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ORIGINAL REPORT

Second Malignant Neoplasms in Survivors of Pediatric Hodgkin's Lymphoma Treated With Low-Dose Radiation and Chemotherapy

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ABSTRACT

Purpose
Survivors of childhood Hodgkin's lymphoma (HL) are at risk for second malignant neoplasms (SMNs). It is theorized that this risk may be attenuated in patients treated with lower doses of radiation. We report the first long-term outcomes of a cohort of pediatric survivors of HL treated with chemotherapy and low-dose radiation.

Patients and Methods
Pediatric patients with HL (n = 112) treated at Stanford from 1970 to 1990 on two combined modality treatment protocols were identified. Treatment included six cycles of chemotherapy with 15 to 25.5 Gy involved-field radiation with optional 10 Gy boosts to bulky sites. Follow-up through September 1, 2007, was obtained from retrospective chart review and patient questionnaires.

Results
One hundred ten children completed HL therapy; median follow-up was 20.6 years. Eighteen patients developed one or more SMNs, including four leukemias, five thyroid carcinomas, six breast carcinomas, and four sarcomas. Cumulative incidence of first SMN was 17% (95% CI, 10.5 to 26.7) at 20 years after HL diagnosis. The standard incidence ratio for any SMN was 22.9 (95% CI, 14.2 to 35) with an absolute excess risk of 93.7 cases per 10,000 person-years. All four secondary leukemias were fatal. For those with second solid tumors, the mean (± SE) 5-year disease-free and overall survival were 76% ± 12% and 85% ± 10% with median follow-up 5 years from SMN diagnosis.

Conclusion
Despite treatment with low-dose radiation, children treated for HL remain at significant risk for SMN. Sarcomas, breast and thyroid carcinomas occurred with similar frequency and latency as found in studies of children with HL who received high-dose radiation.

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INTRODUCTION

With current therapy, most children and adolescents with Hodgkin's lymphoma (HL) are long-term survivors.[1] Survivors are at risk for developing second malignant neoplasms (SMNs) including leukemia, sarcomas, breast, thyroid, gastrointestinal, and lung carcinoma.[2-10] While secondary leukemia is associated with alkylating agents and epipodophyllotoxin chemotherapy, solid SMN risk is more closely linked to radiation, particularly at higher doses.[11,12] Over the past 40 years, treatment for children with HL has evolved from high-dose extended-field radiation to combined-modality therapy with chemotherapy and low-dose involved-field radiation (IFRT). Such treatment protocols have the theoretical benefit of diminished risk of solid SMN due to decreased radiation exposure. Early reports of low SMN incidence in children and young adults after low-dose radiation are promising but suffer from short follow-up (median, 8 to 13 years).[13-15]

In 1970, in an effort to diminish the deleterious effects of high-dose radiation on growth and musculoskeletal development of children with HL, Stanford investigators pioneered a combined modality treatment protocol with low-dose IFRT and mechlorethamine, vincristine, prednisone, procarbazine (MOPP) chemotherapy.[16,17] Children treated on this protocol had normal growth, but secondary leukemias and male infertility were significant concerns. In response, a second protocol was initiated in 1982 combining alternating cycles of MOPP and doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD) chemotherapy with low-dose IFRT.[18] Median follow-up time for patients treated on these protocols is now longer than 20 years, allowing the first long-term

follow-up of pediatric HL survivors treated with chemotherapy and low-dose radiation.

PATIENTS AND METHODS

Patients and Treatment

Between 1970 and 1990, 112 children with newly diagnosed, untreated, biopsy-proven HL were treated at Stanford on two consecutive protocols. Details of eligibility, staging, treatment, and early outcomes have been published previously.[17,18] Protocols were approved by the Stanford institutional review board and the parents/guardians of participants provided informed consent.

Ped HD1 protocol enrolled patients from 1970 to 1982. Treatment included six cycles of MOPP chemotherapy and low-dose radiation with dose determined by bone age (range, 15 to 25.5 Gy) followed by 10 Gy boosts for select patients with bulky disease or partial response to treatment. Radiation volumes were tailored to the involved nodal station with appropriate margins—mantle, minimantle, or hemimantle for disease above the diaphragm and modified spade, para-aortic, or inverted Y fields for infradiaphragmatic disease.[19] Two patients died before receiving radiation and are excluded from SMN analysis.

Ped HD2 protocol enrolled patients from 1982 to 1990. Treatment included six cycles of chemotherapy (three ABVD, three MOPP) administered in alternating fashion. All patients received 15 Gy IFRT with 10 Gy boosts for select patients with bulky disease or partial response following two cycles of chemotherapy. All enrolled children completed primary therapy and are included in this analysis.

Data Collection

Stanford University institutional review board approval was obtained for this retrospective study. The following data were abstracted from medical records: date of birth, sex, date of HL diagnosis, stage, presence of B symptoms, histology, treatment dates, chemotherapy doses, radiation fields and doses, complications of therapy, date and sites of relapse, relapse therapy, date and cause of death, date and clinical status at last contact. Patients without documented death and with last known address in the United States (n = 95) were sent a follow-up questionnaire regarding interval development of SMNs through September 1, 2007; 46 patients (48%) returned the questionnaire. The

Table 1. Characteristics of Pediatric Patients With HL With Solid SMNs

Age at HL Diagnosis (years)	Sex	Stage	Chemotherapy Regimen (No. of cycles)	Radiation		Solid SMN	Time to SMN (years)	Age at SMN (years)	Current Status
				Field	Dose (Gy)				
11.5	Female	IVA	MOPP (6)	Mantle Lung	23.5 16	Breast invasive ductal carcinoma	29.9	41.4	Alive, NED
13.6	Male	IIIA	MOPP (6)	Inverted Y	24.5	Bladder paraganglioma	12.5	26.4	Alive, NED
				Mantle	25	Metastatic papillary thyroid carcinoma	13.5	27.4	
				Inguinal	10	Buttock melanoma (out of radiation field)	22	35.9	
13.4	Female	IVA	MOPP (4.5)	Mantle Lung	25 10	Breast DCIS	22.1	35.5	Alive, NED
5	Male	IA	MOPP (6)	Left hemimantle/spade	15	Papillary thyroid carcinoma, right lobe	8.2	13.3	Dead, refractory leukemia
9.8	Male	IIA	ABVD/MOPP (6)	Mantle	15	Papillary thyroid carcinoma	18.1	27.9	Alive, NED
14.7	Female	IIIA	ABVD/MOPP (6)	Minimantle/spade/Waldeyer	15	Malignant fibrous histiocytoma, right neck	9.4	24.1	Alive, NED
15.8	Female	IVB	ABVD/MOPP (6)	Mantle/inverted Y	25.2	Breast invasive ductal carcinoma	15.4	31.3	Alive, metastatic breast cancer
13.4	Female	IIA	ABVD/MOPP (6)	Mantle	25	Breast DCIS	12.1	25.5	Alive, NED
12.8	Female	IVB	ABVD/MOPP (6)	Mantle/inverted Y	15	Endometrial stromal sarcoma	14.3	27.1	Alive, NED
13.9	Male	IIA	ABVD/MOPP (6)	Mantle	25	Chondrosarcoma, scapula	4	17.9	Alive, disease status unknown
9.3	Female	IIB	ABVD/MOPP (6)	Mantle	22.5	Papillary thyroid carcinoma	24.4	33.7	Alive, NED
14.7	Male	IIIA	ABVD/MOPP (6)	Mantle/spade	15 + 10 Gy boost right neck	Metastatic neuroendocrine tumor (thyroid)	13.3	27.9	Death
15.1	Male	IIIB	ABVD/MOPP (6)	Mantle/spade	15 + 15 Gy boost left neck	MPNST, L3 nerve root	17.7	32.8	Alive, NED
14.6	Female	IIA	ABVD/MOPP (6)	Mantle	15 + 10 Gy boost mediastinum	Breast DCIS	17.6	32.2	Alive, NED
13.9	Female	IIA	ABVD/MOPP (6)	Mantle	15	Breast invasive ductal carcinoma	15.6	29.6	Alive, metastatic breast cancer

NOTE. Radiation fields—mantle: bilateral axillary, mediastinal, hilar, cervical, supra- and infraclavicular lymph nodes; hemimantle: unilateral mantle field; minimantle: bilateral cervical, supraclavicular, and axillary lymph nodes; spade: para-aortic lymph nodes and spleen/splenic pedicle; inverted Y: spleen, para-aortic, iliac, hypogastric, and inguinal lymph nodes.

Abbreviations: HL, Hodgkin's lymphoma; SMN, second malignant neoplasm; MOPP, mechlorethamine, vincristine, procarbazine, prednisone; NED, no evidence of disease; DCIS, ductal carcinoma in situ; ABVD, doxorubicin, bleomycin; vinblastine; dacarbazine; MPNST, malignant peripheral nerve sheath tumor; L3, third lumbar vertebrae.

Social Security Death Index was queried to ascertain unreported deaths. For those with SMN, date of diagnosis, histology, location, proximity to radiation field, treatment, and clinical outcome were determined. All malignancies counted in the population incidence rates of the registry of the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (including breast ductal carcinoma in situ [DCIS]) were considered SMNs. Nonmelanoma skin cancers, meningiomas, and schwannomas were excluded.

Statistical Analysis

Cumulative incidence of SMN from time of HL diagnosis was estimated using the Kaplan-Meier method with adjustment for competing risks to account for those patients who died of recurrent HL or treatment-related complications.[20-22] For patients with multiple SMNs, only the time to the first SMN was included. For patients with solid SMNs, disease-free survival (DFS) was defined as the time from first SMN diagnosis to SMN relapse or death from any cause. Overall survival (OS) was defined as the time from first SMN diagnosis to death. Actuarial curves showing the probability of DFS and OS were constructed according to the Kaplan-Meier method.[20]

Standardized incidence ratios (SIRs) were calculated as the ratio of the observed SMN cases to expected cases. The absolute excess risk (AER) per 10,000 person-years was calculated as the number of observed cases minus the expected cases divided by person-years of follow-up multiplied by 10,000.[23] Age-, sex-, and site-specific SEER cancer incidence rates were applied to person-years of follow-up for the cohort to yield the expected number of cases.[24] For patients with multiple SMNs, each SMN was counted in the numerator of the SIR following the methodology of the SEER program incidence calculations.[25] Patients were considered to be at risk for SMN from the time of HL diagnosis until death or date of last contact. SIR and AER 95% CIs were determined by the Poisson distribution.[26]

Due to a concern of ascertainment bias in which those patients who developed SMN were more likely to seek medical care and therefore have more complete follow-up, SIR and AER calculations were repeated with the assumption that all patients without a documented SMN or death had complete follow-up through September 1, 2007, and were healthy without SMN. This additional analysis allows a conservative estimate of the lower bound of SIRs.

Univariate associations were evaluated by χ^2 test or Fisher's exact test for categoric variables and pooled *t*-test for continuous variables. Multivariate analysis was undertaken to evaluate the association of SMN with a priori defined potential predictors with $P \leq .1$ in univariate analyses. Cox proportional hazards regression was used to evaluate these predictors using chronological age as the time scale to control for the strong association between cancer risk and chronological age.[27-29] All pairs of predictors were evaluated for potential interactions. The proportional hazards assumption was evaluated for all variables by generating log-log survival plots for each predictor from the Cox regression model and evaluating at the means of the covariates. Statistical analyses were performed using SAS version 9.1 (SAS Institute Inc, Cary, NC).

RESULTS

Patient Demographics

Fifty-five children were treated on Ped HD1 and 57 on Ped HD2 (Appendix Table A1, online only). Median age at diagnosis was younger for Ped HD1, likely because eligibility was limited to prepubertal children who were felt to be at highest risk for adverse musculoskeletal outcomes with adult high-dose radiation protocols. Based on the promising early results of Ped HD1, Ped HD2 included older adolescents. In addition, children with stage I lymphocyte predominant HL, who tend to be younger, were excluded from Ped HD2.

Ped HD1 Treatment and Outcomes

Fifty three (96.3%) of 55 patients completed primary therapy including radiation to at least one field (eg, right neck, mantle; Appendix Table A2, online only) with median mantle dose of 24 Gy. Median follow-up of these 53 patients is 25.4 years (range, 2.1 to 32.8 years). For those alive at last contact, 27 (56%) of 48 have documented follow-up in the past 5 years and 34 of 48 (73%) have documented follow-up in the past 10 years. Median age at last contact was 33.9 years (range, 7.4 to 44.9 years). Five patients developed relapse at a median

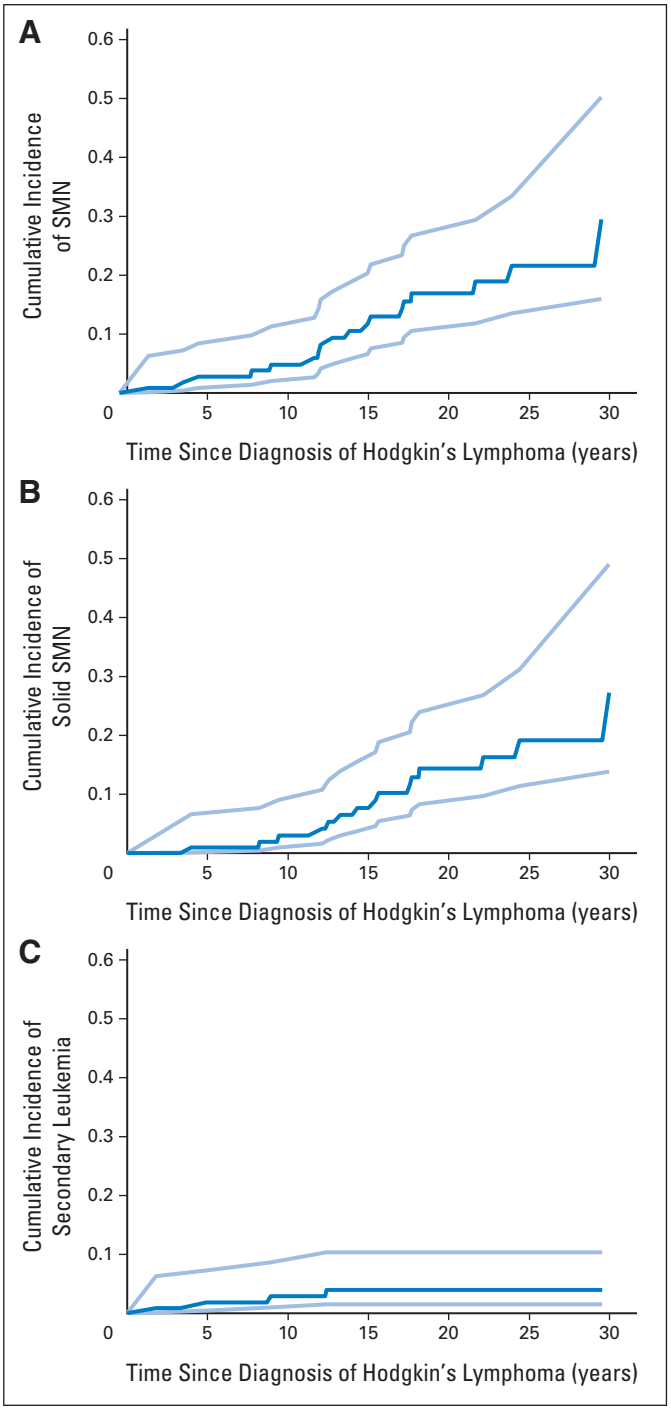

Fig 1. Cumulative incidence (dark blue line) of (A) any second malignant neoplasm (SMN), (B) solid SMN, and (C) secondary leukemia from the date of Hodgkin's lymphoma (HL) diagnosis with 95% CIs (light blue lines). For subjects with multiple SMNs, only the time to the first SMN was included.

Table 2. SIRs and AER of SMN

Parameter	Patients	Person-Years	Observed SMN	Expected SMN	SIR	95% CI	AER*	95% CI
Any SMN	110	2,143.4	21	0.916	22.9	14.2 to 35	93.7	56.4 to 145.5
Sex								
Male	75	1,435.3	11	0.505	21.8	10.9 to 39	73.1	34.7 to 133.6
Female	35	708.1	10	0.392	25.5	12.2 to 46.9	135.7	62.2 to 254.2
Age at HL diagnosis, years								
< 11	53	1,057.8	4	0.357	11.2	3.1 to 28.7	34.4	6.9 to 93.4
≥ 11	57	1,085.6	17	0.557	30.5	17.8 to 48.9	151.5	86.1 to 245.6
SMN site								
Leukemia	110	2,143.4	4	0.044	90.9	24.8 to 232.8	18.5	4.9 to 47.6
Solid tumor	110	2,143.4	17	0.86	19.8	11.5 to 31.7	75.3	42.2 to 123.0
Thyroid	110	2,143.4	5	0.094	53.2	17.3 to 124.1	22.9	7.1 to 54.0
Sarcoma	110	2,143.4	4	0.045	88.9	24.2 to 227.6	18.5	4.9 to 47.6
Breast (females)	35	708.1	6	0.082	72.3	26.5 to 157.3	83.6	29.9 to 183.3

Abbreviations: SIR, standardized incidence ratio; AER, absolute excess risk; SMN, second malignant neoplasm; HL, Hodgkin's lymphoma.
*Calculated per 10,000 person-years.

of 3.2 years off-therapy (range, 0.6 to 10.6 years); one died of secondary acute myeloid leukemia (AML) after salvage therapy, and another died of complications of bone marrow transplant (BMT) for treatment of relapse. Three are long-term survivors with additional therapy and reported no SMN with 6, 27, and 30 years of follow-up.

Four patients developed secondary leukemia (one acute lymphoblastic leukemia, three AML) at a median of 6.9 years (range, 1.8 to 12.4 years) from HL diagnosis; one occurred after additional therapy for relapse. All died of refractory leukemia. Four patients developed six secondary solid tumors at a median of 17.3 years (range, 8.2 to 29.9 years; Table 1). One patient developed papillary thyroid carcinoma (right lobe after 15 Gy to left neck) and B-precursor acute lymphoblastic leukemia. Two patients with prior stage IV HL with lung involvement developed breast cancer: one with infiltrating ductal carcinoma after 23.5/15 Gy to the mantle/whole lung and one with ductal carcinoma in situ after 25.5/10 Gy mantle/whole lung irradiation. One patient developed three SMNs (bladder paraganglioma, metastatic papillary thyroid carcinoma, and left buttock melanoma) after 25.5 Gy to mantle, para-aortic, and pelvic fields. The melanoma was outside the radiation field.

Table 3. Comparison of SIRs Based on Actual Versus Theoretical Complete Follow-Up

	Actual Follow-Up		Complete Follow-Up*	
Parameter	SIR	95% CI	SIR	95% CI (lower bound)
Any SMN	22.9	14.2 to 35	17	10.5
Sex				
Male	21.8	10.9 to 39	14.3	7.1
Female	25.5	12.2 to 46.9	21.1	10.1
Age at HL diagnosis, years				
< 11	11.2	3.1 to 28.7	7.4	2
≥ 11	30.5	17.8 to 48.9	22	12.8
SMN site				
Leukemia	90.9	24.8 to 232.8	74.1	20.2
Solid tumor	19.8	11.5 to 31.7	13.7	8
Thyroid	53.2	17.3 to 124.1	37	12
Sarcoma	88.9	24.2 to 227.6	71.4	19.5
Breast (female)	72.3	26.5 to 157.3	56.1	20.6

Abbreviations: SIR, standardized incidence ratio; HL, Hodgkin lymphoma; SMN, second malignant neoplasm.
*Theoretical complete follow-up assumes that those lost to follow-up are alive without SMN through September 1, 2007.

Table 4. Univariate Analysis of Risk Factors Associated With SMN Development

Parameter	SMN (n = 18)	No SMN (n = 92)	*P*
Sex			
Male	8	67	.02
Female	10	25	
Age at HL diagnosis, years			
< 11	3	50	
≥ 11	15	42	
Mean	12.9	10.3	.003
SD	2.6	3.5	
Range	5-15.8	1.7-17.6	
Stage			
I/II	7	43	.54
III/IV	11	49	
Chemotherapy			
MOPP	7	46	.39
ABVD/MOPP	11	46	
Mean radiation dose, Gy			
Left neck	22.1	19.1	.17
Right neck	19.9	19.9	.99
Mantle/minimantle	22.2	19.8	.21
Spade/inverted Y	10.8	11.5	.79
Relapse			
Yes	1	8	1.00
No	17	84	
Mean follow-up time, years	19	19.6	.79
SD	7.2	8.1	
Range	2.8-30	2-32.9	
Mean age at last contact, years	32	29.8	.34
SD	7.7	8.6	
Range	15.5-41.8	7.4-44.9	

Abbreviations: SMN, second malignant neoplasm; HL, Hodgkin's lymphoma; SD, standard deviation; MOPP, mechlorethamine, vincristine, procarbazine, and prednisone; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine.

Table 5. SIRs, AERs, and Cumulative Incidence of SMN in Pediatric Hodgkin's Lymphoma Cohorts With Median Follow-Up > 15 years

Reference	No. of Subjects	Median Age at Diagnosis (years)	Median Follow-Up (years)	Any SMN: Cumulative Incidence (%) 20 Year	Any SMN: Cumulative Incidence (%) 30 Year	Any SMN: SIR	Any SMN: 95% CI	Any SMN: AER*	Any SMN: 95% CI	Solid SMN: Cumulative Incidence (%) 20 Year	Solid SMN: Cumulative Incidence (%) 30 Year	Solid SMN: SIR
Stanford												
Actual follow-up	110	11.3	20.6	17	29.4	22.9	14.2 to 35	93.7	56.4 to 145.5	14.3	27.2	19.8
Complete follow-up†	110	11.3	20.6			17	10.5 to 25.9	74.3	44.2 to 116			13.7
Bhatia et al[10]	1,380	11.7	17	9.3	23.7	18.5	15.6 to 21.7	65		5.9	20.1	18.5
Green et al[6]	182	15.3 (mean)	17.1	12.7	26.3	Male: 9.4	4 to 18.5					
						Female: 10.2	5.6 to 17					
CCSS[7,37,45]	1,815‡	≈14‡	≈18‡	7.6		9.7	8.1 to 11.6	51.3				

Reference	Solid SMN: SIR 95% CI	Solid SMN: AER*	Solid SMN: 95% CI	Breast Carcinoma: SIR	Breast Carcinoma: 95% CI	Breast Carcinoma: AER*	Breast Carcinoma: 95% CI	Thyroid Carcinoma: SIR	Thyroid Carcinoma: 95% CI	Thyroid Carcinoma: AER*	Thyroid Carcinoma: 95% CI
Stanford											
Actual follow-up	11.5 to 31.7	75.3	42.2 to 123	72.3	26.5 to 157	83.6	29.9 to 183.3	53.2	17.3 to 124	22.9	7.1 to 54.0
Complete follow-up†	8 to 21.9	59.2	32.6 to 97.6	56.1	20.6 to 122	75.2	26.7 to 165.2	37	12 to 86.4	18.3	5.6 to 43.4
Bhatia et al[10]	15.2 to 22.3	51		55.5	39.5 to 75.9	53		36.4	21.9 to 56.8	9	
Green et al[6]				7.8	2.1 to 19.9			Male: 158.8	32.7 to 463.9		
								Female: 38	7.8 to 111.1		
CCSS[7,37,45]				26.3	20.2 to 33.7			18.3	11.4 to 27.6		

NOTE. Values and CIs are presented where available from the published studies.
Abbreviations: SIR, standardized incidence ratios; AER, absolute excess risk; SMN, second malignant neoplasm; CCSS, Childhood Cancer Survivor Study.
*Calculated per 10,000 person-years.
†Assumes that those lost to follow-up are alive without SMN through September 1, 2007.
‡CCSS publications report entire cohort, not simply patients with Hodgkin's lymphoma, so specific follow-up duration and age data for the Hodgkin's lymphoma subgroup are estimated based on data from different CCSS publications.

Ped HD2 Treatment and Outcomes

All 57 patients completed primary therapy including radiation to at least one field (eg, right neck, mantle; Appendix Table A3, online only) with median mantle dose 22 Gy. Median follow-up is 19 years (range, 2 to 25.4 years). For those alive at last contact, 38 (72%) of 53 have documented follow-up in the past 5 years and 43 (81%) of 53 have documented follow-up in the past 10 years. Median age at last follow-up is 30.6 years (range, 8.9 to 41.6 years). Four patients developed relapse at a median of 1.6 years (range, 0.9 to 3.9 years); one is a long-term survivor without SMN 16 years after autologous BMT. Three patients died following relapse—one from refractory HL, one from disseminated cytomegalovirus infection after BMT, and one from pulmonary fibrosis 13 years after BMT.

There were no secondary leukemias. Eleven patients (19.3%) developed a second solid tumor at a median of 15.4 years (range, 4 to 24.4 years). Each SMN occurred in or adjacent to a prior radiation field (Table 1). Three patients developed thyroid carcinoma after receiving 15 to 25.5 Gy radiation to the neck; one died of metastatic undifferentiated neuroendocrine tumor thought to have originated from the thyroid. Four (19%) of 21 women developed breast cancer after receiving 15 to 25.5 Gy to the mantle field including the axillae. Three presented with localized disease, one of whom relapsed with metastatic disease after initial therapy while the fourth presented with widely metastatic disease. Four patients developed localized sarcomas in fields irradiated to 15 to 25.5 Gy.

Survival and Cumulative Incidence of SMN

For the combined cohort of 110 patients, the estimated cumulative incidence of first SMN was 17% at 20 years (95% CI, 10.5 to 26.7) and 29.4% at 30 years (95% CI, 16 to 50) after HL diagnosis (Fig 1). The majority of the risk is due to solid tumors with a cumulative incidence of 14.3% at 20 years (95% CI, 8.4 to 24) and 27.2% at 30 years (95% CI, 13.9 to 49) while the cumulative incidence of secondary leukemia plateaued at 4% at 15 years (95% CI, 1.5 to 10.3). Only one SMN (AML) occurred in a patient who received additional therapy for HL relapse; all other patients who developed SMN had received only primary HL therapy. The actuarial death rate was 4.1% for secondary leukemia, 4.1% for refractory HL or complications of therapy (ie, infection), and 1.3% for secondary solid tumor. Of the 15 patients who developed a solid SMN, two have died and two are alive with metastatic breast cancer, with mean ($\pm$ SE) 5-year OS 85 $\pm$ 10% and 5-year DFS 76 $\pm$ 12%.

SIRs

Observed and expected numbers of SMN by age, sex, and site are presented in Table 2. The SIR for any SMN was 22.9 (95% CI, 14.2 to 35) with an AER of 93.7 cases per 10,000 person-years (95% CI, 56.4 to 145.5). SIRs and AERs were elevated for leukemia, thyroid carcinoma, breast carcinoma, and sarcomas; there were no reported cases of gastrointestinal or lung carcinoma. SIRs remained elevated even when recalculated with the "best-case scenario" assumption that those with incomplete follow-up were alive and free from SMN through September 1, 2007 (Table 3).

Analysis of Factors Associated With SMN

In univariate analysis, only female sex and older age at HL diagnosis (≥ 11 years) were associated with SMN (Table 4) and therefore included in the Cox proportional hazards model. Mean follow-up time and age at the time of last contact did not differ between those with and without SMN. Multivariate analysis revealed nonstatistically significant associations of SMN with older age at HL diagnosis (HR, 2.7; 95% CI, 0.7 to 10.4) and female sex (HR, 2.0; 95% CI, 0.8 to 5.2). Stage, chemotherapy regimen, and maximum radiation doses did not significantly alter parameter estimates. Six (17%) of 35 women developed breast cancer at a median of 16.6 years (range, 12.1 to 29.9 years); univariate analysis revealed no statistically significant risk factors (Appendix Table A4, online only), although only one received pelvic radiation and none reported a history of ovarian failure or early menopause.

DISCUSSION

The Stanford combined modality protocols achieved their original goal of providing curative HL therapy while decreasing the musculoskeletal sequelae associated with radiation doses of 40 to 44 Gy in children. Subsequently, as reports of SMN among HL survivors treated with high-dose radiation accumulated, we theorized that low-dose radiation-based protocols might have the additional benefit of decreased SMN incidence or longer latency time to the development of SMN. However, SMN cumulative incidence, SIR, and AER are similar to those from studies in which most patients received higher radiation doses (Table 5), even in the "best-case scenario" with the assumption of complete follow-up without SMN for those lost to follow-up. The median time to solid SMN (15.4 years) is comparable to that reported for the Late Effects Study Group cohort (16.9 years)[10] and the cohorts reported by Wolden (15.5 years)[2] and Metayer (15 years).[4]

Five patients developed thyroid carcinoma, the only solid SMN among those treated for HL before age 10 years. The young age of the patients in our cohort may contribute to the high observed rate of thyroid cancer, consistent with reports that at radiation doses below 20 Gy, thyroid carcinoma risk is highest among patients diagnosed with their primary cancer before age 10 years.[30-32] The significant incidence of thyroid carcinoma with low-dose radiation is not surprising given the nonlinear radiation dose-response, in which thyroid SMN risk increases from 0 to 20 Gy and then decreases, with few cases occurring at doses above 40 Gy due to cell killing.[33-34] Therefore, with current low-dose radiation regimens, we may expect to see stable or even increasing rates of secondary thyroid carcinoma, particularly in children treated at very young ages.

Breast cancer is the most common SMN among female HL survivors and is strongly linked to supradiaphragmatic radiation and younger age (< 20 years) at the time of HL treatment.[35-40] In our cohort, breast cancer incidence was similar to other pediatric HL studies despite lower radiation doses (Table 5). In contrast, Inskip and colleagues[41] reported a linear relationship between breast cancer risk and radiation dose based on data from the Childhood Cancer Survivor Study, with decreased risk among those women receiving 11.4 to 29.9 Gy compared to those receiving 30 Gy or more. The high breast cancer SIR in our cohort, despite mantle radiation doses between 15 and 25.5 Gy, may be due to small cohort size with wide confidence intervals. In addition, three patients were diagnosed with DCIS through screening; they may represent an ascertainment bias which inflates the SIR. When the DCIS cases are excluded, the SIR remains elevated at 36.1 (95% CI, 7.5 to 105.6) with an AER of 41 cases per 100,000 person-years.

Alternatively, Inskip and colleagues[41] noted that breast cancer risk is substantially mitigated by ovarian radiation ≥ 5 Gy at the time of initial treatment. It is possible that the proportion of women in our cohort who received ovarian radiation is lower than the comparison cohorts in Table 5, diminishing our ability to detect a protective effect of lower mantle radiation doses. Also, in the Inskip et al Childhood Cancer Survivor Study cohort, only 50% of patients received any alkylating agent and 30% received any anthracycline, versus 100% and 52% in our cohort, respectively. It is possible that some of the benefit of low-dose radiation is offset by an increased SMN risk conferred by specific chemotherapy agents.

Sarcoma risk increases significantly at radiation doses higher than 30 Gy; most sarcomas are reported in fields treated to at least 35 Gy.[2,42] Therefore, a notable decrease in secondary sarcoma incidence might be expected with lower radiation doses. However, our SIR for secondary sarcoma remained highly elevated, and of the four sarcomas, three occurred in 15 Gy radiation fields. The four reported sarcomas occurred in patients treated with MOPP/ABVD chemotherapy. Henderson and colleagues[43] found that both alkylating agent and anthracycline chemotherapy are associated with increased risk of secondary sarcomas. In our cohort, the occurrence of more sarcoma cases with fewer cycles of MOPP suggests that the anthracycline exposure from the ABVD cycles may be an important contributor. Alternatively, this finding may reflect the more complete follow-up of the MOPP/ABVD cohort compared to the MOPP only group.

Notably, there were no reported cases of lung or gastrointestinal carcinoma which may reflect the lower radiation doses or the young median age at last follow-up (31 years). It is possible that these SMN subtypes may emerge as cohort members continue to age. However, the lack of these SMN subtypes to date is encouraging because the Late Effects Study Group reported multiple lung and gastrointestinal SMN with younger median age at last follow-up (27.8 years) and shorter median follow-up time (17 *v* 20.6 years).[10]

Due to the long latency to the development of solid SMN, current follow-up data necessarily reflect past therapies. HL treatment has continued to evolve since these early Stanford protocols, with refinements in chemotherapy regimens and radiation techniques to limit exposure of normal tissues. Models suggest that lower radiation doses and smaller volumes will decrease the risk of certain SMNs such as breast cancer,[41] particularly with shielding of the axillae,[44] while risk of thyroid carcinoma is likely to remain elevated. However, the outcomes for this cohort suggest that children who receive combined-modality therapy with low-dose radiation remain at significant risk for morbidity and mortality from sarcomas, thyroid, and breast carcinomas and will continue to require aggressive surveillance. Future therapeutic protocols for pediatric patients with HL should pursue radiation dose reduction or elimination of radiation when feasible. Improved understanding of genetic predisposition and modifying factors such as hormone status and the impact of specific chemotherapy agents such as anthracyclines will help to identify those patients at greatest risk of SMN.

Note Added in Proof

Consistent with the ongoing significant SMN risk observed in this study, two additional patients with SMN have self-identified since the submission of this article. One male from Ped HD2 reported a grade 3 leiomyosarcoma of the groin at 22 years after 15 Gy to pelvic field and MOPP/ABVD chemotherapy, and one male from Ped HD1 reported papillary thyroid carcinoma at 31 years after 25.5 Gy to the neck and MOPP chemotherapy.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

AUTHOR CONTRIBUTIONS

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