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ORIGINAL REPORT

Cardiovascular Disease Mortality After Chemotherapy or Surgery for Testicular Nonseminoma: A Population-Based Study

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ABSTRACT

Purpose
Increased risks of incident cardiovascular disease (CVD) in patients with testicular cancer (TC) given chemotherapy in European studies were largely restricted to long-term survivors and included patients from the 1960s. Few population-based investigations have quantified CVD mortality during, shortly after, and for two decades after TC diagnosis in the era of cisplatin-based chemotherapy.

Patients and Methods
Standardized mortality ratios (SMRs) for CVD and absolute excess risks (AERs; number of excess deaths per 10,000 person-years) were calculated for 15,006 patients with testicular nonseminoma reported to the population-based Surveillance, Epidemiology, and End Results program (1980 to 2010) who initially received chemotherapy (n = 6,909) or surgery (n = 8,097) without radiotherapy and accrued 60,065 and 81,227 person-years of follow-up, respectively. Multivariable modeling evaluated effects of age, treatment, extent of disease, and other factors on CVD mortality.

Results
Significantly increased CVD mortality occurred after chemotherapy (SMR, 1.36; 95% CI, 1.03 to 1.78; n = 54) but not surgery (SMR, 0.81; 95% CI, 0.60 to 1.07; n = 50). Significant excess deaths after chemotherapy were restricted to the first year after TC diagnosis (SMR, 5.31; AER, 13.90; n = 11) and included cerebrovascular disease (SMR, 21.72; AER, 7.43; n = 5) and heart disease (SMR, 3.45; AER, 6.64; n = 6). In multivariable analyses, increased CVD mortality after chemotherapy was confined to the first year after TC diagnosis (hazard ratio, 4.86; 95% CI, 1.25 to 32.08); distant disease ($P < .05$) and older age at diagnosis ($P < .01$) were independent risk factors.

Conclusion
This is the first population-based study, to our knowledge, to quantify short- and long-term CVD mortality after TC diagnosis. The increased short-term risk of CVD deaths should be further explored in analytic studies that enumerate incident events and can serve to develop comprehensive evidence-based approaches for risk stratification and application of preventive and interventional efforts.

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INTRODUCTION

Testicular cancer (TC) is the most common cancer among men age 18 to 39 years and also the most curable.[1] As a result of effective cisplatin-based chemotherapy introduced in the 1970s,[2] the 10-year relative survival for all patients with TC approaches 95%.[3,4] These remarkable successes, however, have been accompanied by potentially life-threatening complications, including cardiovascular disease (CVD).[5] Among survivors of TC (TCSs) given chemotherapy, European studies show that CVD incidence is significantly increased compared with the general population or with TCSs managed with surveillance, with risks ranging from 1.2- to 7-fold, based on five to 49 CVD events.[6-10] Most investigations,[8-10] however, limited the evaluation of incident CVD to long-term TCSs, with no assessment undertaken during or shortly after treatment, and some studies included patients treated in the 1960s,[9,10] before the use of cisplatin-based chemotherapy. In contrast, Dieckman et al[11] reported 25 CVD events during or within 6 weeks of cisplatin-based chemotherapy for TCSs (1996 to 2008) in a

survey of German cancer centers, including five patients with cerebral stroke or arterial thrombosis. However, reporting was voluntary, and risk was not quantified. Recently, O'Reilly et al[12] emphasized the growing literature on platinum-induced thromboembolic events but underscored the scarcity of data for TCS. Thus, the extent to which cisplatin-based chemotherapy for TC contributes to excess CVD incidence during, shortly afterward, and years after treatment remains unclear. Similarly, CVD types and the extent to which increased mortality might result have not been systematically examined. To quantify the relative and absolute risks of major types of CVD mortality in the entire period during and after TC diagnosis among patients given cisplatin-based chemotherapy, we studied 15,006 survivors of testicular nonseminoma managed initially with either chemotherapy or surgery alone without radiotherapy (1980 to 2010).

PATIENTS AND METHODS

Patients

We quantified CVD mortality among men diagnosed with histologically confirmed testicular nonseminoma as a first primary cancer from 1980 to 2010, when cisplatin-based chemotherapy became widely adopted.[13] All patients were initially managed without radiotherapy (n = 15,006) and reported to 16 population-based registries within the Surveillance, Epidemiology, and End Results (SEER) program. Patients with extragonadal germ cell tumors (GCT) were excluded. Because radiotherapy-associated CVD risk is well established[5,14] and radiation is typically not used to treat nonseminoma, we excluded 99 radiotherapy-treated patients.

The SEER program collects data on patient demographics, tumor characteristics, and initial treatment based on broad categories (ie, chemotherapy, radiotherapy, surgery) but does not include any details or any data on subsequent therapy. Patients were grouped into the following four categories based on age at TC diagnosis: less than 30, 30 to 39, 40 to 49, and ≥ 50 years. Attained age at study end was divided into less than 30, 30 to 39, 40 to 49, 50 to 59, and ≥ 60 years. Calendar year of TC diagnosis was categorized into 1980 to 1989, 1990 to 1999, and 2000 to 2010. Extent of disease was grouped into localized, regional, and distant disease. Patients were divided into the following two initial treatment categories: surgery alone (no radiotherapy) or chemotherapy (no radiotherapy). County education level, which is highly correlated with health literacy,[15] was quantified by percentage of county residents without a high school education and grouped into tertiles using prior methods.[16] Marital status was grouped into never married, married, and separated/divorced/widowed.

Person-years of observation were accrued starting at TC diagnosis and ending on the first of the following dates: date of death, date lost to follow-up, or date of study end (December 31, 2010). SEER examines all available sources to accurately establish cause of death (eg, autopsy reports, the National Death Index, and multiple state death registry files).[16] Each International Classification of Diseases code used to assign cause of death is tested for validity before implementation[17] and is grouped by SEER into 26 nonmalignant causes, which were applied here. CVD deaths included diseases of heart, cerebrovascular disease, hypertension without heart disease, atherosclerosis, aortic aneurysm and dissection, and other diseases of arteries, arterioles, and capillaries (International Classification of Diseases codes are itemized in Table 2).

Statistical Methods

Overall mortality risks from CVD and other nonmalignant causes were analyzed according to initial therapy and expressed as the standardized mortality ratio (SMR) with 95% CIs. Numbers of expected deaths for each category were estimated by multiplying general population mortality rates (available through the Centers for Disease Control and Prevention, National Center for Health Statistics),[18] as used previously,[19] for each cause of death by person-years at risk. SMR was calculated as the ratio of observed-to-expected deaths; 95% CIs were obtained using an approximation based on an assumption of a Poisson regression model for mortality; exact methods were used when observed numbers were ≤ 5.[20] Statistical significance was $P < .05$ (two-sided). Absolute excess risk (AER) was calculated as [(observed – expected deaths)/person-years of observation] × 10,000 to yield excess deaths per 10,000 person-years.

Cox regression was used to estimate unadjusted (univariable) and adjusted (multivariable) hazard ratios (HRs), along with 95% CIs and *P* values. The proportional hazards assumption for chemotherapy was found not to apply ($P = .04$) and was remedied by allowing for a separate time-dependent HR for chemotherapy within 0 to 1, 1 to 4, and ≥ 5 years after TC diagnosis. Although piecewise linear splines revealed insufficient evidence of nonlinearity in the log-hazard function, the continuous variables of age and calendar year at diagnosis were both discretized into groups. This did not influence the model fit but simplified the presentation of results and bounded the influence of any extreme observations.

RESULTS

Patient Characteristics

Of 15,006 eligible patients with testicular nonseminoma, 8,097 initially received surgery alone and 6,909 were initially given chemotherapy (Table 1). Both groups were similar in terms of age at diagnosis, attained age at study end, race, calendar year of diagnosis, county educational level, and marital status. However, men in the surgery cohort had predominantly localized disease (84.1%), whereas patients given chemotherapy tended to have regional (35.9%) or distant (35.1%) disease. Average follow-up in the surgery cohort was 10.0 years (median, 7.9 years), with 3,185, 2,061, and 1,215 patients observed for 10, 15, and 20 years, respectively. In the chemotherapy group, average follow-up was 8.7 years (median, 6.5 years), with 2,330, 1,436, and 806 men observed for 10, 15, and 20 years, respectively. Overall, the surgery and chemotherapy groups accrued 81,227 and 60,065 person-years of follow-up, respectively.

Cause-Specific Mortality

Comparisons with general population. Four hundred twenty-nine non–cancer-related deaths were observed among all patients with nonseminoma (Table 2). No increased risk followed surgery alone (SMR, 0.96; 95% CI, 0.84 to 1.11; n = 200), whereas significantly increased 60% excesses (SMR, 1.60; 95% CI, 1.40 to 1.82; n = 229) occurred after chemotherapy. The AER of all non–cancer-related deaths in the latter group was 14.29 per 10,000 person-years.

Of all non–cancer-related deaths, 24.2% were a result of CVD. Significantly increased risks were restricted to patients given chemotherapy (SMR, 1.36; 95% CI, 1.03 to 1.78; AER, 2.40; n = 54), with no excesses observed after surgery alone (SMR, 0.81; 95% CI, 0.60 to 1.70; n = 50). Significantly elevated CVD mortality after chemotherapy occurred only during the first year after nonseminoma diagnosis (SMR, 5.31; 95% CI, 2.65 to 9.51; AER, 13.90) and included cerebrovascular disease (SMR, 21.72; 95% CI, 7.05 to 50.69; AER, 7.43) and heart disease (SMR, 3.45; 95% CI, 1.27 to 7.52; AER, 6.64). Significant excess CVD deaths were not observed in subsequent intervals, although SMRs in the intervals of 1 to 4 and 5 to 9 years were 1.67 and 1.20, respectively. CVD mortality after chemotherapy was significantly increased in patients with attained ages of either less than 30 (SMR, 5.82) or 30 to 39 years (SMR, 2.32), likely reflecting low CVD

Table 1. Description of Population-Based Cohort of 15,006 Survivors of Testicular Nonseminoma

Characteristic	Survivors of Testicular Nonseminoma (N = 15,006)					
	Initial Surgery (no RT)*			Initial Chemotherapy (no RT)		
	No.	%	Person-Years of Follow-Up	No.	%	Person-Years of Follow-Up
Total	8,097	100	81,227	6,909	100	60,065
Age at diagnosis, years						
< 30	4,611	57.0	47,231	4,009	58.0	35,667
30-39	2,349	29.0	24,663	1,905	27.6	17,432
40-49	850	10.5	7,181	752	10.9	5,632
≥ 50	287	3.5	2,152	243	3.5	1,334
Attained age, years†						
< 30	1,877	23.2	7,501	1,892	27.4	6,078
30-39	2,326	28.7	16,378	2,055	29.7	14,036
40-49	2,130	26.3	26,399	1,728	25.0	19,999
50-59	1,349	16.7	23,321	931	13.5	14,711
≥ 60	415	5.1	7,628	303	4.4	5,241
Race						
White	7,616	94.1	77,244	6,471	93.7	56,583
Nonwhite	481	5.9	3,983	438	6.3	3,482
Calendar year of diagnosis						
1980-1989	1,288	15.9	29,935	1,028	14.9	20,267
1990-1999	1,849	22.8	26,768	1,501	21.7	20,076
2000-2010	4,960	61.3	24,524	4,380	63.4	19,722
Extent of disease						
Localized	6,808	84.1	67,392	1,939	28.1	16,162
Regional	1,038	12.8	11,718	2,483	35.9	25,302
Distant	174	2.1	1,180	2,427	35.1	17,739
Unknown	77	1.0	937	60	0.9	862
Initial surgery						
None	0	0	0	201	2.9	927
Orchiectomy ± other types of surgery	7,072	87.3	56,716	5,891	85.3	42,799
Surgery, NOS	1,025	12.7	24,511	817	11.8	16,339
County education level‡						
Education 1 (low)	1,792	22.1	21,577	1,518	22.0	15,761
Education 2 (medium)	3,609	44.6	39,295	2,966	42.9	27,808
Education 3 (high)	2,696	33.3	20,355	2,424	35.1	16,469
Unknown	0	0	0	1	0	27
Marital status§						
Never married	4,347	53.7	41,780	4,003	57.9	33,556
Married	3,096	38.2	33,942	2,385	34.5	22,670
Separated/divorced/widowed	312	3.9	3,013	358	5.2	2,739
Unknown	342‖	4.2	2,492	163	2.4	1,100

NOTE. Population includes 15,006 men diagnosed with testicular nonseminoma as a first primary cancer (International Classification of Diseases for Oncology, Third Edition, codes 9065, 9070 to 9073, 9080 to 9085, and 9100 to 9102) initially managed with chemotherapy (n = 6,909) or surgical approaches alone (n = 8,097). The sparse number of patients with testicular nonseminoma who were given RT (n = 99) precluded further evaluation.

Abbreviations: NOS, not otherwise specified; RT, radiotherapy.

*The Surveillance, Epidemiology, and End Results (SEER) program collects data with regard to general categories of initial treatment (eg, chemotherapy, radiation, surgery) but does not include any details or any data on subsequent therapy. Surgical procedures defined as initial by the SEER program are those that are part of the original treatment plan at diagnosis.

†Attained age was defined as the age of the patient at the time of death or end of follow-up.

‡County education level was categorized based on tertiles of distribution, as follows: education 1 represents the lowest level (composed of counties with ≥ 25% of men without a high school education); education 2 represents the medium level (counties with 15% to < 25% of men without a high school education); and education 3 represents the highest level (counties with < 15% of men without a high school education).

§The median ages at testicular cancer diagnosis of patients who were never married, married, and separated/divorced/widowed are 24.5, 33.2, and 36.3 years, respectively.

‖Includes one patient whose marital status was described as unmarried/domestic partner.

mortality at these ages in the general population. After chemotherapy, elevated risks of CVD deaths were observed among whites (SMR, 1.37) and nonwhites (SMR, 1.22). Significant excesses of CVD mortality occurred in patients with distant nonseminoma.

Cerebrovascular disease mortality accounted for 16.3% of all CVD deaths, with significantly elevated risks after chemotherapy (SMR, 2.40; 95% CI, 1.15 to 4.42; n = 10) but not surgery alone (SMR, 1.07; 95% CI, 0.43 to 2.20; n = 7). Five of 10 deaths after chemotherapy occurred within 1 year after TC diagnosis (range, 3 to 7 months), at a median age of 32 years (range, 29.3 to 65.5 years). In contrast, after initial surgery alone, cerebrovascular disease deaths occurred at a median of 13.7 years (range, 0.75 to 29.58

Table 2. Risk of Death As a Result of Cardiovascular Disease and Other Non–Cancer-Related Causes Compared With the Age-Adjusted US Male Population Among Patients With Testicular Nonseminoma by Initial Treatment

	Survivors of Testicular Nonseminoma (N = 15,006)							
	Surgery Only (no RT) (n = 8,097)				Chemotherapy (no RT) (n = 6,909)			
Cause of Death	No.	SMR	95% CI	AER	No.	SMR	95% CI	AER
Total noncancer causes of deaths	200	0.96	0.84 to 1.11	−0.92	229	1.60[a]	1.40 to 1.82	14.29
Total cardiovascular disease deaths[b]	50	0.81	0.60 to 1.07	−1.41	54	1.36[a]	1.03 to 1.78	2.40
Time since diagnosis of testicular nonseminoma, years								
< 1	2	0.75	0.09 to 2.72	−0.85	11[c]	5.31[a]	2.65 to 9.51	13.90
1-4	9	0.88	0.40 to 1.67	−0.47	12	1.67	0.86 to 2.92	2.48
5-9	9	0.72	0.33 to 1.36	−1.69	10	1.20	0.57 to 2.20	1.05
10-14	8	0.65	0.28 to 1.28	−3.33	7	0.92	0.37 to 1.90	−0.65
15-19	9	0.81	0.37 to 1.54	−2.58	8	1.18	0.51 to 2.33	2.22
≥ 20	13	1.03	0.55 to 1.75	0.52	6	0.79	0.29 to 1.71	−4.16
Age at diagnosis, years								
< 30	8	0.62	0.27 to 1.23	−1.03	15	1.74	0.97 to 2.87	1.79
30-39	17	0.87	0.51 to 1.40	−0.99	17	1.31	0.76 to 2.10	2.32
40-49	12	0.93	0.48 to 1.62	−1.26	11	1.03	0.51 to 1.84	0.57
≥ 50	13	0.80	0.43 to 1.37	−15.15	11	1.51	0.75 to 2.70	27.74
Attained age, years[d]								
< 30	1	0.81	0.02 to 4.50	−0.12	6	5.82[a]	2.14 to 12.67	2.97
30-39	3	0.47	0.10 to 1.37	−1.18	11	2.32[a]	1.16 to 4.15	2.92
40-49	16	0.91	0.52 to 1.48	−0.72	17	1.39	0.81 to 2.22	3.15
50-59	16	0.90	0.51 to 1.46	−2.17	13	1.06	0.57 to 1.82	1.35
≥ 60	14	0.76	0.41 to 1.27	−20.48	7	0.75	0.30 to 1.55	−17.12
Race								
White	47	0.80	0.59 to 1.06	−1.55	51	1.37[a]	1.02 to 1.81	2.46
Nonwhite	3	1.22	0.25 to 3.55	1.34	3	1.22	0.25 to 3.56	1.55
Calendar year of diagnosis								
1980-1989	25	0.75	0.48 to 1.10	−2.85	26	1.38	0.90 to 2.02	3.51
1990-1999	17	0.96	0.56 to 1.54	−0.27	12	0.96	0.49 to 1.67	−0.28
2000-2010	8	0.79	0.34 to 1.55	−0.89	16	1.97[a]	1.13 to 3.20	4.00
Extent of disease								
Localized	36	0.72[a]	0.50 to 0.99	−2.12	10	0.99	0.47 to 1.82	−0.07
Regional	11	1.18	0.59 to 2.11	1.43	23	1.33	0.84 to 2.00	2.27
Distant	3	2.50	0.52 to 7.32	15.27	20	1.74[a]	1.06 to 2.68	4.78
Unknown	0	0	0 to 5.73	−6.87	1	1.50	0.04 to 8.34	3.85
County education level								
Education 1 (low)	20	1.16	0.71 to 1.79	1.25	10	0.97	0.46 to 1.78	−0.22
Education 2 (medium)	20	0.63[a]	0.38 to 0.97	−3.05	33	1.66[a]	1.14 to 2.33	4.70
Education 3 (high)	10	0.82	0.39 to 1.51	−1.06	11	1.18	0.59 to 2.12	1.03
Unknown	0	0	NA	0	0	0	0 to 528.39	−2.57
Marital status								
Never married	17	1.08	0.63 to 1.73	0.30	20	1.73[a]	1.06 to 2.67	2.51
Married	25	0.62[a]	0.40 to 0.92	−4.45	29	1.19	0.80 to 1.71	2.02
Separated/divorced/widowed	5	1.21	0.39 to 2.82	2.87	4	1.44	0.39 to 3.68	4.45
Unknown	3	2.04	0.42 to 5.95	6.13	1	1.24	0.03 to 6.93	1.78
Type of cardiovascular disease death								
Diseases of heart	43[e]	0.83	0.60 to 1.12	−1.09	42[f]	1.25	0.90 to 1.70	1.42
Cerebrovascular diseases	7	1.07	0.43 to 2.20	0.05	10[g]	2.40[a]	1.15 to 4.42	0.97
Other diseases of arteries, arterioles, or capillaries	0	0	0 to 7.54	−0.06	2	6.51	0.79 to 23.53	0.28
Other non–cancer-related deaths								
Diabetes mellitus	6	0.99	0.36 to 2.14	−0.01	5	1.23	0.40 to 2.86	0.15
Septicemia	2	0.95	0.12 to 3.43	−0.01	10	7.14[a]	3.43 to 13.14	1.43
Other infectious and parasitic diseases including HIV	14	1.12	0.61 to 1.88	0.18	14	1.58	0.86 to 2.64	0.85
Chronic liver disease and cirrhosis	10	1.16	0.56 to 2.13	0.17	8	1.35	0.58 to 2.67	0.35
Nephritis, nephrotic syndrome, and nephrosis	3	1.44	0.30 to 4.22	0.11	2	1.48	0.18 to 5.33	0.11
Chronic obstructive pulmonary disease and allied conditions	5	0.86	0.28 to 2.00	−0.10	4	1.15	0.31 to 2.96	0.09
Pneumonia and influenza	4	1.29	0.35 to 3.29	0.11	6	3.05[a]	1.12 to 6.65	0.67
Alzheimer's disease	2	3.47	0.42 to 12.55	0.18	1	3.30	0.08 to 18.37	0.12
Congenital anomalies	3	2.26	0.47 to 6.60	0.21	0	0	0 to 4.29	−0.14

(continued on following page)

Table 2. Risk of Death as a Result of Cardiovascular Disease and Other Non–Cancer-Related Causes Compared With the Age-Adjusted US Male Population Among Patients With Testicular Nonseminoma by Initial Treatment (continued)

Cause of Death	Survivors of Testicular Nonseminoma (N = 15,006)							
	Surgery Only (no RT) (n = 8,097)				Chemotherapy (no RT) (n = 6,909)			
	No.	SMR	95% CI	AER	No.	SMR	95% CI	AER
Certain conditions originating in perinatal period	0	0	0 to 9.49	−0.05	1	16.07	0.41 to 89.56	0.16
Accidents and adverse effects	33	0.75	0.52 to 1.06	−1.33	40	1.22	0.87 to 1.66	1.21
Suicide and self-inflicted injury	19	0.95	0.57 to 1.49	−0.12	16	1.09	0.62 to 1.77	0.22
Homicide and legal intervention	6	0.78	0.29 to 1.70	−0.20	8	1.32	0.57 to 2.61	0.33
Benign neoplasms and those with unknown behavior[h]	4	4.03[a]	1.10 to 10.31	0.37	7	10.62[a]	4.27 to 21.88	1.06
Symptoms, signs, and ill-defined conditions[i]	9	1.94	0.89 to 3.69	0.54	14	4.31[a]	2.36 to 7.23	1.79
Other causes of death[j]	30	1.16	0.78 to 1.66	0.51	39	2.21[a]	1.57 to 3.02	3.56

NOTE. All study registries collect data on the underlying cause of death as classified by International Classification of Diseases (ICD) codes. We used ICD-9 and ICD-10 classifications to establish noncancer causes of death for years 1980 to 1998 and 1999 to 2010, respectively.

Abbreviations: AER, absolute excess risk per 10,000 person-years; NA, not applicable; RT, radiotherapy; SMR, standardized mortality ratio.

[a]SMR with $P < .05$.

[b]Total cardiovascular disease deaths include deaths resulting from diseases of heart (ICD-9: 390 to 398, 402, 404, 410 to 429; ICD-10: 100 to 109, 111, 113, 120 to 151), cerebrovascular diseases (ICD-9: 430 to 438; ICD-10: 160 to 169), other diseases of arteries, arterioles, and capillaries (ICD-9: 442 to 448; ICD-10: 172 to 178), hypertension without heart disease (ICD-9: 401, 403; ICD-10: 110, 112), atherosclerosis (ICD-9: 440; ICD-10: 170), and aortic aneurysm and dissection (ICD-9: 441; ICD-10: 171).

[c]Includes diseases of heart (n = 6; SMR, 3.45; 95% CI, 1.27 to 7.52; AER, 6.64) and cerebrovascular diseases (n = 5; SMR, 21.72; 95% CI, 7.05 to 50.69; AER, 7.43).

[d]The same patient can contribute to multiple time-dependent age groups in the SMR analyses. As a patient ages, he transitions from one age group to the next, until his time of death or end of follow-up.

[e]No statistically significantly increased SMR was observed for any time interval after diagnosis of testicular nonseminoma.

[f]Deaths by time since diagnosis were as follows: < 1 year: n = 6; SMR, 3.45 (95% CI, 1.27 to 7.52); 1 to 4 years: n = 11; SMR, 1.81 (95% CI, 0.91 to 3.25); 5 to 9 years: n = 8; SMR, 1.13 (95% CI, 0.49 to 2.22); 10 to 14 years: n = 5; SMR, 0.78 (95% CI, 0.25 to 1.81); 15 to 19 years: n = 7; SMR, 1.22 (95% CI, 0.49 to 2.52); and ≥ 20 years: n = 5; SMR, 0.78 (95% CI, 0.25 to 1.82).

[g]Deaths by time since diagnosis were as follows: < 1 year: n = 5; SMR, 21.72 (95% CI, 7.05 to 50.69); 1 to 4 years: n = 1; SMR, 1.29 (95% CI, 0.03 to 7.19); 5 to 9 years: n = 1; SMR, 1.16 (95% CI, 0.03 to 6.44); 10 to 14 years: n = 2; SMR, 2.55 (95% CI, 0.31 to 9.21); 15 to 19 years: n = 1; SMR, 1.45 (95% CI, 0.04 to 8.05); and ≥ 20 years: n = 0; SMR, 0 (95% CI, 0 to 4.52).

[h]Of the 11 patients who died, one had a benign brain neoplasm, whereas the remaining 10 had neoplasms of uncertain behavior of digestive and respiratory systems, genitourinary organs, endocrine glands and nervous systems, or other and unspecified sites and tissues. Only one of the 11 patients had had a second malignant neoplasm diagnosed before death and reported to the SEER program.

[i]Includes the following ICD-9 and ICD-10 codes, although the specific ICD code for each identified event is not available in the SEER database: ICD-9: 780 (general symptoms); 781 (symptoms involving nervous and musculoskeletal systems); 782 (symptoms involving skin and other integumentary tissue); 783 (symptoms concerning nutrition, metabolism, and development); 784 (symptoms involving head and neck); 785 (symptoms involving cardiovascular system); 786 (symptoms involving respiratory system and other chest symptoms); 787 (symptoms involving digestive system); 788 (symptoms involving urinary system); 789 (other symptoms involving abdomen and pelvis); 790 (nonspecific findings on examination of blood); 791 (nonspecific findings on examination of urine); 792 (nonspecific abnormal findings in body substances); 793 (nonspecific abnormal findings on radiologic and other examination of body structure); 794 (nonspecific abnormal results of function studies); 795 (other and nonspecific abnormal cytologic, histologic, immunologic, and DNA test findings); 796 (other nonspecific abnormal findings); 797 (senility without mention of psychosis); 798 (sudden death, cause unknown); 799 (other ill-defined and unknown causes of morbidity and mortality); ICD-10: R00 to R99 (symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified).

[j]Included any ICD cause of death not defined in the SEER Stat recode. The specific ICD code for each of the identified events is not available in the SEER data set.

years) after TC diagnosis at older ages (median age, 49.7 years; range, 43.8 to 85.6 years).

Significantly increased mortality after chemotherapy for nonseminoma was also observed for other causes, including septicemia (SMR, 7.14), pneumonia and influenza (SMR, 3.05), and symptoms, signs, and ill-defined conditions including those involving the cardiovascular system (SMR, 4.31). Significant excess deaths as a result of these causes were not observed after surgery.

Internal comparisons: Cox regression analyses. Results of univariable Cox regression analyses of CVD deaths comparing patients with nonseminoma initially given chemotherapy with patients managed with surgery alone are listed in Table 3. Significantly increased CVD deaths were restricted to the first year after TC diagnosis and associated with older age, marital status, and regional and distant TC.

Table 4 lists the results of multivariable Cox regression analyses, which adjust for time since TC diagnosis, age at diagnosis, calendar year of diagnosis, extent of disease, race, county education level, and marital status. Compared with patients with nonseminoma managed initially with surgery only, patients given chemotherapy experienced significantly increased five-fold risks of CVD death during the first year after TC diagnosis (HR, 4.86; 95% CI, 1.25 to 32.08) but not thereafter (HR, 1.35 for 1 to 4 years after diagnosis; HR, 0.90 for ≥ 5 years after diagnosis). Other significant risk factors for CVD mortality included distant nonseminoma (HR, 1.91) and older age at TC diagnosis (HRs of 3.47, 8.97, and 34.26 for ages 30 to 39, 40 to 49, and ≥ 50 years, respectively). The association of marital status with CVD death was no longer significant as a result of adjustment for age.

DISCUSSION

This is the first large population-based investigation, to our knowledge, to quantify CVD mortality during, shortly after, and for two decades after TC diagnosis. On the basis of a population of more than 15,000 patients with nonseminoma, significantly increased CVD mortality (SMR, 1.36) occurred after chemotherapy, with no excesses after surgery alone (SMR, 0.81). Multivariable analyses showed that significantly elevated five-fold CVD mortality occurred within the first year after TC diagnosis among chemotherapy patients compared with patients initially given surgery alone. In contrast to prior studies of

Table 3. Univariable Cox Regression Analyses of CVD Deaths in Men Diagnosed With Testicular Nonseminoma According to Baseline Characteristics

Variable	No. of Patients	All CVD Deaths (n = 104)			
		No. of CVD Deaths	HR	95% CI	*P*
Initial treatment by time since TC diagnosis*					
< 1 year					
Surgery (no RT)	8,097	2	—	—	Ref
Chemotherapy (no RT)	6,909	11	6.52†	1.75 to 42.12	< .01
1-4 years					
Surgery (no RT)	7,388	9	—	—	Ref
Chemotherapy (no RT)	6,014	12	1.73	0.73 to 4.25	.21
≥ 5 years					
Surgery (no RT)	5,369	39	—	—	Ref
Chemotherapy (no RT)	3,973	31	1.15	0.72 to 1.85	.55
Age at TC diagnosis, years					
< 30	8,620	23	—	—	Ref
30-39	4,254	34	3.10†	1.84 to 5.34	< .01
40-49	1,602	23	7.68†	4.27 to 13.80	< .01
≥ 50	530	24	28.96†	16.22 to 51.82	< .01
Calendar year of diagnosis					
1980-1989	2,316	51	—	—	Ref
1990-1999	3,350	29	0.87	0.52 to 1.46	.60
2000-2010	9,340	24	0.87	0.46 to 1.65	.66
Extent of disease					
Localized	8,747	46	—	—	Ref
Regional	3,521	34	1.58†	1.01 to 2.46	.04
Distant	2,601	23	2.20†	1.31 to 3.59	< .01
Unknown	137	1	0.87	0.05 to 3.97	.89
Race					
White	14,087	98	—	—	Ref
Nonwhite	919	6	1.16	0.45 to 2.43	.73
County education level‡					
Education 1 (low)	3,310	30	—	—	Ref
Education 2 (medium)	6,575	53	1.00	0.65 to 1.59	.99
Education 3 (high)	5,120	21	0.83	0.46 to 1.45	.51
Unknown	1	0	0	NA to 68.05	.99
Marital status					
Never married	8,350	37	—	—	Ref
Married	5,481	54	1.92†	1.27 to 2.93	< .01
Separated/divorced/widowed	670	9	3.35†	1.52 to 6.64	< .01
Unmarried/domestic partner/unknown	505	4	2.37	0.71 to 5.91	.10

Abbreviations: CVD, cardiovascular disease; HR, hazard ratio; NA, not applicable; Ref, reference; RT, radiotherapy; TC, testicular cancer.
*The number of person-years (PY) is as follows: < 1 year (surgery: 81,227 PY; chemotherapy: 60,065 PY); 1 to 4 years (surgery: 80,946 PY; chemotherapy: 59,655 PY); and ≥ 5 years (surgery: 75,054 PY; chemotherapy: 54,070 PY).
†HR with $P < .05$.
‡County education level was categorized based on tertiles of distribution, as follows: education 1 represents the lowest level (composed of counties with ≥ 25% of men without a high school education); education 2 represents the medium level (counties with 15% to < 25% of men without a high school education); and education 3 represents the highest level (counties with < 15% of men without a high school education).

CVD incidence,[6-10] significant excesses of CVD mortality were not observed after 1 year. Other new findings include significantly elevated (2.4-fold) overall mortality as a result of cerebrovascular diseases among TCSs given chemotherapy, with 50% of deaths observed within the first year. Notable findings also include significant excesses of CVD mortality associated with extent of disease (regional *v* distant) and increases in CVD mortality with increasing age at TC diagnosis.

Four European groups of investigators[6-10] have quantified CVD incidence, but not mortality, in patients with nonseminoma after chemotherapy (Table 5). Limitations of these studies included the relatively small numbers of patients with TC given chemotherapy (range, 87 to 710 patients), the inclusion of patients treated in the 1960s,[9,10] and the restriction of risk estimation either to selected time intervals (eg, long-term survivors)[8-10] or across all latency periods taken together.[7] No investigation, to our knowledge, quantified CVD risk within 1 year of TC diagnosis.

CVD incidence in TCSs given chemotherapy was compared with that in TCSs managed with surgery in four studies.[6,7,9,10] Among 364 5-year TCSs treated with bleomycin, etoposide, and cisplatin (BEP) alone (median follow-up, 19 years), Haugnes et al[6] found a 5.7-fold significantly increased incidence of coronary artery disease compared with TCSs who underwent surgery alone (n = 206). The incidence of myocardial infarction (MI) after chemotherapy was increased 3.1-fold (95% CI, 1.2 to 7.7) compared with age-matched controls.[6] Increased risks for atherosclerotic disease were observed with increasing cumulative dose of either cisplatin ($P = .04$) or etoposide ($P < .001$). Among

Table 4. Multivariable Cox Regression Analyses of Cardiovascular Disease Deaths in Men Diagnosed With Testicular Nonseminoma According to Baseline Characteristics

Variable	All Cardiovascular Deaths (n = 104)		
	HR	95% CI	*P*
Initial treatment by time since TC diagnosis			
< 1 year			
Surgery (no RT)	—	—	Ref
Chemotherapy (no RT)	4.86*	1.25 to 32.08	.04
1-4 years			
Surgery (no RT)	—	—	Ref
Chemotherapy (no RT)	1.35	0.54 to 3.45	.53
≥ 5 years			
Surgery (no RT)	—	—	Ref
Chemotherapy (no RT)	0.90	0.51 to 1.58	.72
Age at diagnosis, years			
< 30	—	—	Ref
30-39	3.47*	1.99 to 6.13	< .01
40-49	8.97*	4.73 to 17.02	< .01
≥ 50	34.26*	17.81 to 66.17	< .01
Calendar year of diagnosis			
1980-1989	—	—	Ref
1990-1999	0.78	0.46 to 1.32	.35
2000-2010	0.67	0.35 to 1.30	.23
Extent of disease			
Localized	—	—	Ref
Regional	1.45	0.87 to 2.40	.15
Distant	1.91*	1.02 to 3.55	.04
Unknown	0.93	0.05 to 4.30	.94
Race			
White	—	—	Ref
Nonwhite	1.31	0.51 to 2.76	.53
County education level†			
Education 1 (low)	—	—	Ref
Education 2 (medium)	0.94	0.60 to 1.49	.78
Education 3 (high)	0.83	0.46 to 1.48	.54
Marital status‡			
Never married	—	—	Ref
Married	0.76	0.48 to 1.24	.27
Separated/divorced/widowed	1.08	0.47 to 2.23	.85
Unmarried/domestic partner/unknown	1.52	0.45 to 3.86	.44

Abbreviations: HR, hazard ratio; Ref, reference; RT, radiotherapy.
*HR with $P < .05$.
†County education level was categorized based on tertiles of distribution, as follows: education 1 represents the lowest level (composed of counties with ≥ 25% of men without a high school education); education 2 represents the medium level (counties with 15% to < 25% of men without a high school education); and education 3 represents the highest level (counties with < 15% of men without a high school education). One person with unknown county education level and who had no cardiovascular event was excluded from the multivariable regression model.
‡In the multivariable model, the association of marital status with cardiovascular disease death was no longer significant, likely as a result of adjustment for age at testicular cancer diagnosis, because married or separated/divorced/widowed patients were older than never-married men (median ages, 33.2, 36.3, and 24.5 years, respectively).

390 chemotherapy-treated TCSs in the United Kingdom (1982 to 1992; median follow-up, 9.7 years), a significantly elevated 2.6-fold risk for incident cardiac events was reported for all time periods taken together compared with surgery alone (n = 242).[7] Using multivariable analysis, a retrospective study of 455 Dutch 5-year TCSs given BEP chemotherapy[10] found a 1.5-fold (95% CI, 1.0 to 2.2) risk of incident CVD, but excesses of MI (HR, 1.2) or peripheral vascular disease (HR, 0.4) were not apparent compared with surgery alone (n = 362).

Although prior case reports and small series[12,13] have described instances of MI and cerebrovascular disease during or immediately after TC chemotherapy, our study quantifies the associated mortality. Despite the significantly increased 3.5- to 21.7-fold SMRs, the AER of deaths as a result of heart disease or cerebrovascular disease after chemotherapy in the first year after TC diagnosis was small (6.64 and 7.43 excess deaths per 10,000 person-years, respectively). Nonetheless, in a largely curable cancer,[21] the early development of any fatal event is devastating. Despite improvements in stroke outcomes in the US population,[22] this trend did not seem to extend to chemotherapy-treated TCSs. Van den Belt-Dusebout et al[10] reported 50 cerebrovascular accidents among 2,512 5-year TCSs after all treatments taken together (1965 to 1995), but incidence was not increased compared with the general population (standardized incidence ratio, 0.84). Although the number of cerebrovascular accidents among the 664 TCSs given chemotherapy was not specified, multivariable analyses showed that risk (HR, 0.80) was not elevated compared with surgery alone (n = 362). Our results are generally in accord with these observations,[10] because we found elevated risk concentrated within the first year after TC diagnosis, and van den Belt-Dusebout et al[10] studied 5-year TCSs.

In contrast to the development of atherosclerosis that likely contributes to the increased incidence of CVD in long-term TCSs,[6,23] acute direct vascular injury and endothelial dysfunction[24-29] induced by cisplatin-based chemotherapy (reviewed in Feldman et al[23]) may explain in part the increased CVD mortality we observed in the first year after TC diagnosis. A meta-analysis by Seng et al[30] of 38 randomized controlled trials that evaluated cisplatin-based versus non–cisplatin-based chemotherapy in 8,216 patients with solid tumors reported that cisplatin is associated with a significantly increased 1.7-fold risk of venous thromboembolism (VTE), but the analysis included only 130 patients with TC (and one event). Other studies have indicated that, in general, advanced cancer stage[31,32] seems to be associated with a higher risk of thromboembolic events, and we found independent effects for both advanced stage and chemotherapy. In the meta-analysis by Seng et al,[30] patients who received a weekly equivalent cisplatin dose of more than 30 mg/m^2 were at highest risk (relative risk, 2.7) of VTE,[30] and it is noteworthy that a weekly dose of 100 mg/m^2 is typically used to treat advanced TC.[33-36] Further, Alanee et al[37] postulated that the significantly increased overall CVD mortality observed in men with mediastinal or nonmediastinal extragonadal GCT (HR, 4.5 and 2.8, respectively) compared with patients with testicular GCT was a result of the typically larger amounts of primary cisplatin-based chemotherapy and additional salvage chemotherapy needed for treatment. However, treatment data were unavailable to confirm this hypothesis.

In the Khorana scoring system,[38] TC is categorized as a high-risk cancer for chemotherapy-associated VTE. A validation of this score in a retrospective single-institution study of patients with different types of cancer given cisplatin-based chemotherapy included only 39 patients with TC.[39] In a recent retrospective study of 216 men with disseminated TC given cisplatin-based chemotherapy, Srikanthan et al[40] reported that incident VTE was associated with a high-risk Khorana score ≥ 3 points (odds ratio [OR], 11.8; $P < .01$), retroperitoneal lymph nodes (RPLNs) greater than 5 cm (OR, 5.26; $P = .001$),

Table 5. Summary of Studies Reporting CVD and CVAs After Chemotherapy for TC

Study	Study Type	No. of Patients With TC Given Chemotherapy[a]			Calendar Years of Diagnosis	Type of Antecedent Chemotherapy	Time Period Evaluated After TC Diagnosis	CVD (total)		CVAs	
		Total	NS	S				No. of Patients	Overall Risk (95% CI)	No. of Patients	Overall Risk (95% CI)
Current article,[b] 2014	Retrospective population-based cohort	6,909	6,909	0	1980-2010	Not available[c]	Entire time period, stratified into intervals	54[d]	SMR: 1.36 (1.03 to 1.78)	10	SMR: 2.40 (1.15 to 4.42)
Haugnes et al,[6] 2010	Multi-institutional retrospective cohort	364[e]	NA	NA	1980-1994	PVB, BEP	> 2 years	27[f]	HR: 2.60[g] (1.10 to 5.90)	6[h]	Not reported[i]
Dieckmann et al,[11] 2010	Multi-institutional retrospective survey[j]	8,233	6,586	1,647	1996-2008	BEP, VIP	During or within 6 weeks of chemotherapy	25[k]	Not reported	3	Not reported
Van den Belt-Dusebout et al,[9] 2007	Multi-institutional retrospective cohort	710	614	96	1965-1995	PVB, BEP, carboplatin, ifosfamide, and dactinomycin	≥ 5 years	49[l]	SIR: 1.30[m] (1.00 to 1.80)	Not reported	Not reported
Van den Belt-Dusebout et al,[10] 2006	Multi-institutional retrospective cohort	664	572	92	1965-1995	PVB, BEP, carboplatin, ifosfamide, and dactinomycin	≥ 5 years	36[n]	SIR: 1.16[m] (0.81 to 1.61)	Not reported[o]	HR: 0.80[p] (0.40 to 1.70)
Huddart et al,[7] 2003	Single institution	390[q]	329	46	1982-1992	BEP, carboplatin, etoposide, bleomycin, or others	Entire time period taken together[r]	26[s]	RR: 2.59[t] (1.15 to 5.84)	Not reported	Not reported
Meinardi et al,[8] 2000	Single-institution cross-sectional	87[e]	NA	NA	Before 1987	PVB, BEP, VIP	≥ 10 years	5[u]	SIR: 7.10[v] (1.90 to 18.30)	Not reported	Not reported

Abbreviations: BEP, bleomycin, cisplatin, and etoposide; CVA, cerebrovascular accidents; CVD, cardiovascular disease; HR, hazard ratio; NA, not applicable; NS, nonseminoma; PVB, cisplatin, vinblastine, and bleomycin; RR, relative risk; S, seminoma; SIR, standardized incidence ratio; SMR, standardized mortality ratio; TC, testicular cancer; VIP, etoposide, ifosfamide, and cisplatin.

[a]This table lists the number of patients with TC given chemotherapy in each study.

[b]Two thousand five hundred twenty-nine (36.6%) of the patients with NS in the current study who were treated with chemotherapy in the Surveillance, Epidemiology, and End Results program (1980 to 1999) were included in a prior international registry-based study (1943 to 2002; Fossa SD, et al: J Natl Cancer Inst 99:533-544, 2007).

[c]Likely cisplatin-based chemotherapy (refer to text of article).

[d]CVD is defined as diseases of the heart, cerebrovascular diseases, and other diseases of arteries, arterioles, and capillaries (see text).

[e]Numbers of patients with S and NS were not reported.

[f]CVD consisted of all atherosclerotic diseases, including myocardial infarction, angina, stroke, transient ischemic attack, carotid stenosis, aneurysm of aorta/renal artery, and intermittent claudication.

[g]HR compared patients treated with chemotherapy with patients managed with surgery only. In addition, the HR of CVD for patients who received BEP chemotherapy compared with patients managed with surgery only was 5.7 (95% CI, 1.9 to 17.1).

[h]Included patients who had cerebrovascular diseases diagnosed more than 2 years after testicular cancer diagnosis; two patients had stroke, three patients had transient ischemic attacks, and one patient had carotid stenosis.

[i]HR of cerebrovascular disease after chemotherapy compared with control group was not reported in article; however, it was noted that the HR was not statistically significantly different.

[j]In this study, a questionnaire was sent to 355 institutions in Germany inquiring whether cardiovascular events occurred during or within 6 weeks of chemotherapy among survivors of TC treated during 1996 to 2008. Reporting was voluntary without validation of responses, and the survey response rate was 79%. The total number of patients with TC undergoing chemotherapy in the participating institutions was estimated to be 8,233 based on the total number of patients with TC in the national database of the Robert Koch Institute, Berlin (n = 47,651). The following methods and assumptions were used to estimate the total number of patients with TC undergoing chemotherapy, and a reduction of 10% was made to obtain the number of germ cell tumors: the relative proportion of patients requiring chemotherapy was assumed to be approximately 40% and 10% for NS and S, respectively. A further correction was made with respect to the response rate of the survey (ie, 79%), and the authors noted that a proportion of 2% was added to account for relapses requiring chemotherapy.

[k]CVD consisted of 20 patients with myocardial infarction, three patients with cerebral stroke, and two patients with arterial thrombosis.

[l]CVD was defined as myocardial infarction, angina pectoris, and congestive heart failure diagnosed at least 5 years after testicular cancer diagnosis. This study included patients in the prior report from van den Belt-Dusebout et al[10] in 2006.

[m]SIR of CVD compared with the age-specific, sex-specific, and calendar year–specific incidence rates of CVD in the general male population.

[n]CVD defined as myocardial infarction and angina pectoris diagnosed at least 5 years after testicular cancer diagnosis.

[o]The number of cerebrovascular events was not reported for the chemotherapy cohort. However, 50 cerebrovascular events were reported for all patients with TC taken together.

[p]HR compared patients with TC given chemotherapy with patients managed with surgery only and adjusted for recent smoking status, age at diagnosis, and treatment period.

[q]An additional 15 patients with unspecified histology were included in the analysis.

[r]Median follow-up time was 9.7 years (range, 0 to 19.8 years) since TC diagnosis.

[s]Events were restricted to coronary artery disease (defined as myocardial infarction, angina, or sudden cardiac death) based on medical records or general practitioner communication.

[t]Relative risk by age-adjusted regression analysis compared chemotherapy-treated patients with those managed with surveillance (no chemotherapy or radiation) in the same cohort.

[u]CVD defined as myocardial infarction or angina with proven myocardial ischemia.

[v]Represents SIR of CVD compared with the general male Dutch population.

intermediate-/poor-risk disease (OR, 3.76; $P = .005$), and hospitalization during chemotherapy (OR, 4.24; $P = .002$). Thus, a number of factors likely contributed to early CVD mortality among our chemotherapy-treated patients, including the Khorana categorization of TC as a high-risk cancer for chemotherapy-associated VTE,[38] advanced stage,[32,37,40] direct vascular effects of cisplatin-based chemotherapy,[24-29] and other influences.[40] However, clinical data, such as RPLN size or RPLN dissection, are not collected by the SEER program.

Although prior European studies[8-10] reported increased CVD incidence among long-term TCSs given chemotherapy, we did not find elevated CVD mortality ≥ 5 years after diagnosis. Advances in CVD management, as reflected in the 31% decline in US CVD death rates from 2000 to 2010,[41] may account for our observations. Our finding that increasing age at TC diagnosis is significantly associated with increasing CVD mortality after chemotherapy may reflect the operation of platinum-associated toxicities on pre-existing risk factors because CVD mortality increases with increasing age in the US population.[41]

To our knowledge, no other US studies quantify either CVD incidence or mortality after chemotherapy for TCSs. Beard et al[42] evaluated CVD deaths after radiotherapy for stage I seminoma, but patients with nonseminoma were not included, and chemotherapy was not evaluated. An evaluation of cardiac deaths among patients with stage I or II testicular seminoma at The University of Texas MD Anderson Cancer Center was restricted to men given abdominal and/or chest radiotherapy; chemotherapy-treated patients were excluded.[43]

More than 90% of men diagnosed with regional or distant testicular nonseminoma in the SEER program (1999) received chemotherapy,[13] with BEP or cisplatin and etoposide accounting for 88%. Similarly, in our SEER-based investigation, approximately 80% of 6,122 patients with regional and distant testicular nonseminoma initially received chemotherapy. Because approximately one third of patients with stage I testicular nonseminoma may experience relapse,[44] some patients with localized disease in our surgery-alone cohort may have subsequently received chemotherapy. In view of this potential misclassification, our quantifications of CVD mortality (SMR and HR) associated with chemotherapy likely represent minimal estimates.

Strengths of our study include the large number of patients, population-based setting, and wide range of follow-up. Limitations of the SEER program include a lack of data regarding types and doses of initial chemotherapy and subsequent treatments. SEER also does not collect information on general risk factors that may affect CVD risk (eg, tobacco history, diet, physical activity).[41] Inclusion of the surgery-only cohort serves as an internal control for many of these potential confounding factors, but our results should be interpreted with caution, given the lack of detail in SEER. In multivariable analyses, we also adjusted for race,[41,45] county education level,[41] and marital status[46,47] to account for potential effects on CVD mortality. A small percentage of patients with TC with disseminated disease (2% to 3%) present with brain metastases,[48] and it is possible that death as a result of an associated intracranial hemorrhage may be assigned to cerebrovascular disease. However, in view of the strict SEER coding rules[17] and rarity of brain metastases, any residual misclassification is unlikely to materially affect our results.

TC has long been the model of a curable cancer[21,49] and increasingly represents a paradigm for adult-onset cancer survivorship.[50] Although CVD research priorities in TCSs were recently summarized,[49] these focused largely on long-term survivors. The relatively scant attention given to CVD incidence or mortality during or immediately after cisplatin-based chemotherapy in patients with TC[12] is noteworthy, in view of the growing literature in other cancers.[30,39] In particular, in a largely curable cancer, the early development of any potentially fatal and preventable therapy-associated event is devastating. Our findings remain to be confirmed in analytic studies that also identify patients with TC at highest risk of thromboembolic events to formulate comprehensive, evidence-based approaches for risk stratification and reduction.[51] In the interim, the low AER of early CVD mortality reported here should not affect decisions to administer effective TC chemotherapy when clinically indicated. However, until evidence-based data are developed for TC, clinicians should apply general American Society of Clinical Oncology clinical practice guidelines[51] for VTE prophylaxis and treatment.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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GLOSSARY TERMS

cisplatin: an inorganic platinum agent (cis-diamminedichloroplatinum) with antineoplastic activity. Cisplatin forms highly reactive, charged, platinum complexes, which bind to nucleophilic groups such as GC-rich sites in DNA, inducing intrastrand and interstrand DNA cross-links as well as DNA-protein cross-links. These cross-links result in apoptosis and cell growth inhibition. Carboplatin and oxaliplatin are other members of this class.

nonseminoma: a type of cancer that begins in cells that form sperm or eggs. There are several types of nonseminoma tumors, including embryonal carcinoma, malignant teratoma, choriocarcinoma, and yolk sac tumor. These tumors are usually made up of more than one type of cancer cell. Although nonseminomas occur most often in the testicles or ovaries, they can occur in other tissues, such as the brain, chest, or abdomen. This happens when cells that have the ability to form sperm or eggs are found in other parts of the body.

Surveillance, Epidemiology, and End Results (SEER): a national cancer registry that collects information from all incident malignancies in multiple geographic areas of the United States.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Cardiovascular Disease Mortality After Chemotherapy or Surgery for Testicular Nonseminoma: A Population-Based Study

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