ORIGINAL ARTICLE

Secondary Malignancies Following Treatment for Hodgkin's Lymphoma in Childhood and Adolescence

A Cohort Study With More Than 30 Years' Follow-up

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SUMMARY

Background: About 155 persons under age 18 develop Hodgkin's lymphoma (HL) in Germany every year. More than 90% survive at least 20 years. They may, however, suffer from late sequelae of treatment, including secondary malignant neoplasia (SMN).

Methods: 2548 patients from the German, Austrian, and Swiss pediatric Hodgkin's lymphoma studies that were conducted over the period 1978–2002 were asked every 2–3 years about possible late sequelae of treatment, either directly or through their physicians. The documented cases of SMN were analyzed for cumulative incidence, standardized incidence rates (SIR), and absolute excess risk (AER).

Results: 147 cases of SMN were diagnosed in 138 of the 2548 patients, including 47 cases of thyroid cancer, 37 of breast cancer, and 15 of hematopoietic neoplasia. The cumulative incidence of SMN at 20, 25, and 30 years was 7%, 11.2%, and 18.7%, respectively. These percentages are rather low compared to other international studies. For all types of SMN, the SIR was 9.1 and the AER was 16.8. Among the 123 patients with secondary solid tumors, 105 (85%) had a tumor in the irradiated region.

Conclusion: Survivors of pediatric HL must be informed about the risk of late sequelae of treatment for HL, including SMN in the irradiated region, and that they will need regular follow-up examinations. In the future, radiotherapy for children and adolescents should be further reduced or entirely avoided.

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In Germany, survival rates after treatment for Hodgkin's lymphoma (HL) are the highest among all types of cancer that affect children and adolescents (1). Nonetheless, the combination of chemotherapy and radiotherapy has many long-term sequelae (2–4). Pediatric HL studies are conducted to achieve high survival rates, and to make long-term sequelae as rare as possible (5). The “GPOH-HD-Spätfolgen” research project (where GPOH stands for *Gesellschaft für Pädiatrische Onkologie und Hämatologie* [the German Society for Pediatric Oncology and Hematology], and HD stands for Hodgkin's disease; *Spätfolgen* = late sequelae) assessed late sequelae in the patients who were treated for HL in the first seven pediatric HL studies (1978–2002).

In this paper, we report on the occurrence of secondary malignant neoplasia (SMN) in these patients and on its possible causes. The findings have implications for the clinical follow-up of patients already treated for HL, as well as for the design of future treatments for children and adolescents with HL.

Patients and methods

From June 1978 to November 2002, 2548 patients in Germany, Austria, and (from 1995) Switzerland were enrolled and treated in six treatment optimization studies (HD-78 to HD-95) and one registry study (HD-Intervall). Detailed treatment protocols are presented in the *eTable*. 1124 of the patients were female, and 1424 were male. Their age at diagnosis ranged from 1.9 to 18 years (median, 13.3). All were treated with a combination of 3 to 6 chemotherapeutic drugs (prednisone, vincristine, procarbazine, doxorubicin, cyclophosphamide, etoposide, methotrexate) in 15-day cycles, with the number of cycles depending on the stage of disease: 2 cycles in early, 4 in intermediate, and 6–8 in advanced stages (5).

Patients in the DAL-HD-78 study (DAL: *Deutsche Arbeitsgemeinschaft für Leukämie-Forschung und -Behandlung im Kindesalter*; German

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TABLE 1

Secondary malignant neoplasia (SMN) in the studies from DAL-HD-78 to GPOH-HD-Intervall

	Patients (n)	Years to SMN diagnosis: median (range)	Age at SMN diagnosis: median (range)	Cumulative incidence at 30 years (95% CI)	Died (n)
HD-78 to HD-Intervall	2548				170
SMN (total)	138	16.9 (0.8–34.4)	28.4 (11.3–45.9)	0.19 (0.15–0.23)	31
Secondary hematopoietic neoplasia ^{*1}	15	6.7 (0.8–29.1)	17.9 (11.3–39.1)	0.015 (0.006–0.035)	9
Secondary solid tumors ^{*2}	123	17.5 (1.7–34.4)	28.7 (13.4–45.9)	0.17 (0.13–0.21)	22 ^{*3}
Thyroid cancer	47	13.2 (4.0–29.2)	24.7 (13.4–41.1)	0.044 (0.029–0.065)	4 ^{*3}
Breast cancer	37	22.0 (14.3–32.1)	36.9 (24.0–45.7)	0.16 (0.11–0.23)	5

SMN (not including 28 cases of basal-cell carcinoma) in the studies from DAL-HD-78 to GPOH-HD-Intervall (closing date, 30 September 2013).

^{*1} Secondary hematopoietic neoplasia: 1 myelodysplastic syndrome, 7 cases of leukemia, and 7 non-Hodgkin's lymphomas.

^{*2} 47 cases of thyroid cancer, 37 of breast cancer, 8 of colorectal cancer, 9 of sarcoma, 7 of melanoma, 6 of cervical cancer, 3 of schwannoma, 3 of renal-cell carcinoma, 2 of bronchial carcinoma, 2 of gastric carcinoma, 2 of cancer of the parotid gland, 1 germ-cell tumor, 1 brain tumor, 1 urothelial carcinoma, 1 histiocytoma, 1 ependymoma, 1 astrocytoma. 9 of 123 patients had multiple tumors.

^{*3} 7 patients died of causes other than SMN (5 of these 7 patients had solid tumors, including 3 with thyroid cancer).

DAL, German Working Group for Leukemia Research and Treatment in Childhood; GPOH, German Society for Pediatric Oncology and Hematology; HD, Hodgkin's disease; n, number; SMN, secondary malignant neoplasia; 95% CI, 95% confidence interval

Working Group for Leukemia Research and Treatment in Childhood) received extended field radiotherapy, and patients from the DAL-HD-82 study onward received involved field radiotherapy (IF-RT). In the DAL-HD-90 study, local IF-RT was introduced, i.e., radiotherapy restricted to the area of the involved lymph nodes. The radiation dose was gradually reduced from 40 to 20 Gray (Gy) (5).

In the next study thereafter (GPOH-HD-95), radiotherapy was not performed in patients found to be in complete remission after chemotherapy. Higher recurrence rates among patients who were in intermediate and advanced stages of HL in this study led, in turn, to a change in treatment in the next one (the GPOH-HD-Intervall study): radiotherapy was withheld only from patients who were both in complete remission and in the early stages of the disease (stages I–IIA) (6, 7).

Every 2 to 3 years, information was obtained about recurrences and late sequelae, at first from the treating institutions and later from the patients themselves with standardized questionnaires. Further medical information was obtained from the patients' physicians, with their written consent.

By 30 September 2013 (the last day of data collection), we had received data from 2548 study patients with HL of onset before age 18. Their age at the time of the last information received ranged from 2.5 to 49.2 years (median 27.4); their follow-up duration ranged from 0.1 to 35.2 years (median, 14.3). 2378 (93.3%) of the patients were still alive

at the last follow-up. Information from the last 5 years was available for 72% of the patients.

Statistical methods

Cumulative incidences of various types of secondary malignant neoplasia (SMN) were calculated as described by Gooley (8), with death taken into account as a competitive risk. The probability of overall survival was estimated as described by Kaplan and Meier (9). Cox regression and log-rank tests were used for group comparisons. The standardized incidence ratio (SIR, the ratio of observed to expected cases) and absolute excess risk (AER, the difference between the observed and expected cases per 10 000 person-years) were also calculated (10). Expected numbers of cases for the German population were derived from data of the Robert Koch Institute (www.krebsdaten.de/Krebs/DE/Datenbankabfrage/datenbankabfrage_stufe1_node.html).

Results

By 30 September 2013, 147 secondary malignant neoplasms had been diagnosed in 138 patients. 28 cases of basal-cell carcinoma were not included in this total, in accordance with the usual practice of cancer registries and publications around the world.

The SMN diagnoses and the corresponding intervals from HL diagnosis to SMN diagnosis, median ages at the time of diagnosis, and cumulative incidences at 30 years are given in *Table 1*. The calculated SIR and AER values for defined age brackets

TABLE 2

Secondary malignant neoplasia in the studies from DAL-HD-78 to GPOH-HD-Intervall; SIR and AER values relative to the normal German population

SMN diagnosis	Age (years)	Person-years at risk	SMN (n)	Expected MN (RKI) (n)	SIR			AER (per 10 000 py)
					Median	Min.	Max.	
SMN total	10–44	45754	133	15.6	9.1	4.8	10.8	16.8
Thyroid Ca	10–44	45754	47	0.89	66.2	13.6	121	8.5
♂	10–34	23156	25	0.19	133.8	72.3	157.5	11.0
♀	10–34	20255	20	0.55	29.9	19.2	120.3	5.5
Breast Ca ♀	25–44	6041	31	1.61	17.2	14.3	25.7	14.9
Leukemia	10–19	24088	7	0.69	10.4	9.2	11.1	2.9
NHL	10–39	45135	7	0.87	9.6	5.1	9.6	1.1
Colorectal Ca	25–39	11468	7	0.34	9.9	3.4	9.9	1.4
Melanoma	15–39	32673	7	1.9	5.25	2.0	5.25	1.5
♂	15–39	17080	3	0.60	4.19	4.2	12.2	0.7
♀	20–34	9435	4	1.02	1.48	1.5	8.1	0.5
Cervical Ca ♀	25–44	6041	6	0.51	21.1	5.7	21.1	9.1

Secondary malignant neoplasia in the age groups indicated in the studies from DAL-HD-78 to GPOH-HD-Intervall, compared to the expected number of malignant neoplasias based on cancer registry data of the Robert Koch Institute (closing date of the study, 30 September 2013).

DAL, German Working Group for Leukemia Research and Treatment in Childhood; GPOH, German Society for Pediatric Oncology and Hematology; HD, Hodgkin's disease; AER, absolute excess risk; Ca, carcinoma; MN, malignant neoplasia; n, number; RKI, Robert Koch Institute; SIR, standardized incidence ratio; SMN, secondary malignant neoplasia; NHL, non-Hodgkin's lymphoma, py, person years of follow-up

are given in *Table 2*. The SIR for all SMN taken together, compared to the (age-adjusted) normal population, was 9.1. The SIRs for different types of SMN ranged from 4.8 to 10.8. The AER for all SMN taken together was 16.8 per 10 000 person-years. Among all types of SMN, the highest AER was for breast cancer in women, at 14.9 per 10 000 person-years.

Cumulative incidence curves for all types of SMN, leukemia and non-Hodgkin's lymphoma (NHL), solid tumors, thyroid carcinoma, and breast cancer in women are shown in *Figure 1*. The cumulative incidence 30 years after the diagnosis of HL was:

- 19% for all types of SMN (95% confidence interval [CI], 15–23%)
- 17% for solid tumors (95% CI, 13–22%)
- 1.5% for leukemia and NHL together (95% CI, 0.6–3.5%)
- 4.4% for thyroid carcinoma (95% CI, 2.9–6.5%)
- 16% for breast cancer in women (95% CI, 11–24%).

The median interval after HL diagnosis was:

- 6.7 years for leukemia and NHL (range, 0.8–29.1 years)
- 13.2 years for thyroid carcinoma (range, 4.0–29.2 years).

Breast cancer was observed after a median interval of 22 years (range, 14.3–32.1 years); other types of solid tumors also arose only after relatively long intervals.

The cumulative incidence of SMN 30 years after the diagnosis of HL was 28.4% in women (95% CI, 21.8–36.9%) and 11.4% in men (7.6–17.2%) ($p = 0.0001$). The difference is no longer significant if breast cancer in women is not counted (12.7%; 95% CI, 8.5–18.8%) ($p = 0.67$) (*Figure 2*).

No significant difference in the cumulative incidence of secondary thyroid carcinoma 30 years after the diagnosis of HL was found between men and women (women 5.7%, men 3.4%; $p = 0.24$), among different age groups at the time of HL diagnosis (≤ 10 years, 5.4%; > 10 to ≤ 15 years, 4.4%; > 15 years, 2.3%; $p = 0.76$), or among groups of patients treated with different radiation doses to the neck (≤ 20 Gy, 4.1%, 14/941 patients; > 20 to ≤ 30 Gy, 2.9%, 15/66 patients; > 30 Gy, 6.2%, 15/437 patients; $p = 0.77$).

No cases of secondary thyroid carcinoma were diagnosed in 395 patients who had not received radiotherapy to the neck or mediastinum. Among 107 patients who received radiotherapy to the mediastinum, but not to the neck, 3 developed thyroid carcinoma (cumulative incidence, 4.5%).

FIGURE 1

Cumulative incidence of various types of secondary malignant neoplasia (SMN), not including basal-cell carcinoma, in the studies from DAL-HD-78 to GPOH-HD-Intervall. Percentages and 95% confidence intervals are given for patients with up to 30 years of follow-up by the closing date of the study (30 September 2013). Subgroups: SST (secondary solid tumors), Leuk. (leukemia) and NHL (non-Hodgkin's lymphoma), BCa (breast cancer), ThCa (thyroid cancer). n, number; 1st SMN, SMN of primary occurrence (i.e., SMN as narrowly defined); pts., patients; DAL, German Working Group for Leukemia Research and Treatment in Childhood; GPOH, German Society for Pediatric Oncology and Hematology; HD, Hodgkin's disease

The difference between patients irradiated in both the neck and the mediastinum and those irradiated in neither area was significant, with $p = 0.02$.

41 of the 47 patients with thyroid carcinoma had a papillary carcinoma. Of the 4 patients with thyroid carcinoma who died, only one had a follicular carcinoma.

We previously reported on secondary breast cancers in 26 out of 590 women who were treated in the first five HD studies (11). In the seven HD studies that are considered in this article, a total of 37 out of 1124 female patients had developed a secondary breast cancer as of 30 September 2013. 36 of them had received radiotherapy to the breast, at doses of 20–50 Gy. Five died of breast cancer.

There were fifteen cases of secondary hematologic malignant neoplasia of various types, including one case of myelodysplastic syndrome (MDS), seven of leukemia, and seven of NHL. The case of MDS

and four cases of acute myeloid leukemia (AML) arose after intervals of up to 5.3 years; one case of acute lymphoblastic leukemia at 9.2 years, one of AML at 10.4 years, and one of chronic myeloid leukemia at 22.4 years. None of these patients had been treated with either etoposide or mechlorethamine (two agents that are considered highly leukemogenic). Six died of secondary leukemia.

The seven cases of NHL arose 1.6–29.1 years after the diagnosis of HL (median, 16.2 years). Six patients had B-cell NHL, and one had null-cell NHL. Three of these patients died.

105 out of the 123 patients with SMN (85%) had a secondary solid tumor in an irradiated area.

170 of the 2548 patients were dead at the conclusion of the study, including 31 of the 138 patients with SMN and 139 of the remaining 2410 patients. The Kaplan-Meier estimates of overall survival for all patients at 10, 20, and 30 years, respectively, are

FIGURE 2

Cumulative incidences of various types of secondary malignant neoplasia (SMN), not including basal-cell carcinoma, in the studies from DAL-HD-78 to GPOH-HD-Intervall, in men and in women, with a separate curve for SMN in women with breast cancer excluded. Percentages and 95% confidence intervals are given for patients with up to 30 years of follow-up by the closing date of the study (30 September 2013).

BCa, breast cancer; n, number; DAL, German Working Group for Leukemia Research and Treatment in Childhood; GPOH, German Society for Pediatric Oncology and Hematology; HD, Hodgkin's disease

96%, 94%, and 84%. The values at 30 years for patients without and with SMN are 88% and 66%, respectively; the difference is not significant ($p = 0.34$).

Discussion

In all of the pediatric DAL-/GPOH-HD studies from 1982 onward, the 10-year-survival rates have been about 95% (5, 6). The high likelihood of survival is, however, associated with a number of adverse treatment effects, including SMN; this has been demonstrated in studies from abroad as well (3, 4). The Childhood Cancer Survivor Study (CCSS) included 13 581 patients under age 21 who were treated in the USA and Canada for various types of cancer from 1970 to 1986 and survived for at least 5 years. 314 cases of SMN were diagnosed in 298 of these patients. 1815 of the patients had HL as their primary cancer diagnosis; of the 298 patients with SMN, 111 (37.2%) were HL patients (12). In an update of this study with 30 years' follow-up, the cumulative incidence of SMN after treatment for HL was 18.4% (13).

Table 3 contains the cumulative incidences and SIR values for SMN after HL in children and adolescents that were determined by various European and North American institutions and cancer registries (14–21). The cumulative incidence values range from 6.5% to 17% at 20 years and from 18% to 29.4% at 30 years. The SIR values range from 7.7% to 22.9%. These studies varied widely in the ages of the patients treated, the treatments they received, and in cohort sizes and duration of follow-up; as a result, the usefulness of comparing findings across studies, or of comparing the findings of these studies with our own findings, is limited. In the present study, the cumulative incidence of SMN at 20, 25, and 30 years (7%, 11.2%, and 18.7%, respectively; 95% CI for the value at 30 years, 15–23%) is low compared to most of the other studies, and the SIR value of 9.1 is relatively low as well. One reason for this may be that all of the other studies included patients who received the more intensive type of treatment that was standard before 1978. In contrast, none of the patients in our cohort were given mechlorethamine, and radiotherapy with reduced target volumes and

TABLE 3

Cumulative incidence of SMN after treatment for Hodgkin's lymphoma in childhood and adolescence

First author (reference number)	Age at HL diagnosis (years)	Patient recruitment period	Pts. in study (no.)	Median follow-up (years)	Pts. with SMN (no.)	Cumulative incidence at:			SIR	95% CI
						20 years	25 years	30 years		
Sankila (14)	<21	1943–87	1641		62*	6.9%		18%	7.7	5.9–9.9
Wolden (15)	<21	1960–95	694	12.3	56*	m 9.7%			m 10.6	6.6–16.0
						f 16.8%			f 15.4	10.6–21.5
Green (16)	<20	1960–89	182	17.1	28	12.7%		26.3%	m 9.4	4.1–18.5
									f 10.2	5.6–17.1
Metayer (17)	<21	1935–94	5925	10.5	195*	6.5%	11.7%		7.7	6.6–8.8
Bhatia (18)	<16	1955–86	1380	17	212*	10.6%		26.3%	18.5	15.6–21.7
Constine (19)	<19	1960–90	930	16.8	102*		19.0%		14.2	11.6–17.3
O'Brien (20)	"children"	1970–90	110	20.6	18*	17.0%		29.4%	22.9	14.2–35
DAL/GPOH	<18	1978–2002	2548	14.3	138*	7.0%	11.2%	18.7%	9.1	4.8–10.8

Cumulative incidence and standardized incidence ratio of secondary malignant neoplasia after treatment for Hodgkin's lymphoma in childhood and adolescence: data from European and North American studies.

DAL/GPOH: the 7 DAL-/GPOH studies that are analyzed in this article.

CI, confidence interval; f, female; HL, Hodgkin's lymphoma; m, male; SIR, standardized incidence ratio; SMN, secondary malignant neoplasia;

Pts., patients; DAL, the German Working Group for Leukemia Research and Treatment in Childhood; GPOH, the German Society for Pediatric Oncology and Hematology.

*not including basal-cell carcinoma

reduced radiation doses was used from the second study (HD-82) onward.

The findings across the eight different patient cohorts presented in *Table 3* are consistent to some extent, at least with respect to the frequency ranking of different types of SMN after HL. In six of them, breast cancer accounted for the highest absolute number of secondary malignancies. More cases of thyroid cancer than of breast cancer were seen only in the study of Green (16) and in our own; in three further studies (14, 19, 20), thyroid cancer took second place in the ranking of absolute frequencies. All of the other, rarer SMN diagnoses varied in frequency ranking from one study to another.

Nearly all studies of SMN after the treatment of cancer in childhood and adolescence have revealed a higher incidence of SMN in women than in men, particularly among HL patients. In one large-scale American study (but not in the present study), this difference was still significant even when secondary breast cancer in women was not counted (19).

Children are at higher risk for SMN than adults (21–24). The high rate of breast cancer is attributed to increased sensitivity of the mammary gland during the glandular proliferation phase in puberty (11).

Adults, unlike children, often develop secondary lung cancer after treatment for HL (22, 23); the risk is higher in heavy smokers (25).

Secondary leukemias and NHL tend to arise in the first 10 to 12 years after treatment for HL, as our studies have confirmed. The incidence of leukemia is lower due to the avoidance of the leukemogenic drug mechlorethamine in chemotherapeutic DAL/GPOH protocols for HL (3, 26).

Secondary thyroid carcinoma after radiotherapy to the neck has been reported in many publications (27–30) and can arise within a few years of treatment. Most such carcinomas are papillary. In the CCSS cohort, 119 secondary thyroid carcinomas were documented in 12 547 patients, and a direct linear dependence of the rate of thyroid carcinoma on the radiation dose was described, up to a dose of about 20 Gy; a declining incidence was seen at higher doses and was attributed to a cell-killing effect (30). The same authors observed that thyroid carcinoma arises more often as an SMN in women than in men, and that its incidence declines significantly with increasing age at the time of irradiation (the analysis was based on the following age brackets: <5 years, 5–9, 10–14, and ≥ 15 years). 47 thyroid carcinomas arose in 2548 patients, without any significant differences in cumulative incidence with regard to sex, age at the time of treatment (this time in brackets of <10, 10 to <15, and ≥ 15 years), and radiation dose (in brackets of 0, ≤ 20, >20 to ≤ 30, and >30 Gy). When interpreting these data, one should bear in mind that the patients treated with

higher radiation doses in earlier studies were followed up for much longer times than those who were treated with lower doses in later studies. A more refined analysis of the different dose brackets is, unfortunately, not possible, because of the low case numbers in each bracket.

In an earlier publication, we reported extensively on secondary breast cancer arising in women who had received radiotherapy to the breast at the ages of 9 to 18; this observation led to the initiation, in 2012, of an intensified early-detection program in Germany (11). An assessment of the program's effects will be possible a few years from now.

As for the pathogenesis of SMN in patients who have been treated for HL, there are still more questions than answers. Nearly all analyses suggest that chemotherapy mainly causes secondary hematopoietic neoplasia, while radiation therapy mainly causes secondary solid tumors (31, 32). Most patients in the DAL/GPOH-HD study were treated with both chemo- and radiotherapy. 85% of the secondary solid tumors diagnosed to date have been located in an irradiated field and were, therefore, presumably radiogenic. Secondary thyroid carcinoma has been observed exclusively after radiotherapy to the neck or mediastinum. The incidence of most types of solid secondary tumor is presumed to be directly proportional to the radiation dose (19, 32), but doubt has been expressed in recent publications about the ability of lower-dosed radiotherapy—the current standard—to lessen the incidence of SMN (20, 24). As radiotherapy (particularly in children) also has other long-term adverse effects, mainly on the heart, lungs, and thyroid gland, major efforts are now underway around the world to lower the radiation dose in children and adolescents still further, or to avoid radiotherapy for them entirely. In the last European pediatric HL study (EuroNet-PHL-C1) only about half of the affected children are being treated with radiotherapy (personal communication from D. Körholz, August 2014).

Tumor predisposition syndromes and genetic polymorphisms play a role in the pathogenesis of SMN (31–35), but personalized treatment and follow-up for affected patients—involving, e.g., the avoidance of certain chemotherapeutic drugs or of radiotherapy in patients with a known predisposition to SMN—cannot yet be routinely offered.

Survivors of cancer in childhood or adolescence must be told that the treatment can have late complications, including SMN due to radiotherapy. Measures are indicated for the early detection of secondary breast cancer (inclusion criteria: see [11]) and thyroid cancer (for all patients who have received radiotherapy to the neck or mediastinum).

Most survivors of HL in childhood or adolescence do well. They fervently want to lead a normal life, and they are highly motivated to do so. Physicians should support this desire while informing patients of the possibility of late sequelae and the need for regular medical follow-up.

KEY MESSAGES

- In recent decades, the treatment of Hodgkin's lymphoma (HL) in children and adolescents has led to high survival rates, but also to a number of serious long-term sequelae, especially secondary malignant neoplasia (SMN).
- Of the 2548 patients treated in pediatric HL studies from 1978 to 2002, with a mean of 14.3 years of follow-up, 138 patients developed 147 secondary malignant neoplasms. There were 15 cases of hematopoietic neoplasia and 132 secondary solid tumors (SSTs), including 47 cases of thyroid cancer and 37 of breast cancer.
- The cumulative incidence at 30 years was 19% (95% CI:15–23%) for all types of SMN, 16% (11–23%) for breast cancer in women, 4.4% (2.9–6.5%) for thyroid carcinoma, and 1.5% (0.6–3.5%) for hematopoietic neoplasia. The standardized incidence ratio (SIR) and the absolute excess risk (AER) were higher than in the age-adjusted normal German population (source: cancer registry data of the Robert Koch Institute).
- SMN was rarer in this study than in most of the other international studies. In particular, secondary hematopoietic malignancies were less common, perhaps because less leukemogenic chemotherapy was used. Solid secondary tumors (SSTs) were mostly attributable to radiotherapy: of the 123 patients with SSTs, 105 (83%) had them in irradiated areas. Thyroid carcinoma arose only after radiotherapy to the neck or mediastinum.
- All patients who receive radiotherapy for HL in childhood or adolescence should have lifelong medical follow-up for the early detection of long-term sequelae of treatment, particularly SMN. In the future, radiotherapy for children and adolescents with HL should be further reduced or entirely avoided.

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Conflict of interest statement

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ORIGINAL ARTICLE

Secondary Malignancies Following Treatment for Hodgkin's Lymphoma in Childhood and Adolescence

A Cohort Study With More Than 30 Years' Follow-up

Wolfgang Dörffel, Marianne Riepenhausen, Heike Lüders, Jürgen Brämswig, Günther Schellong

eTABLE

Pediatric DAL-/GPOH studies for Hodgkin's lymphoma: chemotherapy and radiotherapy

Study	TG 1 Stage I–IIA	TG 2 Stage IIB–IIIA (I _E , II _E A)	TG 3 Stage IIIB–IV (II _E B, III _E)
HD-78	2 OPPA	2 OPPA + 4(-6) COP(P)	2 OPPA + 4(-6) COP(P)
	EF: IF 36–40 Gy AF 36–40 Gy vs. (randomized) 18–20 Gy		
HD-82	2 OPPA IF 35 Gy	2 OPPA + 2 COP(P) IF 30 Gy	2 OPPA + 4 COP(P) IF 25 Gy
HD-85	2 OPA IF 35 Gy	2 OPA + 2 COM(P) IF 30 Gy	2 OPA + 4 COM(P) IF 25 Gy
HD-87	2 OPA IF 30 Gy	2 OPA + 2 COP(P) IF 25 Gy	2 OPPA + 4 COP(P) IF 25 Gy
HD-90	2 OPPA 2 OEPA IF 25 Gy	2 OPPA + 2 COPP 2 OEPA + 2 COPP IF 25 Gy	2 OPPA + 4 COPP 2 OEPA + 4 COPP IF 20 Gy
HD-95	2 OPPA 2 OEPA CR: 0 Gy, ICR: 20 Gy RIF	2 OPPA + 2 COPP 2 OEPA + 2 COPP CR: 0 Gy, ICR: 20 Gy RIF	2 OPPA + 4 COPP 2 OEPA + 4 COPP CR: 0 Gy, ICR: 20 Gy RIF
HD-Intervall	2 OPPA 2 OEPA CR: 0 Gy, ICR: 20 Gy RIF	2 OPPA + 2 COPP 2 OEPA + 2 COPP 20 Gy RIF	2 OPPA + 4 COPP 2 OEPA + 4 COPP 20 Gy RIF

DAL, German Working Group for Leukemia Research and Treatment in Childhood; GPOH, German Society for Pediatric Oncology and Hematology; HD, Hodgkin's disease; TG, treatment group.

AF, adjacent field; CR, complete remission; EF, extended field; Gy, Gray; ICR, incomplete remission; IF, involved field; RIF, reduced involved field; female/male; COM(P): cyclophosphamide, vincristine, methotrexate, (prednisone); COPP: cyclophosphamide, vincristine, prednisone, procarbazine; OEPA: vincristine, etoposide, prednisone, adriamycin; OPA: vincristine, prednisone, adriamycin; OPPA: vincristine, prednisone, procarbazine, adriamycin