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ORIGINAL REPORT

Risk of Solid Cancer After Treatment of Testicular Germ Cell Cancer in the Platinum Era

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ABSTRACT

Purpose
Testicular cancer (TC) treatment increases risk of subsequent malignant neoplasms (SMNs). It is unknown whether changes in TC treatment over time have affected SMN risk.

Methods
Solid SMN risk was evaluated in a multicenter cohort comprising 5,848 1-year survivors treated for TC before age 50 years between 1976 and 2007. SMN incidence was compared with cancer incidence in the general population. Treatment-specific risks were assessed using multivariable regression in a case-cohort design.

Results
After a median follow-up of 14.1 years, 350 solid SMNs were observed, translating into a 1.8-fold (95% CI, 1.6-2.0) increased risk compared with general population rates. Solid SMN risk was increased in patients with seminoma and those with nonseminoma (standardized incidence ratio, 1.52 and 2.21, respectively). Patients with nonseminoma experienced increased risk of SMNs of the thyroid, lung, stomach, pancreas, colon, and bladder and of melanoma and soft tissue sarcoma, whereas those with seminoma experienced increased risk of SMNs of the small intestine, pancreas, and urinary bladder. The 25-year cumulative incidence of solid SMNs was 10.3% (95% CI, 9.0% to 11.6%). In multivariable analysis, platinum-based chemotherapy was associated with increased risk of a solid SMN (hazard ratio [HR], 2.40; 95% CI, 1.58 to 3.62), colorectal SMN (HR, 3.85; 95% CI, 1.67 to 8.92), and noncolorectal GI SMN (HR, 5.00; 95% CI, 2.28 to 10.95). Receipt of platinum 400 to 499 and $\geq$ 500 mg/m^2 increased solid SMN risk compared with surgery only (HR, 2.43; 95% CI, 1.40 to 4.23 and HR, 2.42; 95% CI, 1.50 to 3.90, respectively), whereas risk was not significantly increased with lower doses (HR, 1.75; 95% CI, 0.90 to 3.43). The HR of a GI SMN increased by 53% (95% CI, 26% to 80%) per 100 mg/m^2 of platinum-containing chemotherapy. The HR of an infradiaphragmatic SMN increased by 8% per Gray of radiation dose administered (95% CI, 6% to 9%; $P < .001$).

Conclusion
Radiotherapy and platinum-containing chemotherapy are associated with increased solid SMN risk, specifically with GI SMNs.

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INTRODUCTION

The introduction of cisplatin-based chemotherapy in the late 1970s,[1] improvements in radiation treatment, and better supportive care have greatly improved testicular cancer (TC) survival. However, TC treatment has previously been associated with late adverse effects, including subsequent malignant neoplasms (SMNs).[2-7]

To decrease risk of late effects of TC treatment, radiation dose and field size and the number of platinum-containing chemotherapy cycles have been reduced over the last decades. Moreover, patients with early-stage disease are now frequently managed under wait-and-see protocols. However, it is unclear whether these changes have affected SMN risk among more recently treated patients.

A few studies have shown that exposure to chemotherapy may increase solid SMN risk in TC

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survivors.[3,7] In a large international cohort study, chemotherapy was associated with a 1.8-fold increased solid SMN risk.[3] Fung et al[7] reported a 1.4-fold increased solid SMN risk among patients with nonseminoma treated with chemotherapy compared with the general population, with three- to seven-fold increased risks of cancers of the kidney, soft tissue, and thyroid. van den Belt-Dusebout et al[4] previously found that chemotherapy for TC increased SMN risk 2.1-fold compared with surgery only. So far, this is the only study investigating solid SMN incidence in TC survivors to have incorporated relapse treatment. Previous studies in TC survivors have not specifically examined whether platinum-containing chemotherapy is associated with a (dose-dependent) increase of site-specific solid SMN risk.[3,4,7,8] This is of special interest because a study in childhood cancer survivors reported that platinum-containing chemotherapy was associated with increased GI SMN risk, although this conclusion was based on only a few patients with a GI SMN.[9]

In this study, we assessed long-term treatment-specific solid SMN risk in a large Dutch cohort of patients with TC treated between 1976 and 2007.

METHODS

To assess late effects of TC treatment, a multicenter cohort was established including 6,175 TC survivors treated for TC before age 50 years between 1976 and 2007 in 13 Dutch hospitals. Patients were identified through hospital tumor registries and the population-based Netherlands Cancer Registry.

A case-cohort design was used to facilitate collection of detailed treatment data while allowing assessment of multiple treatment-associated outcomes.[10] A hospital-stratified subcohort comprising 15% of the base cohort (25% in the coordinating hospitals Antoni van Leeuwenhoek and University Medical Center Groningen) was randomly selected, comprising 1,174 patients with TC. For all patients in the cohort who developed an SMN and all subcohort members, detailed treatment data were abstracted from the medical records, including administered chemotherapy regimens, numbers of cycles and cumulative doses, and radiotherapy fields and doses (excluding booster dose), for primary treatment as well as relapse or contralateral TC (CLTC) treatment.

In total, 327 patients were excluded (5.3%) because they did not meet eligibility criteria (n = 47), had died within 1 year after TC diagnosis (n = 144), were lost to follow-up within 1 year (n = 121), or were diagnosed with a solid SMN within 1 year after TC diagnosis (n = 15), leaving 5,848 1-year survivors for analysis. This cohort comprised 1,437 5-year TC survivors treated between 1976 and 1995, included in previous studies.[4,11] For similar reasons, we excluded 53 patients in the subcohort, leaving 1,121 patients for analysis (Data Supplement).

Information on solid SMNs was collected from either the medical records or the general practitioners or through linkage with the Netherlands Cancer Registry. Oncologic follow-up was complete up to at least January 2012 for 91.5% of all patients with TC (n = 5,350).

Treatment

Standard TC treatment included unilateral orchidectomy followed by elective nodal radiotherapy for patients with stage I or II seminoma and combination chemotherapy for those with disseminated seminoma or nonseminoma (Data Supplement).[12,13] Radiotherapy for stage I or II seminoma was usually administered to the infradiaphragmatic para-aortic nodes and initially also included the ipsilateral iliac and inguinal lymph nodes (dog-leg field), with doses ranging from 26 to 35 Gy.[4,14] Before 1983, 76.5% of all irradiated patients with nonseminoma (n = 26) received doses > 32 Gy (median, 40 Gy). From 1977, patients with stage II to IV seminoma or nonseminoma received platinum-containing combination chemotherapy (initially consisting of cisplatin, vinblastine, and bleomycin; bleomycin, etoposide, and cisplatin [from 1984]; or a combination of both).[15] Maintenance chemotherapy included dactinomycin or vinblastine and bleomycin before the 1980s.[16,17]

Statistical Analysis

Time at risk started 1 year after date of hemiorchidectomy and ended at the date of solid SMN diagnosis, death, emigration, or last follow-up, whichever came first. Basal-cell skin cancers and CLTC were ignored in all analyses. For patients with multiple SMNs, in site-specific analysis, time at risk ended at date of diagnosis of the first solid SMN of interest.

Comparison With General Population

The expected number of solid SMNs was estimated using age-, sex-, calendar period-, and site-specific cancer incidence rates for the Dutch male population. Standardized incidence ratios (SIRs), absolute excess risk (expressed per 10,000 person-years), and corresponding 95% CIs were computed using standard methods.[10] Tests for homogeneity and trend of SIRs were performed within collapsed Poisson regression models.

Within-Cohort Comparisons

Cumulative incidence of SMNs was estimated in the presence of death as competing risk. Missing data in the subcohort at multiple treatment occasions per patient were imputed using ordered multiple imputation by chained equations, ignoring patient clusters, creating 20 data sets.[18,19] Effects of TC treatment on SMN risk were assessed in multivariable Cox regression models. Treatment effects were modeled as a time-dependent variable, allowing a patient to add person-time to a different treatment category at the date treatment of relapse or CLTC was initiated, accounting for the effects of other covariates where appropriate.[19] Models were adjusted for age, unless otherwise stated. Barlow's inverse probability weights were used to adjust the partial likelihood function for case-cohort analysis.[10] To assess an excess hazard ratio (HR) for treatment dose in our case-cohort setting, the linear increase in the HR over categories of administered dose, with more than five cases in each dose category, was estimated separately for each imputed data set using variance weighted least squares regression with weights equal to 1/variance of the HR. Dose-response associations were estimated by first modeling the respective SMN rate as $RR = 1 + \beta dose$, where β is the proportional increase in SMN rate per unit increase in dose. Departure from linearity was evaluated by a test of the null hypothesis $\Phi = 0$ in a model including a quadratic dose term: $RR = 1 + \beta dose + \Phi dose^2$. Regression model estimates were pooled using Rubin's rule.[18] CIs of the HRs were based on Wald test. The proportional hazards assumption was assessed using residual-based methods. A P value $\leq .05$ was considered significant. STATA statistical software (version SE13; STATA, College Station, TX) was used for analysis.

RESULTS

Patient Characteristics

The cohort comprised 2,827 patients with seminoma and 3,021 with nonseminoma (Table 1; Data Supplement). Most patients with seminoma in the subcohort received radiotherapy (82.4%) as primary treatment after orchidectomy, whereas 57.9% of the patients with nonseminoma received platinum-based chemotherapy. Over time, para-aortic irradiation gradually replaced dog-leg irradiation, and administered radiation doses decreased among patients with seminoma (mean dose, 30 Gy from 1976 to

Table 1. Characteristics of All 1-Year Testicular Cancer Survivors (N = 5,848)

Characteristic	Cohort (N = 5,848)		Seminoma (n = 2,827)		Nonseminoma (n = 3,021)	
	No.	%	No.	%	No.	%
Age at diagnosis, years						
Median (IQR)	31.6 (25.9-37.7)		35.0 (30.4-40.4)		27.7 (23.3-33.4)	
< 20	309	5.3	21	0.7	288	9.5
20-29	2,197	37.6	641	22.7	1,556	51.8
30-39	2,317	39.6	1,409	49.8	908	30.6
40-50	1,025	17.6	756	26.7	269	8.9
Treatment period						
1976-1985	908	15.5	331	11.7	577	19.1
1986-1995	1,863	31.9	861	30.5	1,002	33.2
1996-2007	3,077	52.6	1,635	57.8	1,442	47.7
Primary treatment (% yes)*						
Radiotherapy†	2,230	38.1	2,071	73.3	159	5.3
Chemotherapy only	2,202	37.7	367	13.0	1,835	60.7
Surgery only	1,416	24.2	389	13.8	1,027	34.0
Vital status at end of follow-up						
Alive	5,384	92.1	2,655	93.9	2,729	90.3
Died	380	6.5	143	4.7	246	8.1
Emigrated	84	1.4	38	1.3	46	1.5
Duration of follow-up, years						
Median (IQR)	14.1 (9.3-20.1)		13.5 (9.3-19.1)		14.7 (9.3-21.1)	
1-4	331	5.7	130	4.6	201	7.6
5-9	1,355	23.2	698	24.7	657	21.8
10-14	1,494	25.6	804	28.4	690	22.8
15-19	1,192	20.4	584	20.7	608	20.1
20-24	789	13.5	361	12.8	428	14.2
≥ 25	687	11.8	246	8.8	437	14.5
Attained age at end of follow-up, years						
Median (IQR)	47.9 (40.8-55.1)		50.5 (44.1-57.2)		45.0 (37.6-52.3)	
< 45	2,488	42.5	873	30.9	1,615	53.5
45-49	1,035	17.7	545	19.3	490	16.2
50-54	900	15.4	518	18.3	382	12.6
55-59	656	11.2	398	14.1	258	8.5
60-64	419	7.2	260	9.2	159	5.3
≥ 65	350	6.0	233	8.2	117	3.9

Abbreviation: IQR, interquartile range.
*In the cohort, 105 patients (50 with seminoma and 55 with nonseminoma) received both radiotherapy and chemotherapy.
†Of the 121 patients in the subcohort, 12.9% experienced relapse (n = 145). Relapse information was available from medical record abstraction and therefore not available for the full cohort.

1985 and 26 Gy from 1996 to 2007; $P < .001$). Among patients with nonseminoma, the number of cycles of combination chemotherapy decreased from a median of six cycles from 1976 to 1985 to four from 1996 to 2007 ($P < .001$).

Median follow-up was 14.1 years (interquartile range, 9.3-20.1), with 11.8% of patients observed ≥ 25 years. In total, 350 patients (seminoma, n = 180; nonseminoma, n = 170) developed at least one solid SMN (Tables 2 and 3). Nineteen patients had two solid SMNs and three patients had three solid SMNs other than TC (Data Supplement). The median interval until the first solid SMN was 16.9 years (interquartile range, 10.5-23.1 years).

Solid SMN Risk Compared With General Population

Compared with the general population, solid SMN risk was 1.52-fold (95% CI, 1.32- to 1.77-fold) higher among patients with seminoma and 2.21-fold (95% CI, 1.89- to 2.57-fold) higher among those with nonseminoma (Table 3). Patients with nonseminoma experienced increased risks for both supradiaphragmatic and infradiaphragmatic sites, with significantly increased SIRs for thyroid (SIR, 5.45), lung (SIR, 2.14), stomach (SIR, 3.27), pancreatic (SIR, 3.43), colon (SIR, 2.55), bladder (SIR, 5.83), and melanoma skin cancers (SIR, 2.49) and soft tissue sarcoma (SIR, 8.36). Together, these sites accounted for 11.5 excess SMNs per 10,000 person-years. Among patients with seminoma, increased SIRs were restricted to infradiaphragmatic sites, with increased SIRs for small intestine (SIR, 8.90), pancreatic (SIR, 4.41), and urinary bladder cancers (SIR, 3.40), together representing 6.3 excess SMNs per 10,000 person-years. Analysis restricted to primary treatment showed no increased risk of solid SMNs after surgery only, except for soft tissue sarcoma (SIR, 4.9; Data Supplement). Radiotherapy was associated with increased SIRs of stomach, pancreatic, kidney, bladder, melanoma, and squamous cell skin cancers and soft tissue sarcoma, and chemotherapy was associated with increased SIRs of thyroid, lung, pancreatic, small intestine, colon, rectal, bladder, CNS, and melanoma skin cancers and soft tissue sarcoma.

Table 2. Treatment Characteristics of All Patients Who Developed a Solid SMN and All Patients in the Random Sample From the Full Cohort (n = 1,121)

Characteristic	Randomly Sampled Subcohort* (n = 1,121) No.	%	All Patients With Solid SMN (n = 350) No.	%
Histology				
Seminoma	508	45.3	180	51.4
Nonseminoma	613	54.7	170	48.6
Age, years				
Median (IQR)	31.2 (25.6-37.2)		36.5 (29.7-42.0)	
< 30	508	45.3	92	26.3
30-39	428	38.2	130	37.1
40-50	185	16.5	128	36.6
Primary treatment (% yes)†				
Surgery only/wait and see	260	23.2	47	13.4
Radiotherapy only	434	38.7	180	51.4
Chemotherapy only	401	35.8	118	33.7
Radiotherapy and chemotherapy	26	2.3	5	4.1
Relapse (% yes)	145	12.9	52	14.9
CLTC (% yes)	48	4.3	18	5.1
Total treatment (% yes)				
Surgery only/wait and see	196	17.4	28	8.0
Radiotherapy only	410	36.6	164	46.9
Chemotherapy only	439	39.1	124	35.4
Radiotherapy and chemotherapy	78	7.0	34	9.7
Radiotherapy field‡				
No irradiation below diaphragm	642	57.3	153	43.7
Para-aortic	187	16.7	41	11.7
Dog leg	261	23.3	137	39.1
Radiotherapy, field unknown	31	2.8	19	5.4
Infradiaphragmatic irradiation dose, Gy				
Median (IQR)	26 (26-30)		30 (26-36)	
No radiotherapy	642	57.2	153	43.7
< 26	95	8.5	27	7.7
26 to < 32	248	22.1	88	25.1
≥ 32	69	6.2	46	13.1
Missing dose	67	6.0	36	10.3
Supradiaphragmatic irradiation field§				
No irradiation above diaphragm	1,060	94.6	312	98.1
Irradiation above diaphragm	30	2.7	19	5.4
Radiotherapy, field unknown	31	2.8	19	5.4
Platinum dose, mg/m^2‖				
No chemotherapy	604	53.9	192	54.9
No platinum	24	2.1	8	2.3
< 400	111	9.9	19	5.4
400-499	253	22.6	87	24.9
≥ 500	98	8.7	28	8.0
Platinum, dose unknown	31	2.8	16	4.6
Etoposide dose, mg/m^2‖				
No chemotherapy	604	53.9	192	54.9
No etoposide	121	10.8	51	14.6
< 1,500	102	9.1	14	4.0
1,500-2,000	215	19.2	67	19.1
≥ 2,000	55	4.9	19	5.4
Etoposide, dose unknown	24	2.1	7	2.0
Bleomycin dose, U¶				
No chemotherapy	604	53.9	192	54.9
No bleomycin	57	5.2	22	6.3
≤ 120	60	5.4	10	2.9
121-270	143	12.8	30	8.6
271-360	141	12.6	44	12.6
> 360	27	2.4	13	3.7
Bleomycin, dose unknown	88	7.9	39	11.1

Abbreviations: CLTC, contralateral testicular cancer; IQR, interquartile range; SMN, subsequent malignant neoplasm.

*Random subcohort includes 70 patients who subsequently developed an SMN.

†Primary treatment excludes treatment of relapse and/or CLTC.

‡Patients who underwent infradiaphragmatic irradiation (± supradiaphragmatic irradiation) as part of primary or follow-up treatment.

§Supradiaphragmatic irradiation fields: lung, mediastinum, brain, and other, with or without infradiaphragmatic irradiation.

‖Cumulative platinum dose was reported based on number of cycles (ie, for bleomycin, etoposide, and cisplatin [BEP; 20 mg/m^2 daily for 5 days], cisplatin, vinblastine, and bleomycin [PVB; 20 mg/m^2], and etoposide, ifosfamide, and cisplatin [VIP; 20 mg/m^2 for 5 days]). Similarly, etoposide dose was reported based on number of cycles (ie, for BEP [100 mg/m^2 daily for 5 days per cycle]). Platinum dose included 10 subcohort patients receiving carboplatin (carboplatin, etoposide, and bleomycin). A cisplatin dose equivalent to carboplatin of 0.25 times the carboplatin dose was assumed.

¶Administered bleomycin dose accounting for dose reduction. Standard bleomycin dose in BEP chemotherapy is 30 U on days 1, 8, and 15 or on days 2, 8, and 15.

SIRs for solid infradiaphragmatic SMNs remained increased for at least 25 years, among both patients with seminoma and those with nonseminoma (Data Supplement). Among patients with seminoma, SIRs for any infradiaphragmatic SMN (P trend = .007) and GI SMN (P trend = .041) were higher for younger patients. Similarly, SIRs increased with decreasing age at TC diagnosis for any solid SMN (P trend = .002) and for infradiaphragmatic (P trend = .002), GI (P trend = .045), and urologic SMNs (P trend = .008) in those with nonseminoma.

The cumulative incidence of any solid SMN was 10.3% (95% CI, 9.0% to 11.6%) at 25 years of follow-up; it was 12.6% for patients with seminoma and 9.5% for those with nonseminoma, whereas expected cumulative incidences were 8.4% and 4.3%, respectively (Table 3). Cumulative incidence did not differ between treatment periods (Data Supplement).

Case-Cohort Comparisons: Multivariable Regression Analyses

Receipt of platinum-containing chemotherapy was associated with increased risks of solid SMNs (HR, 2.40; 95% CI, 1.58 to 3.62) and colorectal (HR, 3.85; 95% CI, 1.67 to 8.92) and noncolorectal GI SMNs (HR, 5.00; 95% CI, 2.28 to 10.95; adjusted for radiation dose and etoposide use; Table 4) compared with patients who did not receive platinum-containing chemotherapy. Receipt of platinum-containing chemotherapy 400 to 499 mg/m^2 and ≥ 500 mg/m^2 significantly increased solid SMN risk compared

Table 3. SIR and Cumulative Incidence for Selected SMNs

Cancer Site	ICD-10	Total (N = 5,848)				Seminoma (n = 2,827)				Nonseminoma (n = 3,021)			
		Obs	SIR (95% CI)	AER	25-Year Cumulative Incidence (95% CI)	Obs	SIR (95% CI)	AER	25-Year Cumulative Incidence (95% CI)	Obs	SIR (95% CI)	AER	25-Year Cumulative Incidence (95%CI)
Any solid SMN	C00-C80	350	1.8 (1.6 to 2.0)	17.5	10.3 (9.0 to 11.6)	180	1.5 (1.3 to 1.8)	15.0	12.6 (10.5 to 14.9)	170	2.2 (1.9 to 2.6)	19.7	9.5 (7.9 to 11.4)
Supradiaphragmatic SMN	C00-C15, C30-C39, C69-C74	86	3.9 (3.1 to 4.8)	7.0	2.7 (2.0 to 3.5)	40	1.2 (0.8 to 1.6)	1.35	2.6 (1.8 to 3.7)	46	2.1 (1.5 to 2.7)	4.9	1.9 (1.3 to 2.8)
Lip, oral cavity, or pharynx	C00-14	6	0.7 (0.3 to 1.4)	−0.3	0.1 (0.1 to 0.3)	3	0.5 (0.1 to 1.6)	−0.7	0.8 (0.2 to 2.5)	4	1.0 (0.3 to 2.5)	0.0	0.2 (0.1 to 0.5)
Esophagus	C15	7	1.0 (0.4 to 2.0)	−0.2	0.0 (0.0 to 0.2)	3	0.7 (0.1 to 2.0)	−0.3	0.2 (0.2 to 3.8)	4	1.5 (0.4 to 3.8)	0.1	0.1 (0.0 to 0.3)
Lung or bronchus	C34	50	1.5 (1.1 to 1.9)	1.3	1.4 (1.0 to 1.9)	22	1.0 (0.7 to 1.6)	0.2	1.7 (1.0 to 2.6)	28	2.1 (1.4 to 3.1)	3.1	1.2 (0.7 to 1.9)
Thyroid gland	C73	7	4.6 (1.9 to 9.5)	0.6	0.2 (0.1 to 0.4)	3	3.8 (0.8 to 11.2)	0.5	0.2 (0.1 to 0.7)	4	5.5 (1.5 to 14.0)	0.7	0.2 (0.1 to 0.5)
Solid infradiaphragmatic SMN	C16-20, C22-26, C64-C68	150	2.4 (2.0 to 2.8)	9.7	4.5 (3.6 to 5.5)	79	2.1 (1.6 to 2.6)	9.6	6.2 (4.7 to 8.1)	71	2.9 (2.2 to 3.6)	9.7	3.2 (2.5 to 4.6)
GI tract	C16-C20, C22-C26	99	2.1 (1.7 to 2.6)	5.7	3.0 (2.3 to 3.8)	52	1.9 (1.4 to 2.4)	5.7	4.5 (3.1 to 6.1)	47	2.6 (1.9 to 3.5)	6.0	1.9 (1.3 to 2.8)
Stomach	C16	16	2.3 (1.3 to 3.8)	0.8	0.4 (0.2 to 0.8)	7	1.7 (0.7 to 3.5)	0.68	0.7 (0.3 to 1.5)	9	3.7 (1.5 to 6.2)	1.3	0.2 (0.1 to 0.6)
Small intestine	C17	5	5.2 (1.7 to 12.2)	0.4	0.2 (0.1 to 0.4)	5	8.9 (2.9 to 20.8)	1.0	0.4 (0.1 to 1.0)	0	—	—	—
Colon	C18	30	1.8 (1.2 to 2.5)	1.4	0.7 (0.3 to 0.9)	13	1.3 (0.7 to 2.1)	0.6	0.8 (0.4 to 1.7)	17	2.6 (1.5 to 4.1)	2.1	0.7 (0.3 to 1.2)
Rectum	C19-C20	20	1.5 (0.9 to 2.4)	0.7	0.6 (0.3 to 1.0)	8	1.0 (0.4 to 2.0)	0.0	0.9 (0.4 to 1.9)	12	2.3 (1.2 to 4.1)	1.4	0.4 (0.1 to 0.9)
Pancreas	C25	21	4.0 (2.5 to 6.2)	1.7	0.8 (0.3 to 1.0)	14	4.4 (2.4 to 7.4)	2.5	0.8 (0.4 to 1.6)	7	3.4 (1.4 to 7.1)	1.03	0.4 (0.2 to 1.0)
Urinary tract*	C64-C68	52	3.0 (2.3 to 4.0)	3.7	1.5 (1.1 to 2.1)	28	2.7 (1.8 to 3.9)	4.1	1.8 (1.1 to 2.7)	24	3.6 (2.3 to 5.3)	3.6	1.3 (0.8 to 2.2)
Kidney	C64	17	2.1(1.2 to 3.4)	1.0	0.4 (0.2 to 0.8)	10	2.1 (1.0 to 3.8	1.2	0.6 (0.3 to 1.4)	7	2.2 (0.8 to 4.4)	0.8	0.3 (0.1 to 0.7)
Bladder	C67	35	4.3 (3.0 to 6.0)	3.0	1.1 (0.7 to 1.6)	17	3.4 (2.0 to 5.4)	2.8	1.0 (0.6 to 1.8)	18	5.8 (3.5 to 9.2)	3.1	1.1 (0.6 to 1.9)
Prostate	C61	40	1.2 (0.8 to 1.6)	0.7	1.3 (0.8 to 1.8)	26	1.2 (0.8 to 1.8)	1.0	1.5 (0.9 to 2.5)	14	1.1 (0.6 to 1.9)	1.2	1.0 (0.5 to 1.8)
Other malignancies													
Skin, melanoma	C43	33	2.1 (1.5 to 3.0)	1.7	1.1 (0.7 to 1.7)	15	1.8 (1.0 to 2.9)	1.5	1.1 (0.6 to 2.0)	18	2.5 (1.5 to 3.9)	2.3	1.1 (0.6 to 1.8)
Skin, other	C44	21	2.0 (1.3 to 3.1)	1.2	0.8 (0.5 to 1.2)	13	2.1 (1.1 to 3.6)	1.6	1.4 (0.6 to 3.1)	8	2.0 (0.9 to 3.9)	0.8	0.6 (0.3 to 1.3)
Soft tissue sarcoma	C47-C49	13	4.7 (2.4 to 8.2)	1.0	0.2 (0.1 to 0.5)	3	2.2 (0.5 to 6.5)	0.4	0.2 (0.1 to 0.7)	10	8.4 (4.0 to 15.4)	1.8	0.3 (0.1 to 0.5)
CNS	C70-C72	11	1.7 (0.9 to 3.0)	0.5	0.3 (0.1 to 0.5)	4	1.2 (0.3 to 2.9)	0.1	0.2 (0.1 to 0.5)	7	2.3 (0.9 to 4.8)	0.8	0.3 (0.2 to 0.7)
Primary site unknown or ill defined	C80	6	0.9 (0.4 to 2.1)	0.0	0.2 (0.1 to 0.6)	4	1.1 (0.3 to 2.7)	0.0	0.4 (0.1 to 0.9)	2	0.8 (0.1 to 2.8)	−0.1	0.2 (0.0 to 0.7)

NOTE. SIRs reported if ≥ five malignancies observed. Besides the specific tumor sites noted, we observed the following SMNs: liver cancer (C22; n = 1); biliary tract (C24; n = 4); digestive tract, other and ill defined (C26; n = 2); larynx (C32; n = 4); other or unspecified respiratory and intrathoracic sites (C38-39; n = 1); bone and joint (C40-41; n = 3); mesothelioma (C45; n = 4); male breast cancer (C50; n = 2); eye and adnexa (C69; n = 1); and other endocrine glands (C75; n = 1). SIR for contralateral testicular cancer (C62) diagnosed ≥ 1 year after primary testicular cancer diagnosis was 17.2 (95% CI, 14.5 to 20.1; n = 148) among all patients with testicular cancer, 23.2 (95% CI, 18.4 to 28.8; n = 80) among patients with seminoma, and 13.1 (95% CI, 10.2 to 16.7; n = 68) among those with nonseminoma.

Abbreviations: AER, absolute excess risk per 10,000 person-years; ICD-10, International Classification of Diseases (10th revision); Obs, observed; SIR: standardized incidence ratio; SMN, subsequent malignant neoplasm.

*Two patients first developed bladder cancer and subsequently kidney cancer.

with surgery only (HR, 2.43; 95% CI, 1.40 to 4.23 and HR, 2.42; 95% CI, 1.50 to 3.90, respectively), whereas risk was not significantly increased after < 400 mg/m^2 (HR, 1.75; 95% CI, 0.90 to 3.43). Etoposide was not associated with solid SMN risk after adjusting for receipt of platinum-containing chemotherapy (HR, 1.00; 95% CI, 0.63 to 1.62). We observed a nonlinear dose-response relationship between increasing platinum exposure and risk of a solid SMN, with risk leveling off at higher platinum doses (Fig 1), whereas a linear dose-response relationship better described the association with GI SMN risk, with each additional 100 mg/m^2 of platinum-containing chemotherapy increasing SMN risk by 53% (95% CI, 26% to 80%; *P* trend < .001). Urologic SMN risk was significantly increased among patients treated with 400 to 499 mg/m^2 of platinum-containing chemotherapy (HR, 4.41; 95% CI, 1.21 to 16.10) but not among patients who received ≥ 500 mg/m^2 (HR, 2.71; 95% CI, 0.86 to 8.57).

Receipt of ≥ 500 mg/m^2 of platinum-containing chemotherapy was associated with a three-fold increased lung cancer risk (95% CI, 1.18- to 7.50; adjusted for age, radiation dose, etoposide use, and smoking status), whereas lower doses did not increase risk (HR, 1.18; 95% CI, 0.37 to 3.80; Data Supplement). Platinum-containing chemotherapy was not associated with sarcoma risk (HR, 0.88; 95% CI, 0.30 to 2.56) but was associated with increased stomach cancer risk (HR, 11.7; 95% CI, 2.23 to 62.35; adjusted for age, radiation dose, and etoposide use).

Infradiaphragmatic irradiation was associated with increased risk of infradiaphragmatic SMNs compared with no para-aortic irradiation, with risk increasing with a higher administered dose (*P* trend ≤ .001; Table 4). The HR of infradiaphragmatic SMNs increased linearly by 8% for every Gray increase in radiation dose (95% CI, 6% to 9%; *P* trend < .001; Fig 2); the HR increased by 9% per Gray (95% CI, 7% to 11%; *P* trend < .001) for GI SMNs (Fig 2). The HR for infradiaphragmatic SMN risk was 1.88 (95% CI, 0.90 to 3.92) after > 26 Gy to the para-aortic field alone compared with no radiotherapy, whereas patients receiving radiation at similar doses to a dog-leg field experienced a 4.04-fold increased risk (95% CI, 2.27- to 7.18; *P* heterogeneity < .001; adjusted for age and chemotherapy dose). Dog-leg irradiation with > 26 Gy increased noncolorectal GI cancer risk 9.99-fold compared with no radiotherapy (95% CI, 3.63- to 27.48). This risk was significantly higher than the risk conferred by > 26 Gy to the smaller para-aortic field (HR, 5.15; 95% CI, 1.38 to 19.20; *P* heterogeneity < .001). Supradiaphragmatic radiotherapy did not significantly increase risk of supradiaphragmatic solid cancers (HR, 2.42; 95% CI, 0.87 to 6.78; Data Supplement). Complete case analyses provided similar results for all cancer outcomes (Data Supplement).

DISCUSSION

In this large cohort of TC survivors, with long-term follow-up, we show for the first time to our knowledge that platinum-containing chemotherapy is associated with a dose-dependent increase in risk of GI SMNs. Higher platinum doses were associated with increased risks of urologic and lung SMNs, although no significant dose-dependent increase was observed for these sites, likely because of the smaller number of SMNs. Risk of infradiaphragmatic SMNs increased in a dose-dependent manner after infradiaphragmatic irradiation.

An association between chemotherapy and increased risk of various solid SMNs, including soft tissue sarcoma,[7] lung,[7] thyroid,[7] bladder,[4] and kidney cancers,[7] and melanoma,[4] has been reported previously among TC survivors. However, none of these studies specifically addressed the association with platinum-based chemotherapy, and none showed a dose-dependent relationship. Fung et al[7] showed that chemotherapy was associated with increased risks of thyroid and kidney cancers and soft tissue sarcoma, whereas nonsignificantly elevated risks were observed for bladder and lung cancers, compared with surgery only. GI cancer risk was not increased in this study. Travis et al[3] related their finding of an increased lung cancer risk among 1-year TC survivors to exposure to supradiaphragmatic irradiation.

The association between platinum compounds and SMN risk has also been studied in childhood cancer survivors. Friedman et al[20] did not observe a dose-dependent association between platinum-chemotherapy and SMN risk in the US Childhood Cancer Survivor Study cohort. Henderson et al[9] reported a 7.6-fold increased GI cancer risk with exposure to platinum derivatives after longer follow-up of the Childhood Cancer Survivor Study cohort. However, most patients in this study had received both chemotherapy and radiotherapy, and the GI cancer risk estimate was based on four patients exposed to cisplatin.

Although the causal mechanisms underlying an association between platinum-containing chemotherapy and solid SMN risk are not known,[1,2,21] cisplatin-DNA adducts may play a role.[22,23] Residual active platinum has been found in serum and urine up to 20 years after treatment.[24,25] Prolonged exposure to platinum residuals, for instance in organs involved in urine production, could trigger malignant transformation.

One of the most frequent SMNs in our study was bladder cancer, with 35 cases responsible for 17.1% of the overall absolute excess risk. The 5.8-fold increased risk among patients with nonseminoma in this study is comparable to the 2.7-fold increased risk previously reported by Travis et al.[3] However, Fung et al[7] did not observe an elevated bladder cancer risk after chemotherapy exposure, possibly attributable to the rather short follow-up in their study (median < 7 years).

Chemotherapy exposure was associated with a five-fold increased risk of kidney cancer among childhood cancer survivors.[26] We also observed an increased risk among TC survivors for this rare cancer in the general population, although risk was no longer significantly elevated when we restricted our analyses to patients with nonseminoma, likely because of the small number of events (seven cancers). Fung et al[7] observed a 3.4-fold increased risk of kidney cancer after chemotherapy in TC survivors compared with the general population (13 cancers), and risk was also increased 2.1-fold after surgery only (11 cancers), possibly because of missed relapse treatment.

Some SMNs among patients with nonseminoma may be misdiagnosed as dedifferentiated late relapses originating from residual teratoma.[27-31] Approximately 40% of patients with nonseminoma receiving chemotherapy and/or undergoing retroperitoneal lymph node dissection presented with teratoma on pathologic evaluation.[32] Today, most suspect residual lesions are removed pre- or postchemotherapy, but this was not consistently

Table 4. Multivariable Cox Analysis for Treatment-Associated Risk of Selected Subsequent Cancers Among TC Survivors

Variable	Any Solid SMN (n = 350)			Any Infradiaphragmatic SMN (n = 150)			Any GI SMN (n = 99)			Any Urologic SMN C64-C68 (n = 52)[a]			Colorectal SMN C18-C20 (n = 50)			GI SMN Other Than Colorectal C16-C17, C22-C26 (n = 49)		
	No.	HR	95% CI	No.	HR	95% CI	No.	HR	95% CI	No.	HR	95% CI	No.	HR	95% CI	No.	HR	95% CI
Platinum-containing chemotherapy[b]																		
No	199	1	Ref	83	1	Ref	56	1	Ref	28	1	Ref	28	1	Ref	28	1	Ref
Yes	151	2.40	1.58 to 3.62	67	3.81	2.20 to 6.60	43	4.53	2.47 to 8.29	24	2.47	0.74 to 8.30	22	3.85	1.67 to 8.92	21	5.00	2.28 to 10.95
Etoposide[c]																		
No	235	1	Ref	105	1	Ref	73	1	Ref	32	1	Ref	37	1	Ref	37	1	Ref
Yes	115	1.00	0.63 to 1.62	45	0.68	0.34 to 1.37	26	0.50	0.23 to 1.09	20	1.72	0.18 to 16.8	13	0.46	0.14 to 1.46	12	0.53	0.21 to 1.36
Platinum-containing chemotherapy, mg/m^2 [b]																		
No platinum-containing chemotherapy[d]	199	1	Ref	83	1	Ref	56	1	Ref	28	1	Ref	28	1	Ref	28	1	Ref
< 400	28	1.75	0.90 to 3.43	11	2.76	1.08 to 7.10	6	2.26	0.68 to 7.56	5	2.14	0.36 to 12.61	5	3.15	0.71 to 14.01	1	0.96	0.08 to 10.76
400-499	85	2.43	1.40 to 4.23	38	4.13	2.03 to 8.40	21	3.62	1.57 to 8.37	17	2.71	0.86 to 8.57	11	3.30	1.09 to 10.00	10	4.14	1.39 to 12.36
≥ 500	38	2.42	1.50 to 3.90	18	3.45	1.77 to 6.74	16	5.00[e]	2.42 to 10.30	2			6	3.24	1.23 to 8.53	10	7.31	2.75 to 19.45
P trend		< .001			< .001			< .001			.045			.005			< .001	
Infradiaphragmatic irradiation dose, Gy[f]																		
No infradiaphragmatic irradiation	154	1	Ref	62	1	Ref	40	1	Ref	22	1	Ref	25	1	Ref	1	Ref	1
≤ 26	86	1.27	0.88 to 1.82	34	1.37	0.79 to 2.36	18	1.02	0.52 to 2.01	16	2.37	0.96 to 5.84	8	0.61	0.26 to 1.44	1.92	0.68 to 5.41	1.92
>26-32	51	2.41	1.54 to 3.77	26	3.41	1.88 to 6.20	20	3.53	1.79 to 6.98	7	3.56	1.29 to 9.75	8	2.00	0.83 to 4.59	7.02	2.70 to 18.29	7.02
>32-36	12	2.49	1.13 to 5.53	7	3.90	1.46 to 10.41	6	4.66	1.63 to 13.33	1	—	—	4	3.63	0.95 to 13.78	6.17	1.23 to 31.00	6.17
>36	47	3.52	1.13 to 5.53	22	4.17	2.21 to 7.87	5	3.91	1.91 to 7.98	7	5.49	1.74 to 17.28	5	1.58	0.52 to 4.77	8.72	3.42 to 22.25	8.72
P trend		< .001			< .001			< .001			.007			.047			< .001	
Irradiation field and dose[g]																		
No radiotherapy[h]	159	1	Ref	64	1	Ref	41	1	Ref	24	1	Ref	25	1	Ref	17	1	Ref
Para-aortic, Gy																		
≤ 26	9	0.92	0.36 to 2.36	3	—	—	1	—	—	2	—	—	—	—	—	1	—	—
> 26	38	1.45	0.90 to 2.33	16	1.88	0.90 to 3.92[i]	10	1.71	0.69 to 4.20	6	2.13	0.63 to 7.27	3	0.61	0.18 to 2.08	6	5.15	1.38 to 19.20
P trend		.142			.110			.190			.375			.632			.030	
Dog leg, Gy																		
≤ 26[j]	30	2.64	1.55 to 4.48	14	3.76	1.71 to 8.27	9	3.43	1.34 to 8.77	5	4.27	1.15 to 15.88	5	2.40	0.83 to 6.93	2	5.39	1.12 to 25.90
> 26[k]	114	2.88	1.96 to 4.24	53	4.04	2.27 to 7.18[l]	39	4.24	2.21 to 8.13	15	3.57	1.19 to 10.67	17	1.99	0.92 to 4.26	23	9.99[l]	3.63 to 27.48
P trend		< .001			< .001			< .001			.222			.872			< .001	

NOTE. Proportions of missing values for subcohort members and patients with a solid SMN were: stage (6.7%), irradiation field (9.7%), radiation dose (12.2%), chemotherapy type (4.5%), number of cycles (14.8%), weight (32.0%), height (49.1%), and smoking status at start of TC treatment (31.6%). We did not observe interactions between treatment modality and smoking or among treatment modalities (radiotherapy and chemotherapy). Median numbers of patients per exposure category over 20 pooled data sets were rounded. In the subcohort, nine patients received carboplatin only, 441 received cisplatin only, and 52 received both. No. column indicates median number of cases over the 20 imputed data sets.

Abbreviations: HR, hazard ratio; SMN, second malignant neoplasm; TC, testicular cancer.

[a]Of the 52 patients with a urologic malignancy, 33 had bladder cancer, 15 had kidney cancer, two had bladder and kidney cancers, and two had malignancies of the urethra.

[b]Adjusted for age (continuous), radiation dose (categorical), and etoposide (yes or no).

[c]Adjusted for age (continuous), radiation dose (categorical), and chemotherapy dose (categorical).

[d]In the SMN data set including patient cases and subcohort members, patients who did not receive platinum-containing chemotherapy included eight who received dactinomycin only, one who received dactinomycin combined with etoposide and bleomycin, three who received vinblastine combined with bleomycin, one who received bleomycin only, and 16 who received other chemotherapy (without platinum). Four solid SMNs were observed among patients who were treated with chemotherapy other than platinum.

[e]≥ 500 mg/m^2 platinum-containing chemotherapy versus 400 to 499 mg/m^2: *P* hetero = .441.

[f]Adjusted for age (continuous), chemotherapy dose (categorical), and etoposide (yes or no).

[g]Adjusted for age (continuous) and number of chemotherapy cycles (categorical).

[h]No radiotherapy or infradiaphragmatic irradiation field other than dog-leg or para-aortic irradiation.

[i]Dog-leg field, > 26 Gy versus para-aortic field, 26 Gy: *P* hetero < .001.

[j]Administered cumulative dose; no infradiaphragmatic irradiation was used as reference group.

[k]No infradiaphragmatic irradiation was used as a reference group.

[l]*P* heterogeneity for dog-leg versus para-aortic irradiation = < .001.

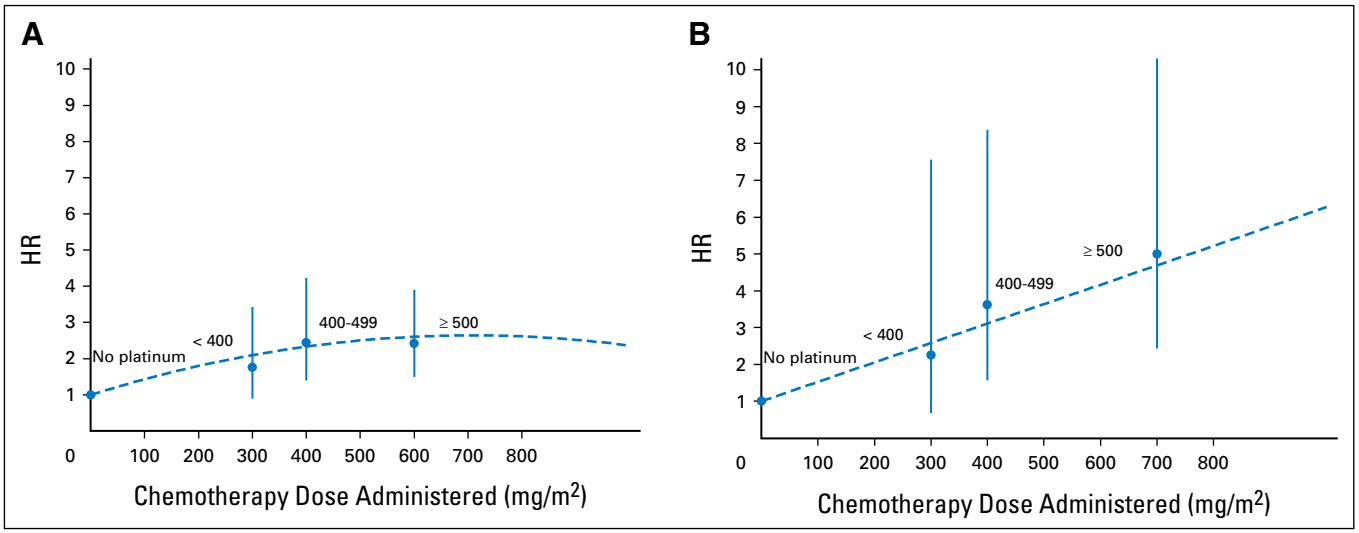

Fig 1. Risk of (A) solid subsequent malignant neoplasm (SMN) and (B) GI SMN by cumulative dose of platinum-containing chemotherapy (in mg/m^2 body surface area) among 1-year testicular cancer survivors. Models adjusted for age (continuous), etoposide use, and subdiaphragmatic irradiation dose. Circles are estimates for dose categories (no platinum-containing chemotherapy and > 0 to 400, 400 to 499, and ≥ 500 mg/m^2 of body surface area) and are plotted at the median dose in each category (ie, 0, 300, 400, and 600 mg/m^2). Vertical lines represent 95% CIs. (A) Dotted curved line indicates the best-fitting dose-response relationship, allowing for curvature (model described in Statistical Analysis). The hazard ratios (HRs) for SMNs were 2.1 for patients who received 300 mg/m^2, 2.3 for a dose of 400 mg/m^2, and 2.6 for a dose of 600 mg/m^2 compared with patients who did not receive platinum-containing chemotherapy ($P < .001$), based on the following model: HR = 1 + 0.46 × dose − 0.03 × dose^2. (B) Dotted straight line indicates the best-fitting dose-response relationship and reflects a linear increase in GI SMN risk, adding 0.53 (95% CI, 0.26 to 0.80; $P < .001$) to the GI SMN rate for each additional dose of 100 mg/m^2 of body surface area of platinum-containing chemotherapy.

done in the past.[12] Although rare, residual teratomatous tissue may ultimately dedifferentiate into a sarcoma or even an adenocarcinoma.[33] We cannot exclude the possibility that the high SIR for sarcomas in patients with nonseminoma is partly a result of dedifferentiated late relapses, however rare.[34] Nonetheless, for most SMNs in our study, a different clinical presentation would have been expected in case of dedifferentiation, not a localized cancer within a clearly defined anatomic structure.

In line with Travis et al,[3] we found an increased risk of infradiaphragmatic SMNs after exposure to infradiaphragmatic irradiation, which was mainly driven by an increased risk of pancreatic, small intestine, and bladder cancers. It has been shown that approximately 64% of all excess cancers after infradiaphragmatic irradiation occur within irradiated tissue.[3,35] The lower SMN risk observed after para-aortic compared with dog-leg irradiation is encouraging but should be confirmed. Previous studies

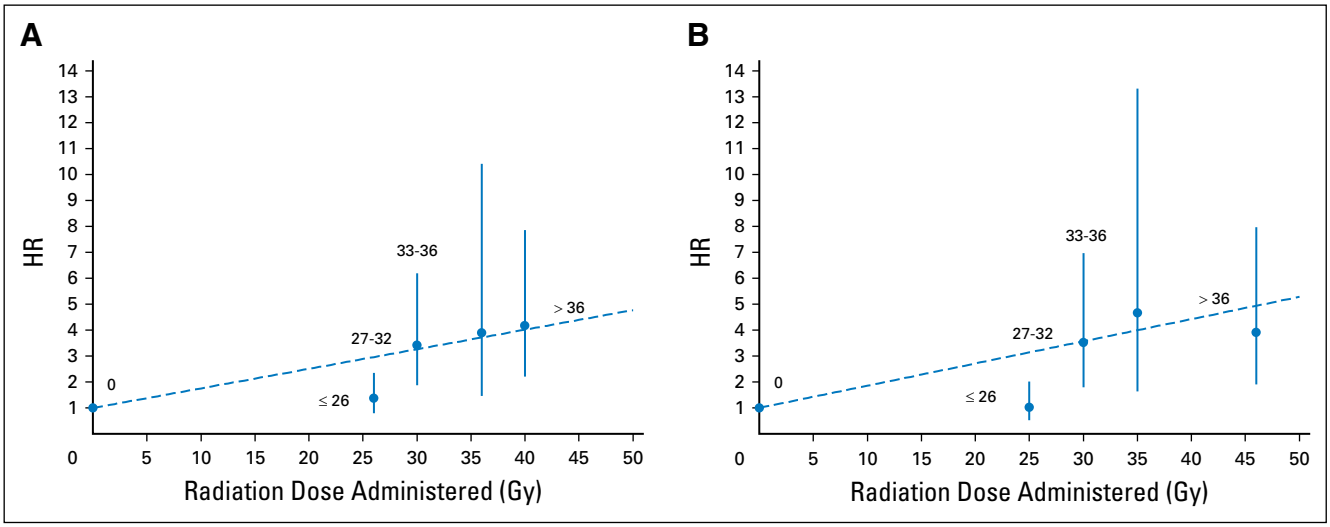

Fig 2. Risk of (A) infradiaphragmatic subsequent malignant neoplasm (SMN) and (B) GI SMN by administered infradiaphragmatic irradiation dose among 1-year testicular cancer survivors. Model adjusted for age (continuous), etoposide use, and platinum-containing chemotherapy cycles. Circles are estimates for dose categories (no infradiaphragmatic radiotherapy and > 0 to 26, 27 to 32, 33 to 36, and > 36 Gy) and are plotted at the median dose within each category (ie, 0, 26, 30, 36, and 40 Gy). Vertical lines represent 95% CIs for dose categories. (A) Dotted straight line indicates the best-fitting dose-response relationship and reflects a linear increase in infradiaphragmatic SMN risk, adding 0.08 (95% CI, 0.06 to 0.09; $P < .001$) to the infradiaphragmatic SMN rate for each additional Gray of infradiaphragmatic irradiation. (B) Dotted straight line indicates the best-fitting dose-response relationship and reflects a linear increase in GI SMN risk, adding 0.09 (95% CI, 0.07 to 0.11; $P < .001$) to the GI SMN rate for each additional Gray of infradiaphragmatic irradiation. HR, hazard ratio.

already reported a significant dose-response relationship between infradiaphragmatic irradiation for TC and various solid SMNs, such as stomach and pancreatic cancers.[36,37] An international case-control study in TC survivors treated between 1959 and 1987 found an increasing stomach cancer risk with increasing dose to affected site in stomach, with an odds ratio of 20.5 for $\geq$ 50 Gy compared with $<$ 10 Gy.[37] No association was observed with chemotherapy use or cumulative cisplatin dose.[37] The absence of an increased stomach cancer risk in our patients with seminoma could be a result of lower radiation doses, because our cohort largely consisted of more recently treated patients.

The absence of a decline in solid SMN risk in patients treated between 1996 and 2007 compared with patients treated in earlier decades may be a result of the relatively low number of patients with nonseminoma receiving high-dose radiotherapy in the earliest treatment periods in our cohort compared with previous cohort studies.[3,7] Fung et al[7] did also not observe a decrease in solid SMN risk for patients treated in the period from 1995 to 2008 compared with 1980 to 1994. Changes in radiotherapy techniques, field size, and dose and reduction of the number of chemotherapy cycles may have been too recent to translate into reduced SMN risk in our cohort.

Despite our efforts to abstract complete treatment exposure information, we have missing data on cumulative platinum dose and body size. We therefore presented cumulative platinum dose based on the number of administered cycles of chemotherapy. This was highly comparable to the actual cumulative administered dose in patients for whom we had complete information on dose and body surface, because dose reductions were rare. Because of the retrospective nature of data collection, we also had limited information on changes in lifestyle factors, such as smoking behavior and alcohol use.

Our study has important implications for TC survivors as well as patients with newly diagnosed TC. The lower SMN risk with lower infradiaphragmatic radiation doses and fewer cycles of chemotherapy is reassuring for current patients.[12]

In conclusion, in this large multicenter cohort, we observed increased risks of various solid SMNs associated with exposure to platinum-based chemotherapy and radiotherapy. Our study provides evidence for a dose-response relationship between platinum-containing chemotherapy and solid SMN risk, in particular for GI SMNs. Therefore, efforts to reduce treatment intensity are important, as are efforts to increase awareness of these late effects and potentially screen if reliable screening tools are available.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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