and BEPX3 treatment groups. P values were >.05 for all AHOs except Raynaud phenomenon ($P<.01$) and peripheral neuropathy ($P=.02$).

^bOutcome was not stated for 3 participants.

^cAmong all 952 participants, 270 (28.4%) reported problems hearing words, sounds, or language in crowds, 13 (1.4%) required a hearing aid, and 2 (0.2%) had complete deafness (questions derived from the hearing handicap inventory by Ventry and Weinstein¹¹¹); 109 (11.4%) had "quite a bit" or "very much" difficulty hearing, and 75 (7.9%) had "quite a bit" or "very much" reduced hearing (EORTC QLQ-CIPN20 questionnaire and SCIN).^{112,113} Outcome was not stated for 48 participants.

^dAmong all 952 participants, the number of patients reporting "quite a bit" or "very much" to the following questions are as follows: 123 (12.9%) tingling fingers or hands, 167 (17.5%) tingling toes or feet, 121 (12.7%) numbness in fingers or hands, 161 (16.9%) numbness in toes or feet, 34 (3.6%) shooting/burning pain in fingers or hands, 70 (7.4%) shooting/burning pain in toes or feet (EORTC QLQ-CIPN20 questionnaire)¹¹²; 134 (14.1%) pain and tingling in toes or feet, and 86 (9.0%) pain and tingling in hands or fingers (SCIN).¹¹³ Outcome was not stated for 16 participants.

^eOutcome was not stated for 11 participants.

^fOutcome was not stated for 3 participants.

^gIncludes CAD, heart failure, and cerebrovascular disease (categories not mutually exclusive and each category was counted as one AHO). Among all participants, 7 (0.7%) reported CAD (3 occurrences of CAD, 5 occurrences of angioplasty or stent, and 5 occurrences of heart attack or myocardial infarction); 1 reported heart failure; and 10 (1.0%) reported cerebrovascular disease (6 occurrences of transient ischemic attacks, 4 occurrences of stroke, and 1 occurrence of carotid artery surgery).

^hOutcome was not stated for 21 participants.

ⁱOutcome was not stated for 12 participants.

^jOutcome was not stated for 19 participants.

^kDVT and pulmonary embolism developed simultaneously in 3 participants and was counted as one thromboembolic event for each. The remaining 2 participants reported DVT only. Outcome was not stated for 19 participants.

^lOutcome was not stated for 26 participants.

^mAmong all participants, 13 (1.4%) and 22 (2.3%) reported use of insulin and oral antidiabetic agents, respectively (categories not mutually exclusive). Outcome was not stated for 15 participants.

ⁿOutcome was not stated for 19 participants.

^oOf the 89 patients, 47 reported persistent dizziness or vertigo and 63 reported symptoms of dizziness when standing up (categories not mutually exclusive). Outcome was not stated for 40 participants.

^pEight participants who underwent bilateral orchiectomy were excluded from this category.

^qOutcome was not stated for 7 participants.

^rParticipants could report >1 psychotropic medication. Psychotropic medications used by the 99 participants include aripiprazole (n=2), alprazolam (n=5), amphetamine-dextroamphetamine (n=9), bupropion (n=10), buspirone (n=1), citalopram (n=6), clonazepam (n=8), desvenlafaxine (n=1), diazepam (n=1), duloxetine (n=7), escitalopram (n=16), fluvoxamine (n=1), fluoxetine (n=4), hydroxyzine (n=1), lisdexamphetamine (n=4), lorazepam (n=6), methylphenidate (n=5), nortriptyline (n=2), olanzapine (n=2), paroxetine (n=7), trazodone (n=5), sertraline (n=11), and venlafaxine (n=7).

Modified from Fung C, Sesso HD, Williams AM, et al. Multi-institutional assessment of adverse health outcomes among North American testicular cancer survivors after modern cisplatin-based chemotherapy. J Clin Oncol 2017;35:1216–1217, with permission.

A multi-institutional investigation⁶³ reported that approximately 38.5% of North American TCS (median age, 38 years) had hypogonadism, defined by testosterone levels ≤ 300 ng/dL. Predominant causes of hypogonadism in long-term TCS include orchiectomy, testicular dysgenesis syndrome, RT, and chemotherapy.⁷⁴ When compared with orchiectomy alone, TCS administered standard cisplatin-based chemotherapy and infradiaphragmatic RT had significant 1.8- and 1.6-fold risks of hypogonadism, respectively, as defined by total testosterone levels less than the lower limit of the reference range or use of testosterone replacement therapy.⁷⁵ The intensity of TC treatment is directly associated with hypogonadism severity.^{74–79} An investigation of 244 long-term TCS reported that cumulative cisplatin doses of >400 mg/m² were associated with significant impairment of Leydig cell function compared with TCS who received no chemotherapy, whereas total cisplatin doses of ≤ 400 mg/m² showed no significant association.⁸⁰ Increased serum platinum levels had a significant association with hypogonadism⁵⁵ and high luteinizing hormone quartiles.⁴⁴

Infertility

Orchiectomy, postorchiectomy chemotherapy or RT, and testicular dysgenesis syndrome⁸¹ have been hypothesized as the predominant etiologies for azoospermia and oligospermia. Overall conception and paternity rates range from 49% to 88% among long-term TCS who intended to conceive a child after treatment, as reported in several studies (median follow-up, 7–12 years).^{79,82–84} Approximately half of the patients with newly diagnosed TC have low sperm counts (<20 million/mL), decreased motility indices ($<40\%$), and large percentages of abnormal sperm cells before receipt of any RT or chemotherapy.⁸⁵ A systematic review⁸⁶ reported that 6% to 24% of TCS are azoospermic and 50% oligozoospermic at TC diagnosis. Because spermatogonia are highly sensitive to RT,⁸⁷ scattered irradiation of the remaining testicle during abdominal RT can adversely affect short-term reproductive function of TCS.⁸⁸ Sperm concentrations nadir approximately 6 months after RT, but most patients ($>90\%$) recover sperm counts by 24 months after RT.⁸⁹ A Norwegian TCS study⁸⁸ (median follow-up, 11 years) confirmed that RT had no significant long-term negative effects on sperm counts when compared with a surgery-only cohort.

Cisplatin-based chemotherapy is also associated with risk of infertility.^{68,84,88} After 2, 3, and 4 cycles of cisplatin-based chemotherapy, 100%, 83%, and 76% of Norwegian TCS (median follow-up, 12 years) self-reported posttreatment paternity success, respectively ($P=.022$).⁸⁴ Another study demonstrated that the 15-year actuarial posttreatment paternity rate among TCS treated with a cumulative cisplatin dose >850 mg (48%) was significantly lower compared with the surveillance group and the group

that received a cumulative cisplatin dose ≤ 850 mg (92% and 60%, respectively; $P<.001$).⁶⁸ Sperm counts and serum level of inhibin B were significantly lower, whereas the serum follicle-stimulating hormone level was significantly higher in TCS who received a cumulative cisplatin dose >850 mg compared with those who received surgery only or ≤ 850 mg of cumulative cisplatin.⁸⁸ RPLND may cause injury to the retroperitoneal postganglionic sympathetic nerve, causing infertility unless cryopreserved sperm are banked presurgery. Rates of retrograde ejaculation after primary and postchemotherapy nerve-sparing RPLND were 1% to 9%^{90,91} and 21% to 29%,^{91,92} respectively.

Anxiety and Depression

Compared with age-adjusted men in the general population, a Norwegian investigation⁹³ (mean follow-up, 11.3 years) showed a higher prevalence of a Hospital Anxiety and Depression Scale–defined anxiety disorder among TCS (19.2% vs 13.5%; $P<.001$). Anxiety disorders were significantly associated with young age, peripheral neuropathy, economic difficulties, excess alcohol use, sexual concerns, and prior treatment of mental illness.⁹³ Another study (mean duration after diagnosis, 11.6 years) reported a 6.1% prevalence of clinically significant anxiety among German TCS, which was associated with younger age and shorter time from diagnosis.⁹⁴ A systematic review⁹⁵ reported that clinically significant anxiety was more prevalent among TCS ($\sim 20\%$) than the general population ($\sim 12.5\%$).

Figure 1. CBM score distribution among 1,214 participants in the Platinum Study. CBM score accounts for the number and severity of the following adverse health outcomes: peripheral sensory neuropathy, autonomic neuropathy, hearing loss/damage, tinnitus, Raynaud phenomenon, pain, kidney disease, hypercholesterolemia, hypertriglyceridemia, hypertension, diabetes, coronary artery disease, transient ischemic attack, stroke, peripheral artery disease, thromboembolic event, obesity, thyroid disease, anxiety/depression, erectile dysfunction, and hypogonadism.

Abbreviations: CBM, cumulative burden of morbidity; GCT, germ cell tumor. From Kerns SL, Fung C, Monahan PO, et al. Cumulative burden of morbidity among testicular cancer survivors after standard cisplatin-based chemotherapy: a multi-institutional study. *J Clin Oncol* 2018;36:1508, with permission.

Table 2. Multivariable Ordinal Logistic Regression^a of Factors Associated With CBM Scores

Variable	OR (95% CI)	P Value ^b
Age at evaluation (per 5 y) ^c	1.18 (1.10–1.26)	<.001
Time since chemotherapy completion, y		
<2	Ref	
2–5	0.91 (0.68–1.23)	.54
6–9	0.61 (0.42–0.89)	.010
≥10	0.55 (0.38–0.85)	.002
Race		
White	Ref	
Black/African American	1.56 (0.49–5.03)	.45
Asian	0.41 (0.23–0.72)	.002
Other	1.05 (0.63–1.76)	.84
Education		
College or postcollege graduate	Ref	
Less than college	1.44 (1.11–1.87)	.006
Current employment status		
Employed	Ref	
Unemployed	0.90 (0.55–1.47)	.66
Retired	1.10 (0.36–3.39)	.87
Disability leave	3.53 (1.57–7.95)	.002
Smoking status		
Never	Ref	
Current or former	1.28 (1.02–1.63)	.037

(continued)

Abbreviations: BEP, bleomycin/etoposide/cisplatin; CBM, cumulative burden of morbidity; EP, etoposide/cisplatin; MET, metabolic equivalent; OR, odds ratio; RPLND, retroperitoneal lymph node dissection; VIP, etoposide/ifosfamide/cisplatin.

^aORs and P values are from an adjusted model that includes all other variables listed in the table as well as enrollment center, with CBM score as the outcome (dependent) variable. The “very high” and “severe” categories were collapsed due to sparse data. Analysis includes 1,013 (83.4%) testicular cancer survivors with nonmissing data for all variables in the model.

^bBold indicates statistical significance at $P < .05$.

^cAge at diagnosis was not included in the model given the strong correlation with age at evaluation ($r = 0.81$), which was included.

Prior studies^{93,94,96–98} reported that the prevalence of depression among TCS ranges from 7.9% to 29.2%, but the extent to which TCS may experience significantly more depressive orders versus the general population is uncertain. Several factors are significantly associated with higher levels of depression, including feeling helpless/hopeless,⁹⁷ less social support,⁹⁷ a higher number of physical symptoms,⁹⁴ and having children.⁹⁴

Other Complications

Cisplatin-based chemotherapy may have neurotoxic effects, causing cognitive impairment, although underlying mechanisms have not yet been elucidated. Two studies of the same cohort of TCS reported that those

Table 2. Multivariable Ordinal Logistic Regression^a of Factors Associated With CBM Scores (cont.)

Variable	OR (95% CI)	P Value ^b
Vigorous physical activity (≥6 METs) ^d		
No	Ref	
Yes	0.68 (0.52–0.89)	.004
RPLND ^e		
No	Ref	
Yes	0.88 (0.69–1.12)	.31
Type of chemotherapy ^f		
BEPX3	Ref	
EPX4	1.09 (0.75–1.60)	.65
BEPX4	1.44 (1.04–1.98)	.028
VIPX4	1.96 (1.04–3.71)	.039

Abbreviations: BEP, bleomycin/etoposide/cisplatin; CBM, cumulative burden of morbidity; EP, etoposide/cisplatin; MET, metabolic equivalent; OR, odds ratio; RPLND, retroperitoneal lymph node dissection; VIP, etoposide/ifosfamide/cisplatin.

^aORs and P values are from an adjusted model that includes all other variables listed in the table as well as enrollment center, with CBM score as the outcome (dependent) variable. The “very high” and “severe” categories were collapsed due to sparse data. Analysis includes 1,013 (83.4%) testicular cancer survivors with nonmissing data for all variables in the model.

^bBold indicates statistical significance at $P < .05$.

^dExercise was assessed in this study using a validated questionnaire that asks participants to report their average time per week (over the past year) spent at each of 9 recreational activities: walking or hiking (including walking to work); jogging (slower than 10-min miles); running (10-min miles or faster); bicycling (including stationary bike); aerobic exercise or dance/exercise machines; lower intensity exercise/yoga/stretching/toning; tennis, squash or racquetball; lap swimming; and weight lifting/strength training. Each physical activity was assigned a MET value. MET values are a commonly used metric for describing the relative energy expenditure of a specific type of physical activity (1 MET = 1 kcal/kg/h, or the energy cost of sitting quietly). The MET values for each activity were then used to calculate MET hours/week for each participant, and these were grouped into categories of vigorous or nonvigorous physical activity following standard definitions.

^eRPLND was retained in the multivariable model to control for potential residual confounding, given its correlation with chemotherapy regimen ($P < .001$); approximately 34%, 55%, 66%, and 44% of TCS treated with BEPX3, EPX4, BEPX4, and VIPX4, respectively, had an RPLND.

^fDisease stage was not significantly associated with CBM score ($P = .48$), suggesting that increased scores after BEPX4 or VIPX4 were not explained by more advanced tumor status.

Modified from Kerns SL, Fung C, Monahan PO, et al. Cumulative burden of morbidity among testicular cancer survivors after standard cisplatin-based chemotherapy: a multi-institutional study. J Clin Oncol 2018;36:1509, with permission.

who received chemotherapy ($n = 22$) had altered global and local brain network properties between baseline and follow-up⁹⁹ and widespread brain gray matter reductions with prefrontal reductions on whole-brain MRI, compared with TCS who underwent surveillance ($n = 43$).¹⁰⁰ Despite these findings, the association of cisplatin-based chemotherapy with cognitive impairment in TCS remains unclear. The prevalence of cognitive impairment in patients with newly diagnosed TC prechemotherapy ranges from 46% to 58%, which is higher than in

normal populations ($P < .01$).^{101,102} Furthermore, although 3 investigations^{103–105} reported significant risks of cognitive impairment after chemotherapy ($n = 69–1,173$; median follow-up, 1–10 years), 3 other studies ($n = 70–112$ TCS; median follow-up, 1–3 years) reported no significant differences in performance on cognitive tests between various TC treatment cohorts (ie, surgery only vs chemotherapy).

Chronic cancer-related fatigue (CRF) is defined as a distressing, persistent physical, emotional, and/or cognitive tiredness/exhaustion with a duration of ≥ 6 months that is related to cancer and/or its treatment, is not proportional to recent activity, and interferes with usual functioning.¹⁰⁶ The prevalence of chronic CRF among Norwegian TCS was 17.1% compared with 9.7% in age-matched men in the general population ($P < .001$).¹⁰⁷ In another study of Norwegian TCS (1980–1994), the prevalence of chronic CRF increased significantly from 15% at survey I (1998–2002) to 27% at survey II (2007–2008).¹⁰⁸ Chronic CRF was significantly associated with peripheral neuropathy, RP, testosterone levels in the lowest quartile, low levels of physical activity, and anxiety/depression.¹⁰⁸ A phase II randomized controlled trial among Canadian TCS¹⁰⁹ reported that high-intensity training significantly improved CRF compared with usual care ($P = .003$), with its effects persisting at a 3-month follow-up. A meta-analysis of cancer survivors¹¹⁰ similarly reported that exercise and psychological interventions were more effective than pharmaceutical options in reducing CRF during and after cancer treatment.

AHOs and Cumulative Morbidity

Characterization of the number and severity of long-term adverse health outcomes (AHOs) among TCS is critically important for the development of risk-stratified, evidence-based follow-up guidelines. A multi-institutional study⁴⁰ among North American TCS (median age, 37 years) after cisplatin-based chemotherapy showed that 37.6% of TCS reported ≥ 3 AHOs with similar prevalence and types after treatment with EPX4 and BEPX3; exceptions were RP (11.6% vs 21.4%; $P < .01$), peripheral neuropathy (29.2% vs 21.4%; $P = .02$), and obesity (25.5% vs 33.0%; $P = .04$) (Table 1). A follow-up investigation³⁶ characterized the cumulative burden of morbidity (CBM) due to AHOs using a score that encompassed both AHO number and severity; approximately 20% of 1,214 TCS had a CBM score of high (14.8%) or very high/severe (3.9%), whereas almost 80% scored medium (29.7%) or low/very low (46.3%) (Figure 1). Higher CBM scores were significantly associated with VIPX4 (OR, 2.0) or BEPX4 (OR, 1.4 vs BEPX3), older attained age (OR, 1.2), current disability leave (OR, 3.5), less-than-college education (OR, 1.4), and current or former smoking status (OR, 1.3) (Table 2). This same study³⁶ identified 6 clusters of AHOs (chi-square $P < .001$): (1) hearing loss/damage, tinnitus (OR, 16.3); (2) hyperlipidemia, hypertension, diabetes (OR, 9.8); (3) neuropathy, pain, RP

(OR, 5.5); (4) cardiovascular and related conditions (OR, 5.0); (5) thyroid disease, erectile dysfunction (OR, 4.2); and (6) depression/anxiety, hypogonadism (OR, 2.8).

Long-Term Survival and Causes of Death

Understanding the long-term effects of TC treatment on mortality risks due to noncancer causes and SMN is important. A population-based investigation³⁷ of 38,907 1-year TCS in North America and Europe (1943–2002) reported that TCS had a significant 6% excess risk of mortality from noncancer causes compared with the general population; including 1.3- and 1.4-fold mortality from infections and digestive diseases, respectively. TCS given chemotherapy (with or without RT) in 1975 or later when cisplatin-based chemotherapy was introduced had significantly higher mortality from noncancer causes (standardized mortality ratio [SMR], 1.4), including circulatory diseases (SMR, 1.6), infections (SMR, 2.5), and respiratory disease (SMR, 2.5).³⁷ Another SEER Program study¹¹⁴ (1973–2009) reported that 15-year non-cancer-related and other-cancer mortality significantly increased with advancing stage and age at diagnosis among TCS using a competing-risks Poisson regression analysis (all $P \leq .001$); no data, however, were reported on the effect of treatment.

Conclusions

TCS account for approximately 4% of all male cancer survivors¹¹⁵ and have become a valuable cohort for research on adult-onset cancer survivorship, given their long-term survival.¹¹⁶ Future research should focus on developing longitudinal cohort studies to investigate the cumulative burden and latency trends of various medical and psychosocial morbidities, stratified by treatment type. By gathering comprehensive exposure and outcomes data, this type of investigation would provide information to help identify predictors of AHOs, with the ultimate goal to not only develop preventive and interventional strategies but also enable risk-adapted follow-up. Another critical research goal is to understand genetic variants that predispose TCS to acute and long-term AHOs. This type of elucidation of etiopathogenetic pathways would provide additional foundational support to develop risk-based, targeted prevention and intervention approaches. Finally, increasing evidence suggests that premature physiologic aging develops in survivors of childhood cancer after cytotoxic therapies, with hypothesized mechanisms including increased cellular senescence, reduced telomere length, epigenetic modifications, somatic mutations, and mitochondrial DNA infidelity.¹¹⁷ This area of research may also serve as a new frontier for TC survivorship.

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Testicular Cancer Survivorship

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eFigure 1: Severity of American Speech-Language-Hearing Association–Defined Hearing Loss According to Cumulative Cisplatin Dose Group

eTable 1: Recommended Management Options for Treatment-Related Complications

eFigure 1. Severity of American Speech-Language-Hearing Association–defined hearing loss according to cumulative cisplatin dose group. From Frisina RD, Wheeler HE, Fossa SD, et al. Comprehensive audiometric analysis of hearing impairment and tinnitus after cisplatin-based chemotherapy in survivors of adult-onset cancer. J Clin Oncol 2016;34:2717, with permission.

eTable 1. Recommended Management Options for Treatment-Related Complications	
Treatment-Related Complications	Recommended Management
Second malignant neoplasms	<ul style="list-style-type: none"> Healthcare providers should advise TCS to adhere to national cancer screening guidelines applicable to the general population⁶ Every effort should be made to reduce the amount of cytotoxic exposure needed to successfully treat the cancer
CVD	<ul style="list-style-type: none"> No established evidence-based CVD screening recommendations exist specifically for TCS Healthcare providers should counsel TCS about CVD risk-factor modification, advising adherence to guidelines⁷ for the general population
Raynaud phenomenon	<ul style="list-style-type: none"> Raynaud phenomenon–associated symptoms can be prevented by avoidance of cold and other aggravating factors, including smoking, sympathomimetic drugs, and selected treatments for either attention-deficit/hyperactivity disorder or migraine headaches⁸
Ototoxicity	<ul style="list-style-type: none"> Although there are no effective pharmacotherapies to prevent or treat cisplatin-related ototoxicity, TCS should minimize noise exposure and avoid other ototoxic agents.
Neurotoxicity	<ul style="list-style-type: none"> ASCO clinical practice guidelines for CIPN⁹ recommend duloxetine for management of pain, because there are no effective agents available to prevent or treat CIPN
Nephrotoxicity	<ul style="list-style-type: none"> During cisplatin-based chemotherapy, healthcare providers should avoid nephrotoxic drugs¹⁰ and administer intense hydration¹¹ to minimize the degree of renal damage
Pulmonary toxicity	<ul style="list-style-type: none"> Before initiation of any bleomycin-containing chemotherapy regimen, healthcare providers should perform a detailed patient history, including consideration of age, smoking status, and preexisting lung disease, and consider baseline pulmonary function Healthcare providers should also withhold bleomycin at the earliest clinical signs or symptoms of bleomycin-induced pulmonary toxicities during chemotherapy
Hypogonadism	<ul style="list-style-type: none"> Healthcare providers should routinely evaluate TCS for hypogonadism symptoms and assess hormonal status accordingly Decisions to administer testosterone replacement therapy should be based on clinical symptoms of hypogonadism, and referrals to endocrinologists should be considered for challenging cases¹⁰
Infertility	<ul style="list-style-type: none"> The ASCO clinical practice guideline for fertility preservation¹² recommends referral of patients with cancer to appropriate reproductive specialists if clinically indicated; sperm cryopreservation remains a standard fertility preservation practice before treatment initiation for interested patients with TC
Cognitive impairment	<ul style="list-style-type: none"> Because subjective cognitive complaints may reflect the effects of underlying anxiety and depression that are prevalent in TCS,¹³ implementation of effective coping strategies should be considered
Chronic CRT	<ul style="list-style-type: none"> Exercise and psychologic interventions should be considered

Abbreviations: CIPN, chemotherapy-induced peripheral neuropathy; CRT, cancer-related fatigue; CVD, cardiovascular disease; TC, testicular cancer; TCS, testicular cancer survivors.