chapter 2

Long-term risk of secondary skin cancers after radiation therapy for Hodgkin lymphoma

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Abstract

Purpose
Survivors of Hodgkin's lymphoma (HL) are at risk of secondary tumors. We investigated the risk of secondary skin cancers after radiotherapy compared to treatment without radiation and to an age-matched population.

Methods
We conducted a retrospective cohort study of 889 HL patients treated between 1965 and 2005. Data on secondary skin cancers and treatment fields were retrieved. Incidence rates were compared to observed rates in the Dutch population.

Results
318 skin cancers were diagnosed in 86 patients, showing significantly higher risks of skin cancers, the majority being BCC. The standardized incidence ratio (SIR) of BCC in HL survivors was significantly increased (SIR 5.2, 95% CI 4.0–6.6), especially in those aged <35 years at diagnosis (SIR 8.0, 95% CI 5.8–10.7). SIR increased with longer follow-up to 15.9 (95% CI 9.1–25.9) after 35 years, with 626 excess cases per 10.000 patients per year. Most (57%) skin cancers developed within the radiation fields, with significantly increased risk in patients treated with radiotherapy compared to chemotherapy alone (p=0.047, HR 2.75, 95% CI 1.01–7.45).

Conclusions
Radiotherapy for HL is associated with a strongly increased long-term risk of secondary skin cancers, both compared to the general population and to treatment with chemotherapy alone.

Introduction

With the introduction of effective chemotherapy agents and the development of modern radiotherapy techniques, the overall and relapse-free survival rates for patients with Hodgkin's lymphoma (HL) have improved dramatically. With increasing numbers of long-term survivors of HL, the evaluation of late treatment sequelae has become of major importance. The increased long-term risk of secondary cancers due to radiotherapy has been established in numerous studies (1-6). The excess risks of several types of secondary tumors in or near the previous radiation fields have been found to be associated with radiation dose, time since radiation and age at initial treatment (7, 8). Patients treated at a young age, those treated to the mediastinal and axillary lymph nodes with relatively high doses of radiotherapy, and especially those treated with extended (subtotal nodal) radiation fields are at risk for developing secondary cancers (7). Increased rates of secondary solid tumors, such as breast cancer, are usually seen from 10 to 15 years after exposure to irradiation onward (9-12).

Epidemiological studies have established previous radiation therapy as a risk factor for the development of skin cancers, mainly basal cell carcinoma (BCC)(13). These studies have predominantly described large cohorts of children, treated at a very early age with moderate radiation doses. Shore *et al.* reported a relative risk of 3.6 for the development of skin cancer when comparing a cohort of 2.224 children irradiated with a median dose of 4.8 Gy to the scalp for tinea capitis to a control group of 1.380 children merely treated with topical medications (14).

Several case-control studies have found similar odds ratios (OR)(15). Watt *et al.* compared 199 childhood survivors of cancer developing BCC during follow-up to 597 age-matched childhood survivors without BCC and found an increased risk for BCC in patients treated with radiotherapy. Risk of developing BCC increased with higher radiation treatment dose(16).

Few studies in HL survivors have focused on the risk of developing secondary skin cancers: Swerdlow *et al.* reported a significantly increased standardized incidence ratio (SIR) of non-melanoma skin cancer of 3.9 in 1039 patients treated for HL(17). Increased risks of melanoma (SIR 8.0) have been described in Australian HL survivors (18).

The present study was undertaken to investigate the long-term risk of developing secondary skin cancer after radiation therapy (RT) in a large cohort of HL survivors compared to those treated without RT and to the general Dutch population, and to relate the location of skin cancers to the radiation fields.

Methods

Patients and treatment

Leiden University Medical Center (LUMC) is a regional center of expertise for diagnosis and treatment of HL patients. Data on all treated oncology patients are collected in a central database. We conducted a retrospective cohort study of all HL patients treated between 1965 and 2005 to establish the incidence of skin cancers in HL patients treated with radiation therapy alone or with combined modality treatment (radiotherapy and chemotherapy, either as primary treatment or at relapse) in comparison to those treated with chemotherapy alone. The timeframe 1965-2005 was chosen to assess long-term risks and have a sufficient time interval since treatment to analyze radiation-induced tumors, which usually develop from 10 to15 years after treatment onwards.

From the LUMC cancer registry system (OncDoc) we collected information on age at diagnosis, gender, stage of HL, treatment modality, treatment phase (primary treatment or for recurrent disease), survival and date of death. OncDoc performs an independent and active follow-up by annually updating their database through the Dutch Municipal Population Registries, supplemented with data from the nationwide network and registry of histo- and cytopathology in the Netherlands (PALGA(19)), patient files and contact with family doctors in case of patients lost to follow-up or with unknown cause of death. This resulted in this study in a nearly complete (95%) follow-up registration up to January 19th 2011.

For information on the occurrence of skin cancers in HL patients we consulted PALGA(19). This is a nationwide organization with a central archive for pathology reports from all pathology laboratories in the Netherlands, which was founded in 1971, and had increasing participation in subsequent years. Since 1989 the registration has nationwide coverage. After the PALGA Internal Review Board approval, a search of subsequent pathology diagnoses in our HL patient cohort was conducted to identify those diagnosed with skin cancers. The search was performed by matching patients on date of birth, sex, and last name.

Skin cancer was defined as a histological diagnosis of basal cell carcinoma (BCC), squamous cell carcinoma (SCC) or melanoma of the skin. Date(s) of diagnosis and site(s) of first and any subsequent occurrence of skin cancer were established from the PALGA reports. Data were extracted on January 19th 2011. For patients who had developed skin cancers, detailed information on HL treatment and location and dose of the radiation treatment fields was collected in order to examine the type and location of the secondary skin cancers in relation to the radiation fields and doses. Follow-up ended at January 19th 2011.

Incidence rates of skin cancers, including BCC which was the predominant form of skin cancer in our cohort, were compared to observed incidence rates in the Netherlands obtained from the population-based Cancer Registry of the Comprehensive Cancer Center South (for BCC) and the Netherlands Cancer Registry (for SCC and melanoma)(20, 21).

Statistical analysis

All statistical analyses were performed using SPSS statistical software for windows version 17 (SPSS inc., Chicago, IL, USA) and STATA statistical software for windows version 11 (StataCorp LP, College Station, Texas, USA). Differences in characteristics of patients treated with chemotherapy alone or with radiotherapy were evaluated using chi-square (categorical variables) and analysis of variance (numerical variables). Correlations of skin cancer locations to the radiation fields were done in a descriptive manner.

The number of first skin cancers (BCC, SCC or melanoma) in the cohort was compared with the expected number in the Dutch population, based on age, sex- and calendar period- specific incidence rates for the period from 1989 through 2005. Time at risk started at date of HL diagnosis. Because the registration of the occurrence of skin cancers by PALGA was not complete until 1988, we left-censored within the timeframe 1965–1988. Therefore, patients at risk between 1965 and 1988 did not contribute person-time to our analysis during this timeframe. Time at risk ended at an event of a first skin cancer occurrence, last date of follow-up, death or other loss to follow-up, whichever occurred first. The SIR, defined as the observed (O) divided by the expected (E) numbers of BCC, SCC and melanoma were determined and corresponding 95% confidence intervals were calculated based on the Poisson distribution of observed numbers. Absolute excess risks (AER) were calculated as the observed incidence of skin cancers minus the number expected, divided by the number of person-years at risk and multiplied by 10,000.

Cumulative incidence of skin cancer in HL survivors treated with and without radiotherapy was estimated accounting for death as competing risk (22). To determine the influence of the possible incomplete event registration between 1965 and 1988, results were calculated both without and with left censoring. Hazard ratios and 95% confidence intervals (CI) were calculated by competing risk regression, both unadjusted and corrected for age, sex, year of diagnosis, and treatment period. A two-sided p-value <0.05 was considered statistically significant.

Table 2.1: Characteristics of HL survivors cohort

	Total number of patients	%	RT	%	No RT	%	P-value
Total	889		750		139		
Median age at diagnosis (range)	30 (5-84)		30 (5-84)		34 (10-78)		p=0.69
Treatment*							
Radiotherapy	251	28					
Chemotherapy	139	16					
Chemo- and radiotherapy	499	56					
Sex							p=0.13
Male	505	57	418	56	87	62	
Female	384	43	332	44	52	38	
Year of diagnosis							p=0.60
1965-1975	216	24	171	23	45	33	
1976-1985	233	26	194	26	39	28	
1986-1995	231	26	200	26	31	22	
1996-2005	209	24	185	25	24	17	
Stage (Ann-Arbor)							$p<0.001$
I	209	23	204	27	5	4	
II	456	51	437	58	19	14	
III	103	12	44	6	59	42	
IV	104	12	51	7	53	38	
Unknown	17	2	14	2	3	2	
Relapse							p=0.86
Yes	187	21	157	20	30	22	
No	702	79	593	80	109	78	

* including treatment for relapse. RT = radiotherapy.

Results

Between January 1st 1965 and December 31st 2005 a total of 889 patients were treated for HL at LUMC. Median age at diagnosis was 30 years (range 5-84 years). Of these, 139 patients (16%) were treated with chemotherapy alone, 251 (28%) with radiotherapy alone and 499 (56%) with a combination of these two modalities, either as primary treatment or as treatment for relapse of disease. Table 2.1 gives an overview of patient characteristics of the HL cohort.

Table 2.2: Characteristics of patients with skin cancer

Treatment	Number	%
Radiotherapy	39	45
Chemotherapy and radiotherapy	43	50
Chemotherapy only	4	5
Mean dose of radiotherapy (Gy, range)	35 (24-45)	
Chemotherapy regimes used	Number	%
MOPP	17	36
MOPP-ABV	12	26
ABVD	7	15
Other	8	17
Unknown	3	6
Age and time interval	Years	Range
Median interval of HL treatment to skin cancer	18	1-37
Median age at diagnosis of first skin cancer	52	25-80
Number of skin cancers	Number	%
Total number of skin cancers	318	
Mean number of skin cancers per patient (range)	4 (1-44)	
1	44	52
2 -5	28	33
6-10	8	8
≥11	6	7
Histology of skin cancers	Number	%
Total	318	100
Basal cell carcinoma	294	93
Squamous cell carcinoma	14	4
Melanoma of the skin	10	3
Relation of skin cancer to radiation field (per skin cancer)	Number	%
No radiotherapy	10	
Radiotherapy	308	
Within radiation field	175	57
Outside radiation field	87	28
* *Head and neck*	**65*	
* *Trunk*	**12*	
* *Limbs*	**10*	
Unknown	46	15
Relation of skin cancer to radiation field (per patient)	Number	%
No radiotherapy	4	
Radiotherapy	82	100
Within radiation field	23	28
Outside radiation field	23	28
* *Head and neck*	**13*	
* *Trunk*	**4*	
* *Limbs*	**6*	
Unknown	21	26

* Subgroup of skin cancers developing outside radiation fields.

Table 2.3: Standardized incidence ratios of first skin cancer in HL survivors

Diagnosis	Observed	Expected	SIR	95 % CI	AER*
Skin, melanoma	6	2.3	2.6	0.9-5.6	3.6
Skin, squamous cell	10	1.9	5.0	2.4-9.2	7.9
BCC of skin, head & neck	17	8.0	2.1	1.2-3.4	8.8
BCC of skin, trunk	36	3.0	11.7	8.2-16.2	32.4
BCC of skin, limbs	3	1.7	1.7	0.3-5.0	1.2
BCC of skin, other & NOS	11	.05	185.6	92.7-332.1	10.8
BCC of skin, total	67	12.9	5.2	4.0-6.6	53.3

Abbreviations: BCC = basal cell carcinoma; SIR = standardized incidence ratio; CI = confidence interval; AER = absolute excess risk; NOS = not otherwise specified.

* per 10.000 persons per year.

Over the time period considered, 86 patients developed a total number of 318 skin cancers at a median interval of 18 years (range 1-37 years). Mean number of subsequent skin cancers was 4 per patient (range 1-44). Among the 318 skin cancers, 294 (93%) were BCC, 14 (4%) were SCC and 10 (3%) melanomas of the skin (Table 2.2).

When comparing the incidence rates of BCC, SCC and melanoma in our patient cohort to the incidence rates found in the Dutch population, the overall SIR for development of BCC was 5.2 (95% CI 4.0-6.6, Table 2.3), resulting in 53 excess cases of BCC per 10,000 persons per year. SIRs for SCC and melanoma were 5.0 (95% CI 2.4-9.2) and 2.3 (95% CI 0.9-5.6), respectively. When comparing incidence rates of BCC at specific anatomic locations, the rates were especially increased in the chest and trunk area (SIR 11.7, 95% CI 8.2-16.2), which is the predominant location of radiotherapy fields since most patients received either mantle fields or mediastinal involved field radiotherapy.

The SIR for BCC was clearly higher in patients who had received radiotherapy as part of their treatment, than in those who received chemotherapy alone (Table 2.4). SIRs after radiotherapy were 7.9 (95% CI 5.5-11.2) for radiotherapy alone and 4.1 (95% CI 2.8-6.0) for combined modality treatment (CMT), compared to 2.6 (95% CI 0.7-6.6) after chemotherapy (CT) alone.

The risks of developing secondary BCC were especially increased in patients treated for HL before the age of 35 years (SIR 8.0 95% CI 5.8-10.7, Table 2.4) and those treated between 35 and 65 years of age (SIR 3.1, 95% CI 1.9-4.9) and close to unity in patients treated after the age of 65. SIRs increased with longer follow-up; after 35 years the SIR was 15.9 (95% CI 9.1-25.9), with 626 excess cases per 10.000 patients per year. There were no significant differences in incidence between men and women.

Table 2.4: Risk of first BCC compared to the general Dutch population

Sex	PY	O	SIR	95% CI	AER*
Male	5415	39	5.7	4.0-7.7	59.4
Female	4740	28	4.6	3.0-6.7	46.2
Age at diagnosis	PY	O	SIR	95% CI	AER*
<35	7341	46	8.0	5.8-10.7	54.9
35-65	2653	20	3.1	1.9-4.9	51.7
>65	161	1	1.1	0-6.2	6.8
Treatment	PY	O	SIR	95% CI	AER*
CT	3073	4	2.6	0.7-6.6	22.5
RT	1086	33	7.9	5.5-11.2	93.9
RT + CT	5996	30	4.1	2.8-6.0	38.0
Treatment period	PY	O	SIR	95% CI	AER*
1965–1975	1747	25	7.1	4.5-10.5	122.9
1976–1985	2749	13	3.5	1.9-6.1	33.9
1986–1995	3726	20	5.1	3.2-7.9	43.3
1996–2005	1932	9	4.8	2.2-9.1	36.9
Follow-up interval	PY	O	SIR	95% CI	AER*
0–1 yrs	395	0	0	-	-
1–5 yrs	1676	2	1.8	0.2-6.3	5.1
5–10 yrs	2082	5	3.0	0.9-7.0	16.0
10–15 yrs	1829	4	2.1	0.6-5.5	11.7
15–20 yrs	1572	6	2.8	1.0-6.2	24.7
20–25 yrs	1215	14	6.7	3.7-11.3	98.1
25–29 yrs	745	10	6.3	3.0-11.7	113.0
30–34 yrs	400	10	8.0	3.8-14.7	218.7
>35 yrs	239	16	15.9	9.1-25.9	626.4

Abbreviations: PY = person years; O = observed; SIR = standardized incidence ratio; CI = confidence interval; AER = absolute excess risk.

* per 10.000 persons per year.

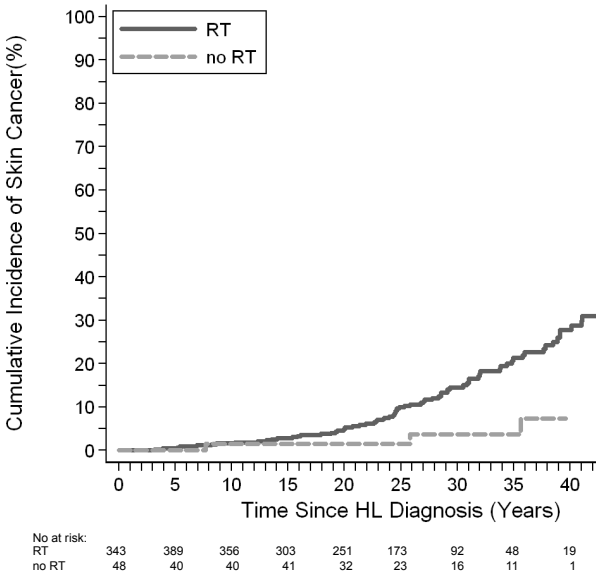

Figure 2.1: Cumulative incidence of developing a first skin cancer in the HL survivor cohort after treatment which included radiotherapy (RT; either RT alone or combined modality treatment) vs. treatment with chemotherapy alone (No RT).

The risk of development of skin cancer was significantly increased in patients who had received RT as (part of) their treatment, when compared to those treated with chemotherapy alone (unadjusted p=0·030, HR 2.95, 95% CI 1.11-7.86, adjusted p=0.047, HR 2.75, 95% CI 1.01-7.45). Cumulative incidences of developing skin cancer were 1.5%, 5% and 15% at 10, 20 and 30 years after treatment with radiotherapy, respectively, compared to 1.5%, 1.5% and 4%, respectively, for those treated with chemotherapy alone (see Figure 2.1).

The correlation of each separate skin cancer to the radiation fields is described in Table 2.2. The majority of skin cancers developed within radiation fields (57%). For those developing outside treatment fields an assessment was made of the distance to the radiation field borders, given that skin cancers in close proximity to the radiation treatment fields could have developed either due to scatter irradiation near the field, or within the radiation penumbra. Of the 87 skin cancers that had developed out of field, 12 (14%) were located close to the radiation field border. For 15% of all

skin tumors no relation to the radiation fields could be established, due to missing descriptions of precise anatomic locations in PALGA pathology reports.

Of the 10 skin cancers developing within five years after initial treatment for HL, 1 developed within the radiation treatment fields (10%). In contrast, of the 210 skin cancers developing more than 20 years after treatment, 127 (60%) developed within the radiation field.

Among patients who developed secondary skin cancers, 28% developed tumors only within radiation fields, 26% developed skin cancers both within and out of the fields, and 28% only outside the radiation fields (18% unknown, Table 2.2). These numbers changed only slightly when limiting the analysis to BCC (31% within fields, 31% both within and out of field). Among the patients with only one BCC, 54% of the tumors developed within field.

Most skin cancers were treated with simple excision, but specific information on subsequent follow up was not available. None of the patients died from the results of basal cell carcinoma, squamous cell carcinoma or melanoma of the skin.

Discussion

This study investigated the long-term risk of developing secondary skin cancers in a large cohort of HL survivors. We found significantly increased risks of subsequent skin cancers in HL patients treated with radiation therapy as compared to those treated with chemotherapy alone. The predominant form of skin cancer observed was BCC. Risks of developing BCC were substantially increased when compared to the general Dutch population and strongly increased with longer follow-up.

To our knowledge, this is one of the largest cohort studies presenting risks of skin cancer in patients treated with moderately to high doses of radiotherapy, with long-term and nearly complete follow-up. We calculated cumulative incidence rates of developing skin cancer with death as competing risk and found incidences of 1.5%, 5% and 15% at 10, 20 and 30 years after treatment with radiotherapy, compared to 1.5%, 1.5% and 4% for those treated with chemotherapy alone. Furthermore, we found a SIR of 5.2 for BCC, resulting in 53 excess cases of BCC per 10.000 persons per year in our HL cohort, when compared to the general population in the Netherlands. As BCC are not registered in the Netherlands Cancer Registry we compared our data to population data from Cancer Registry of the Comprehensive Cancer Center South (CCCS), which is the only registry of BCC incidence in the Netherlands. The increased rates found in our study are comparable those found by Swerdlow *et al.*

(17). When assessing location-specific rates we found increased rates in the chest and trunk area. This observation can be explained by the fact that most patients received radiotherapy to that area either as part of a mantle field or involved field irradiation. The high rates of BCC found in the not otherwise specified (NOS) group are due to the fact that our cohort had more missing anatomic locations than the CCCS registry. With respect to the effect of treatment, data showed the highest rates of BCC in those treated with radiotherapy alone. The lower, but still significantly increased, rates found in the combined modality group, could be due to the fact that these patients were more often treated with smaller, radiotherapy fields.

Several mechanisms for development of radiation-induced malignant neoplasms have been postulated (23). Ionizing radiation can result in sublethal DNA damage which could cause genetic changes. These changes may contribute to malignant transformation in the irradiated tissues, even after low doses of irradiation. This might explain the increased incidence of skin cancers in patients who received RT as (part of) their treatment. The observed interval of 15 years and more for increased risks of developing skin cancers was also found in other studies reporting on secondary malignancies after cancer treatment. Since the majority of our HL cohort has not yet reached a follow-up duration over 15 years, and absolute risks of developing skin cancer increase with older age, the total number of skin cancers is expected to further increase in the upcoming years, implicating a substantial and clinically relevant problem.

Due to the retrospective nature of our study, certain potential confounding factors could not be evaluated. Smoking habits, (work-related) sun exposure, age, light skin type or family history are established risk factors for developing BCC (24-26), which were by far the most frequent skin cancers in our cohort. One patient in our cohort developed a total of 44 subsequent skin cancers in a time period of 20 years. An influence of genetic predisposition for developing skin cancer can therefore not be ruled out. Since medical records of patients in our cohort were often incomplete for skin cancer risk factors other than radiation, our data could not be analyzed with adjustment for these risk factors. It is unlikely, however, that these factors would differ considerably between patients receiving radiotherapy and those who were treated with chemotherapy alone. Given the median time interval of 18 years to development of the first skin cancer after primary treatment, a retrospective study is probably the only feasible type of research for this purpose.

To ensure an independent and complete report on the development of skin cancers in our cohort we used the PALGA database for histological confirmation. In principle it could be that some skin cancers, mainly BCC, were treated without histological confirmation. Therefore it is possible that the observed incidence rates in our cohort slightly underestimate the true occurrence of BCC.

Radiotherapy has played an important role in HL treatment since the 1960s. Extended field radiotherapy has long been (part of) standard treatment. Such extended fields exposed large parts of the patient's body to radiation. Current combined treatment approaches for early stage HL with 3-4 cycles of chemotherapy followed by lower doses of involved field radiotherapy, and more recently involved node radiotherapy, have resulted in significantly reduced irradiated volumes (27, 28). Complete omission of radiotherapy in early stage HL has been shown to lead to increased local relapse rates (29, 30). With radiotherapy as an important element in the treatment of HL, patients will continue to be at risk for late adverse events due to their treatment. Patient and doctor awareness of the increased risk of developing skin cancers in addition to the established risk of secondary solid tumors such as breast cancer, lung cancer or gastrointestinal cancers is therefore essential (31-33). Increased awareness will lead to reduced morbidity by means of preventive measures (such as reduction of sun exposure) and early detection (34-36). In this light, a nationwide network of specialized long-term HL follow-up clinics has been started in the Netherlands, to ensure optimal patient education, aimed at prevention and early detection of late treatment sequelae (37).

In conclusion, our cohort study shows a substantially increased risk of secondary skin cancers in HL survivors receiving radiotherapy as part of their treatment, both compared to the general Dutch population and to those treated with chemotherapy alone. This excess risk remains increased for at least 35 years after treatment. Patients and health care providers should be aware of this risk, in order to facilitate preventive measures and rapid access to early diagnosis and treatment.

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