Second Malignant Neoplasms in Testicular Cancer Survivors

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Abstract

Second malignant neoplasms (SMNs) are a potentially life-threatening late effect of testicular cancer (TC) and its therapy. Although the increased risk for developing solid tumors among TC survivors is largely attributed to radiotherapy, chemotherapy may also be associated with excess risks. However, the baseline risks of developing site-specific SMNs in TC survivors have not yet been quantified, nor have interactions between treatments and other risk factors been elucidated. Studies to date report overall relative risks ranging from 1.4- to 2.8-fold for SMN in TC survivors, with significantly elevated risks apparent for more than 35 years. Analytic investigations show relationships between increasing radiation dose and/or field size and solid tumor risk. Small excess risks of leukemia follow treatment with either chemotherapy or radiotherapy. Recently, concern has been expressed about the increased risk of SMN from radiation exposure during imaging surveillance for recurrence. A small number of studies have examined this issue, generating inconclusive results. Given the current changes in TC treatment that result in lower radiation doses, in the future solid tumors will likely have a considerably lower impact on the lives of TC survivors, although diligent follow-up will be required to accurately quantify long-term risks and to ascertain risks associated with chemotherapy. (*JNCCN* 2012;10:545–556)

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Testicular cancer (TC) is the most common cancer among men aged 18 to 39 years,[1] with a worldwide doubling in incidence over the past few decades.[2] In contrast to the poor survival associated with many young adult cancers, the 5- and 10-year relative survival rates of men with TC are both 95%.[2,3] This success results in not only an average gain of an additional 37 years of life[4] but also the emergence of considerable morbidities. These include second malignant neoplasms (SMNs), which have been linked to treatment of TC,[3,5–13] although the magnitude of any risk after surgery only (without cytotoxic therapy) remains to be defined. This article focuses on the risks of treatment-associated SMNs in patients with TC and evaluates emerging data regarding the possible long-term effects of diagnostic radiation from imaging surveillance in patients who do not undergo adjuvant treatment after orchiectomy for stage I disease.

Overview of Management

Radiotherapy

Radiotherapy has been widely used in the management of early-stage seminoma, with organ-specific radiation doses from various fields shown in Table 1. Adjuvant radiotherapy (20 Gy) to the para-aortic lymph nodes,[14] adjuvant chemotherapy with single-dose carboplatin,[15] and radiographic surveillance[16] are options for stage I seminoma with normal serum tumor markers. In Europe and many areas of North America, due to published data on long-term toxicities of radiotherapy, adjuvant radiation treatment for stage I seminoma is no longer recommended.[17] For stage IIA and IIB seminoma, a higher dose of radiation (30–35 Gy) may be administered to the infradiaphragmatic area, which extends

Table 1 Comparison of Organ-Specific Radiation Doses

Organ	Radiotherapy: Para-Aortic Field Only (20 Gy)	Radiotherapy: Para-Aortic and Iliac Fields (30 Gy)	Single CT, Abdomen/Pelvis (Gy)	Single CT Chest/ Abdomen/Pelvis (Gy)
Esophagus	0.4	1.0	N/A	N/A
Stomach	10.0	14.8	0.018	0.019
Small intestine	4.7	13.5	N/A	N/A
Colon	0.5–9.4	1.7–30	0.017	0.017
Rectum	0.2	22.8	N/A	N/A
Liver	7.0	9.5	0.016	0.018
Gallbladder and ducts	7.3	4.8	N/A	N/A
Pancreas	12.9	16.8	N/A	N/A
Lung	0.3	0.6	0.0035	0.020
Prostate	0.1	4.3	N/A	N/A
Kidneys	5.7	4.2	N/A	N/A
Bladder	0.2	10.2	0.0199	0.020
Thyroid	0.03	0.06	0.00007	0.0038
Active bone marrow	N/A	10.8[8,a]	0.0081	0.013

Organ-specific doses for radiotherapy modified from Travis et al.[8,10] Organ-specific doses from CT scans modified from Tarin et al.[31]
Abbreviation: N/A, data not provided.
[a]Includes patients who received radiotherapy to para-aortic and inguinal/iliac lymph nodes. The average treatment dose to the abdomen and pelvis for all patients in this category was 32.7 Gy (median, 30.5 Gy), with an average dose to active bone marrow of 10.9 Gy.

from the para-aortic region to the proximal ipsilateral iliac lymph nodes.[18–20] For selected patients with stage IIB or IIC seminoma, chemotherapy with 4 cycles of etoposide and cisplatin (EP) or 3 cycles bleomycin, etoposide, and cisplatin (BEP) are options.[21]

Cisplatin-based chemotherapy[22] and retroperitoneal lymph node dissection (RPLND)[23–25] are the cornerstones of nonseminoma management. Radiation treatment is generally reserved for patients with symptomatic metastases that are resistant to chemotherapy and not amenable to surgical resection.[26]

Orchiectomy and Surveillance

Because approximately 70% of patients with stage I nonseminoma and 80% to 85% with stage I seminoma are cured with orchiectomy alone, and 97% to 99% of those who experience relapse are ultimately cured with chemotherapy, surveillance emerged as an attractive management strategy for stage I TC.[27–29] To identify recurrent disease in the retroperitoneum, routine surveillance with abdominal and pelvic CT scan is recommended.[16] For stage I seminoma, patients generally undergo 3 CT scans per year for the first 3 years, followed by 2 scans annually in years 4 to 7, with 1 annual CT until year 10.[30–32] For stage I nonseminoma, the surveillance protocol generally includes 3 to 4 CT scans per year for the first 2 years, followed by 2 to 3 scans annually in years 3 and 4, with another scan at 5 years.[30–32] These protocols translate into approximately 13 to 20 abdominal and pelvic CT scans, with a cumulative effective radiation dose of at least 200 mSv during the first 5 years.[30–32] Estimated organ-specific radiation doses resulting from typical CT scans[31] are listed in Table 1, and are several orders of magnitude smaller than those associated with radiotherapy.

Chemotherapy

Cisplatin-based chemotherapy, which was introduced by Einhorn and Donohue[22] in the 1970s, remains standard treatment for patients with metastatic disease. These patients are categorized into prognostic risk groups using criteria defined by the International Germ Cell Cancer Consensus Classification Group.[33] Patients with low-risk disease generally receive 3 cycles of BEP or 4 cycles of EP. For patients with intermediate- or high-risk disease, the standard therapy is 4 cycles of BEP or 4 cycles

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of etoposide, ifosfamide, and cisplatin. Salvage chemotherapy options include chemotherapy consisting of paclitaxel, ifosfamide, and cisplatin or high-dose chemotherapy followed by autologous stem cell transplant.[34–39]

Second Malignant Neoplasms

Compared to the general population, TC survivors experience a 1.7- to 3.5-fold increased overall risk for SMNs (Table 2).[3,5–7,9–13] Travis et al.[9,10] determined that SMN risk after radiotherapy remains statistically significantly elevated for at least 35 years, and that earlier age at TC diagnosis was associated with a higher cumulative risk of SMN.

Risks After Radiotherapy

Leukemia: Radiotherapy for TC is associated with an increased risk for developing leukemia[8] and solid tumors.[9,10] The largest analytic study of leukemia (n = 36 cases, 106 matched controls) to date in TC survivors (18,567 patients) consisted of an international population-based collaboration by Travis et al.[8] The median latency of the 36 leukemias, 22 of which occurred after radiotherapy alone, was 5.0 years, with 25% occurring after 1 decade (maximum latency, 17.3 years). The increased risk of leukemia occurring after abdominal and pelvic radiotherapy (mean dose to active bone marrow, 10.9 Gy) was on the order of 3-fold.[8] Nonetheless, the absolute risk of leukemia was low, estimated at approximately 9 excess cases per 10,000 patients per year followed for 15 years after 25 Gy of abdominal and pelvic radiation.[8]

Solid Cancers: Compared with the general population, TC survivors have an overall relative risk of 1.4 to 1.9 for developing second solid cancers,[9–11] with risks increasing approximately 5 years after treatment. In an international population-based survey of 40,576 TC survivors,[10] significantly elevated 1.5- to 4-fold relative risks were noted for malignant melanoma and cancers of the lung, thyroid, esophagus, pleura, stomach, pancreas, colon, rectum, kidney, bladder, and connective tissue among 10-year survivors (Table 3).[10,40] By 75 years of age, men who were diagnosed with seminomas or nonseminomatous tumors at 35 years of age experienced cumulative risks of solid cancer of 36% and 31%, respectively.[10] Among TC survivors treated with radiotherapy alone, relative risks (RRs) of SMN at sites included in typical infradiaphragmatic radiotherapy fields were significantly larger than risks at nonexposed sites (RR, 2.7 vs. 1.6; $P < .05$), and remained elevated for 35 or more years.[10] Although supradiaphragmatic radiotherapy is rarely used today, its historical importance likely explains in part the observed increased risks of supradiaphragmatic cancers, including those of the esophagus, pleura, and lung.[3,6,7,10,11,13]

In a case-control investigation of 42 patients with stomach cancer after a diagnosis of either TC (n = 23 cases) or Hodgkin lymphoma (n = 16 cases),[41] a significant relationship (P-trend < .001) with increasing radiation dose was observed, although controls were not matched on primary cancer diagnosis. Other studies of TC survivors[5,11,42] have found associations between increasing treatment dose of radiotherapy and increasing SMN risk. In one study, van den Belt-Dusebout et al.[11] reported that subdiaphragmatic radiotherapy given at doses of 40 to 50 Gy compared with 26 to 35 Gy resulted in an increase in the hazard ratio for SMN from 2.3 to 3.2, respectively, when using the surgery-only group as a control. Based on the linear dose–response model, Zwahlen et al.[42] predicted a 45% decrease in the cumulative risk of second solid cancers by 75 years of age for a patient with TC treated at 35 years of age with para-aortic radiation using 20 Gy instead of 30 Gy. For the same hypothetical patient, Zwahlen et al.[42] estimated that para-aortic radiotherapy decreased the cumulative second solid cancer risk by 48% to 63%, depending on the type of applied dose–response model (linear, plateau, or linear-exponential), when compared with para-aortic and ipsilateral iliac lymph node radiation.

Since there is likely a correlation between either dose or extent of radiotherapy and SMN risk, limiting the total amount of radiation without compromising TC cure rates is imperative.[5,8,11,42] In a randomized trial of 30 versus 20 Gy in the adjuvant treatment of stage I testicular seminoma, no statistically significant difference in relapse rate was observed between the groups.[14] Similarly, Fossa et al.[43] found no statistically significant difference in relapse-free rates at 3 years for patients with stage I seminoma who received para-aortic or para-aortic with ipsilateral iliac lymph node radiation. Finally, Classen et al.[18] reported that radiotherapy with reduced portals

Table 2 Relative Risks of Second Malignant Neoplasms in Testicular Cancer Survivors

Study Populations[a]	No. of Patients	Calendar Years of Testicular Cancer Diagnosis	Duration of Follow-Up (y)	Treatment	Obs	RR	(95% CI)
All Second Malignant Neoplasms							
Norwegian Radium Hospital (Wanderas et al.,[13] 1997)	2006	1952–1990	Mean: 12.5	Any	153[b]	1.7	1.4–1.9
				RT	130	1.6	1.3–1.9
				CT	4	1.3	0.4–3.4
				RT + CT	15	3.5	2.0–5.8
Fourteen population-based tumor registries[c] in Europe and North America (Travis et al.,[10] 2005)	40,576	1943–2001	Mean: 11.3	Any	1694	1.9	1.8–2.1
				RT	892	2.0	1.9–2.2
				CT	35	1.8	1.3–2.5
				RT + CT	25	2.9	1.9–4.2
Thirteen international cancer registries[d] (Richiardi et al.,[3] 2007)	29,511	1943–2000	Median: 8.3	Any	1811[e]	1.7	1.6–1.7
Netherlands Testicular Cancer Survivor cohort (van den Belt-Dusebout et al.,[11] 2007)	2707	1965–1995	Median: 17.6	Any	270[f]	1.7	1.5–1.9
				RT	199	1.7	1.5–2.0
				CT	23	1.4	0.9–2.1
				RT + CT	29	3.0	2.0–4.4
				SDRT	N/A	2.6[g]	1.7–4.0
				SDRT + MRT	N/A	3.6[g]	2.1–6.0
				PVB/BEP	N/A	2.1[g]	1.4–3.1
				SDRT (26-35 Gy)	N/A	2.3[g]	1.5–3.6
				SDRT (40-50 Gy)	N/A	3.2[g]	2.1–5.1
Swedish Family-Cancer Database (Hemminki et al.,[7] 2010)	5533	1980–2006	N/A	Any	274[h]	2.0	1.8–2.2
Leukemia							
Nested case-control study of leukemia in 8 population-based tumor registries[i] in Europe and North America (Travis et al.,[8] 2000)	18,567	1970–1993	N/A	No RT/CT	4	1.0[j]	–
				RT	22	3.1	0.7–2.2
				CT	8	5.0	1.1–40
				RT + CT	2	5.1	0.5–58

Abbreviations: BEP, bleomycin, etoposide, cisplatin; CT, chemotherapy; MRT, mediastinal radiation; N/A, data not provided; Obs, observed number of cases; PVB, cisplatin, vinblastine, bleomycin; RR, relative risk; RT, any radiation treatment; SDRT, supradiaphragmatic radiation.

[a]There was overlap in the cancer registries included in the cohort studies by Richiardi et al.[3] and Travis et al.,[10] with the following countries contributing patients to both studies: Denmark, Finland, Norway, and Sweden.

[b]Six cases of leukemia were observed, with an RR of 1.9 (95% CI, 0.7–4.1).

[c]Fourteen population-based tumor registries: Canada (Ontario, 1964–2000), Denmark (1943–1998), Finland (1953–2001), Norway (1953–1999), Sweden (1958–2001), and 9 registries that participated in the SEER programs in the United States (1973–1999), including Connecticut (from 1973), Hawaii (from 1973), metropolitan areas of San Francisco-Oakland (from 1973), Detroit (from 1973), Seattle-Puget Sound (from 1974), and Atlanta (from 1975).

[d]Thirteen international cancer registries: Australia, New South Wales (1972–1997); Canada, British Columbia (1970–1998); Canada, Manitoba (1970–1998); Canada, Saskatchewan (1967–1998); Denmark (1943–1997); Finland (1953–1998); Iceland (1955–2000); Norway (1953–1999); Singapore (1968–1992); Slovenia (1961–1998); Spain, Zaragoza (1978–1998); Sweden (1961–1998); United Kingdom, Scotland (1975–1996).

[e]Thirty-eight cases of myeloid leukemia were observed, with an RR of 3.6 (95% CI, 2.6–5.0); 13 cases of lymphoid leukemia were observed, with an RR of 1.0 (95% CI, 0.5–1.7); 23 cases of other types of leukemia were observed, with an RR of 3.5 (95% CI, 2.2–5.2).

[f]Six cases of leukemia were observed, with an RR of 1.6 (95% CI, 0.6–3.5).

[g]Hazard ratios (HRs) are shown, with the referent group consisting of patients treated with surgery alone (HR, 1.0).

[h]Twelve cases of leukemia were observed, with an RR of 3.8 (95% CI, 2.0–6.7).

[i]Eight population-based tumor registries (1970–1993): Iowa, Connecticut, New Jersey, Ontario, Denmark, the Netherlands, Sweden, and Finland.

[j]The referent group in the nested case-control study of leukemia.

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for stage IIA/B seminoma resulted in excellent TC control, with actuarial relapse-free survival rates at 6 years of 95.3% and 88.9% for stage IIA and IIB, respectively, although chemotherapy may also be an option for these conditions.

Risks After Chemotherapy

Leukemia: Both etoposide and cisplatin are associated with increased risks of secondary leukemia.[8,34,44,45] The cumulative incidence of leukemia 5 years after a cumulative etoposide dose of less than 2000 mg/m^2 and of 2000 mg/m^2 or greater is approximately 0.5% and 2.0%, respectively.[45] Travis et al.[8] reported a highly significant relationship between increasing cumulative dose of cisplatin for TC and leukemia risk (*P*-trend = .001) in a multivariable model that adjusted for radiation dose. These investigators estimated that a cumulative dose of 650 mg of cisplatin is associated with a 3.2-fold risk of leukemia, although the excess risk is small (a total of 16 excess cases among 10,000 patients with TC followed up for 15 years). Remarkably similar results were found in an analytic study[46] of leukemia after ovarian cancer, in which a highly significant relationship (*P*-trend < .001) between cumulative cisplatin dose and leukemia risk was observed, with a total of 21 excess leukemias estimated among 10,000 women followed for 15 years after a cumulative dose of 500 to 1000 mg.

Solid Cancers: Chemotherapy for TC also appears to be associated with increased risks of solid tumors (Table 2).[8,10,11] In the international series of more than 40,000 patients,[10] Travis et al.[2,10] reported that the RR of solid tumors (RR, 1.8) was significantly increased after chemotherapy alone, although data on specific cytotoxic drugs were not available. A subsequent study[11] showed a significantly increased 2-fold risk of solid tumors with cisplatin-based regimens (BEP and cisplatin, vinblastine, and bleomycin) compared with surgery alone, confirming other reports.[13,47] Prolonged accumulation of platinum in specific organs may in part provide a biologic explanation for the increased risk of SMN, although information regarding long-term sites of tissue deposition is lacking.[2] Elevated concentrations of cisplatin in most organs, including the lung, are detected for up to 17 months after administration.[48–51] However, the risk of solid tumors after cisplatin-based chemotherapy in the modern era remains to be elucidated, because most epidemiologic studies included patients treated before current cisplatin-based chemotherapy became widely adopted. Moreover, tobacco use may increase the risk (RR, 1.8) of SMN after TC to a similar extent as either radiotherapy or chemotherapy.[11]

Risks After Radiotherapy Combined With Chemotherapy

Whether patients with TC treated with both radiation and chemotherapy have a significantly higher risk of SMN than those treated with either modality alone has not been definitively established (Table 2).[10,11,13] Compared with patients treated with radiation alone, Travis et al.[10] reported that the RR of second solid tumors increased from 2.0 to 2.9 for those given both radiation and chemotherapy, but differences were not statistically significant. A study by Wanderas et al.,[13] however, showed that the risk of SMN in patients who received both radiation and chemotherapy was significantly higher than in those receiving radiation alone (RR, 3.5 vs. RR, 1.6). Similarly, van den Belt-Dusebout et al.[11] showed that SMN risk is 1.8-fold significantly higher among patients who received both radiation and chemotherapy, compared with those given radiation alone. Platinum is used clinically as a radiosensitizer, and patients with ovarian cancer who received radiotherapy and platinum-based chemotherapy had a significantly higher risk of developing leukemia than those who received platinum alone (*P* = .006) in a multivariate model adjusted for cumulative amount of drug.[46] A similar finding was not apparent in TC survivors, but few patients had received both treatments.[8]

Mortality After Second Malignant Neoplasms

Concern exists that survival after an SMN may be inferior to that after a first cancer at the same anatomic site. Prior treatment for TC may not only limit therapeutic options for SMN but also adversely affect the response of SMN to anticancer treatment due to mechanisms of therapy-related carcinogenesis.[52–54] Prior irradiation may limit the ability to apply sufficient radiation doses or to perform major surgery.[55–57] Based on a large number of patients reported to the SEER program, Schairer et al.[58] reported that the rate ratios for both cancer-specific and all-cause mortality for SMN (n = 621) among 29,356 TC survivors were not significantly different from those of matched first cancers (n = 12,420). However, a subgroup analysis showed that all-cause mortality after either lung cancer or SMN at subdiaphragmatic sites

Table 3 Estimated Relative Risk of Second Cancers According to Time Since Testicular Cancer Diagnosis for Patients Diagnosed With Testicular Cancer at 35 Years of Age

	All ≥ 10 y Intervals		Time Since Testicular Cancer Diagnosis						Excess Number[a] (%)
			10–19 y		20–29 y		≥ 30 y		
	Obs	RR (95% CI)	Obs	RR (95% CI)	Obs	RR (95% CI)	Obs	RR (95% CI)	
Cancer Site									
All solid tumors	1694	1.9 (1.8–2.1)	802	2.1 (1.9–2.3)	563	2.0 (1.8–2.2)	329	1.7 (1.6–1.9)[b]	698 (100)[c]
Esophagus	26	1.7 (1.0–2.6)	13	2.0 (< 1.0–3.8)	7	0.9 (< 1.0–2.3)	6	2.1 (< 1.0–4.0)	9 (1.3)
Stomach	129	4.0 (3.2–4.8)	64	4.9 (3.7–6.4)	49	4.5 (3.3–5.9)	16	1.9 (1.0–3.2)[d]	88 (12.6)
Colon	153	2.0 (1.7–2.5)	62	1.8 (1.3–2.6)	52	2.1 (1.5–2.8)	39	2.2 (1.6–3.0)	66 (9.5)
Rectum/anus	101	1.8 (1.4–2.3)	60	2.7 (1.9–3.8)	22	1.3 (< 1.0–1.9)	19	1.7 (1.1–2.6)	39 (5.5)
Pancreas	95	3.6 (2.8–4.6)	44	4.1 (2.8–5.9)	38	4.3 (3.0–6.0)	13	2.3 (1.3–3.7)	63 (9.0)
Lung	256	1.5 (1.2–1.7)	148	2.2 (1.7–2.7)	73	1.4 (1.1–1.8)	35	1.0 (< 1.0–1.4)[d]	65 (9.3)
Pleura	12	3.4 (1.7–5.9)	7	6.0 (2.3-12)	3	2.6 (0.5–6.6)	2	1.9 (0.4-6.1)	8 (1.1)
Prostate	249	1.4 (1.2–1.6)	88	1.1 (< 1.0–1.6)	91	1.4 (1.1–1.8)	70	1.5 (1.2–1.8)	52 (7.4)
Kidney	80	2.4 (1.8–3.0)	29	1.7 (1.0–2.6)	30	2.5 (1.7–3.6)	21	3.0 (1.9–4.4)[e]	43 (6.2)
Bladder	211	2.7 (2.2–3.1)	75	2.0 (1.4–2.7)	85	3.2 (2.5–4.0)	51	2.6 (2.0–3.5)	115 (16.4)
Malignant melanoma	70	1.8 (1.3–2.3)	43	1.9 (1.3–2.6)	23	2.1 (1.4–3.1)	4	0.8 (0.3–1.7)	30 (4.2)
Thyroid	16	2.3 (1.0–4.4)	15	4.2 (1.8–8.2)	1	1.0 (< 1.0–3.4)	0	—	9 (1.2)
Connective tissue	19	4.0 (2.3–6.3)	9	3.7 (1.7–7.0)	9	6.1 (2.8–11.0)	1	1.6 (< 1.0–5.8)	14 (2.0)
Other solid tumors[f]	277	1.6 (1.4–1.9)	145	1.5 (1.2–1.9)	80	1.6 (1.3–2.0)	52	1.9 (1.4–2.4)	98 (14.1)
Radiotherapy Only									
All solid tumors	892	2.0 (1.9–2.2)	399	2.2 (1.9–2.5)	300	2.0 (1.8–2.3)	193	1.8 (1.6–2.1)[g]	387 (100)[c]
Sites in-field[h]	445	2.7 (2.4–3.0)	174	2.6 (2.1–3.2)	165	2.9 (2.4–3.4)	106	2.5 (2.0–3.0)	246 (63.7)
Other sites	447	1.6 (1.4–1.8)	225	1.9 (1.6–2.3)	135	1.5 (1.3–1.8)	87	1.4 (1.1–1.7)[i]	141 (36.3)

The table is restricted to sites for which significantly increased RR were observed in 10-year survivors of testicular cancer. The RR is a decreasing function of age at testicular cancer diagnosis; results are presented for patients 35 years of age, which is the mean age of the cohort.
Abbreviations: Obs, observed number of cases; RR, relative risk.
[a]Percentage contribution to the total excess is shown within the parentheses; percentages may not sum to 100 because of rounding.
[b]*P*-trend (negative) = .007.
[c]Obtained as sum of site-specific excesses.
[d]*P*-trend (negative) < .001.
[e]*P*-trend (positive) = .02.
[f]Includes 172 tumors for which site was specified and 105 tumors of unknown or ill-defined primary site.
[g]*P*-trend (negative) = .013.
[h]Restricted to those sites that are included in typical infradiaphragmatic radiotherapy fields for testicular cancer: stomach, small intestine, colon, rectum, liver, gallbladder and ducts, pancreas, kidney, and bladder.
[i]*P*-trend (negative) = .005.
Adapted from Travis LB, Fossa SD, Schonfeld SJ, et al. Second cancers among 40,576 testicular cancer patients: focus on long-term survivors. J Natl Cancer Inst 2005;97:1354–1365; with permission.

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was increased among patients with TC diagnosed during 1973 to 1979.[58] The higher radiation doses delivered and possible inclusion of the chest in radiation fields during earlier years were hypothesized to cause more bone marrow suppression, which may have subsequently limited patients' ability to tolerate full-dose chemotherapy.[58]

Diagnostic Radiation Exposure

Recently, there are growing concerns regarding risk resulting from radiation due to CT scans.[59,60] Brenner et al.[59] estimated that approximately 1.5% to 2.0% of all cancers in the United States may be attributable to radiation from CT studies, with the largest concern expressed for the very young. Not only are children more sensitive to the carcinogenic effects of radiotherapy than adults, but also imaging modalities are not usually adjusted to their smaller body sizes, which can in turn result in higher doses of scattered radiation.[59] These results, however, must be put into perspective, because the estimated lifetime attributable risk (LAR) of mortality from cancer for an individual is extremely small (e.g., 0.02%) after an abdominal CT (240 mAs) at 35 years of age.[59]

Second Malignancies and Surveillance Imaging for TC

Three recent studies[30–32] that addressed the risk of SMN associated with radiation during surveillance for stage I TC yielded conflicting results. To estimate the LAR of SMN among patients with stage I TC, Tarin et al.[31] applied cancer incidence data from the BEIR VII report.[61] They showed that the organ-specific LAR after a single abdomen and pelvic CT for stomach, colon, liver, lung, bladder, and bone marrow malignancies in an 18-year-old man were 0.008%, 0.03%, 0.005%, 0.006%, 0.02%, and 0.008%, respectively. After 13 to 16 abdominal and pelvic CT studies, as recommended by current surveillance protocols, the investigators estimated that the LAR of SMN ranged from 1.9% for an 18-year-old to 1.2% for a 40-year-old patient.[31] With the inclusion of chest CT, this risk increased to 2.6% and 1.6% for patients aged 18 and 40 years, respectively.[31] However, the authors did not adjust for known cancer risk factors,[31] such as smoking.[11]

Chamie et al.[30] conducted a retrospective study to determine if patients with stage I nonseminoma who forewent RPLND had higher risks of SMN than those who underwent RPLND, with the assumption that most patients in the former group underwent surveillance only.[30] Although no statistically significant increase in the incidence of SMN was seen for the entire cohort, an absolute excess incidence of 73 SMN was shown for every 10,000 patients older than 45 years without RPLND at 15 years.[30] However, a major weakness of this study was that subjects in the group without RPLND may have received chemotherapy. Furthermore, other risk factors for SMN, such as genetic influences and lifestyle choices, including tobacco and alcohol use, physical activity, and dietary patterns, were not taken into account.

Unlike the previous 2 studies,[30,31] van Walraven et al.[32] found no association between diagnostic radiation and risk of SMN among 2569 TC survivors in Canada. The hazard ratio for SMN per 10 mSv increase was 0.99 (95% CI, 0.95–1.04).[32] The median number of abdominal and pelvic CT scans within this cohort was 10, with a median radiation dose of 110 mSv.[32] However, the authors pointed out that a follow-up longer than 11 years may be necessary to detect any increased risk.

Given the heightened awareness regarding any potential risk from the very low levels of ionizing radiation associated with CT scans, low-dose CT protocols have been developed to replace standard-dose CTs. A prospective study of 100 patients with TC who each underwent low- and standard-dose CT showed that low-dose CT provided diagnostically acceptable images for 99% of patients and achieved a 55% reduction in ionizing radiation dose.[62] In many institutions, low-dose CT is now the standard of care for surveillance protocols involving repetitive imaging.

Second Malignancies and Survivorship Issues

Currently, no consensus exists regarding interventions to prevent SMN in TC survivors.[2,63] In general, adoption of practices that are consistent with a healthy lifestyle, including exercise, dietary modification, and smoking cessation, should be encouraged. Moreover, all patients should undergo age-appropriate cancer screening.[63] Because approximately 2% of TC survivors will develop a second TC that is unrelated to treatment,[64] self-examination of the contralateral testicle is recommended. However,

evidence for frequent cancer screening with blood tests or radiographic studies is lacking. A retrospective study conducted by Buchler et al.[65] reported that only 27% of second cancers were detected through frequent oncology follow-up visits.

Genetic Predisposition to Radiation-Induced Second Malignancies

In the past decade, the research community has made significant progress in elucidating the treatment-associated risks of SMN.[66] However, understanding of the molecular basis of genetic susceptibility to SMN remains limited.[67–69] Two recent studies identified genetic variants associated with radiation-related SMN,[67,68] albeit not in TC survivors. In 189 survivors of Hodgkin lymphoma treated with radiation as children, 2 single nucleotide polymorphisms (SNPs) at chromosome 6q21 were associated with all second solid cancers taken together.[67] The largest number of sites comprised cancers of the breast (n = 59), thyroid (n = 15), and skin (n = 5). Knight et al.[68] identified 3 SNPs associated with therapy-related myeloid leukemia. Identifications of similar genetic markers in TC survivors could provide a strategy to identify those patients at greatest risk of SMN and potentially help guide the development of targeted therapeutic agents.

Future Research Directions

Future research priorities with regard to SMN in TC survivors were recently summarized (Table 4).[2,40] In particular, it will be important to determine the effect of reductions in field size and dose of radiotherapy on the risk of SMN, and to further investigate the relationship between the effect of modern platinum-based chemotherapy on the site-specific risk of solid tumors, including associated temporal patterns, and the influence of age at exposure and attained age. It will also be critical to compare the risk of SMN in TC survivors managed with surgery alone versus cancer incidence in the general male population; to examine the delaying influence of platinum-based chemotherapy (and duration and magnitude of this effect) on the development of contralateral testicular cancer; and to characterize the evolution of cured testicular cancer.[2] In addition, more focus is needed on the construction of a comprehensive infrastructure that would facilitate research in this area, with the inclusion of a coordinated system for biospecimen collection, to eventually identify the genetic and molecular underpinnings of not only SMN[2,69] but also other late toxicities. An ultimate goal is the development of a risk classification system that would allow appropriate screening and early intervention with the goal of decreasing the morbidity and mortality from SMN in TC survivors.

Conclusions

Second malignant neoplasms are a potentially life-threatening late effect of TC and its therapy. Although the increased risk of solid tumors among TC survivors is largely attributed to radiotherapy, especially as it was administered decades ago, chemotherapy may also be associated with increased risks. Given the current changes in TC treatment that result in lower radiation doses, in the future solid tumors will likely have a considerably lower impact on the lives of TC survivors, although diligent follow-up will be required to accurately quantify long-term risks and to ascertain risks associated with chemotherapy. Although theoretical concerns exist with regard to an increased risk of SMN due to diagnostic radiation based on mathematical risk models,[59,60,70] several recent retrospective studies[30–32] that addressed this question in TC survivors generated conflicting results.

As data continue to accrue, it seems prudent for TC survivors to adopt practices consistent with a healthy lifestyle, including smoking cessation, and to follow guidelines published by the American Cancer Society Nutrition and Physical Activity Advisory Committee.[71] They should also be encouraged to seek medical advice for any persistent changes in health status, and to follow cancer screening guidelines applicable to the general population. These and other recommendations were recently summarized in a commentary published in the *Journal of the National Cancer Institute*[2] based on the results of an international workshop focused on TC survivors.

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Table 4 Summary of Major Research Recommendations: Late Effects of Testicular Cancer and Its Treatment

Overarching Recommendation: Lifelong Follow-Up of All Testicular Cancer Survivors (TCS)

- Integrate observational and analytic epidemiologic studies with molecular and genetic approaches to ascertain the risk of emerging toxicities and to understand the evolution of known late effects, especially with the aging of TCS.
- Evaluate the influence of race and socioeconomic status on the late effects of TC and its treatment.
- Characterize long-term tissue deposition of platinum (sites, reactivity), serum levels, and correlation with late effects.
- Evaluate the life-long burden of medical and psychosocial morbidity by treatment.
- Use research findings to establish evidence-based, risk-adapted, long-term follow-up care.

Specific Recommendations

- Second malignant neoplasms (SMN) and late relapses
  - ➤ Determine the effect of reductions in field size and dose of radiotherapy, along with the use of carboplatin as adjuvant therapy in seminoma patients, on the risk of SMN.
  - ➤ Examine relation between platinum-based chemotherapy and site-specific risk of solid tumors, the associated temporal patterns, and the influence of age at exposure and attained age.
  - ➤ Compare risk of SMN in TCS managed with surgery alone to cancer incidence in the general male population.
  - ➤ Examine delaying influence of platinum-based chemotherapy (and duration and magnitude of effect) on development of contralateral testicular cancer.
  - ➤ Characterize the evolution of cured testicular cancer, in particular, the molecular underpinnings of late recurrences.
- Cardiovascular disease (CVD)
  - ➤ Evaluate the contributions and interactions of subclinical hypogonadism, platinum-based chemotherapy, radiotherapy, lifestyle factors (diet, tobacco use, physical activity), body mass index, family history of CVD, race, socioeconomic status, abnormal laboratory values, and genetic modifiers.
  - ➤ Develop comprehensive risk prediction models, considering the above variables, to stratify TCS into risk groups in order to customize follow-up strategies and develop evidence-based interventions.
- Neurotoxicity
  - ➤ Evaluate evolution of neurotoxicity across TCS lifespan, role of genetic modifiers, and extent to which symptoms affect work ability and quality of life.
- Nephrotoxicity
  - ➤ Determine whether the natural decline in renal function associated with aging is accelerated in TCS, any influence of low-level platinum exposure, and the impact of decreased glomerular filtration rate on CVD and all-cause mortality.
  - ➤ Determine the incidence of hypomagnesemia, together with the role of modifying factors and resultant medical consequences, in long-term TCS.
- Hypogonadism and decreased fertility
  - ➤ Address the incidence, course, and clinical effects of subclinical hypogonadism.
  - ➤ Evaluate effect of all levels of gonadal dysfunction in TCS on CVD, premature aging, fatigue, osteoporosis, mental health, quality of life, and sexuality.
- Pulmonary function
  - ➤ Examine role of platinum compounds on long-term pulmonary damage in TCS, and interactions with other influences, including bleomycin, tobacco use, and occupational risk factors.

(Cont.)

Table 4 Summary of Major Research Recommendations: Late Effects of Testicular Cancer and Its Treatment (Cont.)

Specific Recommendations (cont.)

- Psychosocial effects
  - ▸ Identify prevalence and predictors of depression, cancer-related anxiety, fatigue, infertility-related distress, problems with sexuality and paired relationships, and posttraumatic growth.
  - ▸ Examine the impact of different cultural backgrounds on posttreatment quality of life.
  - ▸ Evaluate TCS work ability throughout life.
  - ▸ Determine whether normal age-related declines in cognitive function are accelerated in TCS.

Interventions

- Conduct targeted intervention trials aimed at promoting smoking cessation, healthy dietary habits, and an increase in physical activity.
- Evaluate the role of information and communication technologies in promoting a healthy lifestyle among TCS.
- Consider randomized, pharmacologic intervention trials among TCS with biochemical parameters approaching threshold values to avoid accelerated development into treatment-requiring CVD.
- Determine optimal schedule of testosterone replacement therapy among TCS with clinical hypogonadism.
- Consider screening strategies for selected SMN.

Genetic and Molecular Considerations

- Evaluate genetic risk factors (identified in the general male population) as modifiers for all late effects in TCS, in particular, CVD, SMN, neurotoxicity, nephrotoxicity, hypogonadism, and psychosocial effects.
- Investigate the role of genome-wide association studies, epigenetics, mitochondrial DNA, microRNA, proteomics, and related approaches in identifying genetic variants that contribute to the late effects of treatment.
- Develop standardized procedures for biospecimen collection to support genetic and molecular studies, as reviewed previously.

Risk Prediction Models

- Develop comprehensive risk prediction models that incorporate genetic modifiers of late sequelae.

Adapted from Travis LB, Beard C, Allan JM, et al. Testicular cancer survivorship: research strategies and recommendations. J Natl Cancer Inst 2010;102:1114–1130; with permission.

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