Adverse Health Outcomes among U.S. Testicular Cancer Survivors after Cisplatin-Based Chemotherapy vs. Surgical Management

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ABSTRACT

We evaluated for the first time adverse health outcomes (AHOs) among U.S. testicular cancer survivors (TCS) given chemotherapy (n=381) vs. surgery-only patients (n=98) managed at a single institution, accounting for non-treatment-related risk factors to delineate chemotherapy's impact. Chemotherapy consisted largely of bleomycin-etoposide-cisplatin (BEP) administered in 3 or 4 cycles (BEPX3, n=235; BEPX4, n=82). Incidence of ≥3 AHOs was lowest in surgery-only TCS and increased with BEPX3, BEPX4 and other cisplatin-based regimens (12.2%, 40.8%, 52.5%, 54.8%; *P*<0.0001). Multivariate modeling assessed associations of risk factors and treatment with hearing impairment, tinnitus, peripheral neuropathy, and Raynaud phenomenon. Risk for each AHO significantly increased with both increasing chemotherapy burden (P<0.0001) and selected modifiable risk factors (P<0.05): hypertension (OR=2.40) and noise exposure (OR≥2.3) for hearing impairment; noise exposure for tinnitus (OR≥1.69); peripheral vascular disease for neuropathy (OR=8.72), and current smoking for Raynaud phenomenon (OR=2.41). Clinicians should manage modifiable risk factors for AHOs among TCS.

BRIEF COMMUNICATION

Testicular cancer (TC) is the most common cancer in men aged 18-39 years (1). Since cisplatin-based chemotherapy was introduced in the 1970s (2), the overall 5-year relative survival rate is over 95% (3). As a result, one in 600 U.S. men is a TC survivor (TCS), representing a growing need to evaluate the subsequent development of adverse health outcomes (AHOs). Nonetheless, the few single-institution investigations of U.S. TCS (4,5,6,78) have been limited in scope, generally either not addressing AHOs (5,7,8) or evaluating fewer than five conditions (6). Additionally, only Oh et al. (6) included a control group of TCS managed with surgical approaches alone, but examined only four AHOs.

In view of these gaps, our goal was study AHOs among U.S. TCS after contemporary cisplatin-based chemotherapy compared with a surgery-only cohort. The study was IRB-approved at Indiana University. Eligible TCS had a histologic/serological germ cell tumor (GCT) diagnosis at ≤55 years; all administered treatment/management was completed ≥1 year prior to enrollment. All participants were disease-free at routine follow-up and completed AHO-focused health questionnaires. AHO definitions and statistical methods are provided in Supplementary Methods. Two-sided P <0.05 defined statistical significance.

Overall, 479 patients were evaluated (Table 1)**.** Chemotherapy (n=381) consisted largely of 3 or 4 cycles of bleomycin, etoposide, and cisplatin (BEPX3, n=235; BEPX4, n=82), with 64 patients receiving other cisplatin-based chemotherapy regimens (OtherPlat). Median cumulative cisplatin doses were 300 mg/m^2 (BEPx3) and 400

mg/m^2 (BEPx4 and OtherPlat). 98 patients were managed only surgically. No patient received radiotherapy.

Median age at evaluation (overall=38.3 years) and median time since chemotherapy/surgery completion (overall=4.1 years) were similar between groups. Surgery-only patients had a smaller percentage of nonseminomatous histology compared to chemotherapy-treated TCS receiving BEPx3, BEPx4, and OtherPlat (43.3% vs. 77.6%, 92.6%, 77.0%, respectively; P<0.0001) and were more likely to have primary testicular GCT (100% vs. 88.4%, 67.9%, 63.9%, respectively; P<0.0001). Other clinical characteristics, physical examination results, and health behaviors were similar between groups, but more surgery-only TCS reported the absence of noise exposure than did chemotherapy-treated TCS (61.2% vs. 51.1%, 37.5%, 43.5%, respectively; P=0.0073). Median number of AHOs increased from 1 (range: 0-11) after surgery-only to 2 (range: 0-10) after BEPx3 and 3 (range:0-9) after BEPx4 and OtherPlat. Fewer TCS had ≥3 AHOs after surgery-only (12.2%) than after BEPX3 (40.8%), BEPX4 (52.5%), and OtherPlat (54.8%) (P<0.0001). Significant differences between surgery-only, BEPX3, BEPX4 and OtherPlat were observed for the following AHOs (each P<0.05): hearing impairment (11.5%, 36.0%, 41.8%, 45.9%); tinnitus (16.3%, 39.3%, 43.9%, and 50.0%); peripheral neuropathy (4.1%, 27.8%, 33.8%, 46.9%); hypertension (0%, 15.7%, 15.0%, 15.0%); Raynaud phenomenon (2.0%, 20.3%, 29.6%, 20.6%); and balance/vertigo/dizziness (6.1%, 11.0%, 19.5%, 14.3%). For cardiovascular disease (CVD), differences were of borderline significance (1.0%, 5.6%, 9.9%, 7.9%; P=0.0648).

Table 2 shows the results of multivariate modeling for selected AHOs. TCS given BEPX3, BEPX4, and OtherPlat experienced significant tinnitus excesses (OR=3.0, 3.71,

and 3.99 [P=0.0005 each]), with risk increased by 1.44-fold (P<0.0001) for each 100 mg/m^2 of cisplatin. Prior work-related (OR=1.69, P=0.0426), non-work-related (OR=2.1, P=0.0399) and cumulative (OR=2.13, P=0.0078) noise exposure were associated with significantly increased 2-fold tinnitus risks, but no interaction with cisplatin dose existed (P=0.5892).

Hearing loss increased significantly with increasing age at clinical evaluation (OR=1.16 per 5 years, P=0.0259), hypertension (OR=2.40, P=0.0101), and in each chemotherapy group (P<0.01 each). With each 100 mg/m^2 increase in cisplatin, hearing loss increased by 1.4-fold (P=0.0002). Work-related (OR=2.30, P=0.0033), non-work-related (OR=3.64, P=0.0009), and cumulative (OR=2.75, P=0.0012) noise exposure conferred increased hearing loss, but no interaction with cisplatin dose existed (P=0.3672).

Raynaud phenomenon was increased 12-fold (P=0.0009) and 21-fold (P<0.0001) following BEPx3 and BEPx4, respectively, and 12-fold after OtherPlat (P=0.0018). Risk increased with increasing bleomycin dose (OR=1.36 per 90,000 IU, P=0.0016). Current smoking was associated with significantly increased 2.4-fold risks.

Peripheral neuropathy was increased by 9-, 13-, and 18-fold, respectively, after BEPx3, BEPx4, and OtherPlat (P<0.0001 each). Increasing age at assessment (OR=1.23 per 5 years, P=0.0033), higher cumulative cisplatin dose (OR=1.75 per 100 mg/m^2, P<0.0001) and peripheral vascular disease (OR=8.72, P=0.0010) were associated with higher neuropathy risks.

Our study investigates for the first time the prevalence and risk factors for chemotherapy-related AHOs in U.S. TCS, with surgery-only patients as the control

group. We took into account previously identified AHO-specific risk factors, thus, furthering our understanding of the specific impact of chemotherapy. Risk of treatment-related AHOs increased proportionately with increasing chemotherapy burden. Importantly, modifiable risk factors were also associated with AHOs even when controlled for chemotherapy.

It is noteworthy that even after a short median follow-up, about 1 in 7 TCS in each chemotherapy group had hypertension compared with no cases after surgery-only (P=0.0007). A similar trend of borderline significance was noted for CVD.

Major strengths of our study are that all TCS were managed at one large, well-established U.S. institution. However, AHOs were largely self-reported without baseline data pre-therapy. Cross-sectional designs have potential inherent limitations and do not permit causal inference, although prospective follow-up is planned. Although the control group (surgery-only patients) had a lower disease burden initially than did chemotherapy-treated TCS, no TCS had active disease at the time of study enrollment. We cannot rule out, however, any potential influence of initial disease burden on AHO development.

Nonetheless, we provide for the first time estimates of the magnitude of AHOs associated with current chemotherapy in U.S. TCS compared with surgery-only patients. This may potentially guide clinical decision-making, such as recommending surgical approaches with primary retroperitoneal lymph node dissection (RPLND) in patients with low-bulk stage II disease in an attempt to avoid chemotherapy-related AHOs. Future studies should address AHO incidence when adjuvant chemotherapy is

applied in early stage disease, or in guiding decisions regarding primary RPLND vs. chemotherapy in early stage II disease.

The incidence of several AHOs (e.g., hypertension, CVD) will likely increase with the aging process (9). Thus, patients should be encouraged to adopt practices consistent with a healthy lifestyle and to avoid noise exposure, ototoxic drugs, and other factors that may further impact AHOs. Health care providers should diligently manage co-morbidities to minimize the development or exacerbation of AHOs.

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NOTES

Conflicts of Interest: The authors of this study do not have any conflicts of interest to disclose in the subject matter or materials discussed in this manuscript.

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Table 1: Clinical and Other Characteristics and Adverse Health Outcomes in Testicular Cancer Survivors by Type of Management

Characteristic	Treatment regimen					
	All patients	Surgery	BEPx3	BEPx4	Other chemotherapy[a]	P-Value[b]
Total	**N =479**	**N=98**	**N=235**	**N=82**	**N=64**	
			Clinical characteristic			
Age at diagnosis, years						
Median [range]	31.0 [10.0, 56.2]	33.9 [15.4, 56.2]	30.0 [10.0, 53.0]	27.0 [16.0, 49.0]	31.5 [13.0, 55.0]	0.0092
Age at clinical evaluation, years						
Median [range]	38.3 [18.3, 74.5]	39.0 [20.2, 62.3]	38.4 [18.3, 74.5]	36.3 [20.1, 71.3]	40.6 [20.8, 71.1]	0.2468
Category						0.3384
<20 years	3 (0.6%)	0	3 (1.3%)	0	0	
20-29 years	101 (21.1%)	20 (20.4%)	47 (20.0%)	21 (25.6%)	13 (20.3%)	
30-39 years	169 (35.3%)	35 (35.7%)	84 (35.7%)	32 (39.0%)	18 (28.1%)	
40-49 years	135 (28.2%)	30 (30.6%)	65 (27.7%)	23 (28.0%)	17 (26.6%)	
50+ years	71 (14.8%)	13 (13.3%)	36 (15.3%)	6 (7.3%)	16 (25.0%)	
Stage of germ cell tumor at diagnosis[c]						<0.0001
I	190 (40.9%)	88 (90.7%)	82 (36.1%)	6 (7.4%)	14 (23.3%)	
II	173 (37.2%)	9 (9.3%)	110 (48.5%)	32 (38.3%)	23 (38.3%)	
III	102 (21.9%)	0	35 (15.4%)	44 (54.3%)	23 (38.3%)	
Histologic type[d]						<0.0001
Seminoma	127 (27.0%)	55 (56.7%)	52 (22.4%)	6 (7.4%)	14 (23.0%)	
Nonseminoma	344 (73.0%)	42 (43.3%)	180 (77.6%)	75 (92.6%)	47 (77.0%)	
Site[e]						<0.0001
Testis	397 (84.1%)	98 (100.0%)	205 (88.4%)	55 (67.9%)	39 (63.9%)	
Extragonadal	75 (15.9%)	0	27 (11.6%)	26 (32.1%)	22 (36.1%)	

Cisplatin-based chemotherapy						**<0.0001**
BEP[f]	329 (68.7%)	0	235 (100.0%)	82 (100.0%)	12 (18.8%)	
EP[g]	20 (4.2%)	0	0	0	20 (31.3%)	
None	98 (20.5%)	98 (100.0%)	0	0	0	
Other[h]	32 (6.7%)	0	0	0	32 (50.0%)	
Cumulative dose of cisplatin, mg/m2						
Median [range]	300 [0, 700]	0 [0, 0]	300 [276, 334]	400 [370, 414]	400 [198, 700]	<0.0001
Category						<0.0001
0	98 (20.5%)	98 (100.0%)	0	0	0	
< 300	25 (5.2%)	0	16 (6.8%)	0	9 (14.1%)	
300	216 (45.1%)	0	212 (90.2%)	0	4 (6.3%)	
301-399	28 (5.8%)	0	7 (3.0%)	13 (15.9%)	8 (12.5%)	
400	95 (19.8%)	0	0	62 (75.6%)	33 (51.6%)	
>400	17 (3.5%)	0	0	7 (8.5%)	10 (15.6%)	
Cumulative dose of bleomycin, IU						
Median [range]	270,000 [0.0,630,000]	0.0 [0.0, 0.0]	270,000 [90,000, 270,000]	360,000 [0.0, 360,000]	0.0 [0.0, 630,000]	<0.0001
Category						<0.0001
0	143 (29.9%)	98 (100.0%)	0	2 (2.4%)	43 (67.2%)	
>0-180,000	27 (5.6%)	0	8 (3.4%)	8 (9.8%)	11 (17.2%)	
181,000-270,000	254 (53.0%)	0	227 (96.6%)	22 (26.8%)	5 (7.8%)	
271,000-360,000	52 (10.9%)	0	0	50 (61.0%)	2 (3.1%)	
360,000+	3 (0.6%)	0	0	0	3 (4.7%)	
Retroperitoneal lymph node dissection[i]						<0.0001
No	303 (64.3%)	80 (81.6%)	157 (68.6%)	30 (37.0%)	36 (57.1%)	
Yes	168 (35.7%)	18 (18.4%)	72 (31.4%)	51 (63.0%)	27 (42.9%)	

Time from chemotherapy/surgery to clinical evaluation, years						
Median [range]	4.1 [1.0, 34.9]	3.8 [1.0, 30.7]	4.3 [1.0, 25.5]	4.5 [1.0, 34.9]	3.8 [1.0, 25.1]	0.7518
Category						0.0081
<2 years	149 (31.1%)	24 (24.5%)	79 (33.6%)	23 (28.0%)	23 (35.9%)	
2-5 years	136 (28.4%)	44 (44.9%)	55 (23.4%)	23 (28.0%)	14 (21.9%)	
6-9 years	70 (14.6%)	15 (15.3%)	36 (15.3%)	13 (15.9%)	6 (9.4%)	
≥10 years	124 (25.9%)	15 (15.3%)	65 (27.7%)	23 (28.0%)	21 (32.8%)	
Sociodemographic Characteristic						
Race						0.1817
White	453 (95.0%)	94 (95.9%)	225 (96.2%)	73 (90.1%)	61 (95.3%)	
Non-white	24 (5.0%)	4 (4.1%)	9 (3.8%)	8 (9.9%)	3 (4.7%)	
Marital Status[j]						0.4641
Not married	163 (34.2%)	32 (32.7%)	78 (33.3%)	34 (41.5%)	19 (30.2%)	
Married/Living as married	314 (65.8%)	66 (67.3%)	156 (66.7%)	48 (58.5%)	44 (69.8%)	
Education[k]						0.2391
High school or less	85 (17.8%)	15 (15.3%)	35 (15.0%)	17 (20.7%)	18 (28.1%)	
Some college/College Graduate	296 (62.1%)	62 (63.3%)	146 (62.7%)	51 (62.2%)	37 (57.8%)	
Post-Graduate Level/Other	96 (20.1%)	21 (21.4%)	52 (22.3%)	14 (17.1%)	9 (14.1%)	
Noise Exposure[l]						0.0073
None	236 (49.9%)	60 (61.2%)	119 (51.1%)	30 (37.5%)	27 (43.5%)	
Work-related only	111 (23.5%)	22 (22.4%)	60 (25.8%)	17 (21.3%)	12 (19.4%)	
Non-work related only	41 (8.7%)	3 (3.1%)	21 (9.0%)	10 (12.5%)	7 (11.3%)	
Both	85 (18.0%)	13 (13.3%)	33 (14.2%)	23 (28.8%)	16 (25.8%)	
Physical Examination Results						
Body mass index, kg/m2[m]						
Median [range]	28.3 [18.0, 66.6]	28.0 [18.0, 54.3]	28.2 [19.0, 66.6]	28.2 [20.5, 46.1]	29.2 [20.0, 42.0]	0.6641
Category						0.5166
<25 kg/m2 (normal)	105 (22.2%)	24 (25.3%)	54 (23.2%)	16 (19.8%)	11 (17.2%)	
25-<30 kg/m2 (overweight)	194 (41.0%)	40 (42.1%)	95 (40.8%)	33 (40.7%)	26 (40.6%)	

30-<40 kg/m2 (obese)	148 (31.3%)	28 (29.5%)	66 (28.3%)	29 (35.8%)	25 (39.1%)	
≥40 kg/m2 (morbidly obese)	26 (5.5%)	3 (3.2%)	18 (7.7%)	3 (3.7%)	2 (3.1%)	
Health behavior						
Smoking status[n]						0.0938
Never smoker	284 (59.4%)	60 (61.2%)	150 (64.1%)	45 (54.9%)	29 (45.3%)	
Former smoker	147 (30.8%)	31 (31.6%)	59 (25.2%)	30 (36.6%)	27 (42.2%)	
Current smoker	47 (9.8%)	7 (7.1%)	25 (10.7%)	7 (8.5%)	8 (12.5%)	
Average number of alcoholic drinks in past year[o]						0.3286
Rarely/never	147 (30.8%)	30 (30.6%)	68 (29.1%)	29 (35.4%)	20 (31.3%)	
≤4/week	182 (38.1%)	46 (46.9%)	90 (38.5%)	23 (28.0%)	23 (35.9%)	
5/week-1/day	92 (19.2%)	16 (16.3%)	44 (18.8%)	20 (24.4%)	12 (18.8%)	
≥2 per day	57 (11.9%)	6 (6.1%)	32 (13.7%)	10 (12.2%)	9 (14.1%)	
Moderate-intensity exercise[p]						0.0759
Yes	450 (94.5%)	95 (97.9%)	221 (94.0%)	79 (96.3%)	55 (88.7%)	
No	26 (5.5%)	2 (2.1%)	14 (6.0%)	3 (3.7%)	7 (11.3%)	
Vigorous-intensity exercise[q]						0.0664
Yes	313 (65.8%)	69 (71.1%)	159 (67.7%)	53 (64.6%)	32 (51.6%)	
No	163 (34.2%)	28 (28.9%)	76 (32.3%)	29 (35.4%)	30 (48.4%)	
Adverse Health Outcomes						
Total number of adverse health outcomes						
Median [range]	2.0 [0.0, 11.0]	1.0 [0.0, 11.0]	2.0 [0.0, 10.0]	3.0 [0.0, 9.0]	3.0 [0.0, 9.0]	<0.0001
Category						<0.0001
0	82 (17.1%)	33 (33.7%)	41 (17.4%)	5 (6.1%)	3 (4.7%)	
1	115 (24.0%)	39 (39.8%)	47 (20.0%)	20 (24.4%)	9 (14.1%)	
2	96 (20.0%)	14 (14.3%)	51 (21.7%)	14 (17.1%)	17 (26.6%)	
3	66 (13.8%)	7 (7.1%)	32 (13.6%)	15 (18.3%)	12 (18.8%)	
4	43 (9.0%)	2 (2.0%)	25 (10.6%)	10 (12.2%)	6 (9.4%)	
5 or more	77 (16.1%)	3 (3.1%)	39 (16.6%)	18 (22.0%)	17 (26.6%)	

	Type of Adverse Health Outcome					
Tinnitus[r]						<0.0001
Yes	176 (36.8%)	16 (16.3%)	92 (39.3%)	36 (43.9%)	32 (50.0%)	
No	302 (63.2%)	82 (83.7%)	142 (60.7%)	46 (56.1%)	32 (50.0%)	
Hearing impairment[s]						<0.0001
Yes	152 (33.2%)	11 (11.5%)	80 (36.0%)	33 (41.8%)	28 (45.9%)	
No	306 (66.8%)	85 (88.5%)	142 (64.0%)	46 (58.2%)	33 (54.1%)	
Peripheral neuropathy[t]						<0.0001
Yes	126 (26.5%)	4 (4.1%)	65 (27.8%)	27 (33.8%)	30 (46.9%)	
No	349 (73.5%)	93 (95.9%)	169 (72.2%)	53 (66.3%)	34 (53.1%)	
Ototoxicity and peripheral neuropathy						<0.0001
Yes	80 (16.7%)	1 (1.0%)	41 (17.4%)	16 (19.5%)	22 (34.4%)	
No	399 (83.3%)	97 (99.0%)	194 (82.6%)	66 (80.5%)	42 (65.6%)	
Raynaud phenomenon[u]						<0.0001
Yes	86 (18.2%)	2 (2.0%)	47 (20.3%)	24 (29.6%)	13 (20.6%)	
No	387 (81.8%)	96 (98.0%)	184 (79.7%)	57 (70.4%)	50 (79.4%)	
Hypogonadism with testosterone therapy[v]						0.3004
Yes	52 (10.9%)	8 (8.2%)	28 (12.0%)	6 (7.4%)	10 (15.9%)	
No	423 (89.1%)	90 (91.8%)	205 (88.0%)	75 (92.6%)	53 (84.1%)	
Erectile dysfunction[w]						0.0548
Yes	67 (14.0%)	8 (8.2%)	30 (12.8%)	15 (18.5%)	14 (21.9%)	
No	410 (86.0%)	89 (91.8%)	205 (87.2%)	66 (81.5%)	50 (78.1%)	
Hypertension and on prescription medication[x]						0.0007
Yes	57 (12.2%)	0	36 (15.7%)	12 (15.0%)	9 (15.0%)	
No	410 (87.8%)	97 (100.0%)	194 (84.3%)	68 (85.0%)	51 (85.0%)	
Hypercholesterolemia and on prescription medication[y]						0.7902
Yes	58 (12.2%)	14 (14.3%)	25 (10.8%)	10 (12.2%)	9 (14.1%)	
No	418 (87.8%)	84 (85.7%)	207 (89.2%)	72 (87.8%)	55 (85.9%)	
Cardiovascular disease[z]						0.0648

Yes	27 (5.7%)	1 (1.0%)	13 (5.6%)	8 (9.9%)	5 (7.9%)	
No	448 (94.3%)	97 (99.0%)	220 (94.4%)	73 (90.1%)	58 (92.1%)	
Peripheral vascular disease[aa]						0.1063
Yes	19 (4.0%)	1 (1.0%)	8 (3.4%)	5 (6.2%)	5 (8.1%)	
No	455 (96.0%)	97 (99.0%)	225 (96.6%)	76 (93.8%)	57 (91.9%)	
Thromboembolic disease[bb]						
Yes	0	0	0	0	0	
No	474 (100.0%)	98 (100.0%)	233 (100.0%)	81 (100.0%)	62 (100.0%)	
Renal disease[cc]						0.1983
Yes	6 (1.3%)	0	4 (1.7%)	0	2 (3.3%)	
No	462 (98.7%)	97 (100.0%)	227 (98.3%)	80 (100.0%)	58 (96.7%)	
Diabetes and on prescription medication[dd]						0.4671
Yes	14 (3.0%)	5 (5.1%)	6 (2.6%)	1 (1.2%)	2 (3.2%)	
No	460 (97.0%)	93 (94.9%)	227 (97.4%)	80 (98.8%)	60 (96.8%)	
Thyroid disease[ee]						0.6403
Yes	5 (1.1%)	2 (2.0%)	2 (0.9%)	1 (1.2%)	0	
No	469 (98.9%)	96 (98.0%)	231 (99.1%)	80 (98.8%)	62 (100.0%)	
Problems with balance/vertigo/dizziness[ff]						0.0483
Yes	55 (11.8%)	6 (6.1%)	25 (11.0%)	15 (19.5%)	9 (14.3%)	
No	410 (88.2%)	92 (93.9%)	202 (89.0%)	62 (80.5%)	54 (85.7%)	
Psychotropic prescription medication for anxiety and/or depression[gg]						0.1420
Yes	58 (12.1%)	9 (9.2%)	25 (10.6%)	11 (13.4%)	13 (20.3%)	
No	421 (87.9%)	89 (90.8%)	210 (89.4%)	71 (86.6%)	51 (79.7%)	

Abbreviations: BEPx3, three cycles of bleomycin, etoposide, cisplatin; BEPx4, four cycles of bleomycin, etoposide, cisplatin; EPx4, four cycles of etoposide, cisplatin; RPLND, retroperitoneal lymph node dissection

[a] Patients in this category received BEP chemotherapy other than three or four cycles (n=12), EP chemotherapy (n=20), and other cisplatin-based regimens (n=32).
[b] P-value comparisons are based on Chi-square test for categorical variables and Kruskal-Wallis Test (normal approximation) for continuous variables. Missing values were not used in the calculation of the p-values.
[c] Includes 14 patients for whom the clinical stage was missing.
[d] Includes 8 participants with not-otherwise-specified germ cell tumor or unknown histology.
[e] Includes 7 patients with primary site not stated.

[f] The standard BEP chemotherapy cycle that all of our patients received consists of bleomycin 30,000 IU days 1,8,15; etoposide 100 mg/m^2 days 1 through 5; and cisplatin 20 mg/m^2 days 1 through 5. Includes 12 patients that received BEP other than three or four cycles.
[g] The standard dosing and standard EP schedule that all of our patients received consists of etoposide 100 mg/m^2 days 1 through 5 and cisplatin 20 mg/m^2 days 1 through 5.
[h] Includes 32 patients with other cisplatin-based regimens: 11 participants with VIP and 1 with VeIP. Each standard VIP chemotherapy cycle that our patients received consists of etoposide 75 mg/m^2 days 1 through 5, cisplatin 100 mg/m^2 days 1through 5, and ifosfamide 1,200 mg/m^2 days 1 through 5.
[i] Includes 8 patients for whom retroperitoneal lymph node dissection status was not available.
[j] Includes 2 participants with marital status not available.
[k] Includes 2 patients for whom education level was not available.
[l] Noise exposure data was not available for 6 patients.
[m] Includes 6 patients with body mass index information not available.
[n] Reported health behavior was not available for 1 patient.
[o] Reported health behavior was not available for 1 patient
[p] Reported health behavior was not available for 3 patients.
[q] Reported health behavior was not available for 3 patients.
[r] Category includes 1 patient for whom this outcome was not available.
[s] Category includes 21 patients for whom this outcome was not available.
[t] Category includes 4 patients for whom this outcome was not available.
[u] Category includes 6 patients for whom this outcome was not available.
[v] Category includes 4 patients that received bilateral orchiectomy that were not included in the comparison of hypogonadism, but were included elsewhere if the data was available.
[w] Category includes 2 patients for whom this outcome was not available.
[x] Category includes 12 patients for whom this outcome was not available.
[y] Category includes 3 patients for whom this outcome was not available.
[z] Category includes 4 patients for whom this outcome was not available. Includes coronary artery disease, heart failure, and cerebrovascular disease (categories not mutually exclusive and each category was counted as one AHO).
[aa] Category includes 5 patients for whom this outcome was not available.
[bb] Category includes 5 patients for whom this outcome was not available.
[cc] Category includes 11 patients for whom this outcome was not available.
[dd] Category includes 5 patients for whom this outcome was not available.
[ee] Category includes 5 patients for whom this outcome was not available.
[ff] Category includes 14 patients for whom this outcome was not available.
[gg] Participants could report more than one psychotropic medication.

Table 2: Logistic Multivariable Regression Analyses of Selected Adverse Health Outcomes (AHO) in 479 Testicular Cancer Survivors

Characteristic	Adverse Health Outcome							
	Tinnitus: Yes (Ref. = "No")		Hearing Loss: Yes (Ref. = "No")		Raynaud Phenomenon: Yes (Ref. = "No")		Peripheral Neuropathy: Yes (Ref. = "No")	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Clinical Characteristic								
Treatment		$P_{overall}$ =0.0011		$P_{overall}$ =0.0016		$P_{overall}$ =0.0014		$P_{overall}$ <0.0001
Surgery only	Ref.		Ref.		Ref.		Ref.	
BEPx3[a]	3.00 (1.61, 5.60)	0.0005	3.52 (1.71, 7.28)	0.0007	11.85 (2.74, 51.29)	0.0009	8.93 (3.04, 26.29)	<.0001
BEPx4	3.71 (1.77, 7.78)	0.0005	3.80 (1.63, 8.85)	0.0020	20.56 (4.49, 94.19)	<.0001	12.82 (4.01, 40.94)	<.0001
Other chemotherapy[b]	3.99 (1.83, 8.72)	0.0005	5.20 (2.14, 12.63)	0.0003	12.04 (2.52, 57.62)	0.0018	17.63 (5.47, 56.83)	<.0001
Age at clinical evaluation, per 5 years	1.11 (0.99, 1.26)	0.0764	1.16 (1.02, 1.33)	0.0259	1.02 (0.87, 1.18)	0.8260	1.23 (1.07, 1.41)	0.0033
Time since chemo-therapy completion, per 1 year	1.00 (0.96, 1.04)	0.9636	1.01 (0.97, 1.06)	0.4898	1.02 (0.97, 1.06)	0.5031	0.96 (0.92, 1)	0.0658
Cumulative dose of cisplatin, per 100 mg/m^2[c]	1.44 (1.22, 1.69)	<.0001	1.40 (1.17, 1.66)	0.0002	*	*	1.75 (1.41, 2.17)	<.0001
Health Behavior								
Smoking status		$P_{overall}$ =0.4704		$P_{overall}$ =0.6835		$P_{overall}$ =0.0402		$P_{overall}$ =0.5185
Never smoker	Ref		Ref		Ref		Ref	
Former smoker	0.83 (0.52, 1.31)	0.4261	0.81 (0.49, 1.33)	0.4002	0.93 (0.52, 1.67)	0.8146	1.27 (0.75, 2.12)	0.3740
Current smoker	1.27 (0.65, 2.48)	0.4800	0.85 (0.40, 1.78)	0.6655	2.41 (1.16, 5.02)	0.0183	1.43 (0.68, 2.99)	0.3485
Average number of alcoholic drinks in past year	*	*	*	*	*	*		$P_{overall}$ =0.6080
Rarely or never	*	*	*	*	*	*	Ref	
≤4 per week	*	*	*	*	*	*	1.08 (0.6, 1.94)	0.7885
5 per week to 1 daily	*	*	*	*	*	*	1.25 (0.63, 2.48)	0.5178
≥ 2 daily	*	*	*	*	*	*	1.61 (0.78, 3.34)	0.2017
AHO-Specific Risk Factor								
Cumulative dose of bleomycin, per 90,000 IU**Error! Bookmark not defined.**	*	*	*	*	1.36 (1.12, 1.65)	0.0016	*	*

Characteristic	Adverse Health Outcome							
	Tinnitus: Yes (Ref. = "No")		Hearing Loss: Yes (Ref. = "No")		Raynaud Phenomenon: Yes (Ref. = "No")		Peripheral Neuropathy: Yes (Ref. = "No")	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Noise exposure		$P_{overall}$ =0.0189		$P_{overall}$ =0.0003				
None	Ref		Ref		*	*	*	*
Work-related noise only	1.69 (1.02, 2.79)	0.0426	2.30 (1.32, 4.00)	0.0033	*	*	*	*
Non-work-related noise only	2.1 (1.03, 4.25)	0.0399	3.64 (1.70, 7.81)	0.0009	*	*	*	*
Both	2.13 (1.22, 3.72)	0.0078	2.75 (1.49, 5.06)	0.0012	*	*	*	*
Hypertension	1.08 (0.57, 2.02)	0.8175	2.40 (1.23, 4.67)	0.0101	1.13 (0.53, 2.39)	0.7529	1.23 (0.62, 2.43)	0.5468
Cardiovascular disease	1.33 (0.57, 3.13)	0.5118	1.05 (0.41, 2.68)	0.9245	0.58 (0.18, 1.91)	0.3720	0.95 (0.36, 2.48)	0.9086
Peripheral vascular disease	*	*	*	*	0.84 (0.22, 3.12)	0.7895	8.72 (2.41, 31.62)	0.0010
Diabetes and on prescription medication	*	*	*	*	2.23 (0.47, 10.66)	0.3164	1.53 (0.37, 6.35)	0.5614

Abbreviations: AHO=adverse health outcome; BEP=bleomycin, etoposide, cisplatin; CI=Confidence Interval; EP=etoposide, cisplatin; VIP=etoposide, cisplatin, ifosfamide; VeIP=vinblastine, ifosfamide, cisplatin; IU=international unit

[a] The standard BEP chemotherapy cycle that all of our patients received consists of bleomycin 30,000 IU days 1,8,15; etoposide 100 mg/m^2 days 1 through 5; and cisplatin 20 mg/m^2 days 1 through 5.

[b] Includes 32 patients with other cisplatin-based regimens: 11 participants with VIP and 1 with VeIP. Each standard VIP chemotherapy cycle that our patients received consists of etoposide 75 mg/m^2 days 1 through 5, cisplatin 100 mg/m^2 days 1through 5, and ifosfamide 1,200 mg/m^2 days 1 through 5.

[c] Reported results are calculated utilizing the statistical model that included the cumulative dose variable instead of the treatment group variable. Please refer to Supplementary Methods for details on statistical analysis modeling used.

* Variable not included in the analysis for the indicated AHO. Please refer to Supplemental Methods.