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Article

Solid and Hematologic Neoplasms After Testicular Cancer: A US Population-Based Study of 24 900 Survivors

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Abstract

Background: No large US population-based study focusing on recent decades, to our knowledge, has comprehensively examined risks of second malignant solid and hematological neoplasms (solid-SMN and heme-SMN) after testicular cancer (TC), taking into account initial therapy and histological type. **Methods:** Standardized incidence ratios (SIR) vs the general population and 95% confidence intervals (CI) for solid-SMN and heme-SMN were calculated for 24 900 TC survivors (TCS) reported to the National Cancer Institute's Surveillance, Epidemiology, and End Results registries (1973–2014). All statistical tests were two-sided. **Results:** The median age at TC diagnosis was 33 years. Initial management comprised chemotherapy (n = 6340), radiotherapy (n = 9058), or surgery alone (n = 8995). During 372 709 person-years of follow-up (mean = 15 years), 1625 TCS developed solid-SMN and 228 (107 lymphomas, 92 leukemias, 29 plasma cell dyscrasias) developed heme-SMN. Solid-SMN risk was increased 1.06-fold (95% CI = 1.01 to 1.12), with elevated risks following radiotherapy (SIR = 1.13, 95% CI = 1.06 to 1.21) and chemotherapy (SIR = 1.36, 95% CI = 1.12 to 1.41) but not surgery alone (SIR = 0.83, 95% CI = 0.75 to 0.92). Corresponding risks for seminoma were 1.13 (95% CI = 1.06 to 1.21), 1.28 (95% CI = 1.02 to 1.58), and 0.87 (95% CI = 0.74 to 1.01) and for nonseminoma were 1.05 (95% CI = 0.67 to 1.56), 1.25 (95% CI = 1.08 to 1.43), and 0.80 (95% CI = 0.70 to 0.92), respectively. Thirty-year cumulative incidences of solid-SMN after radiotherapy, chemotherapy, and surgery alone were 16.9% (95% CI = 15.7% to 18.1%), 10.1% (95% CI = 8.8% to 11.5%), and 8.8% (95% CI = 7.8% to 9.9%), respectively ($P < .0001$). Increased leukemia risks after chemotherapy (SIR = 2.68, 95% CI = 1.70 to 4.01) were driven by statistically significant sevenfold excesses of acute myeloid leukemia 1 to 10 years after TC diagnosis. Risks for lymphoma and plasma cell dyscrasias were not elevated. **Conclusions:** We report statistically significant excesses of solid-SMN affecting 1 in 6 TCS 30 years after radiotherapy, and 2.7-fold risks of leukemias after chemotherapy, mostly acute myeloid leukemia. Efforts to minimize chemotherapy and radiotherapy exposures for TC should continue. TCS should be counseled about cancer prevention and screening.

Testicular cancer (TC) is the most common malignancy among men aged 18-39 years (1), with global incidence rates doubling over the last few decades (2). Given the introduction of effective chemotherapy in the 1970s (3), the overall 10-year relative survival rate now approaches 95% (4). Nonetheless, this success has been accompanied by late life-threatening complications, including second malignant neoplasms (SMN). To date, SMN risk estimates have been largely based on European data, reporting statistically significantly increased 1.5- to 3.5-fold risks (5-8) compared with the general population. Estimates have varied widely based on differing calendar years of TC diagnosis, follow-up duration, study design, treatment patterns, and underlying population rates.

To our knowledge, there have been no US-based studies that have comprehensively examined SMN risk after TC in terms of histological type and therapy and focused on recent decades. US-based investigations have been restricted to either seminomatous (9,10) or nonseminomatous (11,12) germ cell tumors and largely confined to evaluations of radiotherapy (9,10). An investigation of nonseminoma TC survivors (TCS) addressed only chemotherapy-associated SMN risks (11). Two studies [one restricted to seminoma (9) and another to nonseminoma (11)] provided risk estimates for all solid-SMN taken together. Secondary leukemias (n = 15 patients) were evaluated only by Lewinshtein et al. (9).

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To provide new comprehensive information on site-specific relative and absolute risks of second solid-SMN and hematological SMN (heme-SMN) in US TCS treated in the modern era, we studied 24 900 TCS managed initially with surgery only, chemotherapy, or radiotherapy.

Patients and Methods

Patients

We quantified risks of histologically confirmed solid-SMN and heme-SMN, collectively termed SMN, among patients diagnosed with histologically confirmed TC (nonseminoma, seminoma) as a first primary malignancy between January 1, 1973, and December 31, 2014. Patients were reported to 9 population-based registries within the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program (13). Based on age at TC diagnosis, patients were divided into 4 groups: younger than 30 years, 30–39 years, 40–49 years, and age of 50 years and older. Calendar year of TC diagnosis was divided into 1973–1999 and 2000–2014 in view of the pivotal 1999 study (14) showing that smaller radiotherapy fields (ie, ipsilateral para-aortic lymph nodes) were as effective as larger fields (ie, ipsilateral iliac and para-aortic lymph nodes) for Stage 1 seminoma. The extent of TC was categorized into localized, regional, and distant disease. Patients were divided into 3 groups based on initial treatment: surgery alone (no or unknown radiotherapy or chemotherapy), chemotherapy only (no or unknown radiotherapy), and radiotherapy only (no or unknown chemotherapy). The SEER program acknowledges underreporting of radiotherapy (15,16) and chemotherapy (15). For simplicity, we refer to no or unknown radiotherapy administration as "no radiotherapy" and no or unknown chemotherapy administration as "no chemotherapy." Because few TCS (n = 354) received both radiotherapy and chemotherapy, they were not analyzed separately or included in the three treatment groups but included only in analyses of risks for all 24 900 TCS. Types of surgery included orchiectomy alone or orchiectomy plus resection of regional or distant metastatic sites with lymph node dissection.

Statistical Methods

To calculate standardized incidence ratios (SIR), person-years of observation were accrued starting 1 year after TC diagnosis until SMN diagnosis, death, or study end (December 31, 2015), whichever occurred first. To derive SIR, observed numbers of cancers were divided by numbers expected based on age-, sex-, and race-specific cancer incidence rates in the general population, specific for each SEER Program registration area, using previously described methods (17); 95% confidence intervals (CIs) were derived using SEER Program guidelines (18). Absolute excess risk (AER) was defined as the absolute excess (observed minus expected) number of SMN per person-years at risk/10 000. SIR and AER calculations were performed using the Multiple-Primary-SIR session of SEER*Stat (19). Statistical significance was defined as $P < .05$ (two-sided). Actuarial cumulative incidence rates of SMN were generated using SAS version 9.4; death and occurrence of other cancers were considered competing events. Gray's test (20) was used to test the marginal effect (ie, ignoring other predictors) of each potential predictor on SMN incidence. The Fine and Gray competing risk model (21) was fitted using variables with $P \leq .15$ by Gray's test. Bonferroni corrections were used for multiple test adjustment for pairwise comparisons between the 3 treatments. Temporal trends in SIR were analyzed for statistical significance using the methods of Breslow (22).

Results

Study Population

The study population comprised 24 900 1-year TCS diagnosed at a median age of 33 years (36 for seminoma, 28 for nonseminoma); the interquartile range was 26–40 years. Mean follow-up time was 15 years, with 20 446, 16 169, 8550, and 2952 TCS followed for 5, 10, 20, and 30 years, respectively (Table 1). Most (92%) patients were white. TC stage was localized, regional, and distant in 17 274 (69.4%), 4841 (19.4%), and 2412 (9.7%) patients, respectively. Initial management consisted of surgery only (n = 8995), radiotherapy (n = 9058), and chemotherapy (n = 6340), with 2% of patients receiving other treatments (see Table 1 footnote). During 372 709 person-years of follow-up (mean follow-up = 15 years), 1625 TCS developed a solid-SMN and 228 developed a heme-SMN, including 107 lymphomas, 92 leukemias, and 29 plasma cell dyscrasias.

Solid-SMN

Overall risk of solid-SMN was increased by 1.06-fold (n = 1625, 95% CI = 1.01 to 1.12) (Table 2). Statistically significantly increased risks were observed after radiotherapy (n = 925; SIR = 1.13, 95% CI = 1.06 to 1.21) or chemotherapy (n = 286; SIR = 1.26, 95% CI = 1.12 to 1.41) but not after surgery alone (SIR = 0.83, 95% CI = 0.75 to 0.92). After radiotherapy, TCS had 10%-12% excesses of solid-SMN for up to 30 years follow-up, which then increased at 30–34 years (SIR = 1.25, 95% CI = 0.99 to 1.57) and age of 35 years and older (SIR = 1.38, 95% CI = 0.97 to 1.91) after TC diagnosis ($P_{trend} = .33$). Radiotherapy was associated with statistically significantly elevated risks for cancers of stomach (SIR = 1.70), rectum or recto-sigmoid (SIR = 1.44), pancreas (SIR = 2.65), soft tissue (SIR = 2.16), bladder (SIR = 1.54), and thyroid (SIR = 2.01). Statistically significantly increased risks of solid-SMN were apparent 1–5 years after chemotherapy (SIR = 1.74, 95% CI = 1.27 to 2.33), with 20–50% excesses in intervals, beginning 10 years after TC diagnosis, but without discernible temporal trends. Chemotherapy was associated with statistically significantly elevated risks for cancers of pancreas (SIR = 2.17), soft tissue (SIR = 4.01), kidney (SIR = 1.71), and thyroid (SIR = 3.25).

Hematologic SMN

Overall risk of heme-SMN was statistically significantly increased 1.25-fold (n = 228; 95% CI = 1.10-fold to 1.43-fold) (Table 2). Risks for lymphoma (SIR = 1.02) and plasma cell dyscrasias (SIR = 1.27) were not statistically significantly increased overall or after any treatment modality. In contrast, a statistically significantly increased 1.7-fold (95% CI = 1.37-fold to 2.08-fold) leukemia risk occurred among all TCS, with the most common type being acute myeloid leukemia (AML; n = 44), followed by chronic lymphocytic leukemia (CLL; n = 20) and chronic myeloid leukemia (CML; n = 14). An overall statistically significantly increased 2.68-fold (95% CI = 1.70-fold to 4.01-fold) risk of leukemia occurred after chemotherapy, with excesses restricted to 1–5 years (SIR = 7.18, 95% CI = 3.28 to 13.62) and 5–10 years (SIR = 4.16, 95% CI = 1.53 to 9.05) after TC diagnosis. Surgery

Table 1. Description of US population-based cohort of 24 900 1-year survivors of TC*

Characteristics	Patients, No.	Person-years of follow-up†	Second solid tumors‡, No.	Second hematologic malignancies§, No.
All patients‖	24 900	372 709	1625	228
GCT, seminoma	14 364	210 472	1174	150
GCT, nonseminoma	10 536	162 237	451	78
Age at TC diagnosis, y				
<30	9434	154 266	305	65
30–39	8803	136 653	539	70
40–49	4527	60 326	432	49
50+	2136	21 463	349	44
Calendar year of TC diagnosis				
1973–1999	13 682	295 356	1433	180
2000–2014	11 218	77 353	192	48
Race				
White	22 916	348 667	1518	210
African American	564	6819	45	7
Asian or other	1209	14 792	62	11
Unknown	211	2432	0	0
Extent of disease				
Localized	17 274	258 901	1094	159
Regional	4841	76 114	341	43
Distant	2412	30 515	149	22
Unknown	373	7178	41	4
Initial treatment for TC¶				
Surgery only	8995	128 039	372	73
Radiotherapy, no chemotherapy	9058	156 735	925	108
Chemotherapy, no radiotherapy	6340	80 700	286	43
Radiotherapy and chemotherapy	354	4861	28	1
Initial treatment for seminoma				
Surgery only	3498	38 441	165	28
Radiotherapy, no chemotherapy	8865	152 392	901	106
Chemotherapy, no radiotherapy	1742	16 036	82	14
Radiotherapy and chemotherapy	174	2410	18	0
Initial treatment for nonseminoma				
Surgery only	5497	89 598	207	45
Radiotherapy, no chemotherapy	193#	4343	24	2
Chemotherapy, no radiotherapy	4598	64 664	204	29
Radiotherapy and chemotherapy	180	2451	10	1
Patients entering follow-up interval**, no.				
1 to <5 y	24 900	89 635	173	42
5 to <10 y	20 446	91 420	217	45
10 to <20 y	16 169	122 367	548	68
20 to <30 y	8550	55 610	481	54
30 to <35 y	2952	10 108	140	13
≥35 y	1213	3569	66	6

*All patients were diagnosed with TC as a first primary cancer and survived 1 year or more. Mean follow-up was 14.7 years and 15.4 years for men with seminomatous and nonseminomatous GCT, respectively. GCT = germ cell tumor; no chemotherapy = either no chemotherapy was delivered or it is unknown whether chemotherapy was delivered because of known underreporting of chemotherapy to SEER Program registries (see Methods); no radiotherapy = either no radiotherapy was delivered or it is unknown whether radiotherapy was delivered because of known underreporting of radiotherapy to SEER Program registries (see Methods). ICD-O-3 = International Classification of Diseases for Oncology, Third Edition; NOS = not otherwise specified; SEER = National Cancer Institute's Surveillance, Epidemiology, and End Results; TC = testicular cancer.

†The total person-years in some groups do not total 372 709 because of rounding. The total person-years for the initial treatment groups of TC totals 370 335, given the exclusion of 533 patients for reasons that are provided in Table 1, footnote ¶.

‡Numbers of solid tumors exclude contralateral TC. Second primary miscellaneous cancers (as defined by the SEER Program; n = 25) are not shown in the table.

§Second hematologic malignancies included 107 lymphomas, 92 leukemias, and 29 multiple myelomas or plasmacytomas. Leukemias included acute lymphocytic leukemia (n = 6), acute monocytic leukemia (n = 4), acute myeloid leukemia (n = 40), chronic lymphocytic leukemia (n = 20), chronic myeloid leukemia (n = 14), and other leukemias (n = 8). Lymphomas include non-Hodgkin lymphoma (n = 98, including 30 extranodal) and Hodgkin lymphoma (n = 9).

‖The seminoma category includes ICD-O-3 histologic codes of 9060/3: dysgerminoma, 9061/3: seminoma, NOS, 9062/3: seminoma, anaplastic, 9063/3: spermatocytic seminoma, 9064/3: germinoma. The nonseminoma category includes ICD-O-3 histologic codes of 9065/3: GCT, nonseminomatous, 9070/3: embryonal carcinoma, NOS, 9071/3: yolk sac tumor, 9072/3: polyembryoma, 9073/3: gonadoblastoma, malignant, 9080/3: teratoma, malignant, NOS, 9081/3: teratocarcinoma, 9082/3: malignant teratoma, undifferentiated, 9083/3: malignant teratoma, intermediate, 9084/3: teratoma with malignant transformation, 9085/3: mixed GCT, 9100/3: choriocarcinoma, NOS, 9101/3: choriocarcinoma combined with other germ cell elements, 9102/3: malignant teratoma, trophoblastic.

¶A total of 467 patients did not undergo surgery (n = 422) or it is unknown whether surgery was performed (n = 45). Of these 467 patients, 153 were registered as not having received (or unknown if they received) chemotherapy and/or radiotherapy; these 153 patients are not represented in the above treatment subgroups though are included in the total 24 900 patients. Of the remaining 314 patients, those who underwent radiotherapy (n = 58) or chemotherapy (n = 230) are included in the treatment subgroups of the table. A total 354 patients who underwent chemotherapy and radiotherapy (including 26 for whom surgery was not performed) are not included in the treatment subgroups, though they are included in the total of 24 900 patients.

#Calendar years of diagnosis for the 193 patients with nonseminoma treated with radiotherapy, no chemotherapy were 1973–1978 (n = 132), 1979–1981 (n = 13), 1982–1999 (n = 30), and 2000–2014 (n = 18).

**For patients with seminoma, 14 364, 11 947, 9345, 4677, 1434, and 567 were followed 1, 5, 10, 20, 30, and 35 years and more, respectively. For patients with nonseminoma, 10 536, 8499, 6824, 3873, 1518, and 646 were followed 1, 5, 10, 20, 30, and 35 years or more, respectively.

Table 2. Risk of second solid and hematologic malignancies according to time since diagnosis of TC and type of initial treatment among 24 900 1-year survivors of TC

	All patients[†] (N = 24 900)			Surgery only (no RT, no chemotherapy) (N = 8995)			Radiotherapy (no chemotherapy) (N = 9058)			Chemotherapy (no radiotherapy) (N = 6340)		
Event	No.	SIR (95% CI)	AER	No.	SIR (95% CI)	AER	No.	SIR (95% CI)	AER	No.	SIR (95% CI)	AER[‡‡]
All nontestis solid tumors	1625	1.06 (1.01 to 1.12)*	2.6	372	0.83 (0.75 to 0.92)	−5.9	925	1.13 (1.06 to 1.21)*	6.8	286	1.26 (1.12 to 1.41)*	7.3
Time since TC diagnosis [‡,§]												
1 to <5 y	173	1.13 (0.97 to 1.31)	2.2	41	0.86 (0.61 to 1.16)	−2.2	85	1.12 (0.89 to 1.38)	2.6	45	1.74 (1.27 to 2.33)*	8.9
5 to <10 y	217	0.98 (0.85 to 1.12)	−0.5	47	0.76 (0.56 – 1.01)	−4	134	1.10 (0.93 to 1.31)	3.3	29	0.86 (0.58 to 1.24)	−2.3
10 to <20 y	548	1.05 (0.96 to 1.14)	2.0	111	0.78 (0.64 to 0.94)	−7.5	326	1.11 (0.99 to 1.23)	5.8	97	1.27 (1.03 to 1.55)*	8.2
20 to <30 y	481	1.06 (0.97 to 1.16)	4.8	119	0.88 (0.73 to 1.05)	−8.6	269	1.12 (0.99 to 1.26)	12.0	80	1.19 (0.94 to 1.48)	11.4
30 to <35 y	140	1.13 (0.95 to 1.33)	15.7	33	0.78 (0.54 to 1.10)	−23.8	75	1.25 (0.99 to 1.57)	37.3	27	1.48 (0.97 to 2.15)	45.5
≥35 y	66	1.23 (0.95 to 1.57)	35.0	21	1.15 (0.71 to 1.76)	21.2	36	1.38 (0.97 to 1.91)	63.8	8	1.28 (0.55 to 2.52)	32.9
Age at TC diagnosis[§]												
<40 y	844	1.17 (1.09 to 1.25)*	4.1	197	0.82 (0.71 to 0.95)	−3.9	427	1.26 (1.14 to 1.39)*	3.9	194	1.50 (1.30 to 1.73)*	9.5
≥40 y	781	0.97 (0.90 to 1.04)	−3.0	175	0.84 (0.72 to 0.97)	−16.2	498	1.04 (0.95 to 1.13)	8.0	92	0.93 (0.75 to 1.15)	−5.3
Extent of disease (TC)[‖]												
Localized	1094	1.00 (0.94 to 1.06)	−0.2	302	0.82 (0.73 to 092	−6.3	720	1.09 (1.01 to 1.17)*	4.4	65	1.18 (0.91 to 1.51)	4.7
Regional	341	1.14 (1.03 to 1.27)*	5.7	59	0.95 (0.73 to 1.23)	−1.6	154	1.21 (1.03 to 1.42)*	12.1	117	1.18 (0.97 to 1.41)	5.1
Distant	149	1.45 (1.23 to 1.71)	15.3	6	0.65 (0.24 to 1.41)	−15.0	35	2.07 (1.44 to 2.88)*	66.7	97	1.43 (1.16 to 1.75)*	12.4
Solid cancer site[¶]												
Oral cavity and pharynx	58	0.78 (0.59 to 1.01)	−0.4	10	0.45 (0.22 to 0.83)	−1.0	26	0.68 (0.44 to 0.99)	−0.8	16	1.31 (0.75 to 2.13)	0.5
Esophagus	26	0.98 (0.64 to 1.44)	0	8	1.05 (0.45 to 2.06)	0.0	11	0.77 (0.39 to 1.38)	−0.2	6	1.54 (0.56 to 3.35)	0.3
Stomach	40	1.35 (0.97 to 1.84)	0.3	7	0.81 (0.33 to 1.68)	−0.1	27	1.70 (1.12 to 2.47)*	0.7	5	1.16 (0.38 to 2.71)	0.1
Colon	101	0.96 (0.78 to 1.16)	−0.1	29	0.94 (0.63 to 1.34)	−0.2	49	0.86 (0.64 to 1.14)	−0.5	20	1.32 (0.81 to 2.04)	0.6
Rectum or recto-sigmoid	79	1.30 (1.03 to 1.62)*	0.5	19	1.06 (0.64 to 1.65)	0.1	46	1.44 (1.06 to 1.93)*	0.9	12	1.27 (0.66 to 2.21)	0.3
Liver	26	0.72 (0.47 – 1.06)	−0.3	4	0.38 (0.10 to 0.98)	−0.5	15	0.8 (0.45 to 1.32)	−0.2	7	1.18 (0.47 to 2.43)	0.1
Pancreas	97	2.35 (1.90 to 2.87)*	1.5	21	1.75 (1.08 to 2.67)*	0.7	59	2.65 (2.01 to 3.41)*	2.3	13	2.17 (1.16 to 3.71)*	0.9
Lung and bronchus	189	0.92 (0.80 – 1.06)	−0.4	30	0.52 (0.35 to 0.74)	−2.2	123	1.07 (0.89 to 1.27)	0.5	33	1.25 (0.86 to 1.75)	0.8
Soft tissue	29	2.13 (1.43 – 3.06)*	0.4	3	0.69 (0.14 to 2.03)	−0.1	14	2.16 (1.18 to 3.62)*	0.5	10	4.01 (1.92 to 7.38)*	0.9
Melanoma	115	0.94 (0.77 – 1.12)	−0.2	24	0.63 (0.40 to 0.93)	−1.1	63	1.04 (0.80 to 1.33)	0.2	28	1.3 (0.87 to 1.89)	0.8
Prostate	408	0.87 (0.79 – 0.96)	−1.6	97	0.73 (0.60 to 0.90)	−2.7	252	0.97 (0.85 to 1.10)	−0.5	53	0.82 (0.62 to 1.08)	−1.4
Bladder	152	1.50 (1.27 – 1.76)*	1.4	44	1.50 (1.09 to 2.01)*	1.1	86	1.54 (1.23 to 1.90)*	1.9	20	1.47 (0.9 to 2.26)	0.8
Kidney	78	1.1 (0.87 – 1.37)	0.2	27	1.27 (0.84 to 1.84)	0.5	27	0.74 (0.49 to 1.08)	−0.6	20	1.71 (1.04 to 2.64)*	1.0
Brain and nervous system	31	0.95 (0.64 – 1.35)	0	6	0.58 (0.21 to 1.26)	−0.3	18	1.15 (0.68 to 1.81)	0.2	5	0.84 (0.27 to 1.97)	−0.1
Thyroid	60	1.95 (1.49 to 2.52)*	0.8	11	1.09 (0.55 to 1.96)	0.1	28	2.01 (1.34 to 2.91)*	0.9	20	3.25 (1.99 to 5.02)*	1.7
Kaposi sarcoma	11	0.64 (0.32 to 1.15)	−0.2	5	0.85 (0.28 to 1.98)	−0.1	3	0.41 (0.08 to 1.19)	−0.3	3	0.84 (0.17 to 2.45)	−0.1
All hematologic malignancies	228	1.25 (1.10 to 1.43)*	1.2	73	1.30 (1.02 to 1.64)*	1.3	108	1.18 (0.97 to 1.42)	1.0	43	1.42 (1.03 to 1.94)*	1.6
All lymphomas#	107	1.02 (0.84 to 1.23)	0.1	38	1.16 (0.82 to 1.59)	0.4	52	1.01 (0.75 to 1.32)	0.0	14	0.76 (0.42 to 1.28)	−0.5
Plasma cell dyscrasias	29	1.27 (0.85 to 1.83)	0.2	6	0.90 (0.33 to 1.95)	−0.1	17	1.39 (0.81 to 2.23)	0.3	6	1.77 (0.65 to 3.86)	0.3
All leukemias**	92	1.69 (1.37 to 2.08)*	1.0	29	1.76 (1.18 to 2.52)*	1.0	39	1.39 (0.99 to 1.91)	0.7	23	2.68 (1.70 to 4.01)*	1.8
Time since TC diagnosis												
1 to <5 y	26	3.96 (2.59 to 5.80)*	2.2	10	4.57 (2.19 to 8.40)*	2.5	7	2.34 (0.94 to 4.82)	1.2	9	7.18 (3.28 to 13.62)*	3.6
5 to <10 y	20	2.33 (1.42 to 3.60)*	1.3	5	1.96 (0.64 to 4.58)	0.8	9	2.03 (0.93 to 3.86)	1.2	6	4.16 (1.53 to 9.05)*	2.3
10 to <20 y	22	1.22 (0.76 to 1.84)	0.3	5	0.97 (0.31 to 2.26)	0.0	11	1.13 (0.56 to 2.02)	0.2	5	1.77 (0.58 to 4.14)	0.9
20 to <30 y	19	1.28 (0.77 to 1.99)	0.7	8	1.77 (0.76 to 3.48)	1.8	9	1.16 (0.53 to 2.20)	0.5	2	0.89 (0.11 to 3.22)	−0.2

(continued)

Table 2. (continued)

Event	All patients† (N = 24 900)			Surgery only (no RT, no chemotherapy) (N = 8995)			Radiotherapy (no chemotherapy) (N = 9058)			Chemotherapy (no radiotherapy) (N = 6340)		
	No.	SIR (95% CI)	AER	No.	SIR (95% CI)	AER	No.	SIR (95% CI)	AER	No.	SIR (95% CI)	AER‡‡
30 to <35	3	0.71 (0.15 to 2.07)	−1.2	0	0 (0 to 2.58)	−3.8	2	0.97 (0.12 to 3.52)	−0.1	1	1.62 (0.04 to 9.05)	2.0
≥35 y	2	1.02 (0.12 to 3.69)	0.1	1	1.51 (0.04 to 8.42)	2.6	1	1.03 (0.03 to 5.74)	0.2	0	0 (0 to 16.76)	−4.1
Specific leukemias††												
AML	44	2.98 (2.17 to 4.00)*	0.8	14	3.09 (1.69 to 5.19)*	0.7	13	1.73 (0.92 to 2.95)	0.4	17	7.13 (4.15 to 11.41)*	1.8
CLL	20	0.89 (0.54 to 1.37)	−0.1	7	1.06 (0.43 to 2.19)	0.0	12	0.99 (0.51 to 1.72)	0.0	0	0 (0 to 1.14)	−0.4
CML	14	1.76 (0.96 to 2.96)	0.2	5	2.00 (0.65 to 4.68)	0.2	7	1.80 (0.72 to 3.70)	0.2	2	1.46 (0.18 to 5.27)	0.1

*Statistically significant elevated SIR. AER = absolute excess risk (observed – expected) * person-years at risk/10 000; AML = acute myeloid leukemia; CI = confidence interval; CLL = chronic lymphocytic leukemia; CML = chronic myeloid leukemia; RT = radiotherapy; SIR = standardized incidence ratio; SMN = second-malignant neoplasms; TC = testicular cancer; TCS = testicular cancer survivors.

†A total of 467 patients did not undergo surgery (n = 422) or it is unknown whether surgery was performed (n = 45). Of these 467 patients, a total of 153 were registered as not having received (or unknown if they received) chemotherapy and/or radiotherapy; these 153 patients are not represented in the above treatment subgroups though are included in the "all patients" analysis for the total 24 900 patients. Of the remaining 314 patients, those who underwent radiotherapy (n = 58) or chemotherapy (n = 230) are included in the treatment subgroups of the table. A total of 354 patients who underwent chemotherapy and radiotherapy (including 26 for whom surgery was not performed) are not included in the treatment subgroups though are included in the analysis of all 24 900 TCS.

‡Among TCS diagnosed between 2000 and 2014 for whom latencies beyond 15 years were not yet attainable, for the 192 second solid nontestis cancers that developed, the 1- to <5-, 5- to 10-, and 10- to 15-year SIRs were 1.11 (95% CI = 0.88 to 1.39), 0.84 (95% CI = 0.64 to 1.08), and 1.26 (95% CI = 0.95 to 1.65), respectively; these values were similar to the 1- to <5-, 5- to 10-, and 10- to 20-year data from TCS diagnosed between 1973 and 1999 in whom 1433 second solid nontestis cancers have developed, with SIRs of 1.14 (95% CI = 0.93 to 1.39), 1.05 (95% CI = 0.89 to 1.23), and 1.03 (95% CI = 0.94 to 1.12), respectively.

§Risks of solid, nontestis cancers were statistically significantly increased among those aged younger than 30 years (SIR = 1.29, 95% CI = 1.15 to 1.44; AER = 4.4) and 30–39 years (SIR = 1.11, 95% CI = 1.01 to 1.20; AER = 3.8) at time of TC diagnosis but not for those aged 40–49 years (SIR = 0.96, 95% CI = 0.87 to 1.05; AER = −3.0) and 50 years and older (SIR = 0.98, 95% CI = 0.88 to 1.09; AER = −3.0).

‖Patients with unknown TC stage (see Table 1) are not shown.

¶Solid-SMN not shown in the table include (as classified by the SEER program) mesothelioma (n = 7) and cancers of the anus and anal canal (n = 5), bones and joints (n = 2), eye and orbit (n = 3), gallbladder (n = 3), intrahepatic bile duct (n = 5), larynx (n = 25), male breast (n = 2), nose, nasal cavity and middle ear (n = 4), biliary tract (n = 11), other digestive organs (n = 4), other endocrine sites (n = 1), other nonepithelial skin (n = 13), other urinary organs (n = 1), penis and other male genitalia sites (n = 3), renal pelvis (n = 7), retroperitoneum (n = 4), small intestines (n = 14), thymus (n = 2), and ureter (n = 9), with "other" referring to sites not categorized by SEER as described at: https://training.seer.cancer.gov/modules_site_spec.html.

#Among patients treated for seminoma, 75 developed lymphoma (SIR = 1.10, 95% CI = 0.87 to 1.38), and among patients treated for nonseminoma, 32 developed lymphoma (SIR = 0.87, 95% CI = 0.59 to 1.23). For both seminoma and nonseminoma histologies, SIRs were not statistically significantly elevated or decreased within any treatment subgroup (surgery alone, chemotherapy, or radiotherapy) or within any specific time frame (1–5, 5–10, 10–20, 20–30, 30–35 and ≥35 y) after TC diagnosis.

**Second leukemias include acute lymphocytic leukemia (n = 6), acute monocytic (n = 4) and myeloid (n = 40) leukemias (n = 44), CLL (n = 20), CML (n = 14), and other leukemias (n = 8). Risks of leukemias were statistically significantly increased among those aged <30 years (SIR = 3.14, 95% CI = 2.16 to 4.40; AER = 1.5) and 50 years and older (SIR = 1.72, 95% CI = 1.05 to 2.65; AER = 3.9) at the time of TC diagnosis but not the age groups of 30–39 years (SIR = 1.37, 95% CI = 0.88 to 2.04) or 40–49 years (SIR = 1.02, 95% CI = 0.57 to 1.69).

††Results are shown for the 3 most common leukemias occurring after TC. For acute lymphocytic leukemia (n = 6), the SIR was 1.90 (95% CI = 0.70 to 4.14) and for acute monocytic leukemia (n = 4) the SIR was 4.58 (95% CI = 1.25 to 11.7).

‡‡No radiotherapy" implies either no radiotherapy was administered or it is unknown whether radiotherapy was delivered; likewise "No chemotherapy" implies either no chemotherapy or it is unknown whether chemotherapy was delivered (please refer to Methods).

alone was associated with increased leukemia risks (SIR = 1.76, 95% CI = 1.18 to 2.52), confined to 1-5 years (SIR = 4.57, 95% CI = 2.19 to 8.40) after TC diagnosis. Radiotherapy was associated with nonstatistically significant 2- to 2.3-fold excess leukemias during the first decade after TC diagnosis but decreased to expectation thereafter. Among the most common secondary leukemias (AML, CLL, and CML), only AML was associated with statistically significantly elevated risks (SIR = 7.13, 95% CI = 4.15 to 11.41) after chemotherapy, with statistically significant excesses (SIR = 3.09, 95% CI = 1.69 to 5.19) also following surgery alone.

Solid-SMN After Seminoma and Nonseminoma

Seminoma. Among patients with seminoma, statistically significant overall excesses of solid-SMN followed either radiotherapy (SIR = 1.13, 95% CI = 1.06 to 1.21) or chemotherapy (SIR = 1.28, 95% CI = 1.02 to 1.58), but not surgery alone (SIR = 0.87, 95% CI = 0.74 to 1.01) (Table 3). After radiotherapy, statistically nonsignificant 1.11- to 1.12-fold risks of solid-SMN occurred during the first 30 years of follow-up, with statistically significant excesses thereafter (SIR = 1.28, 95% CI 1.04 to 1.55; P_{trend} = .07). Radiotherapy was associated with statistically significantly elevated risks of pancreatic cancer in 10- to 20-year (SIR = 2.61), 20- to 30-year (SIR = 2.88), and 30 or greater-year (SIR = 4.83) intervals (P_{trend} = .006), whereas statistically significant bladder cancer excesses occurred at 1–10 years (SIR = 1.69) and 30+ years (SIR = 2.00). Excesses of soft tissue cancer were restricted to the 1- to 10-year interval (SIR = 2.88, 95% CI = 1.06 to 6.26), with nonstatistically significant 2-fold risks for 10–30 years (median latency = 11.7 years; range = 5.2–28.3 years). After chemotherapy for seminoma, statistically significantly increased excesses were observed for AML (n = 6, SIR = 10.2, 95% CI = 3.75 to 22.2; data not shown in Table 3), but not for any site-specific solid-SMN.

Nonseminoma. Among patients with nonseminoma, chemotherapy was associated with overall excesses of solid-SMN (SIR = 1.25, 95% CI = 1.08 to 1.43), with statistically significantly increased risks for cancers of thyroid (SIR = 3.65), pancreas (SIR = 2.60), kidney (SIR = 2.13), and soft tissue (SIR = 4.24) (Table 3) and AML (n = 9, SIR = 5.44, 95% CI = 2.49 to 10.3; data not shown in Table 3). Given the relatively small numbers of cancers at each site (n = 8–18), strong discernible temporal trends were not apparent. No overall increased solid-SMN risk was observed after surgery alone (SIR = 0.80) or radiotherapy (SIR = 1.05), but few patients received radiotherapy (n = 193). Site-specific excesses of solid-SMN after surgery alone were confined to kidney cancer (SIR = 1.64), with no apparent temporal trend.

Cumulative Incidence of Solid-SMN

Figure 1 shows the cumulative incidence of solid-SMN (accounting for competing risks of death or other cancers) among TCS by treatment group. Following surgery alone, chemotherapy, and radiotherapy, 15-year cumulative incidences of solid-SMN were 2.2% (95% CI = 1.9% to 2.6%), 2.8% (95% CI = 2.3% to 3.3%), and 4.9% (95% CI = 4.4% to 5.4%), whereas 30-year cumulative incidences were 8.8% (95% CI = 7.8% to 9.9%), 10.1% (95% CI = 8.8% to 11.5%), and 16.9% (95% CI = 15.7% to 18.1%), respectively. Differences between each treatment group were statistically significant: radiotherapy vs surgery alone ($P < .001$), chemotherapy vs surgery alone ($P = .050$), and radiotherapy vs chemotherapy ($P < .001$). Among TCS diagnosed from 1973 to 1999 vs 2000 to 2014 and treated with radiotherapy, 15-year cumulative incidences of solid-SMN did not differ statistically significantly ($P = .41$): 4.8% (95% CI = 4.3% to 5.3%) and 5.2% (95% CI = 4.1% to 6.5%), respectively. Table 4 shows the Fine and Gray competing risk model of solid-SMN cumulative incidence with statistically significant variables, including age of 40 years and older (hazard ratio [HR] = 2.96, 95% CI = 2.67 to 3.28), seminoma histology (HR = 1.42, 95% CI = 1.21 to 1.66), and chemotherapy or radiotherapy (HR = 1.26, 95% CI = 1.08 to 1.47 and HR = 1.35, 95% CI = 1.17 to 1.57, respectively) vs surgery alone. Figure 2 shows the cumulative incidence of leukemias (accounting for competing risks of death or other cancers) by treatment group. Following surgery alone, chemotherapy, and radiotherapy, 15-year cumulative incidences were 0.2% (95% CI = 0.1% to 0.3%), 0.4% (95% CI = 0.3% to 0.7%), and 0.3% (95% CI = 0.2% to 0.5%), respectively, and 30-year cumulative incidences were 0.7% (95% CI = 0.4% to 1.0%), 0.6% (95% CI = 0.3% to 0.9%), and 0.6% (95% CI = 0.4% to 0.9%), respectively.

Discussion

In the largest population-based study of US TCS to date, we identified statistically significant 6% excesses of all solid-SMN taken together and almost 2-fold increased risks of leukemias. With more than 8000 survivors followed for over 20 years and more than 1600 solid-SMN, we described long-term patterns of risk. After radiotherapy, the 30-year cumulative incidence of solid-SMN among all TCS was almost 20% and after chemotherapy was approximately 10%. Statistically significantly elevated leukemia risks persisted for up to 10 years among all TCS and then decreased to expectation. These and other new findings are discussed below.

No US-based investigation (9-12) to date, to our knowledge, has comprehensively examined solid-SMN risk in TCS according to both initial management and histological type focusing on recent decades (Table 5). Two European studies (5,23) examined solid-SMN risks without analyses by treatment type, whereas another European investigation (6) focused only on patients with stage I seminoma given radiotherapy (Table 6). The international investigation of TCS by Travis et al. (17) included population-based registries in Europe (two-thirds of patients) with TC diagnosed as early as 1943. Our estimates are based on considerably larger numbers of solid-SMN (n = 1625) than those in recent European cohorts (range n = 256–427) (5–8,23). The lower overall risks of solid-SMN reported in the current study compared with recent European series (5-8,23) (Table 6) are partially attributable to the population-based nature of our cohort. In contrast, several European series were hospital based (6,8), leading to potential selection biases; another included contralateral TC in SMN risk estimates (23). Lower SMN risks in our survey may also reflect considerable changes in TC treatments in recent decades. These include the use of adjuvant chemotherapy [ie, 1–2 cycles of bleomycin, etoposide, and cisplatin for stage I nonseminoma (24,25) and single-dose carboplatin for stage I seminoma] (26), which reduces the need for salvage therapy (typically 3–4 cycles of platinum-based chemotherapy or radiotherapy) (27). Increased adoption of active surveillance (28,29) for stage I TC might also result in reduced overall risks of SMN; however, approximately 13% and 19% of stage I seminomas and nonseminomas, respectively, relapse within a few years (30); thus, subsequent salvage

Table 3. Site-specific risks of selected second solid cancers after TC according to time since diagnosis of TC, histologic type, and type of initial treatment among 24 900 1-year survivors of TC

Second cancer site[†] and type of initial treatment for TC		1 to <10 y		10 to <20 y		20 to <30 y		≥30 y		Total	
		No.	SIR (95% CI)	No.	SIR (95% CI)	No.	SIR (95% CI)	No.	SIR (95% CI)	No.	SIR (95% CI)
Seminoma: time since diagnosis											
All solid (nontestis) cancer sites	SURG	47	0.76 (0.56 to 1.01)	52	0.82 (0.61 to 1.07)	47	1.00 (0.73 to 1.33)	19	1.12 (0.67 to 1.75)	165	0.87 (0.74 to 1.01)
	RT	218	1.12 (0.97 to 1.28)	321	1.11 (0.99 to 1.24)	262	1.12 (0.99 to 1.27)	100	1.28 (1.04 to 1.55)*	901	1.13 (1.06 to 1.21)*
	CHEMO	36	1.35 (0.95 to 1.87)	25	1.04 (0.67 to 1.53)	16	1.38 (0.79 to 2.24)	5	2.67 (0.87 to 6.23)	82	1.28 (1.02 to 1.58)*
Thyroid cancer	SURG	3	1.96 (0.40 to 5.72)	3	2.69 (0.56 to 7.87)	0	0 (0 to 6.03)	0	0 (0 to 19.8)	6	1.74 (0.64 to 3.79)
	RT	11	2.38 (1.19 to 4.26)*	10	1.98 (0.95 to 3.64)	4	1.31 (0.36 to 3.36)	1	1.15 (0.03 to 6.41)	26	1.91 (1.25 to 2.80)*
	CHEMO	3	3.77 (0.78 to 11.0)	0	0 (0 to 7.51)	0	0 (0 to 20.0)	0	0 (0 to 164.5)	3	2.01 (0.41 to 5.87)
Gastric cancer	SURG	1	0.75 (0.02 to 4.17)	1	0.81 (0.02 to 4.53)	1	1.18 (0.03 to 6.60)	1	3.22 (0.08 to 17.8)	4	1.08 (0.29 to 2.75)
	RT	3	0.71 (0.15 to 2.07)	10	1.79 (0.86 to 3.29)	9	2.16 (0.99 to 4.09)	4	2.80 (0.76 to 7.18)	26	1.69 (1.11 to 2.47)*
	CHEMO	1	1.85 (0.05 to 10.3)	0	0 (0 to 8.22)	0	0 (0 to 18.1)	0	0 (0 to 102.6)	1	0.81 (0.02 to 4.54)
Pancreatic cancer	SURG	6	3.65 (1.34 to 7.94)*	1	0.59 (0.01 to 3.28)	2	1.51 (0.18 to 5.45)	3	5.48 (1.13 to 16.0)*	12	2.30 (1.19 to 4.02)*
	RT	6	1.21 (0.44 to 2.63)	20	2.61 (1.60 to 4.04)*	19	2.88 (1.74 to 4.50)*	12	4.83 (2.50 to 8.44)*	57	2.63 (1.99 to 3.41)*
	CHEMO	1	1.44 (0.04 to 8.01)	0	0 (0 to 5.55)	1	2.99 (0.08 to 16.7)	0	0 (0 to 60.7)	2	1.14 (0.14 to 4.12)
Rectum or recto-sigmoid cancer	SURG	2	0.74 (0.09 to 2.69)	3	1.16 (0.24 to 3.40)	3	1.82 (0.38 to 5.33)	0	0 (0 to 7.72)	8	1.08 (0.47 to 2.13)
	RT	13	1.49 (0.79-2.55)	16	1.34 (0.77 to 2.18)	14	1.73 (0.95 to 2.91)	2	0.90 (0.11 to 3.27)	45	1.45 (1.06 to 1.94)*
	CHEMO	2	1.67 (0.20 to 6.04)	2	2.02 (0.25 to 7.31)	1	2.43 (0.06 to 13.6)	0	0 (0 to 67.0)	5	1.89 (0.61 to 4.40)
Bladder cancer	SURG	6	1.46 (0.54 to 3.18)	8	1.86 (0.80 to 3.66)	7	2.05 (0.82 to 4.22)	1	0.68 (0.02 to 3.77)	22	1.65 (1.04 to 2.50)*
	RT	21	1.69 (1.04 to 2.58)*	24	1.28 (0.82 to 1.90)	25	1.51 (0.98 to 2.23)	13	2.00 (1.07 to 3.43)*	83	1.53 (1.22 to 1.89)*
	CHEMO	1	0.65 (0.02 to 3.60)	5	3.35 (1.09 to 7.81)*	0	0 (0 to 4.84)	1	6.52 (0.17 to 36.4)	7	1.77 (0.71 to 3.65)
Kidney cancer	SURG	3	1.04 (0.21 to 3.03)	1	0.35 (0.01 to 1.94)	1	0.50 (0.01 to 2.80)	1	1.41 (0.04 to 7.86)	6	0.71 (0.26 to 1.54)
	RT	7	0.78 (0.32 to 1.62)	7	0.53 (0.21 to 1.10)	10	1.00 (0.48 to 1.84)	2	0.61 (0.07 to 2.19)	26	0.73 (0.48 to 1.08)
	CHEMO	0	0 (0 to 2.57)	0	0 (0 to 3.06)	2	3.67 (0.44 to 13.3)	0	0 (0 to 45.6)	2	0.61 (0.07 to 2.21)
Soft tissue cancer	SURG	0	0 (0 to 5.60)	1	2.00 (0.05 to 11.1)	0	0 (0 to 12.1)	0	0 (0 to 33.7)	1	0.64 (0.02 to 3.54)
	RT	6	2.88 (1.06 to 6.26)*	5	2.22 (0.72 to 5.18)	3	2.01 (0.42 to 5.88)	0	0 (0 to 7.56)	14	2.22 (1.21 to 3.72)*
	CHEMO	1	3.2 (0.08 to 17.8)	0	0 (0 to 18.4)	1	12.8 (0.32 to 71.1)	0	0 (0 to 300.0)	2	3.31 (0.40 to 12.0)
Nonseminoma: time since diagnosis											
All solid (nontestis) cancer sites	SURG	41	0.86 (0.62 to 1.16)	59	0.76 (0.58 to 0.97)	72	0.81 (0.63 to 1.02)	35	0.81 (0.56 to 1.12)	207	0.80 (0.70 to 0.92)
	RT	1	0.43 (0.01 to 2.41)	5	0.97 (0.31 to 2.26)	7	0.91 (0.37 to 1.87)	11	1.44 (0.72 to 2.58)	24	1.05 (0.67 to 1.56)
	CHEMO	38	1.15 (0.82 to 1.58)	72	1.38 (1.08 to 1.74)*	64	1.15 (0.89 to 1.47)	30	1.32 (0.89 to 1.89)	204	1.25 (1.08 to 1.43)*
Thyroid cancer	SURG	0	0 (0 to 1.87)	2	0.89 (0.11 to 3.21)	2	1.15 (0.14 to 4.14)	1	1.56 (0.04 to 8.72)	5	0.76 (0.25 to 1.77)
	RT	0	0 (0 to 63.4)	1	12.9 (0.33 to 71.7)	0	0 (0 to 74.3)	1	10.8 (0.27 to 60.0)	2	6.33 (0.77 to 22.9)
	CHEMO	8	5.29 (2.28 to 10.4)*	4	2.48 (0.68 to 6.35)	1	0.85 (0.02 to 4.75)	4	11.0 (3.00 to 28.2)*	17	3.65 (2.13 to 5.84)*
Gastric cancer	SURG	0	0 (0 to 3.74)	1	0.65 (0.02 to 3.62)	2	1.25 (0.15 to 4.53)	0	0 (0 to 4.90)	3	0.62 (0.13 to 1.80)
	RT	0	0 (0 to 57.7)	0	0 (0 to 30.5)	0	0 (0 to 24.1)	1	7.4 (0.19 to 41.2)	1	2.11 (0.05 to 11.8)
	CHEMO	0	0 (0 to 5.56)	2	1.97 (0.24 to 7.10)	1	1.00 (0.03 to 5.59)	1	2.55 (0.06 to 14.2)	4	1.30 (0.36 to 3.34)
Pancreatic cancer	SURG	1	0.94 (0.02 to 5.22)	3	1.52 (0.31 to 4.44)	5	2.05 (0.67 to 4.79)	0	0 (0 to 2.81)	9	1.32 (0.61 to 2.52)
	RT	0	0 (0 to 60.0)	0	0 (0 to 28.8)	0	0 (0 to 18.8)	2	8.71 (1.06 to 31.5)*	2	3.25 (0.39 to 11.7)
	CHEMO	0	0 (0 to 5.10)	5	3.81 (1.24 to 8.90)*	5	3.29 (1.07 to 7.69)*	1	1.46 (0.04 to 8.15)	11	2.60 (1.30 to 4.65)*

(continued)

Table 3. (continued)

Second cancer site† and type of initial treatment for TC		1 to <10 y		10 to <20 y		20 to <30 y		≥30 y		Total	
		No.	SIR (95% CI)	No.	SIR (95% CI)	No.	SIR (95% CI)	No.	SIR (95% CI)	No.	SIR (95% CI)
Rectum or recto-sigmoid cancer	SURG	2	0.96 (0.12 to 3.46)	5	1.43 (0.46 to 3.34)	3	0.83 (0.17 to 2.44)	1	0.72 (0.02 to 4.00)	11	1.04 (0.52 to 1.86)
	RT	0	0 (0 to 32.8)	0	0 (0 to 16.2)	0	0 (0 to 12.2)	1	4.31 (0.11 to 24.0)	1	1.14 (0.03 to 6.36)
	CHEMO	1	0.69 (0.02 to 3.87)	2	0.85 (0.10 to 3.09)	3	1.32 (0.27 to 3.85)	1	1.32 (0.03 to 7.35)	7	1.03 (0.41 to 2.12)
Bladder cancer	SURG	3	1.12 (0.23 to 3.26)	7	1.49 (0.60 to 3.07)	7	1.25 (0.50 to 2.57)	5	1.60 (0.52 to 3.74)	22	1.36 (0.86 to 2.07)
	RT	0	0 (0 to 22.8)	0	0 (0 to 10.4)	2	3.76 (0.46 to 13.6)	1	1.69 (0.04 to 9.43)	3	1.83 (0.38 to 5.35)
	CHEMO	0	0 (0 to 2.12)	9	3.03 (1.38 to 5.74)*	3	0.88 (0.18 to 2.58)	1	0.63 (0.02 to 3.54)	13	1.34 (0.71 to 2.30)
Kidney cancer	SURG	6	2.57 (0.94 to 5.59)	5	1.22 (0.40 to 2.85)	6	1.36 (0.50 to 2.97)	4	2.00 (0.55 to 5.13)	21	1.64 (1.01 to 2.50)*
	RT	0	0 (0 to 40.2)	0	0 (0 to 18.4)	1	3.42 (0.09 to 19.0)	0	0 (0 to 11.3)	1	1.10 (0.03 to 6.12)
	CHEMO	4	2.35 (0.64 to 6.02)	7	2.49 (1.00 to 5.12)	5	1.76 (0.57 to 4.10)	2	1.86 (0.22 to 6.71)	18	2.13 (1.26 to 3.37)*
Soft tissue cancer	SURG	1	1.16 (0.03 to 6.48)	1	1.11 (0.03 to 6.18)	0	0 (0 to 5.24)	0	0 (0 to 12.8)	2	0.73 (0.09 to 2.62)
	RT	0	0 (0 to 121.2)	0	0 (0 to 88.7)	0	0 (0 to 74.3)	0	0 (0 to 77.4)	0	0 (0 to 21.8)
	CHEMO	3	4.63 (0.96 to 13.5)	2	3.17 (0.38 to 11.5)	2	4.39 (0.53 to 15.9)	1	6.46 (0.16 to 36.0)	8	4.24 (1.83 to 8.35)*

*Statistically significantly elevated SIR. CHEMO = administration of chemotherapy without (or unknown) radiotherapy administration; CI = confidence interval; RT = administration of radiotherapy without (or unknown) chemotherapy administration; SIR = standardized incidence ratio; SURG = surgery without (or unknown) administration of radiotherapy or chemotherapy; TC = testicular cancer.
†Solid cancers listed in this table are restricted to those for which statistically significantly increased risks were observed in Table 2.

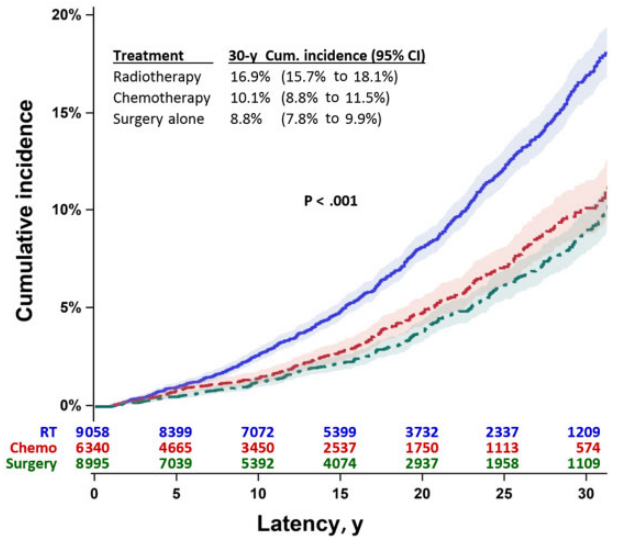

Figure 1. Cumulative incidence of nontestis solid malignant neoplasms after initial testicular cancer (TC) diagnosis, accounting for competing risks of death or development of another cancer after initial TC diagnosis (see Methods), grouped by initial treatment. The 95% confidence intervals are shown as shaded regions. The cumulative incidence functions were statistically different between the 3 treatment curves ($P < .001$). Pairwise comparisons (with Bonferroni correction applied to control for type I error) surgery alone vs radiotherapy ($P < .001$), surgery alone vs chemotherapy ($P = .05$), and chemotherapy vs radiotherapy ($P < .001$) were statistically significant. Chemo = chemotherapy; RT = radiotherapy.

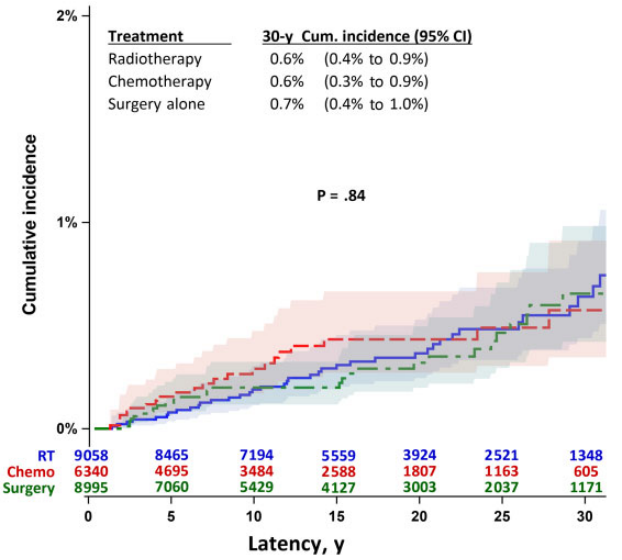

Figure 2. Cumulative incidence of leukemias after initial testicular cancer (TC) diagnosis, accounting for competing risks of death or development of another cancer after initial TC diagnosis (see Methods), grouped by initial treatment. The 95% confidence intervals are shown as shaded regions. The cumulative incidence functions were similar between the three treatment curves ($P = .84$). Chemo = chemotherapy; RT = radiotherapy.

Table 4. Multivariable competing-risk model of potential risk factors affecting the cumulative incidence of second primary solid cancers in TCS

Variables	HR (95% CI)	$P_{adjusted}$
Age, ≥40* vs <40 y	2.96 (2.67 to 3.28)*	<.001*
Race, other race* vs white	1.17 (0.95 to 1.43)	.14
Histology, seminoma* vs nonseminoma	1.42 (1.21 to 1.66)*	<.001*
Chemotherapy* vs surgery alone	1.26 (1.08 to 1.47)*	.01*
Radiotherapy* vs surgery alone	1.35 (1.17 to 1.57)*	.001*
Radiotherapy vs chemotherapy	1.07 (0.91 to 1.27)	1.00

*Statistically significant P values after multiple test adjustment for pairwise treatment comparisons by Bonferroni corrections and hazard ratios (refer to Methods) are denoted by an asterisk. Variables associated with statistically significantly increased risk are denoted by an asterisk. In addition, by univariate Gray's test (not shown in Table 6), age ($P < .0001$), race ($P = .041$), seminoma histology ($P < .001$), and treatment (univariate comparison across 3 groups, $P < .001$) statistically significantly affected risk of second primary solid cancers but not calendar year of TC diagnosis ($P = .18$) or stage of TC ($P = .29$). Clinical variables with univariate $P \leq .15$ were included in the Fine and Gray model shown in this table (refer to Methods). CI = confidence interval; HR = hazard ratio; TCS = testicular cancer survivors.

therapies might result in increased SMN risks after initial surgery alone for TC compared with the general population.

Within the radiotherapy-alone group, the increase in SIR for solid-SMN with more advanced TC (Table 2) likely represents underreporting of chemotherapy use and/or greater radiation exposure (with respect to dose and treatment field) with more advanced TC stage. Reductions in both radiotherapy fields (ipsilateral para-aortic lymphatics vs ipsilateral iliac and para-aortic lymphatics) (14) and doses (20 vs 30 Gy) (31) were adopted in Europe after randomized trials in stage I testicular seminoma reported that these modifications resulted in no statistically significant difference in relapse rates. In contrast, a 20- vs 30-Gy radiotherapy dose was not as widely adopted in the United States until more recently. Glaser et al. reported that the use of lower radiotherapy doses for stage I seminoma increased from 1.5%, 10%, and then 34% in 1999, 2010, and 2012, respectively (32). Commensurately, we reported that the 15-year cumulative incidence of solid-SMN following radiotherapy did not differ among TCS diagnosed in 1973–1999 vs 2000–2014. Given the typical more than 5- to 10-year latency periods for radiation-induced cancer (33), any reduction in risk as a result of a decrease in radiotherapy doses and fields may not manifest until much later. Thus, it will be important to determine whether decreases in radiotherapy dose exposure first recommended in the 1990–2000s (14,31) will eventually result in reduced risks of SMN.

After radiotherapy, pancreatic cancer contributed to the largest AER of solid-SMN, followed by malignancies of the bladder, thyroid, rectum or recto-sigmoid, stomach, and soft tissue. A prior analytic study (34) reported statistically significant 2.9-fold increased risks of pancreatic cancers after TC radiotherapy, with risks associated with higher radiation doses ($P_{trend} < .001$), and remaining elevated for 20 and more years after exposure ($P < .01$). In our series, statistically significantly increased 5-fold risks of pancreatic cancer were apparent for over 30 years after radiotherapy for seminoma.

The urinary bladder (33) is susceptible to carcinogenic effects of radiotherapy. Travis et al. (17) reported statistically significant 2.7-fold increased risks of bladder cancer after radiotherapy alone for TC, similar to twofold increased risks 30+ years after seminoma radiotherapy reported here. The thyroid receives negligible radiation exposure during TC treatment (aside from the relatively few patients treated with supraclavicular nodal radiotherapy) (35). Accordingly, statistically significant thyroid cancer excesses 1–10 years after nonseminoma TC diagnosis were not consistent with radiation carcinogenesis

Table 5. Overview of US studies providing risk estimates for incidence of second primary leukemias or solid cancers in TCS*

Characteristics	First author (citation) (year)								
	Lewinshtein (9) (2012)		Fung (11) (2013)		Patel (12) (2017)		This study		
Patients, no.	5994		12 691		16 463		24 900		
Calendar years of TC diagnosis	1973–2000		1980–2008		1988–2013		1973–2014		
TC histology	Seminoma		Nonseminoma		Nonseminoma		Seminoma and nonseminoma		
Treatment group	RT	No RT	Chemo.	Surgery only	RT	No RT	Surgery only	RT; no chemo	Chemo; no RT
No. patients	4757	1237	6013	6678	9126	7337	8995	9058	6340
Median or mean follow-up, y (range)	15.1 [mean] (0–34.9)	12.3 (N/A)	7.3 (N/A)	7.4 (IQR: 3.3–12.1)	8.3 [mean](IQR: 3.3–12.1)		14.7 for seminoma [mean]15.4 for nonseminoma [mean]		
Second leukemias, no.	13	2	N/A	N/A	N/A	N/A	29	39	23
SIR, overall	1.26	0.85	N/A	N/A	N/A	N/A	1.76	1.39	2.68
95% CI	0.67 to 2.16	0.10 to 3.09	N/A	N/A	N/A	N/A	1.18 to 2.52	0.99 to 1.91	1.70 to 4.01
Second solid cancers, no.	347	53	111	99	N/A	N/A	372	925	286
SIR, overall	1.16	0.77	1.43	0.93	N/A	N/A	0.83	1.13	1.26
95% CI	N/A	N/A	1.18 to 1.73	0.76 to 1.14	N/A	N/A	0.75 to 0.92	1.06 to 1.21	1.12 to 1.41
No. SMN*	506	89	N/A	N/A	661	298	N/A	N/A	N/A
SIR or RR, overall	SIR: 1.51	SIR: 1.16	N/A	N/A	Adjusted† RR: 1.84		N/A	N/A	N/A
95% CI	1.38 to 1.64	0.93 to 1.43	N/A	N/A	1.61 to 2.10		N/A	N/A	N/A
Site-specific risks of solid cancers‡	Yes	Yes	Yes	Yes	No		Yes	Yes	Yes

*All SMN was defined by Lewinshtein et al. as "all malignancies," including cancers of testis, central nervous system, oral cavity, pharynx, thyroid, lung, hepatobiliary, pancreas, stomach, small bowel, colon, rectum, anus, kidney, upper urinary tract, urethra, bladder, prostate, and hematological malignancies including leukemia, lymphoma, non-Hodgkin lymphoma, Hodgkin lymphoma, and a category of "any hematological malignancy." In the study by Patel et al., the cancers comprising SMN were not specified. Chemo = chemotherapy; CI = confidence interval; IQR = interquartile range; PR = prevalence ratio; RR = risk ratio; RT = radiotherapy; SIR = standardized incidence ratio; SMN = second malignant neoplasm; TC = testicular cancer; TCS = testicular cancer survivors.

†Mortality due to SMN was also reported: 82 deaths occurred after radiotherapy and 30 deaths occurred among patients not receiving radiotherapy, resulting in a prevalence ratio of 2.20 (95% CI not available).

‡Lewinshtein et al. also reported site-specific risks for hematological malignancies. All hematological malignancies after radiotherapy SIR = 1.44 (95% CI = 1.08 to 1.89), no radiotherapy SIR = 1.14 (95% CI = 0.52 to 2.17); all lymphomas after radiotherapy SIR = 1.67 (95% CI = 1.17 to 2.31), no radiotherapy SIR = 1.52 (95% CI = 0.61 to 3.13); non-Hodgkin lymphoma after radiotherapy SIR = 1.77 (95% CI = 1.22 to 2.48), no radiotherapy SIR = 1.50 (95% CI = 0.55 to 3.27); Hodgkin lymphoma after radiotherapy SIR = 1.03 (95% CI = 0.21 to 3.00), no radiotherapy SIR = 1.61 (95% CI = 0.04 to 8.95).

Table 6. Overview of major European studies providing risk estimates for incidence of second primary leukemias or solid cancers in TCS*

	First author (citation) (year)										
Characteristics	Robinson (20) (2007)	Hemminki (5) (2010)	Horwich (6) (2014)	Kier (7) (2016)					Groot (8) (2018)		
Patients, no.	9288	5533	2629	5190					5848		
Calendar years of TC diagnosis	1960–2004	1980–2006	1960–1992	1984–2007					1976–2007		
Country or countries	England	Sweden	United Kingdom, Norway	Denmark					Netherlands		
Cohort description	Pop.-based: London, S.E. England	Nationwide	Hospital-based‡ (N = 12)	Nationwide					Hospital-based (N = 13)†		
TC histology	Seminoma, nonseminoma	Seminoma, nonseminoma	Seminoma (Stage 1)	Seminoma, nonseminoma§					Seminoma, nonseminoma		
Treatment group	N/A	N/A	RT	Surgery Only	BEP	RT	MTOL	Total	Surgery Only	RT (with or without Chemo.)	Chemo. Only
No. patients	9288	5533	2629	3335	1862	787	304	5848	2230	1416	2202
Median follow-up, y (range)	N/A	N/A	21.8 (IQR: 17.5–27.5)	14.4 (IQR: 8.6–20.5)					14.1 (IQR: 9.3–20.1)		
Second leukemias, no.	26	18	9	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
SIR, overall	N/A[e]	3.91	1.76	HR = 0.8	HR = 6.3	HR = 2.6	N/A	N/A	N/A	N/A	N/A
95% CI	N/A	2.32 to 6.18	0.92 to 3.38	0.1 to 6.0	2.2 to 18.2	0.3 to 18.9	N/A	N/A	N/A	N/A	N/A
Second solid cancers, no.	383	256	427	N/A	N/A	N/A	N/A	350	47	185	118
SIR, overall	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1.8	1.03	1.91	2.25
95% CI	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1.6 to 2.0	0.75 to 1.36	1.64 to 2.20	1.86 to 2.70
No. SMN¶	409	274	436	152	104	78	27	N/A	N/A	N/A	N/A
SIR or HR, overall‖	N/A‖	SIR = 1.99	SIR = 1.53	HR = 1.0	HR = 1.7	HR = 1.8	HR = 3.7	N/A	N/A	N/A	N/A
95% CI	N/A	1.76 to 2.24	1.39 to 1.68	0.9 to 1.2	1.4 to 2.0	1.5 to 2.3	2.5 to 5.5	N/A	N/A	N/A	N/A
Site-specific risks of solid cancers	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

*Table is restricted to investigations including only European patients and published in the last 15 years. BEP = bleomycin, etoposide, cisplatin; chemo = chemotherapy; CI = confidence interval; HR = hazard ratio; IQR = interquartile range; MTOL = more than one line of treatment; NPop. = population; RT = radiotherapy; SIR = standardized incidence ratio; SMN = second malignant neoplasm; TC = testicular cancer; TCS = testicular cancer survivors.

†All study patients were treated at one of 13 Dutch hospitals.

‡Included 11 radiotherapy centers in the UK and one radiotherapy center in Norway.

§Included gonadal and extragonadal tumors.

‖No overall results were presented. All results were shown only in terms of specific follow-up periods.

¶All SMN was defined as follows. Robinson et al.: all cancers excluding nonmelanoma skin cancer; Hemminki et al.: all cancers excluding TC; Horwich et al.: all cancers excluding nonmelanoma skin cancer and TC; Kier et al.: all cancers excluding nonmelanoma skin cancer and TC.

and may have resulted from more frequent screening in TCS compared with the general population.

Similar to our investigation, two recent studies (36,37) reported statistically significantly increased risks of colorectal and stomach cancers after radiotherapy. The Childhood Cancer Survivor Study (37) found a statistically significant 8.5-fold increased risk of colorectal cancer after abdominal radiotherapy, albeit based on 12 cases. An analytic study of 5-year TCS (36) reported a statistically significantly increased 5.9-fold risk of stomach cancer, with over 20-fold risks ($P_{trend} < .001$) associated with gastric doses of at least 50 Gy vs less than 10 Gy.

Statistically significant excesses of soft tissue cancers after radiotherapy for seminoma likely reflect known treatment effects (33). In contrast, early-onset sarcomas following chemotherapy for nonseminomatous TC may partially represent somatic-type malignancies arising from teratoma (38,39), whereas those with a longer latency may reflect late effects of alkylating agents (40) or radiotherapy (33).

Within the chemotherapy-only group, a statistically significant SIR was observed only among those with metastatic disease (Table 2), suggestive of greater chemotherapy dose intensification within that subgroup. Platinum-based chemotherapy comprises the backbone of metastatic TC therapy (27), but cisplatin binds to and damages DNA, producing partly reactive platinum in the serum and platinum–DNA adducts in organs, detectable up to 20 years later (41). We found statistically significantly elevated 1.7- to 4.0-fold risks for SMN of pancreas, soft tissue, kidney, and thyroid following TC chemotherapy, with thyroid cancer contributing the largest AER, followed by kidney, pancreas, and soft tissue cancers. Wilson et al. (42) reported a 3.5-fold increased risk of renal carcinoma after cisplatin exposure in childhood cancer survivors, albeit based on four cases. Cisplatin is renally excreted, with urine platinum levels detectable for decades after cisplatin administration (43). Thus, acute and ongoing exposure of genitourinary epithelium to cisplatin may contribute to increased risks.

Prior reports showed that radiotherapy (44,45) and cytotoxic drugs (46), including etoposide (47) and cisplatin (44), are associated with excess secondary leukemias in TCS, albeit based on few (n = 3–36) cases. Among more than 18 000 TCS followed-up for a mean of 10.2 years, Travis et al. (44) identified 36 cases of leukemia, 22 after radiotherapy alone. Median time to leukemia diagnosis was 5.0 years, with 25% occurring after one decade. Compared with a surgery-only referent group, increased risks of leukemia after radiotherapy alone and alkylating agents alone were 3- and 5-fold, respectively (44).

Based on the largest number of leukemias identified to date among TCS (n = 92), we found an overall statistically significantly increased 1.7-fold risk. AML comprised 44 cases, with an overall statistically significantly increased sevenfold risk after chemotherapy (n = 17), with statistically significant 13.7-fold and 5.2-fold risks 1–10 years and >10–20 years after TC diagnosis, respectively (data not shown). Consistent with a prior report (48), CLL was not associated with elevated SIRs overall, or for any treatment group; similarly, elevated SIRs were not observed for CML.

The statistically significant 1.8-fold increased risks of leukemia we observed in the surgery-alone group and confined to the first few years after TC diagnosis likely reflect underreporting of subsequent therapies to SEER registries (discussed below) (15,16).

Strengths of our study include the large number of TCS (n = 24 900) and SMN (n = 1853) derived from population-based registries, histological confirmation of all SMN, and long-term follow-up. Limitations inherent to the SEER Program include lack of data regarding types or doses of initial chemotherapy, doses and fields of radiotherapy, and information on subsequent courses of treatments. In our series, 85% TCS in the surgery-alone group had localized TC (data not shown). Some of these TCS subsequently received chemotherapy or radiotherapy (not reported to the SEER program) for relapse (30), which likely contributed to risks of SMN. SEER also does not collect data on other factors that may contribute to cancer excesses (eg, tobacco use, alcohol use, diet, physical activity levels, or comorbid conditions) or the type or frequency of radiologic imaging (49). Our results may also underestimate risks due to underreporting of SMN to SEER program registries when patients emigrate from SEER geographic areas in which TC was diagnosed (16). Such underascertainment may partially account for the lower SIRs observed here vs in European studies, which used nationwide registries (5–8).

Given our results demonstrating statistically significant excesses of solid-SMN and heme-SMN among large numbers of TCS in a population-based setting, efforts to minimize chemotherapy and radiotherapy exposures should continue. Future studies should quantify SMN risks during long-term (>30–40 year) follow-up of TCS and determine the impact of decreases in treatment intensity, including reductions in radiotherapy dose and field size (14,31). Ideally, survivorship care strategies should include counseling TCS with regard to age-appropriate cancer prevention, screening practices applicable to the general population (41,50), smoking cessation, weight control, physical activity, and other factors consonant with adoption of a healthy lifestyle. A better understanding of tumor, genetic, and environmental factors affecting SMN risks could also help personalize treatment and follow-up recommendations (51,52).

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