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Risk of Radiation-related Salivary Gland Carcinomas Among Hodgkin Lymphoma Survivors: A Population-based Analysis

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Abstract

Background—Radiotherapy for Hodgkin lymphoma (HL) increases the risk of salivary gland carcinomas (SGC); however the magnitude of the risk has not been assessed.

Methods—We evaluated risks of SGC among 20,928 one-year survivors of HL diagnosed between 1973 and 2003 in 11 population-based cancer registry areas of the Surveillance, Epidemiology and End Results (SEER) program. Observed-to-expected ratios (O/E) were assessed by radiation treatment, gender, age at HL diagnosis, calendar year of diagnosis, attained age, time since HL diagnosis, histologic type of SGC, and site of occurrence in the major salivary glands.

Results—Among 11,047 HL patients who received radiotherapy as part of initial treatment for HL, 21 developed subsequent invasive SGC (O/E=16.9; 95% confidence interval (CI) 10.4 to 25.8). Risk of radiation-related SGC was highest for younger HL patients (age <20 years: O/E=45.5, CI 12.4 to 116.5) and among 10-year survivors (O/E=23.9, CI 13.1 to 40.1), with risks remaining elevated for at least two decades after irradiation. Significant differences in risk by histologic type were observed with particularly high risk of developing mucoepidermoid

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carcinomas (O=14, O/E=44.2, CI 24.2 to 74.2) and adenocarcinomas (O=4, O/E=30.6, CI 8.3 to 78.2).

Conclusion—HL patients treated with radiotherapy experienced significantly increased risk of SGC particularly when exposed at young ages or for at least two decades following exposure. Although our results reflect the late effects of former HL treatment approaches, they point to the importance of long-term follow-up and heightened awareness of SGC risk in this population.

Keywords

Hodgkin lymphoma; subsequent salivary gland carcinoma; mucoepidermoid carcinoma; radiotherapy; risk

Introduction

Although radiotherapy (RT) is effective in the treatment of Hodgkin lymphoma (HL), it has been associated with the development of subsequent cancers, including salivary gland carcinomas (SGC) (1–5). Ionizing radiation also has been shown to increase the risk of SGC in other populations, including individuals with prior radiation exposure to the head and neck region (6–10) and survivors of the atomic bombings in Japan (11–13). However, the magnitude of radiation-related risk of SGC is uncertain. Furthermore, few studies have assessed risk of SGC by histologic subtype and site of salivary gland cancer, accounting for such factors as age, gender, and time since radiation exposure (latency). HL patients treated with supradiaphragmatic RT often receive high doses of radiation to the neck, depending upon the treatment fields, and thus comprise an identifiable group of individuals at potentially increased risk of subsequent SGC. We undertook this population-based study using data from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) (14) program to quantify the risk of SCG by histologic subtype, site of occurrence, and other factors among 1-year survivors of HL initially treated with RT.

Methods

We evaluated the risk of subsequent SGC among 20,928 one-year HL survivors diagnosed between 1973 and 2003 in the catchment areas of 11 population-based cancer registries contributing to the SEER registry program: Connecticut, Iowa, New Mexico, Utah, Hawaii, the San Francisco-Oakland and Detroit metropolitan areas, and the metropolitan areas of Seattle-Puget Sound, Atlanta, Los Angeles, and San Jose-Monterey in the SEER Program. All registries have participated since 1973 except for Seattle-Puget Sound and Atlanta which began in 1974 and 1975, respectively, and Los Angeles and San Jose-Monterey which have participated since 1992. The SEER program classifies morphology and topography information according to the International Classification of Diseases for Oncology (ICD-O) (15). Cancer treatment information is limited to the initial course of therapy and is available in terms of broad categories, such as RT and/or chemotherapy (CT). Data on subsequent therapy are not collected.

Since the late 1960's, treatment for HL has included RT and CT. Selection of treatment modality (RT, CT or both) depends upon stage of HL and associated clinical features (e.g., bulk disease). From the mid-1970s through the mid-1990s, RT doses of 30 to 40 Gy were commonly used (16–19). Effective CT regimens including MOPP (mechlorethamine, vincristine, procarbazine and prednisone) and ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) were introduced into general clinical practice in the 1970s and 1980s, respectively. However, with the increasing recognition of late-effects of RT and CT, the combination of smaller radiation fields (involved field) and lower radiation doses (< 30 Gy)

in conjunction with shorter duration of CT began to be used in an effort to maintain treatment effectiveness while minimizing potential long-term sequelae (20–22).

Typical radiation doses to the salivary glands based on tumor doses used in standard supradiaphragmatic fields during the period of this study are provided in Appendix 1. These estimations, which are for illustrative purposes only, were performed with a three-dimensional mathematical phantom based on measurements in water, using methods previously described (23). The estimates indicate that the majority of patients treated in the past with a typical full mantle field (neck, mediastinum, axilla, and supraclavicular regions) likely received high radiation doses to the parotid and submandibular gland and substantially lower mean doses to the sublingual gland. In contrast, patients treated with RT fields involving only the mediastinum, the supraclavicular region, or the axilla (or infradiaphragmatic fields) likely received minimal doses to the salivary glands.

We used the Multiple Primary-Standardized Incidence Ratio (MP-SIR) module from SEER*Stat (version 6.3.5) (14) to calculate the SIRs of observed (O)-to-expected (E) number of second or higher order (third, fourth, etc) SGC and their exact 95% confidence intervals (CI) among ≥1-year survivors of HL diagnosed between January 1, 1973 and December 31, 2003 with follow-up for subsequent SGC through December 31, 2004. Person years (PY) were accumulated and tabulated according to gender, race, 5-year age group, 5-year calendar interval, and SEER registry, beginning one year after the diagnosis of HL and continuing to the study end date (December 31, 2004), date of last known follow-up, or date of death, whichever occurred first. To estimate the expected numbers of SGC in the general SEER population, cancer incidence rates were calculated according to gender, race, 5-year age groups, 5-year calendar intervals, and SEER registry, and multiplied by the accumulated PY at-risk in each category. After searching cancer registry files for second or later invasive cancers of the major salivary glands, SIRs or O/Es for HL cases were estimated overall and by gender, age at HL diagnosis, initial treatment for HL, latency, attained age at SGC, and calendar year of HL diagnosis. We also estimated O/E ratios according to SGC histology (ICD-O-3 code): mucoepidermoid (M-8430), adenocarcinoma (M-8140), and all other carcinomas; and topography: parotid gland (C07.9), submandibular gland (C08.0), sublingual gland (C08.1), and overlapping sites and site not specified (C08.8–C08.9). The excess absolute risk (EAR), which measures the overall cancer burden due to a subsequent cancer, was calculated as the difference between the observed number of cancers and the expected number of cases expressed per 100,000 PY, (e.g., [(O-E)/PY]× 100,000). Tests of heterogeneity (P_{HET}) and linear trend (P_{Trend}) were conducted using the methods of Breslow *et al* (24).

Results

Of the 20,928 one-year HL survivors diagnosed between 1973 and 2003, 55% were male and the mean age at diagnosis was 37 years (Table 1). Fifty three percent (n=11,047) of the patients were initially treated with RT and 37% (n=7,811) received CT only. Among patients treated with RT, 56% were diagnosed with HL before 1992 and 49% at 30 years or older. Patients diagnosed at a younger age (< 30 years) and those diagnosed before 1992 more frequently received RT for their first course of therapy than others. Overall, HL patients had more than an 11-fold risk (O/E=11.2, 95% CI 7.3 to 16.4) of developing a subsequent SGC compared with the SEER general population and the EAR was 11.8 cases per 100,000 PY.

Because of the established carcinogenic effect of radiation, we focused our investigation on patients who received RT as part of initial therapy for HL. Overall, 5,745, 3,764 and 2,205 patients treated with RT were followed 10+, 15+, and 20+ years after HL diagnosis,

respectively. The mean age at HL diagnosis was 34 years, the mean interval between diagnosis of HL and SGC was 9.6 years, and the mean age at diagnosis of SGC was 48 years.

Patients treated with RT had a significant 17-fold risk of SGC compared to general population rates (O=21, O/E=16.9, 95% CI 10.4 to 25.8). This risk was significantly higher than patients initially treated with CT without RT (O=4, O/E=4.8, 95% CI 1.31 to 12.29, P_{HET}=0.01). Patients treated with combined modalities (RT and CT) at first treatment (O=7, O/E=18.8, 95% CI 7.6 to 38.7) had a risk similar to that of those treated with RT alone (O=14, O/E=16.1, 95% CI 8.81 to 27.05). Markedly elevated risks of 30–40-fold were seen for mucoepidermoid carcinoma (O=14, O/E=44.2, 95% CI 24.2 to 74.2) and adenocarcinoma (O=4, O/E=30.6, 95% CI 8.3 to 78.2). The risk of SGC was substantially lower for other salivary gland histologic types combined (O=3, O/E=3.8, 95% CI 0.8 to 11.0, $P_{HET} < 0.0001$).

Two-thirds of SGC (14/21) were diagnosed in females (Table 2). Risk of SGC was three times higher among women compared to males when measured in relative terms (P_{HET}=0.02). This gender difference was also seen for mucoepidermoid SGC. When measured on an absolute scale, radiation-related risk for SGC was 2-fold higher for females compared to males (EAR=22.6 and 10.0 per 100,000 PY for females and males, respectively, P_{HET}=0.09) and for mucoepidermoid SGC (EAR=16.5 and 6.1 per 100,000 PY for females and males, respectively, P_{HET}=0.09) however, statistically, the differences were not significant.

Risk of radiation-related SGC was higher for HL patients treated between 1973 and 1991 compared withthose treated from 1992 to 2003 (P_{HET}=0.06) (Table 2). However, the median follow-up period for HL survivors treated during 1992–2003 was relatively short (4.80 years), and thus risk for this later time period may rise when patients are followed for 15 or more years.

A strong pattern of decreasing O/Es with increasing age at HL diagnosis was observed for SGC of all subtypes combined (P_{Trend}<0.001) (Table 2). Based on only four cases, there was a 45-fold risk of developing a subsequent SGC among patients first irradiated before age 20 years, whereas significantly elevated, but lower O/Es were observed for patients treated at later ages. EARs were 14.6, 16.6, 17.6, and 15.3 per 100,000 PY for age categories <20, 20–29, 30–39, and 40+ years, respectively (P_{Trend}=0.78). The age at irradiation pattern for mucoepidermoid carcinomas was attenuated somewhat (P_{Trend}=0.15).

A less pronounced age effect was noted for age attained at follow-up. The risk of developing SGC before age 40 years was larger (O/E=28.6) than for those who developed a SGC at age 40+ years (O/E=13.5) (Table 2). However, this difference was statistically significant only for mucoepidermoid carcinoma.

A significantly increased risk for SGC was noted beginning 5 years after RT for HL. Risk continued to rise with longer follow-up time (P_{Trend}=0.008) reaching over 30 times that expected for those followed for 15 or more years (Table 2). The EAR indicated that the risk of developing a secondary SGC continues even after 20 years of follow-up (EAR=44.0 per 100,000 PYR). For mucoepidermoid carcinomas, significant increased risk was observed within 5 years following initial RT (Table 2), however, no significant trend with increasing follow-up was noted (P_{Trend}=0.4).

Most SGC occurred in the parotid gland (O=17) with only 3 cases observed in the submandibular gland and none in the sublingual gland (Table 2), but there was no statistical evidence that risk differed by site of SGC (P_{HET}=0.97). Among the mucoepidermoid SGC,

12 of the 14 occurred in the parotid gland, one in the submandibular gland and one at an unspecified site. Similar to the results for all SGC, no significant difference in relative risk was noted by site of occurrence (P_{HET}=0.7).

Among 21 survivors initially treated with RT for HL who developed subsequent SGC, 2 died from SGC, 4 died from HL, 3 died from other cancers and 12 were alive at the end of study follow-up.

Discussion

To our knowledge, this is the largest study of radiation-related salivary gland cancers after high-dose RT to the head and neck region, and the first to estimate risks by histologic type, tumor location, sex, age at irradiation, attained age, and latency. We found that risk of SGC after HL was significantly larger among patients who received RT as part of initial treatment for HL than for those who received CT without initial RT. Radiation-related risk was higher among females than males, was more pronounced among patients who developed mucoepidermoid carcinomas, increased with time since diagnosis of HL and decreased with increasing age at irradiation. Risks were greater for those irradiated for HL before 1992, when doses to the head and neck region from full mantle RT fields were likely to be highest.

Previous studies have linked exposure to low to moderate levels of ionizing radiation to an increased risk of benign and malignant salivary gland tumors (25–28). However, the limited data regarding high dose RT comes from case reports and small series (29;30). While several surveys have reported an increased risk of SGC following HL, the studies were based on fewer than 16 cases and none provided risks by RT (1–5). Our findings add to the very sparse literature on the relation between RT and salivary gland malignancies and provide strong evidence that SGC is a radiogenic cancer.

Our analyses showing mucoepidermoid carcinomas to be most strongly associated with radiation are consistent with the especially strong dose response found for mucoepidermoid carcinomas in studies of atomic bomb survivors (11;13). Patients treated with external irradiation to the head, neck or upper chest, have also shown a higher frequency of mucoepidermoid carcinoma compared to other SGC cell types (8;25).

During typical mantle RT with delivered doses of 35 Gy, dose to the salivary glands varies considerably depending on gland location, with the submandibular gland receiving about 32 Gy, the parotid about 18 Gy and the sublingual about 7 Gy (Appendix 1). While Land et al. reported a higher risk for parotid tumors than for tumors at other sites (11), we did not find a significant difference in risks by cancer site. With the advent of increasing use of lower doses and more focused RT fields in the management of HL, radiation doses to all of the salivary glands have been reduced substantially for many patients. Our observation of a higher risk in patients irradiated for HL before 1992 compared with those treated in later years probably reflects the higher doses received in the earlier period, as well as longer follow-up.

Our study provides new data showing that the relative risk of SGC remains elevated among long-term survivors of HL. The significantly increased absolute risk (EAR=44.0 per 100,000 PYR), 20 years after initial exposure to radiation indicates the need for continued surveillance of HL patients.

Another new finding is the significantly increased relative risk of SGC for women compared to men. On an absolute scale the risk was twice higher for females compared to males, however, this difference was not statistically significant (Table 2). In contrast, Dores et al. reported no significant difference in risk of SGC between males and females and no

significant gender difference was observed among atomic bomb survivors (11;12), or among children irradiated with low doses to the head or neck for benign medical conditions (8). Given the inconsistent results, additional data are needed before any conclusions about gender differences can be drawn.

Although our data showed a significantly increased risk of subsequent SGC following RT at young, as well as older HL ages, we observed a strong trend for decreasing relative risk with increasing age at RT. When we evaluated the effects of age at exposure on an absolute scale, we found no significant difference in the EARs indicating that there was a constant excess over background rates for all age groups. High relative risks among persons irradiated before age 20 also have been observed in the Life Span Study of atomic bomb survivors (12), bone marrow transplant patients (30) and patients receiving RT for a brain tumor (29). However within the narrow age range of childhood exposure, there is little or no evidence of an age at exposure trend (8). These findings coupled with an increased risk for early onset SGC (attained age less than 40 years) suggest an increased sensitivity to radiation-related SGC among persons exposed at younger ages.

Although we describe the largest number of radiation-related SGC following HL reported to date, our study is associated with limitations inherent in many population-based studies, including the lack of risk factor information, such as tobacco smoking and alcohol intake. Treatment information in SEER is limited to the first course of therapy, and no information is available on RT dose or fields, specific CT regimens, or subsequent therapy. Thus the significantly increased risk of SGC among HL patients initially treated with CT without RT in comparison to the general population may be due to treatment with subsequent RT not captured by SEER. In addition, some of the SGC excesses could be related to increased screening of HL patients, resulting in the early detection of asymptomatic or indolent cancers.

In conclusion, our study found that the major salivary glands are highly susceptible to the induction of malignancy after high dose RT and that exposure at young ages appears to confer a particularly high risk. The enhanced risk among long-term survivors highlights the importance of routinely following HL patients throughout their lifetime for early detection of any new malignancies. Future studies will be needed to determine if current efforts to diminish radiation exposures for HL patients, such as restricting radiation to involved fields with lower doses, will reduce the risk of secondary SGC among long-term survivors.

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Table 1

Characteristics of 20,928 One-year Survivors of Hodgkin Lymphoma Diagnosed Between 1973 and 2003 and Followed-up Through 2004, SEER-11 Registries

	Total			Initial radiotherapy		
Characteristics	**No. of patients**	**%**	**Person-years at-risk**	**No. of patients**	**%**	**Person-years at-risk**
All patients	20,928	100	201,142	11,047	100	122,268
Gender						
Males	11,578	55.3	108,898	5,758	52.1	62,622
Females	9,350	44.7	92,244	5,289	47.9	59,646
Calendar year of HL diagnosis						
1973–1991	10,610	50.7	147,576	6,229	56.4	96,023
1992–2004	10,318	49.3	53,566	4,818	43.6	26,245
Age at HL diagnosis (years)						
< 20	3,253	15.5	39,323	1,984	18.0	26,786
20–29	6,265	29.9	71,514	3,655	33.1	46,482
30–39	4,511	21.6	44,135	2,439	22.1	26,928
≥ 40	6,899	33.0	46,170	2,969	26.9	22,072
Time since HL diagnosis (years)						
1–4	20,928	100	69,297	11,047	100	38,195
5–9	14,536	69.5	58,585	8,327	75.4	34,677
10–14	9,304	44.5	36,630	5,745	52.0	23,588
15–19	5,620	26.9	21,587	3,764	34.1	14,829
≥ 20	3,137	15.0	15,044	2,205	20.0	10,981

Abbreviations: SEER: Surveillance, Epidemiology and End Results Program; No.: number; HL: Hodgkin lymphoma.

Table 2

Risk of Subsequent Salivary Gland Carcinoma Overall and Mucoepidermoid Carcinoma Among 11,047 One-year Survivors of Hodgkin Lymphoma Diagnosed Between 1973–2003, Initially Treated With Radiotherapy, and Followed-up Through 2004, SEER-11 Registries.

	Total				Mucoepidermoid			
Characteristics	**O**	**O/E**	**95%CI**	***P****	**O**	**O/E**	**95%CI**	***P****
Total	21	16.9	10.4–25.8	~	14	44.2	24.2–74.2	~
Gender								
Males	7	9.6	3.9–19.8		4	24.5	6.7–62.7	
Females	14	27.1	14.8–45.4	0.02	10	65.2	31.3–119.9	0.08
Calendar year of HL diagnosis								
1973–1991	20	20.5	12.5–31.6		13	52.4	27.9–89.7	
1992–2003	1	3.7	0.1–20.8	0.06	1	14.5	0.4–81.0	0.2
Age at HL diagnosis (years)								
< 20	4	45.5	12.4–116.5		2	64.0	7.8–231.2	
20–29	8	30.5	13.2–60.0		5	60.4	19.6–140.9	
30–39	5	18.8	6.1–44.0		4	54.8	14.9–140.4	
≥40	4	6.4	1.7–16.3	< 0.001†	3	23.1	4.8–67.6	0.15†
Attained age (years)								
< 40	8	28.6	12.4–56.4		8	79.8	34.4–157.2	
≥40	13	13.5	7.2–23.0	0.08	6	27.7	10.2–60.3	0.04
Latency (years)								
1–4	2	5.9	0.7–21.4		2	22.5	2.7–81.2	
5–9	5	15.5	5.0–36.3		5	59.5	19.3–138.8	
10–14	2	8.2	1.0–29.7		1	16.0	0.4–89.1	
15–19	7	39.2	15.7–80.7		5	115.7	37.6–270.1	
≥20	5	30.6	9.9–71.5	0.008†	1	26.4	0.7–147.0	0.4†
SGC site								
Parotid	17	17.5	10.2–28.0		12	44.7	23.1–78.0	
Submandibular	3	14.9	3.1–43.6		1	31.1	0.8–173.2	
Sublingual	0	(E=0.01)	~		0	(E=0.01)	~	
Not specified	1	17.5	0.4–97.6	0.97	1	100.8	2.6–561.7	0.7

Abbreviations: SEER: Surveillance Epidemiology and End Results Program; O: Observed number of cases; E: Expected number of cases; O/E: Observed-to-expected ratio; CI: confidence interval; HL: Hodgkin lymphoma; SGC: salivary gland carcinoma; ~not applicable.

*P_{HET}: P for heterogeneity (refer to text for details).

†P_{Trend} P for trend (refer to text for details).

Appendix 1

Estimated Radiation Dose to the Salivary Gland From Typical Radiotherapy Fields Used in the Treatment of Hodgkin Lymphoma.

		Dose to salivary gland (Gy)* (Range across the gland)		
Technique	**HL tumor dose delivered (Gy)**	**Parotid**	**Submandibular**	**Sublingual**
Full mantle†	35	17.5 (1.75–30)	31.5 (30–35)	7 (3.5–17.5)
	20	10 (1–20)	18 (17–20)	4 (2–10)
Supraclavicular only	20	0.21 (0.12–0.30)	0.43 (0.20–0.56)	0.15 (0.14–0.16)
Neck only	20	10 (1–20)	18 (17–20)	4 (2–10)
Mediastinum only	20	0.12 (0.08–0.16)	0.25 (0.21–0.27)	0.14 (0.13–0.15)
Axilla only	20	0.06 (0.04–0.08)	0.10 (0.06–0.14)	0.07 (0.06–0.08)

Abbreviations: Gy: Gray; HL: Hodgkin lymphoma.

*Radiation doses to major salivary glands were estimated using methods described by Stovall et al (23).

†Upper field border at ear/jaw. Dose to the parotid and sublingual glands have high uncertainty due to their location on the edge of these fields.