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ORIGINAL REPORT

Solid Tumors After Chemotherapy or Surgery for Testicular Nonseminoma: A Population-Based Study

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ABSTRACT

Purpose
Increased risks of solid tumors after older radiotherapy strategies for testicular cancer (TC) are well established. Few population-based studies, however, focus on solid cancer risk among survivors of TC managed with nonradiotherapy approaches. We quantified the site-specific risk of solid cancers among testicular nonseminoma patients treated in the modern era of cisplatin-based chemotherapy, without radiotherapy.

Patients and Methods
Standardized incidence ratios (SIRs) for solid tumors were calculated for 12,691 patients with testicular nonseminoma reported to the population-based Surveillance, Epidemiology, and End Results program (1980 to 2008) and treated initially with either chemotherapy (n = 6,013) or surgery (n = 6,678) without radiotherapy. Patients accrued 116,073 person-years of follow-up.

Results
Two hundred ten second solid cancers were observed. No increased risk followed surgery alone (SIR, 0.93; 95% CI, 0.76 to 1.14; n = 99 solid cancers), whereas significantly increased 40% excesses (SIR, 1.43; 95% CI, 1.18 to 1.73; n = 111 solid cancers) occurred after chemotherapy. Increased risks of solid cancers after chemotherapy were observed in most follow-up periods (median latency, 12.5 years), including more than 20 years after treatment (SIR, 1.54; 95% CI, 0.96 to 2.33); significantly increased three- to seven-fold risks occurred for cancers of the kidney (SIR, 3.37; 95% CI, 1.79 to 5.77), thyroid (SIR, 4.40; 95% CI, 2.19 to 7.88), and soft tissue (SIR, 7.49; 95% CI, 3.59 to 13.78).

Conclusion
To our knowledge, this is the first large population-based series reporting significantly increased risks of solid cancers among patients with testicular nonseminoma treated in the modern era of cisplatin-based chemotherapy. Subsequent analytic studies should focus on the evaluation of dose-response relationships, types of solid cancers, latency patterns, and interactions with other possible factors, including genetic susceptibility.

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INTRODUCTION

Testicular cancer (TC) is the most common cancer among men age 18 to 39 years,[1] with a worldwide doubling in incidence over the last few decades.[2] In contrast to the poor survival associated with many adult cancers, the 10-year relative survival rate of men with TC now approaches 95%,[3] as a result of the introduction of effective chemotherapy.[4] These remarkable successes,[4] however, have been accompanied by the emergence of late complications, including second malignant neoplasms (SMNs). Survivors of TC experience significantly increased 1.7- to 3.5-fold risks of SMNs,[5-13] which have been largely attributed to radiotherapy,[7,8,10,11,13] with risks remaining significantly elevated for at least 35 years.[10]

In contrast to what has become compelling evidence for the role of radiation in the development of solid cancers after TC,[10,14,15] the extent to which modern cisplatin-based chemotherapy might contribute to excess risk is less clear. Whereas metastatic seminoma may be cured by either radiotherapy or chemotherapy, treatment of metastatic nonseminoma consists more uniformly of cisplatin-based chemotherapy.[16] Radiotherapy is almost never part of curative treatment of nonseminoma.[16] Greene[17] first suggested that cisplatin might be a human carcinogen, and subsequent international investigations of patients with ovarian cancer[18] or TC[19] documented strong dose-response relationships between cumulative cisplatin dose and secondary leukemia risk ($P < .001$). Most studies[10-13] of solid cancers after TC, however, have focused on patients

treated before modern cisplatin-based chemotherapy was widely adopted, when other alkylating agents were applied, including those convincingly linked to the development of solid tumors.[15,20-24]

Significantly increased 1.8-fold risks of solid tumors were observed after chemotherapy among 10-year survivors of TC in a large international series,[10] but this study included many patients treated as far back as 1943. Moreover, the site-specific risks of solid cancers after chemotherapy were not reported, because the study focused on long-term radiotherapy effects. Results of smaller studies of survivors of TC (ranging from 346 to 710 patients) found no significant excesses of solid tumors after chemotherapy,[11,13,25] but again, most series consisted mostly of patients treated before the widespread use of platinating agents. To quantify site-specific relative and absolute risks of solid cancers treated in the modern era of cisplatin-based chemotherapy, we studied 12,691 survivors of testicular nonseminoma initially managed with either chemotherapy or surgery alone.

PATIENTS AND METHODS

Patients

We evaluated the risks of second solid cancers among men diagnosed with histologically confirmed testicular nonseminoma as a first primary malignancy between 1980 and 2008, when cisplatin-based chemotherapy was increasingly adopted for treatment.[26] All patients were initially managed without radiotherapy (n = 12,691) and reported to 16 population-based registries within the Surveillance, Epidemiology, and End Results (SEER) program. Patients with extragonadal germ cell tumors were excluded. Because the risk of radiotherapy-associated SMNs is well established in survivors of TC[5-13] and this treatment modality is typically not used to treat nonseminoma,[16] we excluded 93 patients initially managed with radiotherapy.

The SEER program collects data on patient demographics, tumor characteristics, and type of initial treatment. On the basis of age at TC diagnosis, patients were categorized into the following four groups: less than 25, 25 to 29, 30 to 39, and ≥ 40 years. Calendar year of TC diagnosis was divided into 1980 to 1989, 1990 to 1999, and 2000 to 2008. Extent of disease was grouped into localized, regional, and distant disease. Patients were divided into the following two broad groupings of initial treatment: surgery alone (no radiotherapy) or chemotherapy (no radiotherapy). Types of surgery included orchiectomy alone or orchiectomy plus resection of regional or distant metastatic sites with lymph node dissection.

Treatment for testicular nonseminoma depends on disease stage. Until the late 1990s, standard management for stage I nonseminoma in the United States included orchiectomy with retroperitoneal lymph node dissection,[16] with active surveillance[27,28] becoming an acceptable management strategy afterward. In the mid-2000s, adjuvant chemotherapy with two cycles of cisplatin, etoposide, and bleomycin[29] emerged as an additional treatment option for patients with high-risk stage I testicular nonseminoma. Among men with stage II nonseminoma, management with cisplatin-based chemotherapy and retroperitoneal lymph node dissection[16] was applied after the late 1970s. For stage III disease, cisplatin-based chemotherapy followed by the resection of residual metastatic lesions is now standard treatment.[4] Beginning in the mid-1970s, advanced testicular nonseminoma was treated with chemotherapy that included cisplatin, vinblastine, and bleomycin,[4] with etoposide replacing vinblastine in the mid-1980s.[30] In subsequent years, other chemotherapy regimens were developed, including cisplatin and etoposide[31]; cisplatin, etoposide, and ifosfamide[32,33]; and cisplatin, ifosfamide, and paclitaxel.[34] Radiation treatment was generally reserved for the few patients with symptomatic chemotherapy-resistant metastases not amenable to surgical resection.[35]

Histologically confirmed second solid cancers (excluding second contralateral TC) were identified in the SEER registries. To exclude synchronous cancers, person-years of observation were accrued starting from 2 months after time of TC diagnosis; follow-up continued until death or study end date (December 31, 2008), whichever occurred first.

Statistical Methods

Overall and site-specific relative risks of second solid cancers were expressed as the standardized incidence ratio (SIR) with 95% CIs. SIR is calculated by dividing the observed number of cancers by the number expected based on cancer incidence rates in the general population specific for each registration area as provided by the SEER program, using previously reported methods.[10,36] Statistical significance was defined as $P < .05$ (two-sided). We calculated the absolute excess risk (AER) of SMNs by subtracting the expected number from the observed number; the difference was then divided by person-years at risk (PYR), and number of excess cancers was expressed per 10,000 PYR—[(observed number – expected number)/PYR] × 10,000. SIR and AER calculations were performed using the MP-SIR session of SEER*Stat.[37] The 95% CIs for AER were calculated according to Breslow and Day.[38]

RESULTS

Patient Characteristics

Of the 12,691 eligible patients with testicular nonseminoma, 6,678 received surgery alone and 6,013 also received chemotherapy (Table 1). Median age at diagnosis was 28.8 years, and 94.2% were white. Men in the surgery cohort had predominantly localized disease (n = 5,666; 84.9%), whereas patients who also received chemotherapy tended to have either regional (37.1%) or distant (33.7%) disease. Median follow-up time in the surgery cohort was 7.3 years, with 2,621, 1,642, and 944 patients observed for 10, 15, and 20 years, respectively. In the chemotherapy group, median follow-up time was 6.5 years, with 2,071, 1,342, and 688 men observed for 10, 15, and 20 years, respectively. Overall, the surgery and chemotherapy groups accrued 64,106 and 51,967 person-years of follow-up, respectively.

Overall and Site-Specific Risks of Second Solid Cancers

A total of 210 second solid cancers was observed among all patients with nonseminoma. No increased risk (SIR, 0.93; 95% CI, 0.76 to 1.14; n = 99 solid cancers) followed management with surgery alone, whereas significantly increased 40% excesses (SIR, 1.43; 95% CI, 1.18 to 1.73; n = 111 solid cancers) occurred after chemotherapy. Nonetheless, the AER after chemotherapy was only 6.47 per 10,000 person-years (Table 2). When stratified by treatment, there was no difference in SMN risk among patients diagnosed in earlier years (1980 to 1994) versus those diagnosed in later years (1995 to 2008). Median time to solid cancer diagnosis after chemotherapy was 12.5 years (range, 0.1 to 28.0 years), and risks were elevated in most latency intervals, including ≥ 20 years after treatment (SIR, 1.54; 95% CI, 0.96 to 2.33; P for trend = .5). Marked upswings in absolute risks of SMN were observed in the 15 to 19 and 20+ year intervals after chemotherapy (20.76 and 27.22 excess cases per 10,000 person-years, respectively). In contrast, among patients managed with surgery alone, excess solid cancers were restricted to the first year after TC diagnosis, consistent with a surveillance effect.

Patients with nonseminoma treated with chemotherapy experienced significantly increased three- to seven-fold risks of cancers of the kidney (SIR, 3.37; 95% CI, 1.79 to 5.77), thyroid (SIR, 4.40; 95% CI, 2.19 to 7.88), and soft tissue (SIR, 7.49; 95% CI, 3.59 to 13.78). Kidney cancer accounted for 27.2% of the excess risk (AER, 1.8 excess cases per 10,000 person-years), with all tumors being renal cell carcinoma. Nonsignificant two- to three-fold risks were observed for cancers of the bladder (SIR, 1.86; 95% CI, 0.80 to 3.66), brain and nervous system

Table 1. Description of Population-Based Cohort of Survivors of Testicular Nonseminoma Managed With Surgery and/or Chemotherapy

Demographic or Clinical Characteristic	Survivors of Testicular Nonseminoma (N = 12,691)					
	Initial Surgery Only (no RT)			Initial Chemotherapy (no RT)		
	No. of Patients	%	Person-Years of Follow-Up	No. of Patients	%	Person-Years of Follow-Up
Total	6,678	100	64,106	6,013	100	51,967
Age at diagnosis, years						
< 25	2,165	32.4	21,151	2,136	35.5	18,727
25-29	1,607	24.1	16,436	1,326	22.1	12,120
30-39	1,973	29.5	19,469	1,716	28.5	15,462
≥ 40	933	14.0	7,050	835	13.9	5,658
Race						
White	6,311	94.5	61,035	5,643	93.8	49,055
Nonwhite	367	5.5	3,071	370	6.2	2,912
Calendar year of diagnosis						
1980-1989	1,242	18.6	26,767	1,111	18.5	20,629
1990-1999	1,795	26.9	22,617	1,598	26.6	18,751
2000-2008	3,641	54.5	14,722	3,304	54.9	12,587
Extent of disease						
Localized	5,666	84.9	53,591	1,687	28.1	13,705
Regional	834	12.5	8,953	2,234	37.1	22,554
Distant	116	1.7	871	2,028	33.7	14,791
Unknown	62	0.9	691	64	1.1	917
Initial surgery*						
None	0	0	0	147	2.4	712
Orchiectomy ± other types of surgery	5,691	85.2	42,088	4,990	83.0	34,647
Surgery, NOS	987	14.8	22,018	876	14.6	16,608

NOTE. Population includes 12,691 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, 9100 to 9102), initially managed with chemotherapy (n = 6,013) or surgical approaches alone (n = 6,678) and who survived ≥ 2 months. The sparse number of patients with testicular nonseminoma who were given radiotherapy (n = 93) precluded further evaluation.

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

*Surgical procedures defined as initial by the Surveillance, Epidemiology, and End Results program are those that are part of the original treatment plan at diagnosis.

(SIR, 2.07; 95% CI, 0.76 to 4.50), and pancreas (SIR, 2.77; 95% CI, 0.89 to 6.47). Significantly increased site-specific risks of solid cancers after surgery were restricted to kidney cancer (SIR, 2.14; 95% CI, 1.07 to 3.84), all with renal cell carcinoma histology.

Treatment-related risks of selected solid tumors according to time since diagnosis of testicular nonseminoma are listed in Table 3. Several general temporal patterns emerged, despite sparse numbers in several strata. After chemotherapy, significantly elevated four- to 4.5-fold risks of cancers of the bladder (SIR, 4.01; 95% CI, 1.61 to 8.26; n = 7) and kidney (SIR, 4.52; 95% CI, 1.81 to 9.31; n = 7) occurred at 10 to 19 years, with nonsignificant excesses of a similar magnitude (SIR, 4.35) persisting for kidney cancer among 20-year survivors. Similar patterns were not observed among patients managed with surgery alone. Thus, the risks for all urologic cancers considered together were 3.6-fold higher ≥ 10 years after chemotherapy, compared with the nonsignificant 1.1-fold increase after surgery alone.

Significant excesses of thyroid cancer emerged 1 to 9 years after chemotherapy (SIR, 6.51), with nonsignificant excesses (SIR, 3.51) in the 10- to 19-year interval. Papillary thyroid cancers accounted for 91% (n = 10) of tumors. Two of five thyroid cancers among men in the surgery group were diagnosed within the first year after nonseminoma diagnosis, consistent with a surveillance effect. Among men given chemotherapy, the overall significantly increased 7.5-fold risk of soft tissue tumor was largely a result of significant 10-fold risks observed 1 to 9 years later (SIR, 10.13; 95% CI, 4.06 to 20.87; n = 7). A similar pattern was not observed after surgery alone (n = 3). Nonsignificant excesses (SIR, 1.63; 95% CI, 0.89 to 2.73; n = 14) of lung cancer after chemotherapy (Table 2) were a result of large risks (SIR, 4.57; 95% CI, 1.97 to 9.00; n = 8) among 20-year survivors. Among patients managed with surgery alone, lung cancer risk did not exceed expectation (SIR, 0.81; 95% CI, 0.39 to 1.49).

DISCUSSION

To our knowledge, this is one of the first studies to demonstrate a significantly increased risk of solid cancers after modern-era chemotherapy for testicular nonseminoma, with no excesses among patients treated with surgery alone. Elevated relative risks of solid tumors after chemotherapy persisted for more than 20 years. Indeed, upswings in absolute excesses were observed in the intervals of 15 to 19 years and 20+ years. Other new findings include significantly increased site-specific risks of cancers of the kidney, thyroid, and soft tissue after chemotherapy.

Quantification of the late effects of cancer and its therapy is especially important for patients diagnosed at a young age, who receive curative therapy, and who have a long life expectancy. Men with testicular nonseminoma are typically in their 20s to 30s at diagnosis. With modern treatment principles, they meet the aforementioned criteria. Cisplatin-based chemotherapy for testicular nonseminoma[4] was quickly adopted by the oncology community. On the basis of a population-based SEER registry study of men diagnosed with regional

Table 2. Risk of Second Solid Cancers According to Time Since Diagnosis and Site Among 12,691 Survivors of Testicular Nonseminoma Managed With Surgery and/or Chemotherapy

	Surgery Only (no RT) (n = 6,678)					Chemotherapy (no RT) (n = 6,013)				
Time Since Diagnosis and Site	No. of Solid Tumors	SIR	95% CI	AER	95% CI	No. of Solid Tumors	SIR	95% CI	AER	95% CI
All solid tumors*	99	0.93	0.76 to 1.14	−1.11	−4.00 to 2.25	111	1.43†	1.18 to 1.73	6.47	2.68 to 10.83
Time since diagnosis of testicular nonseminoma, years										
< 1	9	2.27†	1.04 to 4.32	9.44	0.28 to 24.58	7‡	2.24	0.90 to 4.62	8.21	−0.67 to 23.94
1-4	19	1.02	0.62 to 1.60	0.21	−3.40 to 5.31	24§	1.77†	1.13 to 2.63	6.02	1.04 to 12.78
5-9	22	1.00	0.62 to 1.51	−0.05	−4.92 to 6.66	12	0.74	0.38 to 1.30	−3.01	−7.25 to 3.55
10-14	17	0.78	0.45 to 1.25	−4.53	−11.21 to 5.07	21	1.35	0.83 to 2.06	6.40	−3.08 to 19.56
15-19	12	0.60	0.31 to 1.06	−12.37	−21.51 to 1.75	25‖	1.70†	1.10 to 2.51	20.76	2.98 to 44.74
≥ 20	20	1.01	0.62 to 1.56	0.41	−19.25 to 27.89	22	1.54	0.96 to 2.33	27.22	−1.78 to 67.13
Site of solid tumor¶										
Oral cavity and pharynx	5	0.89	0.29 to 2.09	−0.09	−0.62 to 0.95	5	1.18	0.38 to 2.76	0.15	−0.50 to 1.43
Esophagus	1	0.60	0.01 to 3.36	−0.10	−0.26 to 0.61	1	0.83	0.01 to 4.60	−0.04	−0.23 to 0.84
Stomach	0	0	0 to 1.71	−0.33	0 to 0.24	3	1.90	0.38 to 5.56	0.27	−0.19 to 1.38
Colon	11	1.46	0.73 to 2.62	0.54	−0.32 to 1.90	1	0.19	0.002 to 1.04	−0.84	−1.03 to 0.04
Rectosigmoid junction	1	0.84	0.01 to 4.69	−0.03	−0.18 to 0.68	1	1.16	0.02 to 6.46	0.03	−0.16 to 0.90
Rectum	1	0.30	0.004 to 1.66	−0.37	−0.52 to 0.35	2	0.81	0.09 to 2.92	−0.09	−0.43 to 0.91
Liver	1	0.45	0.01 to 2.50	−0.19	−0.35 to 0.52	3	1.77	0.36 to 5.18	0.25	−0.21 to 1.36
Pancreas	3	1.20	0.24 to 3.51	0.08	−0.30 to 0.98	5	2.77	0.89 to 6.47	0.62	−0.04 to 1.90
Lung and bronchus	10	0.81	0.39 to 1.49	−0.37	−1.18 to 0.94	14	1.63	0.89 to 2.73	1.04	−0.18 to 2.87
Melanoma	11	0.96	0.48 to 1.72	−0.07	−0.93 to 1.29	10	1.14	0.55 to 2.10	0.24	−0.76 to 1.85
Prostate	20	0.76	0.46 to 1.17	−0.98	−2.20 to 0.72	16	0.87	0.50 to 1.41	−0.46	−1.78 to 1.46
Bladder	7	1.13	0.45 to 2.33	0.13	−0.53 to 1.29	8	1.86	0.80 to 3.66	0.71	−0.17 to 2.20
Kidney#	11	2.14†	1.07 to 3.84	0.92	0.05 to 2.27	13	3.37†	1.79 to 5.77	1.76	0.59 to 3.54
Thyroid	5	1.58	0.51 to 3.69	0.29	−0.24 to 1.33	11	4.40†	2.19 to 7.88	1.64	0.57 to 3.31
Kaposi sarcoma	2	0.58	0.06 to 2.08	−0.23	−0.51 to 0.59	1	0.37	0.005 to 2.04	−0.33	−0.52 to 0.55
Soft tissue including heart	3	1.76	0.35 to 5.14	0.20	−0.17 to 1.10	10	7.49†	3.59 to 13.78	1.67	0.66 to 3.28
Brain and nervous system	4	1.07	0.29 to 2.74	0.04	−0.41 to 1.02	6	2.07	0.76 to 4.50	0.60	−0.14 to 1.96

Abbreviations: AER, absolute excess risk per 10,000 person-years; RT, radiotherapy; SIR, standardized incidence ratio.

*Second malignant neoplasms risks by calendar year (1980 to 1994 or 1995 to 2008) of testicular nonseminoma diagnoses were as follows: for patients treated with surgery only (no RT), 1980 to 1994: SIR, 0.83; 95% CI, 0.64 to 1.06; n = 65; 38,752 person-years of follow-up; for 1995 to 2008: SIR, 1.22; 95% CI, 0.85 to 1.71; n = 34; 25,354 person-years of follow-up; for patients treated with chemotherapy (no RT), 1980 to 1994: SIR, 1.40; 95% CI, 1.11 to 1.75; n = 79; 31,219 person-years of follow-up; for 1995 to 2008: SIR, 1.52; 95% CI, 1.04 to 2.14; n = 32; 20,748 person-years of follow-up. Increased risks of second solid cancers after chemotherapy occurred after localized (SIR, 1.26; 95% CI, 0.81 to 1.88), regional (SIR, 1.45; 95% CI, 1.09 to 1.91), and distant (SIR, 1.62; 95% CI, 1.12 to 2.26) testicular cancer.

†SIRs with $P < .05$.

‡Second malignant neoplasms include cancers of stomach (n = 2; SIR, 29.70; 95% CI, 3.34 to 107.23), prostate (n = 2; SIR, 4.37; 95% CI, 0.49 to 15.76), kidney (n = 1; SIR, 6.91; 95% CI, 0.09 to 38.44), and brain and nervous system (n = 2; SIR, 10.37; 95% CI, 1.16 to 37.44).

§Second malignant neoplasms include cancers of rectosigmoid (n = 1; SIR, 6.66; 95% CI, 0.09 to 37.05), rectum (n = 1; SIR, 2.33; 95% CI, 0.03 to 12.98), pancreas (n = 1; SIR, 3.64; 95% CI, 0.05 to 20.27), melanoma (n = 5; SIR, 2.60; 95% CI, 0.84 to 6.07), prostate (n = 4; SIR, 1.95; 95% CI, 0.52 to 4.99), kidney (n = 2; SIR, 3.01; 95% CI, 0.34 to 10.87), thyroid (n = 3; SIR, 4.91; 95% CI, 0.99 to 14.34), Kaposi sarcoma (n = 1; SIR, 1.08; 95% CI, 0.01 to 6.00), and soft tissue including heart (n = 6; SIR, 16.73; 95% CI, 6.11 to 36.42).

‖Second malignant neoplasms include cancers of oral cavity and pharynx (n = 3; SIR, 3.74; 95% CI, 0.75 to 10.93), esophagus (n = 1; SIR, 3.94; 95% CI, 0.05 to 21.91), pancreas (n = 2; SIR, 5.40; 95% CI, 0.61 to 19.51), lung and bronchus (n = 4; SIR, 2.29; 95% CI, 0.62 to 5.86), melanoma (n = 1; SIR, 0.70; 95% CI, 0.01 to 3.91), prostate (n = 2; SIR, 0.47; 95% CI, 0.05 to 1.69), bladder (n = 2; SIR, 2.34; 95% CI, 0.26 to 8.46), kidney (n = 5; SIR, 6.67; 95% CI, 2.15 to 15.57), brain and nervous system (n = 1; SIR, 2.58; 95% CI, 0.03 to 14.38), thyroid (n = 2; SIR, 5.42; 95% CI, 0.61 to 19.58), and soft tissue including heart (n = 2; SIR, 11.27; 95% CI, 1.27 to 40.70).

¶Four cancers are not itemized in Table 2. In the surgery cohort, these included one cancer designated only as a cancer of other digestive organs, one mesothelioma, and one breast cancer. In the chemotherapy cohort, one cancer of the small intestine was observed.

#All cancers occurred in renal parenchyma, with no cancers of the renal pelvis observed in either treatment group.

and distant testicular nonseminoma in 1999,[26] more than 90% received chemotherapy. Cisplatin and etoposide, with or without bleomycin, accounted for 88% of all administered chemotherapy. Similarly, in our investigation (SEER based), approximately 82% of 5,212 patients with testicular nonseminoma with regional and distant disease received chemotherapy.

The success of platinum-based chemotherapy has been accompanied by various late effects, including SMN.[39] Several analytic studies have shown highly significant dose-response relationships between cumulative cisplatin amount and treatment-related leukemia.[18,19] Cisplatin also causes solid tumors in laboratory animals.[17] However, prior analytic clinical studies[10,11,13,25] of solid cancers after chemotherapy for testicular nonseminoma have yielded conflicting results based on small numbers (Table 4). All investigations also included precisplatin alkylating agent chemotherapy dating back to 1952. The relationship between these various alkylating agents and subsequent solid tumors (eg, soft tissue sarcomas[20,23] and cancers of lung,[22] thyroid,[24] stomach,[15] and bladder[21]) have now been established.

Circulating platinum remains partly reactive[40] and is detectable for ≥ 10 years after completion of chemotherapy.[41] Platinum-DNA

Table 3. Site-Specific Risks of Selected Second Solid Cancers According to Time Since Diagnosis of Testicular Nonseminoma

Cancer Site and Initial Treatment for Testicular Nonseminoma	Time Since Diagnosis of Testicular Nonseminoma														
	< 1 Year			1-9 Years			10-19 Years			≥ 20 Years			Total		
	No.	SIR	95% CI	No.	SIR	95% CI	No.	SIR	95% CI	No.	SIR	95% CI	No.	SIR	95% CI
Bladder*															
Surgery only, no RT	1	4.71	0.06 to 26.21	3	1.34	0.27 to 3.93	2	0.79	0.09 to 2.86	1	0.82	0.01 to 4.59	7	1.13	0.45 to 2.33
Chemotherapy, no RT	0	0	0 to 23.07	0	0	0 to 2.37	7	4.01†	1.61 to 8.26	1	1.16	0.02 to 6.46	8	1.86	0.80 to 3.66
Kidney‡															
Surgery only, no RT	1	5.62	0.07 to 31.26	5	2.60	0.84 to 6.06	4	1.94	0.52 to 4.97	1	1.04	0.01 to 5.77	11	2.14†	1.07 to 3.84
Chemotherapy, no RT	1	6.91	0.09 to 38.44	2	1.36	0.15 to 4.91	7	4.52†	1.81 to 9.31	3	4.35	0.88 to 12.72	13	3.37†	1.79 to 5.77
Thyroid§															
Surgery only, no RT	2	12.17†	1.37 to 43.93	1	0.66	0.01 to 3.66	2	1.84	0.21 to 6.63	0	0	0 to 9.44	5	1.58	0.51 to 3.69
Chemotherapy, no RT	0	0	0 to 25.91	8	6.51†	2.80 to 12.83	3	3.51	0.71 to 10.25	0	0	0 to 13.36	11	4.40†	2.19 to 7.88
Soft tissue including heart‖															
Surgery only, no RT	0	0	0 to 34.65	2	2.31	0.26 to 8.35	1	1.81	0.02 to 10.05	0	0	0 to 20.25	3	1.76	0.35 to 5.14
Chemotherapy, no RT	0	0	0 to 40.48	7	10.13†	4.06 to 20.87	2	4.71	0.53 to 17.01	1	7.77	0.10 to 43.24	10	7.49†	3.59 to 13.78
Lung and bronchus¶															
Surgery only, no RT	0	0	0 to 8.62	5	1.11	0.36 to 2.60	3	0.59	0.12 to 1.74	2	0.83	0.09 to 2.98	10	0.81	0.39 to 1.49
Chemotherapy, no RT	0	0	0 to 11.84	0	0	0 to 1.22	6	1.70	0.62 to 3.71	8	4.57†	1.97 to 9.00	14	1.63	0.89 to 2.73

NOTE. Histologic types of solid tumors were defined according to International Classification of Diseases for Oncology, Third Edition, as follows: bladder: urothelial carcinoma (8120 and 8130); kidney: papillary adenocarcinoma (8260), clear cell adenocarcinoma (8310), and renal cell carcinoma (8312); thyroid: papillary carcinoma (8050), papillary adenocarcinoma (8260), follicular adenocarcinoma (8330), and papillary carcinoma follicular variant (8340); soft tissue including heart: fibrosarcoma (8810), malignant fibrous histiocytoma (8830), myxoid liposarcoma (8852), squamous cell carcinoma (8070), sarcoma (8800), spindle cell sarcoma (8801), epithelioid sarcoma (8804), mixed type liposarcoma (8855), rhabdomyosarcoma (8900), synovial sarcoma (9040), hemangiosarcoma (9120), and hemangiopericytoma (9150); and lung and bronchus: carcinoma (8010), large-cell carcinoma (8012), small-cell carcinoma (8041), non–small-cell lung carcinoma (8046), squamous cell carcinoma (8070), adenocarcinoma (8140), pleomorphic rhabdomyosarcoma (8901), atypical carcinoid tumor (8249), and meningioma (9530).

Abbreviations: RT, radiotherapy; SIR, standardized incidence ratio.

*All bladder cancers comprised transitional cell carcinoma.

†SIRs with $P < .05$.

‡Histology in the surgery group (n = 11) included one papillary adenocarcinoma (9.1%), four clear cell adenocarcinomas (36.4%), and six renal cell carcinomas (54.5%). Histology in the chemotherapy group (n = 13) included four papillary adenocarcinomas (30.8%), four clear cell adenocarcinomas (30.8%), and five renal cell carcinomas (38.4%).

§Histology in the surgery group (n = 5) included one papillary carcinoma (20%), three papillary adenocarcinomas (60%), and one papillary carcinoma with follicular variant (20%). Histology in the chemotherapy group (n = 11) included one papillary carcinoma (9.1%), seven papillary adenocarcinomas (63.6%), one follicular adenocarcinoma (9.1%), and two papillary carcinomas, follicular variant (18.2%).

‖Histology in the surgery group (n = 3) included one fibrosarcoma (33.3%), one malignant fibrous histiocytoma (33.3%), and one myxoid liposarcoma (33.3%). Histology in the chemotherapy group (n = 10) included one squamous cell carcinoma (10%), one sarcoma (10%), one spindle cell sarcoma (10%), one epithelioid sarcoma (10%), one mixed type liposarcoma (10%), two rhabdomyosarcomas (20%), one synovial sarcoma (10%), one hemangiosarcoma (10%), and one hemangiopericytoma (10%).

¶Histology in the surgery group (n = 10) included one carcinoma (10%), one large-cell carcinoma (10%), two small-cell carcinomas (20%), one non–small-cell lung carcinoma (10%), one squamous cell carcinoma (10%), three adenocarcinomas (30%), and one pleomorphic rhabdomyosarcoma (10%). Histology in the chemotherapy group (n = 14) included one small-cell carcinoma (7.1%), three non–small-cell lung carcinomas (21.4%), eight adenocarcinomas (57.2%), one atypical carcinoid tumor (7.1%), and one meningioma (7.1%).

adducts have been found in most human organs,[41,42] including kidney and thyroid. Urine and serum platinum concentrations at 5.3 to 16.8 years after chemotherapy are quantified up to 1,000 times greater than in unexposed controls.[43] Because renal clearance constitutes the primary means of short- and long-term cisplatin excretion,[43] the extent to which platinum-based chemotherapy may be later associated with urinary tract cancers is of interest.

Significant excesses of kidney cancer occurred after either chemotherapy or surgery. Cancers reported within the first few years may reflect in part the diagnosis of incidental lesions[44,45] observed during routine radiologic studies to detect recurrence. However, the temporal pattern of significantly increased 4.5-fold risks 10 to 19 years after chemotherapy, with four-fold risks thereafter, was not evident after surgery. Wilson et al[46] reported a 3.5-fold increased risk of renal cell carcinoma after cisplatin exposure in childhood cancer survivors, albeit based on four patients. We also observed increased risks of bladder cancer 10 to 19 years after chemotherapy, although not later. On the basis of three patients, van den Belt-Dusebout et al[11] reported an overall increased risk of bladder cancer (SIR, 4.7; 95% CI, 1.0 to 13.6) among patients with TC (seminoma and nonseminoma) given chemotherapy (1965 to 1995), with no excess after surgery only. The bladder is susceptible to the carcinogenic effects of radiotherapy and cyclophosphamide.[21] Whether long-term ongoing exposure of bladder epithelium to low platinum concentrations might result in excess cancers should be examined in analytic series, along with any role of cisplatin in renal cell carcinoma.[46]

The thyroid gland is highly radiocarcinogenic,[14] with a strong inverse age dependency. Chemotherapy may increase this risk or by itself be carcinogenic.[24] Veiga et al[24] recently reported a significantly increased 2.4-fold risk of thyroid cancer after alkylating agents in

Table 4. Summary of Studies Evaluating Mortality or Incidence of Second Solid Cancers After Chemotherapy for Testicular Cancer

Study	Year of Publication	No. of Patients	Calendar Years of Diagnosis	Histology of Testicular Cancer	No. of Second Solid Cancers	Overall SMR or RR of Second Solid Cancers	95% CI	Antecedent Chemotherapy in Patients With Second Solid Cancers	Site-Specific Risks Associated With Chemotherapy
Bokemeyer and Schmoll[25]	1993	413	1970-1990	NS, S	4	SMR: 2.7	0.7 to 6.9	PVB, BEP, Mtx, Mitox	Reported*
Wanderas et al[13]	1997	346	1952-1990	NS, S	4	RR: 1.3	0.4 to 3.4	Not available	Reported†
Travis et al[10]	2005	3,799	1943-2001	NS	28	RR‡: 1.8	1.3 to 2.5	Not available	Not reported
van den Belt-Dusebout et al[11]	2007	710	1965-1995	NS, S	21	SIR§: 1.5	0.9 to 2.3	PVB, BEP, dactinomycin, unknown	Reported‖
Current article	2013	6,013	1980-2008	NS	111	SIR: 1.4	1.2 to 1.7	Not available	Reported

Abbreviations: BEP, bleomycin, cisplatin, and etoposide; Mitox, mitoxantrone; Mtx, methotrexate; NS, nonseminoma; PVB, cisplatin, bleomycin, and vinblastine; RR, relative risk; S, seminoma; SIR, standardized incidence ratio; SMR, standardized morbidity ratio.

*Only the observed numbers of the total of four deaths were reported (without associated SMRs). There was one case each of gastric cancer, carcinoid tumor, rectum cancer, and rhabdomyosarcoma.

†Site-specific cancer risks were as follows: GI: n = 1; RR, 1.72; 95% CI, 0.0 to 9.7; and melanoma of the skin: n = 2; RR, 6.26; 95% CI, 0.8 to 22.6. Site for the remaining one cancer was not indicated.

‡The reported RR included only 10-year survivors of testicular nonseminoma.

§The reported SIR included only 5-year survivors of testicular cancer.

‖Site-specific cancer risks were as follows: digestive tract: n = 3; SIR, 0.8; 95% CI, 0.2 to 2.4; colon: n = 2; SIR, 1.9; 95% CI, 0.2 to 6.2; lung: n = 1; SIR, 0.3; 95% CI, 0.0 to 1.9; genitourinary tract: n = 5; SIR, 1.4; 95% CI, 0.4 to 3.3; prostate: n = 2; SIR, 1.2; 95% CI, 0.1 to 4.2; urinary bladder: n = 3; SIR, 4.7; 95% CI, 1.0 to 13.6; and melanoma: n = 6; SIR, 6.3; 95% CI, 2.3 to 13.8. Sites for the remaining six cancers were not indicated.

12,000 survivors of childhood cancer also receiving organ radiation doses of 20 Gy or less. Risk increased with increasing dose of alkylating agents (P for heterogeneity = .009). Among children not given radiotherapy, a significantly increased 4.6-fold risk of thyroid cancer occurred after bleomycin, albeit based on small numbers, possibly providing an explanation for the increased risk of thyroid cancer observed in our chemotherapy group. Future studies should address interactions between chemotherapy and known thyroid cancer risk factors, including radiation,[14,24] family history,[47] and obesity.[48] The high prevalence of increased body mass index as a component of metabolic syndrome is well established in survivors of TC[49] and may serve as an additional explanation for our observations.

Teratoma may undergo malignant transformation to any histologic subtype,[16] with soft tissue sarcoma being the most frequent (63%).[50] In our study, 90% of soft tissue tumors after chemotherapy were soft tissue sarcoma, with six of the nine sarcomas detected within 4 years after TC diagnosis. These early-onset sarcomas may represent transformation of teratoma after chemotherapy, whereas late-onset sarcomas may reflect in part the late effects of alkylating agents.[51] Among 16,541 3-year survivors of childhood cancer given alkylating agents in Britain,[51] a 16.1-fold increased risk (95% CI, 9.4 to 25.8) of soft tissue sarcoma was observed with an average latency of 16.3 years (P trend dose = .05).

In nonanalytic studies,[9,12] significantly increased risks of lung cancer after TC have been observed, with excesses attributed largely to the past use of thoracic radiotherapy. The prevalence of current smoking in US survivors of TC (20%)[52] is similar to that of the general population.[53] Thus, it is not surprising that lung cancer risk among survivors with TC managed with surgery alone in our study is similar to that of the general population (SIR, 0.8) and mitigates concern that a TC diagnosis may confer an inherently increased risk. However, the overall 60% excesses of lung cancer after chemotherapy (with a significantly increased five-fold risk in 10-year survivors) are notable. Alkylating agents for Hodgkin lymphoma are associated with significantly elevated risks of lung cancer,[22,54] with a strong dose-response relationship ($P < .001$).[22] Excess risks, however, emerged as early as 1 to 4 years after treatment, unlike the later excesses noted here. Future analytic studies of lung cancer among survivors of TC should consider not only the cumulative dose of cisplatin, but also other cytotoxic drugs (eg, bleomycin) and tobacco use.

An important new observation is the upswing in the absolute excesses of solid cancers 15 to 19 years after chemotherapy, which then persisted in 20-year survivors. Although this may be, in part, a result of the aging of this population and an increase in background cancer rates, no such increase occurred among patients treated with surgery only. Although it is unknown whether similar increases will be observed for longer follow-up periods, these findings could have implications regarding future cancer risks among these young men as they enter the age range in which underlying cancer rates increase.

Strengths of our study include the large number of patients, population-based setting, histologic confirmation of all SMNs, and long-term follow-up. Limitations are those inherent to the SEER program, including lack of data regarding types and doses of initial chemotherapy and the absence of information on subsequent courses of treatment. SEER also does not collect data on other factors that may contribute to cancer risk (eg, tobacco use, diet, physical inactivity, radiologic imaging).[55] Inclusion of the surgery-only cohort, however, serves as a valuable internal control group for many of these factors. To exclude the effect of radiotherapy in the development of SMN, we included only patients with testicular nonseminoma for whom radiation is not integral treatment.[16] Thus, we do not expect an appreciable number of patients in the chemotherapy cohort to have received any radiation treatment, and if so, they most likely contributed only a few person-years of follow-up after palliative radiotherapy. Among patients in the surgery cohort, 84.9% had localized disease; thus, some may have subsequently received chemotherapy, because about one third of patients with stage I testicular nonseminoma may experience relapse.[56] Nonetheless, despite this potential misclassification favoring

underestimation of our analyses' differences, we still found no increased risk of SMN (SIR, 0.93) after surgery.

Platinum compounds now comprise one of the most widely used and successful groups of cytotoxic drugs worldwide, given their efficacy in treating many types of cancer. Each year, more than 5.8 million patients globally[57,58] are diagnosed with cancers of the colon, rectum, cervix, endometrium, bladder, stomach, head and neck, lung, esophagus, pancreas, osteosarcoma, ovary, and testis, for which first-line therapy can potentially include platinating agents. It will be important in analytic studies to further determine the extent to which dose-response relationships between platinum and solid tumors may exist, the types of cancers, latency patterns, and interactions with other factors,[59] including genetic susceptibility[60] and other drugs. In the interim, it is important for health care providers to be aware of the significantly increased risk of solid cancers in survivors of TC after cisplatin-based chemotherapy. Assessment tools for SMN and strategies for risk reduction in providing follow-up care to survivors of cancer were recently reviewed by Wood et al,[61] with these recommendations also applicable to survivors of TC. The importance of smoking cessation, weight control, physical activity, and other factors consonant with adoption of a healthy lifestyle should also be consistently conveyed to patients.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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