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Risk of thyroid disorders in adult and childhood Hodgkin lymphoma survivors 40 years after treatment

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ABSTRACT

Thyroid abnormalities are well reported following childhood treatment for Hodgkin Lymphoma (HL). Limited information exists for adult patients and after modern treatments. We analyzed risks of thyroid disorders in 237 female participants treated at the Royal Marsden Hospital 1970–2015. Multivariable analyses of risk according to treatment and time-related factors, survival analyses, and Cox regression modeling were undertaken. Overall, 33.8% of patients reported thyroid disorders (hypothyroidism 30.0% and thyroid nodules 6.8%). Cumulative prevalence was 42.9% by 40 years follow-up. Risks were greatest after supradiaphragmatic radiotherapy (RR = 5.0, $p < 0.001$), and increasing dose (RR = 1.03/Gy, $p < 0.001$). There was no association with a chemotherapy agent. Risks of thyroid disease were as raised following adult as childhood treatment. There was no trend in risk by decade of supradiaphragmatic radiotherapy treatment. Risks of thyroid disease after supradiaphragmatic radiotherapy are as great after adult as childhood treatment and persist after more recent treatment periods.

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Lymphoma and Hodgkin disease; radiation; chemotherapeutic approaches

Introduction

Hodgkin Lymphoma (HL) survival has improved greatly. In the 1970s, <50% of patients survived beyond 10 years, compared with over 80% now [1]. This success followed the introduction of combination high dose chemotherapy and radiotherapy [2,3] but has come at a cost, with an increasing pool of long-term survivors at risk of developing treatment-related late toxicities [4–7].

Irradiation to the thyroid is a well-established risk factor for a range of thyroid disorders including hypothyroidism, thyroid nodular disease, and thyroid malignancies [8–16]. Chemotherapy agents used historically in HL, such as alkylating agents have also been associated with a small increased risk of hypothyroidism [12], and thyroid cancer [17]. Modern treatment approaches focus on establishing optimal disease control whilst simultaneously reducing late toxicity. This has involved smaller more targeted radiotherapy


fields, improved radiotherapy planning and delivery techniques, lower doses of radiotherapy, and less toxic chemotherapy agents. However, it remains unclear whether modification of radiotherapy and more modern chemotherapy agents have mitigated the risks of thyroid disease.

Much of the existing literature on thyroid outcomes after HL treatment focuses on patients treated in childhood, not adulthood, and there are few data following more modern treatments. We conducted a study investigating the risk of developing a range of thyroid disorders in both childhood and adult-treated female HL survivors who have been treated at the Royal Marsden Hospital, London, UK.

Methods

With ethics approval from the National Health Research Authority (HRA) Research Ethics Committee,

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 Supplemental data for this article can be accessed [here](#).

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we identified all women under age 46 treated for HL at The Royal Marsden Hospital between 1970 and 2015.

A questionnaire was sent to UK residents, eligible subjects who had not died, and were deemed clinically appropriate to contact. The questions included demographic details and assessment of several late effects related to HL treatment, including the occurrence of a range of thyroid disorders—hypothyroidism, thyroid nodules or cysts, hyperthyroidism, thyroid malignancy, the occurrence of thyroid operations, and the reason for the operation. The most commonly occurring thyroid outcomes were validated through medical case notes for a subgroup of respondents. Treatment and disease-related and demographic variables were collected from medical records.

Treatment variables included radiotherapy field, dose delivered to specified anatomical fields (Gy), chemotherapy class, and numbers of cycles delivered. High-intensity multi-drug regimens (MDRs) were defined as regimens containing >4 drugs [18]. The class of chemotherapy agents was classified according to the SEER Antineoplastic Drugs Database [19]. ACORN score (a residential measure of socioeconomic status) [20] was derived from the postcode of residence.

Validation of thyroid outcomes

For a random sample of 80 patients responding to the questionnaire, medical records were reviewed for all thyroid outcomes and dates of diagnoses. Thyroxine treatment was presumed to indicate a diagnosis of hypothyroidism.

Sensitivity and specificity of the questionnaire responses compared with medical records as ‘the gold standard’ were calculated for hypothyroidism, thyroid nodules or cysts, and hyperthyroidism. ‘Sensitivity’ was defined as the proportion of those with the disorder recorded within the medical records correctly classified by the questionnaire. ‘Specificity’ was the proportion of patients who did not have the complication in medical records who were so classified by the questionnaire.

Medical records were also examined for incidence of all thyroid outcomes for 80 non-respondents, matched to respondents by time since treatment, calendar period, and age at first treatment.

Statistical analysis

Differences in age at diagnosis, treatment period, UK location, and occurrence of thyroid disorders between

respondents and non-respondents were analyzed by Chi-Square test.

Univariate analyses using robust Poisson regression [21] were used to explore the relationship between developing one or more thyroid disorders, and hypothyroidism separately (the most frequently occurring condition), according to time and treatment-related risk factors. Multivariable analyses were undertaken to adjust treatment-related analyses for age at treatment and duration since treatment. Analyses of age at first treatment (adjusted for follow-up time) and duration since treatment and calendar period of treatment (adjusted for age at first treatment) were undertaken for the entire population and separately in those treated with supradiaphragmatic radiotherapy.

Proportions of patients affected by thyroid disorders were compared to proportions affected in reference groups within the study population (ratios of proportions reported as relative risks), indicated in the tables. *p*-values are two-sided and considered significant if <0.05. Tests for linear trend were undertaken using continuous variables; with unknown values excluded.

Further analyses were undertaken to treat the study population as a cohort followed from the date of HL diagnosis. Cumulative prevalence of hypothyroidism, hyperthyroidism, and thyroid nodules or cysts were calculated by dividing total numbers of each event occurring during 5 year intervals by the number of women at risk at these time points.

Kaplan Meier analyses [22] investigated the time-related occurrence of any thyroid disorder stratified according to treatment modality. Women were censored at the time of first thyroid disorder or time of questionnaire completion if the event had not occurred.

Estimated rates of hypothyroidism per 1000 person-years were calculated according to period of follow-up. Cox proportional hazards regression modeling was used to calculate hazard ratios and corresponding 95% confidence intervals.

All analyses were undertaken in STATA v.16.0 [23].

Results

A total of 645 patients were eligible, of whom 185 were excluded (Figure 1), so 460 were mailed an invitation by their treating physician.

Of the 460 invited, 21 (4.6%) had emigrated or were uncontactable, 6 (1.4%) declined, and 196 did not reply. Completed questionnaires were received from 237 patients (53.9%) (Figure 1).

There was no difference in age at HL diagnosis ($p = 0.15$) between respondents and non-respondents. Respondents

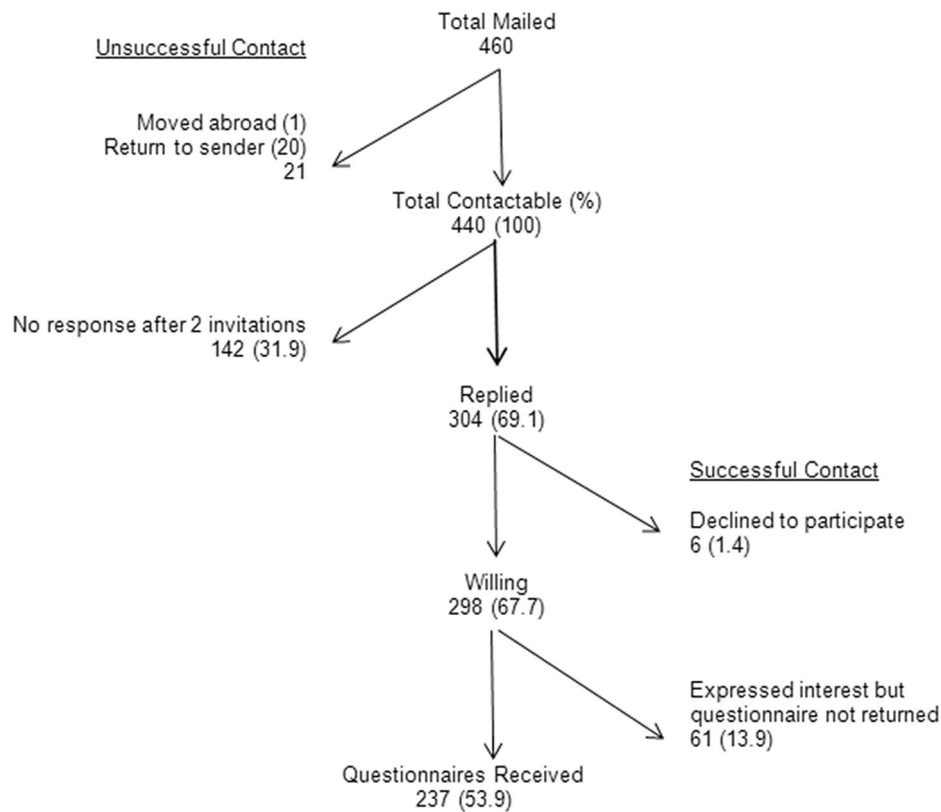


Figure 1. Response rate of a questionnaire study.

were older at the time of questionnaire response ($p = 0.001$) and therefore more likely to have been treated longer ago (54.1% of respondents before 1995 compared with 35.8% of non-respondents, $p = 0.001$).

Demographic and treatment characteristics of participants

The mean age at HL diagnosis of respondents was 22.8 years (range 6–45 years) (Table 1). The mean age at questionnaire completion was 47.5 years (range 18–76 years) and the mean time since the first HL treatment was 23.5 years (range 2–48 years).

Within those whose stage was known (75%), 63.1% were diagnosed stage I–II and 36.9% more advanced stages III–IV. Most patients (83.6%) had the nodular sclerosing histological subtype.

Most patients (86.5%) received chemotherapy, 62.9% received radiotherapy, and half (49.4%) received both. Of those receiving chemotherapy, under half (47.3%) received a classic alkylator and 72.7% received an anthracycline. A total of 25 (12.2%) were treated with a multi-drug regimen (MDR).

Thyroid disorders

A third of patients (33.8%) reported developing thyroid disorders (Supplementary Table 1). Of these 18

reported two thyroid disorders, two participants (0.8%) reported three separate thyroid conditions. The first event occurred an average of 13.5 years (range 0–38) after HL treatment.

The most commonly reported abnormality was hypothyroidism affecting 30.0% of patients at a mean of 12.9 years (range 1–38) after HL treatment. Thyroid nodules developed in 16 patients (6.8%). Of the 80 patients who developed a thyroid disorder, 23.8% were operated on, including two cases of thyroid cancer (Supplementary Table 1).

Risk factors

A significantly increased risk of developing a thyroid disorder (adjusted for the duration since treatment) appeared in patients treated with radiotherapy alone compared with chemotherapy (RR = 6.8, $p < 0.001$, Table 2). A dose-response relationship was seen with supradiaphragmatic radiotherapy dose (RR per Gy = 1.03, $p_{\text{trend}} < 0.001$). There was no significant association with any chemotherapy agent or number of chemotherapy cycles.

There was no significant association between age at first HL treatment and risk of developing a thyroid disorder. The risk of developing a thyroid disorder (after adjusting for the duration since treatment) in

Table 1. Demographic and treatment characteristics of respondents with Hodgkin lymphoma treated at ages ≤ 45 years at The Royal Marsden Hospital, 1970–2015.

Characteristic	n (%)
Age at HL diagnosis (years)	
0–19	84 (35.4)
20–29	103 (43.5)
30–39	39 (16.5)
40–45	11 (4.6)
Socioeconomic status (ACORN score)*	
1 (Highest)	102 (43.0)
2	33 (13.9)
3	60 (25.3)
4	19 (8.0)
5	19 (8.0)
6 (Lowest)	4 (1.7)
Calendar period of first treatment	
1970–1974	12 (5.1)
1975–1984	45 (19.0)
1985–1994	70 (29.5)
1995–2004	50 (21.1)
2005–2015	60 (25.3)
Years since treatment: median (range)	24 (2–48)
Age at questionnaire completion (years)	
18–29	32 (13.5)
30–39	34 (14.3)
40–49	52 (21.9)
50–59	71 (30.0)
60–79	48 (20.3)
Stage at diagnosis	
I	20 (8.4)
II	91 (38.4)
III	26 (11.0)
IV	39 (16.5)
NK	61 (25.7)
B symptoms at diagnosis	
Yes	55 (23.2)
No	112 (47.3)
NK	70 (29.5)
Subtype of HL	
Nodular sclerosis	153 (64.6)
Mixed cellularity	16 (6.8)
Lymphocyte rich	1 (0.4)
Lymphocyte depleted	2 (0.8)
NLPHL	3 (1.3)
Other	8 (3.4)
NK	54 (22.8)
Treatment modality	
Chemotherapy and radiotherapy	117 (49.4)
Radiotherapy only	32 (13.5)
Chemotherapy only	88 (37.1)
Stem cell transplant	
No transplant	218 (92.0)
Autologous	19 (8.0)
Allogeneic	0 (0.0)
Radiotherapy	
SupraRT \pm InfraRT	147 (98.7)
SupraRT only	130 (87.2)
SupraRT + InfraRT	17 (11.4)
InfraRT only	2 (1.3)
SupraRT \pm InfraRT	147 (98.7)
Including neck	114 (76.5)
Excluding neck	33 (22.1)
Including axilla(e)	85 (57.0)
Excluding axilla(e)	64 (43.0)
Total radiotherapy dose (Gy)	
1–29	12 (8.1)
30–39	74 (49.7)
40–49	32 (21.5)
≥ 50	17 (11.4)
NK	14 (9.4)
Total radiotherapy	149
Chemotherapy	

(continued)

Table 1. Continued.

Characteristic	n (%)
Total no. chemotherapy cycles	
1–4	51 (24.9)
5–6	100 (48.8)
>6	43 (21.0)
NK	11 (5.3)
Chemotherapy regimen containing	
Vinca-alkaloid	201 (98.0)
Classic alkylator	97 (47.3)
Anthracycline	149 (72.7)
Platinum	10 (4.9)
MDR	25 (12.2)
Lines of chemotherapy	
1	158 (77.1)
2	39 (19.0)
3	4 (2.0)
4	3 (1.5)
Total chemotherapy	205
Total	237

NLPHL: nodular lymphocyte predominant Hodgkin Lymphoma; NK: not known; InfraRT: infradiaphragmatic radiotherapy; SupraRT: supradiaphragmatic radiotherapy; MDR: multi-drug regimen.

*ACORN score is based on socioeconomic characteristics of the postcode of residence [20].

those treated in adulthood (>21 years) was not statistically different from those treated in childhood (≤ 21 years, Table 3).

There was an increased risk associated with duration since treatment (RR trend 1.04 per year, $p_{\text{trend}} < 0.001$, Table 3), most pronounced in patients who developed two or more thyroid conditions (RR trend 1.10 per year, $p_{\text{trend}} < 0.001$, Supplementary Table 2).

More recent treatment decades showed a significant trend of reducing risk of a thyroid disorder largely resulting from markedly reduced risks in the most recent treatment decade (RR = 0.3 in 2005–2015 compared with 1965–1974, RR trend 0.7 per decade, $p_{\text{trend}} < 0.001$, Table 3). It was not possible to adjust risks by treatment decade for time since treatment as these variables were strongly correlated.

To investigate further this relationship between risk of any thyroid disorder and time-related factors, accounting for treatment modality, risk of developing a thyroid disorder was analyzed in the highest risk treatment group—those treated with supradiaphragmatic radiotherapy. In this group, the increased risk seen with duration since treatment and decreasing risk in more recent calendar periods disappeared.

Further exploration to compare the cumulative prevalence of any thyroid disorder over time for groups of patients treated in each decade (Figure 2) showed no significant difference in cumulative events in those more recently treated compared with those treated long ago.

The prevalence of the most commonly reported thyroid conditions continued to rise steadily over time

Table 2. Relative risks of thyroid disorders by treatment modality.

Treatment modality	No. with disorder	No. treated	%*	RR	95% CI	p-value
Chemotherapy alone	7	88	8.0	1.0	–	–
Chemotherapy and radiotherapy	51	117	43.6	5.0	2.2–11.3	<0.001
Radiotherapy only	22	32	68.8	6.8	2.6–18.0	<0.001
Any SupraRT	72	147	49.0	5.0	2.2–11.4	<0.001
Including neck	57	114	50.0	5.0	2.1–11.6	<0.001
Excluding neck	15	33	45.5	5.1	2.0–12.6	<0.001
InfraRT	1	2	50.0	4.6	0.5–38.5	0.2
Dose of SupraRT (Gy)						
No SupraRT**	8	90	8.9	1.0	–	–
1–29	1	11	9.1	1.0	0.1–7.7	0.97
30–39	41	85	48.2	4.7	2.3–9.8	<0.001
>40	24	37	64.9	6.0	2.8–12.7	<0.001
NK dose SupraRT	6	14	42.9	3.9	1.5–10.1	0.005
Linear trend per Gy ^{††}				1.03	1.02–1.05	<0.001
Total	80	237				
Patients treated with chemotherapy alone						
Chemotherapy agents						
Classic alkylators	3	27	11.1	2.9	0.5–17.6	0.2
Anthracycline	6	79	7.6	0.7	0.08–6.3	0.8
Vinca-alkaloid	6	87	6.9	– [†]	–	–
MDR	1	10	10.0	1.4	0.2–12.9	0.7
Platinum	1	5	20.0	3.1	0.4–26.0	0.3
Total no. of chemo cycles						
1–4	2	18	11.1	1.0	–	–
5–6	3	51	5.9	0.5	0.09–3.3	0.5
>6	1	17	5.9	0.5	0.04–7.3	0.6
NK no. of cycles	1	2	50.0	4.3	0.4–50.6	0.3
Linear trend per cycle ^{††}				0.88	0.6–1.3	0.5
Total	7	88				

HL: Hodgkin Lymphoma; SupraRT: supradiaphragmatic radiotherapy; InfraRT: infradiaphragmatic radiotherapy; Gy: Gray; RR: relative risk; CI: confidence interval.

All analyses adjusted for the duration since the first HL treatment and age at first treatment.

*Proportion of total with risk factor (% by row).

**Includes 2 pts treated with InfraRT only.

[†]No events in the comparator group.

^{††}Excluding NK Gy/no. of cycles.

since diagnosis, increasing to a cumulative prevalence of 42.9% for any type of thyroid condition by 39 years follow up (Figure 3).

Figure 4 shows the cumulative proportion of patients developing any thyroid disorder according to treatment modality. At 30 years after HL treatment, nearly three-quarters of participants who were treated with radiotherapy alone had developed any thyroid disorder compared with ~10% of those treated with chemotherapy alone.

Hypothyroidism

A total of 71 participants reported developing hypothyroidism. Increased relative risks associated with radiotherapy treatment compared with no radiotherapy were, in general, more pronounced for hypothyroidism than for thyroid disorders overall (RR 10.2 after radiotherapy alone compared with RR 6.8 radiotherapy for all thyroid disorders, Supplementary Table 3). A dose-response effect for hypothyroidism was seen, with a 4% increased risk per 1 Gy received, and a clear association of risk with neck irradiation (RR 9.7, $p < 0.001$, Supplementary Table 3).

As for thyroid disorders overall, the risk of having ever developed hypothyroidism increased with longer follow up time (RR = 4.9 in patients 40–49 years after treatment compared with patients with under 10 years follow up, $p = 0.003$, data not shown), but in analyses restricted to patients treated with supradiaphragmatic radiotherapy, this trend disappeared.

Rates of developing hypothyroidism by duration since treatment, adjusted for attained age, were highest within 0–4 years following treatment and reduced markedly over follow up time (rate 15.6/1000 at 0–4 years follow up vs. 7.3/1000 at >30 years follow up, HR = 0.51, Supplementary Table 4). There was no significant change in rates of hypothyroidism with attained age (adjusted for the duration since treatment, Supplementary Table 4).

There was no difference in reported frequency of hypothyroidism in those who replied to the questionnaire compared with those who did not ($p = 0.49$).

Validation of self-reported thyroid disorders

Among 80 patients who responded to the questionnaire, for whom we reviewed the case notes, self-

Table 3. Relative risks of thyroid disorders by demographic and time-related factors.

Risk factor	All patients					SupraRT treated						
	No. with any thyroid disorder	No. with risk factor	%*	RR	95% CI	p-value	No. with any thyroid disorder	No. with risk factor	%*	RR	95% CI	p-value
Age at first HL treatment ^a (years)												
0–19	31	84	36.9	1.0	–	–	27	48	56.3	1.0	–	–
20–29	34	103	33.0	0.9	0.6–1.5	0.7	32	68	47.1	0.9	0.5–1.5	0.7
30–39	14	39	35.9	1.1	0.6–2.0	0.8	12	26	46.2	0.9	0.4–1.8	0.8
40–45	1	11	9.1	0.4	0.05–2.8	0.3	1	5	20.0	0.5	0.1–3.6	0.5
Linear trend per year				1.00	0.98–1.03	0.8				1.00	0.96–1.03	0.9
Age ≤21 at first treatment	37	103	35.9		$\chi^2 = 0.4$	0.5	33	62	53.2		$\chi^2 = 0.8$	0.4
Age >21 at first treatment	43	134	32.1				39	85	45.9			
Duration since first HL treatment ^b (years)												
0–9	5	43	11.6	1.0	–	–	2	9	22.2	1.0	–	–
10–19	7	46	15.2	1.3	0.4–4.1	0.6	5	23	21.7	1.0	0.2–5.0	0.98
20–29	28	70	40.0	3.4	1.3–8.9	0.011	27	47	57.5	2.6	0.6–10.8	0.2
30–39	27	55	49.1	4.2	1.6–11.0	0.003	26	46	56.5	2.5	0.6–10.5	0.2
40–49	13	23	56.5	4.9	1.7–13.6	0.003	12	22	54.6	2.4	0.5–10.8	0.3
Linear trend per year				1.04	1.02–1.06	<0.001				1.02	0.99–1.04	0.1
Treatment decade ^c												
1970–1974	5	12	41.7	1.0	–	–	5	12	41.7	1.0	–	–
1975–1984	25	45	55.6	1.3	0.5–3.5	0.6	23	39	59.0	1.4	0.5–3.7	0.5
1985–1994	28	70	40.0	1.0	0.4–2.5	0.9	27	47	57.5	1.4	0.5–3.6	0.5
1995–2004	14	50	28.0	0.7	0.2–1.9	0.4	13	30	43.3	1.0	0.4–2.9	0.9
2005–2015	8	60	13.3	0.3	0.1–1.0	0.046	4	19	21.1	0.5	0.1–1.9	0.3
Linear trend per decade				0.7	0.6–0.9	<0.001				0.9	0.7–1.1	0.1
Total	80	237					72	147				

HL: Hodgkin lymphoma; RR: relative risk; CI: confidence interval; SupraRT: supradiaphragmatic radiotherapy.

^aAdjusted for time since treatment.^bAdjusted for age at first treatment.^cProportion with a thyroid disorder (% by row).^dUnable to adjust for the duration since treatment due to co-linearity of variables.

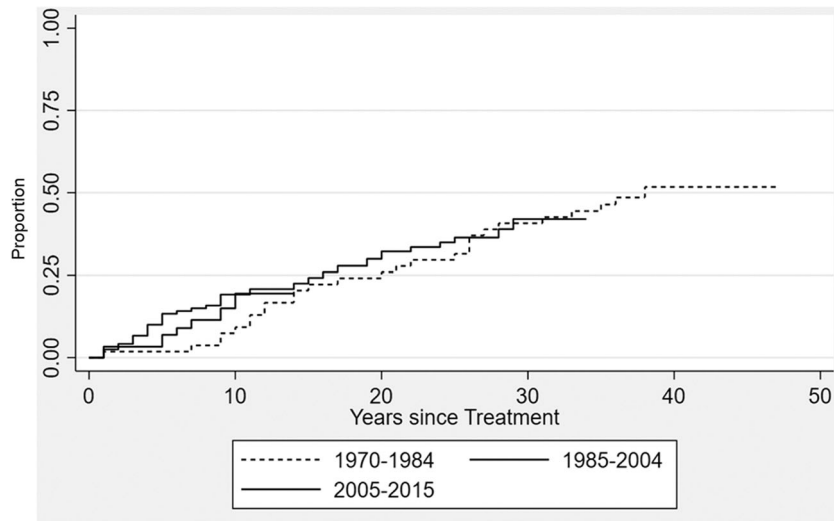


Figure 2. Cumulative proportion developing any thyroid disorder by calendar period of treatment.

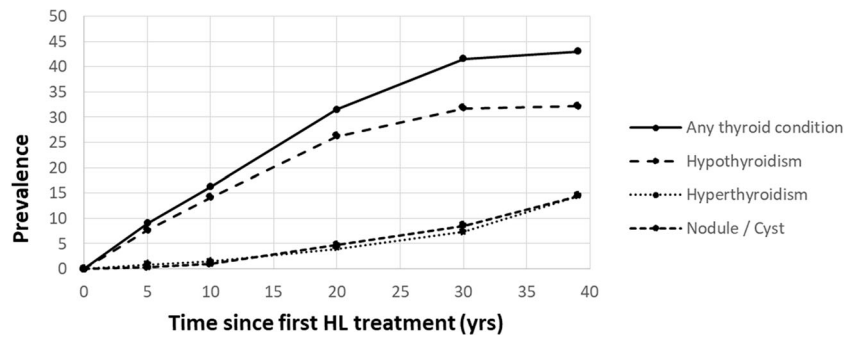


Figure 3. Cumulative prevalence of thyroid disorders by duration since HL treatment.

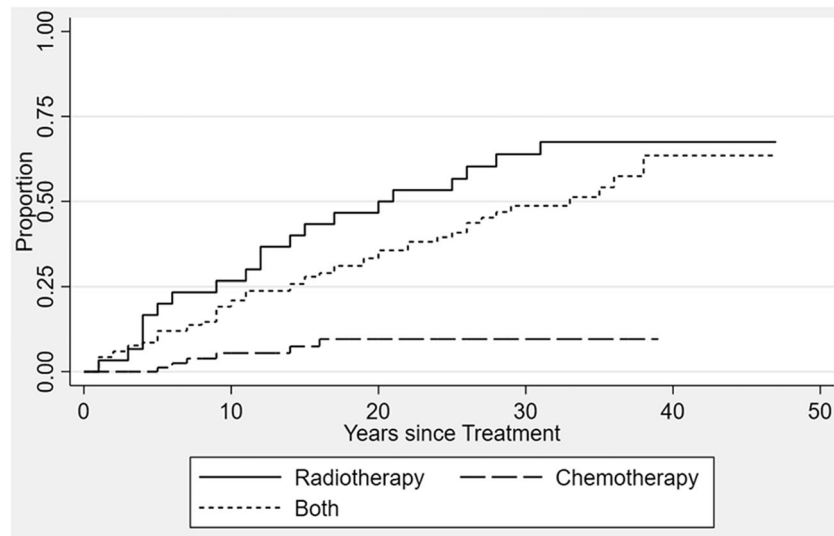


Figure 4. Cumulative proportion developing any thyroid disorder by the modality of treatment.

reported hypothyroidism demonstrated high specificity (53/59, 89.8%) and sensitivity (14/17, 82.3%) compared with medical records. There was high specificity (95.4%, 62/65) for thyroid nodules and reasonably high sensitivity (5/7, 71.4%).

Discussion

In this study, the risk of developing thyroid disorders increased consistently over time since treatment. For adults, our follow-up was longer than any study

previously. Almost half (43%) of the treated population had developed a thyroid abnormality by 40 years of follow-up and risks were as raised in those treated in adulthood as in childhood. Hypothyroidism was the most commonly occurring abnormality, radiotherapy significantly increased risk, with a dose-response relationship, as seen in other studies [15,24–26].

The proportion of patients affected by thyroid disease in this study is in keeping with other studies that have investigated the occurrence of a comparable range of thyroid conditions after HL (ranging from 32% to 60% [10,12,15,26–28]), although the vast majority of these studies were undertaken in childhood survivors [10,12,15,28]. The US-based Childhood Cancer Survivorship Study reported 60.1% of HL survivors were affected by thyroid disease and is the only study with comparable follow-up duration [28]. Their greater prevalence may be explained by a greater proportion having been treated with radiotherapy (67% compared with 57% of our patients aged under 21 years) and in more historical treatment periods when larger fields and higher doses of radiotherapy were applied. Enrollment within the CCSS also involved intensive follow-up and screening for thyroid conditions [29]. We have shown a significant cumulative rise in the numbers of survivors affected over time, irrespective of age at first treatment, which emphasizes the importance of appropriate monitoring for a range of thyroid disorders for these survivors, including those treated outside of pediatric services.

Irradiation to fields involving the thyroid has been demonstrated as the greatest treatment-related risk factor for inducing pathological thyroid changes, in a dose-dependent manner [12,25,26]. The most commonly reported thyroid abnormalities in our study, hypothyroidism and thyroid nodules, are known to be associated with direct radiation-induced damage to the thyroid [11,16,24,30–32]. Increasing radiation dose results in a reduction in the size of the thyroid [13,25]. Although pathological mechanisms for inducing hypothyroidism remain unclear; autoimmune and vascular-induced changes have been proposed [33]. Cohort studies from the UK general population report female-specific prevalence of primary hypothyroidism as 3–4% at all age groups, with a mean age at diagnosis of 58–60 [34,35]. Our self-reported prevalence of 30.0% at a mean age of 35.7 years is ~10-fold greater than would be expected overall in the UK general population with a much younger age at diagnosis than would be expected.

Irradiation was also likely to be the cause of the two thyroid cancers occurring in this study, both after

mantle field radiotherapy, leading to a prevalence that appears to be ~10–15 times higher than would be expected based on the national UK estimated prevalence rates [36].

The administration of chemotherapy alone did not confer an increased risk of thyroid disease. The patients in our study treated with chemotherapy alone had shorter follow up (mean 16.1 years) than patients treated with radiotherapy (mean 27.8 years), so an increased risk of thyroid disorders may become apparent with longer follow up. However, other studies of HL survivors of comparable size have concurred with our finding [15,26,37]. A larger study from the CCSS reported an increased risk of hypothyroidism associated with certain older chemotherapy agents like CCNU and Cyclophosphamide administered to children [12], which were not frequently used in our patients although other classic alkylators were. However, the CCSS study included patients treated for a range of childhood tumor types so these findings may not be relevant specifically to HL survivors.

Another important future question is whether the current direction of HL treatment incorporating novel immunomodulatory treatments alongside chemotherapy, such as PD-1 checkpoint inhibitors [38], may lead to the risk of thyroid disease increasing in the future. Such agents are already known to cause thyroid dysfunction in up to a quarter of those treated [39]. Our population was treated before the introduction of such agents into routine clinical practice so we were unable to address this question, but it is important to highlight that measuring thyroid disorder incidence will continue to be a key question to address for future HL survivors.

We did not find any association with risk of developing a thyroid disorder and age at first treatment, nor a change in risk for those treated specifically with high-risk supradiaphragmatic radiotherapy. Importantly the risks of developing thyroid conditions remained as greatly raised for those treated in adulthood (>21) as in childhood. This has clinical implications for improving follow-up of the adult patient population who may be less comprehensively followed up as pediatric, teenage, and young adult population.

Although duration since treatment initially appeared to be associated with increased risk of developing a thyroid disorder and hypothyroidism specifically, this effect disappeared when analyses focused on the highest risk treatment group, those treated with supradiaphragmatic radiotherapy. The association with time since treatment was clearly confounded by the more widespread use of extended

field supradiaphragmatic radiotherapy and at higher doses in patients treated longer ago (mean dose 37.9 Gy and 100% treated with supraRT in the earliest calendar treatment period compared with only 32% treated with mean dose 9.5 Gy in 2005–2015). Our results suggest it is the radiotherapy treatment and use of higher doses more historically rather than duration since treatment that contributes the most significant risk to these patients.

Due to long follow-up after treatment, we were able to compare proportions of developing thyroid disorders in different calendar periods. The use of extended high dose mantle field radiotherapy was common in the first three decades of this study, after which time involved field radiotherapy (IFRT) and subsequently involved site radiotherapy (ISRT) was adopted. The use of computer tomography (CT) planning over the last 20 years has contributed significantly to the reduced field and more targeted treatment. Interestingly there did not appear to be a significant difference in the cumulative prevalence of thyroid disorder in those treated in more recent decades compared with those treated longer ago (Figure 2). This is somewhat surprising considering the above described secular reduction in field and dose of supradiaphragmatic radiotherapy. It may be that improved clinical awareness and thus more frequent detection of thyroid disorders, with the publication of late effects follow up guidelines over the last 20–30 years, has mitigated against a drop in prevalence in those more recently treated, who are more likely to be under active surveillance.

Due to the historic treatment periods included in this study, it was not possible to establish from medical records, precise estimates of the received dose of radiotherapy to the thyroid. There is therefore likely to be an element of confounding of the contribution of field and dose-effect with the dose-response seen in our analyses with higher doses being more likely to have been given with larger extended fields. The thyroid dose received can reasonably be presumed to approximately equate to the recorded overall dose for extended mantle fields due to relative homogeneity of dose delivery. However it is much more difficult to assess dose to the thyroid accurately with more recent and more variable IFRT and ISRT [40,41] based on medical records review, and retrospective dose reconstruction was not possible within the scope of this study. Another important and related question is whether the evolution of the use of unilateral compared with bilateral supradiaphragmatic field delivery over the last 20 years has impacted on reduced risk of

thyroid disease and both of these issues will be addressed as part of future work.

A potential weakness of our study is that it is based on the self-reported occurrence of thyroid disease. However, we were able to validate hypothyroidism prevalence through the use of medical records, which confirmed reasonably high sensitivity and specificity of self-reports for this outcome. Furthermore, medical records, although unlikely to be inaccurate, could nevertheless be incomplete. There were six patients in our study who convincingly reported hypothyroidism but for whom there was no diagnosis recorded in hospital medical records, and five of these patients had been seen at Royal Marsden Hospital for Lymphoma follow-up after the occurrence of the hypothyroidism. The Royal Marsden Hospital Lymphoma Unit policy specifies annual thyroid function checks in those treated with radiotherapy that includes the neck, but these can be undertaken in the community which may be why they were not captured. Other studies in cancer patients have shown high levels of concordance between patient-reported and clinician-assessed hypothyroidism, likely because it is a binary non-fluctuating event and patients tend to have an awareness and understanding of the condition [42,43]. Once diagnosed, hypothyroidism is usually treated with Thyroxine which also makes inaccurate recall less likely.

Another important consideration is the potential role of selection bias in our study since not all eligible patients responded to the questionnaire request. Patients were more likely to respond if they were currently older and treated longer ago. It is possible that patients who have developed long-term side effects may be more, or less, likely to respond to questionnaires than others. The questionnaire asked about several late effects not just thyroid disease, so it is not likely that patients would respond specifically because they had developed a thyroid condition. Thyroid disease would also not cause disability sufficient to prevent response to a questionnaire, nor is thyroid disease associated with higher death rates (even thyroid cancers, which may be diagnosed post-irradiation are generally associated with good outcomes).

To check this, we examined case notes for a subgroup of non-respondents matched to respondents by age and time since treatment. We found no significant difference in the occurrence of hypothyroidism ($\chi^2 = 0.31$, $p = 0.58$) and thyroid nodules ($\chi^2 = 0.34$, $p = 0.56$) between respondents ($n = 9$ hypothyroidism, $n = 2$ thyroid nodules) and non-respondents ($n = 7$ hypothyroidism, $n = 1$ thyroid nodules) suggesting

response was not influenced by the presence of these disorders. The numbers of events were too small to assess for the difference in hyperthyroidism or thyroid operations in this subgroup. Furthermore, the proportion of respondents who reported being affected by the most common thyroid outcomes was comparable to other studies using self-reported outcomes [27,28], supporting the validity of our findings.

In summary, in our data radiotherapy was significantly associated in a dose-dependent manner with raised risks of developing a range of thyroid disorders, most frequently hypothyroidism, with cumulative prevalence continuing to rise many decades after treatment. This risk of over 40% by 40 years after treatment, was similar in patients treated in adulthood to that after treatment in childhood. With the advancing use of thyrotoxic immunotherapy agents, this issue will remain an important outcome to monitor in survivors over the coming decades. Implementing risk-stratified surveillance, including education of patients of their risk and symptoms of these outcomes, remains an important component for long-term early detection and treatment of thyroid disease in HL survivors.

Author contributions

A.M.D. and A.J.S. designed the study. D.C., I.C., E.A., S.I., M.T., and P.C. provided patient information and assisted with data collection and management. A.M.D., M.J., and C.B. undertook data analysis, all authors contributed to completing the final manuscript.

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