Original Research Article

Second malignancies in patients with Hodgkin's Lymphoma: Half a century of experience

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ABSTRACT

Purpose: Therapeutic improvements for Hodgkin's Lymphoma (HL) has resulted in excellent survival outcomes. Thus, patients are increasing susceptible to developing secondary malignancy (SM) a feared iatrogenic complication.

Materials & Methods: We evaluated the SM risk in a cohort of patients with HL treated over a 50-year period. In total, 1653 patients were treated for HL from 1956 to 2009 at a tertiary-cancer-center. A cumulative incidence function was used to quantify SM risk and the Fine and Gray competing risk model was used to identify disease and treatment related correlates.

Results: Two-hundred-ninety patients (19%) developed SMs. Paradoxically, SM risk was higher in the modern era with 20-year cumulative incidence rates of 11.1%, 11.9%, 17% and 21.8%, for patients treated <1970, 1971–1986, 1986–1995 and 1996–2009, respectively. We hypothesized that the disproportionately high rate of early deaths in the early era may skew the assessment of SM risks, a much-delayed event. When the analysis was restricted to patients with early-stage favorable HL treated >1980, we found a reversal of the trend, especially on the risk of solid tumor, with a hazard ratio of 0.57 (p = 0.0651) in patients treated after 1996.

Conclusion: Our findings highlight the limitations of comparing the risk of a late event between groups with disparate rates of early deaths, despite the use of a competing risk model. When partially corrected for, patients treated in the more recent time period experienced a lower solid tumor risk.

Introduction

Hodgkin lymphoma (HL) is an excellent example of how survival gains can be realized by reducing the long-term side effects related to therapy. A "more is better" approach to therapy, although successful in other types of cancer, has proven to be not applicable for the treatment of HL. Patients who were cured succumb to second malignancies (SM) decades later [1–3], especially among those treated with extensive radiation fields and chemotherapy that includes alkylating agents. Several trials published since the early 1980s have produced clear evidence that reducing the intensity of both chemotherapy and radiation by switching to less toxic chemotherapeutic agents, lower radiation doses and more conformal radiation therapy techniques are safe and maintain the high cure rates in HL [4–11]. The purpose of this single-institution retrospective analysis is to examine how patients fared over time in terms of the development of SM, as various treatments for HL evolved over the past 5 decades.

Materials & methods

Study group

This study was approved by our Institutional Review Board. HL patients were identified by searching an institutional lymphoma database during the period from January 1956 through June 2009 with follow-up until February 12, 2020. Patient's demographics, stage, treatment delivered, recurrence, and occurrence of secondary malignancies were extracted from medical records and our institutional tumor registry. Further confirmatory information was gathered through systematic review of social security records, death certificates, and when possible, further confirmatory phone calls were made to patients and/or their families. The following characteristics were recorded: date of birth, gender, date of diagnosis, age at diagnosis, primary site of disease, number of sites, disease stage, presence of B symptoms, presence of bulky disease, type of chemotherapy used, type of radiation used, number of fields, number of courses, dose, any relapse, use of stem cell transplantation, any SM, date of SM occurrence, type, and location. Since our current therapeutic decisions follow the German Hodgkin's Study group staging criteria, we converted patient's staging into the three groups: early favorable, early unfavorable and advanced. The primary objectives of this study are to determine the frequency and types of SM over time, to compare cumulative incidence rates of SM according to diagnosis and treatment time period, and to identify patient, disease or treatment factors associated with the SM risks.

We first grouped patients according to the date of diagnosis into one of four periods that roughly correspond to changes in institutional practice: the first period was before 1970 (when radiation was the primary treatment modality); the second was 1971–1985 (when extended-field radiation was combined with MOPP [mechlorethamine, vincristine, procarbazine, and prednisone]–based chemotherapy); the third was 1986–1995 (when ABVD [doxorubicin, bleomycin, vinblastine, and dacarbazine] chemotherapy was combined with less-extensive radiation that still included mantle and paraaortic-spleen fields); and the fourth period was 1996–2009 (when radiation therapy transitioned to involved-field). During this 5-decade period, several other chemotherapy regimens were used as well, including combinations similar to MOPP such as CVPP [cyclophosphamide, vinblastine, procarbazine, prednisone] and COPP [cyclophosphamide, vincristine, procarbazine, prednisone]), or similar to ABVD such as NOVP [mitoxantrone, vincristine, vinblastine, prednisone]. Regarding radiation fields, extended-field radiation (EFRT) was defined as radiation therapy that included 2 or 3 of the following fields: mantle (included the neck, supraclavicular area, bilateral axilla, and mediastinum); paraaortic-spleen (included the spleen and paraaortic lymph nodes from T10-T11 through L4-L5); or inverted-Y (included the common iliac nodes, pelvic nodes, obturator, and inguinal femoral nodes). Finally we grouped patients by type of SM as either solid or liquid, given that the later tends to occur on the order of a few years after treatment while the former occurs decades after [12,13].

Statistical analysis

Frequencies and percentages are reported for categorical variables. The clinical endpoint was the cumulative incidence rate of SM after diagnosis. The variables of interest include gender, age at diagnosis, year of diagnosis, disease stage, B symptoms, bulky disease, type of chemotherapy, MOPP chemotherapy, radiation alone, cobalt radiation, number of radiation courses, total radiation dose, radiation field, relapse, and transplant.

To quantify the risk of developing SM, we used the cumulative incidence function because the usual Kaplan–Meier survival-based estimates are biased due to patients who die without SM being counted as simple censoring events rather than as competing risks [14]. To compare the cumulative incidence functions, we used Gray's test [15]. To assess the effects of covariates on the cumulative incidence function, we used the univariate and multi-covariate proportional hazards models of Fine and Gray [16]. For the multivariate competing risk regression model analysis, we first evaluated a model with all the covariates of interest with p-values <0.20 in the univariate model and then kept only the covariates with p-values <0.05 for the final multi-covariate model. All analyses were performed using SAS 9.4 and R version 2.14.2 (R Foundation for Statistical Computing), including the cmprsk package.

Results patient characteristics

The dataset included 1,653 patients diagnosed with and treated for HL between 1956 and 2009. The clinical characteristics are summarized in Table 1.

The median follow-up time for the entire group was 22 years (range

Table 1
Patient characteristics.

Variable		N	%
Gender	Female	770	46.6
	Male	883	53.4
Age	≤20	354	21.4
	>20–40	930	56.3
	>40	369	22.3
Year of Diagnosis	1970 or earlier	62	3.8
	1971-1985	669	40.5
	1986-1995	413	25.0
	1996-2009	509	30.8
	1996 or earlier	1090	70.6
	1997-2009	454	29.4
Stage	Early-favorable	1149	71.6
	Early-unfavorable	330	20.6
	Advanced	126	7.9
	Unknown	48	2.9
B Symptoms	No	1261	76.4
	Yes	389	23.6
	Unknown	3	0.2
Bulky Disease	No	1260	76.5
	Yes	387	23.5
	Unknown	6	0.4
Chemotherapy	ABVD	414	25.0
	Any MOPP	278	16.8
	Other chemo	262	15.8
	No chemo	656	39.7
	Unknown	43	2.6
Radiation Alone	No	968	59.6
	Yes	656	40.4
	Unknown	29	1.8
Cobalt Radiation	No	954	57.8
	Yes	697	42.2
	Unknown	2	0.1
Number of Radiation Courses	1	941	56.9
	2	539	32.6
	≥3	173	10.5
Radiation Dose (Gy)	≤30	165	10.0
	30.1-36	348	21.1
	36.1-60	887	53.7
	Unknown	253	15.3
Radiation Field	Total nodal irradiation	68	4.1
	Mantle paraaortic-splenic	374	22.6
	Paraaortic-pelvic (Inverted-Y)	83	5.0
	Mantle alone	439	26.6
	Involved-field	573	34.7
	Unknown	116	7.0
Relapsed Disease	No	1291	78.1
	Yes	362	21.9
Transplant	No	1434	86.8
	Yes	142	8.6
	Unknown	77	4.7
Secondary Malignancy	Liquid	66	4.3
	Solid	195	12.6
	Breast	54	7.4
	Lung	35	2.3
	Thyroid	24	1.6

11.8–49.6 years). The median age at diagnosis was 28 years (range, 4.1–88.4 years). The majority (59%) were treated with combined chemotherapy and radiation while 40% of patients received radiation alone. Of the 1,611 patients who received radiation, either alone or with chemotherapy, 697 (42.2%) received cobalt therapy. Radiation fields evolved over the study period: 68 patients (4.1%) received total nodal irradiation, which included mantle, *para*-aortic, spleen, and inverted Y; 374 (22.6%) patients received mantle and paraaortic-splenic radiation, 83 patients (5.0%) received paraaortic and pelvic radiation (or inverted Y), 439 (26.6%) patients received mantle radiation only, and 573 (34.7%) received involved-field radiation therapy (IFRT). The majority (54%) received a radiation dose of > 36 Gy. Chemotherapy with MOPP was given to 278 patients (16.8%), ABVD chemotherapy to 414 (25%), and other combinations to 262 (15.8%).

Risk of second malignancy

After excluding 109 patients with missing SM information, 1,544 patients were included in the SM analysis. Of these patients, 290 (18.8%) developed a SM (excluding skin cancers) with 195 (12.6%) being solid tumors and 66 (4.3%) being a liquid malignancy (Table 1). Breast cancer was the most common SM as it occurred in 54 (7.4%) of patients. The median time to the appearance of any SM was 12.8 years. Consistent with previous data a majority of liquid SM occurred within the first 5 years of follow-up in contrast to solid malignancies where the risk persisted over time (Fig. 1). On univariate analysis (Supplementary Table 1), the following factors were associated with a significantly higher SM risk: ≥3 (HR = 1.66, p = 0.003) and 2 radiation courses (HR = 1.49, p = 0.002) compared to 1 radiation course, radiation dose of 30.1–36 Gy (HR = 2.02, p = 0.012) compared to a dose of ≤30 Gy, and history of relapse (HR = 1.34, p = 0.025). Presence of B symptoms was associated with a significantly lower risk of SM (HR = 0.71, p = 0.023). Contrary to expectations, the receipt of cobalt radiation or total nodal irradiation (as compared with IFRT) has a non-significant protective effect against SM (p = 0.120). In addition, there was a non-significant trend of a lower SM risk in patients with early-stage unfavorable (p = 0.089) and advanced-stage disease (p = 0.072) compared to those with early-stage favorable disease.

On multivariable analysis (Table 2), ≥3 radiation courses versus 1–2 radiation courses (HR = 1.89, p = 0.002) and radiation dose of 30.1–36 Gy (HR = 2.03, p = 0.015) were associated with significantly higher SM risk, while advanced-stage disease (HR = 0.47, p = 0.029) was associated with a significantly lower SM risk.

Table 2
Multivariate analysis of the Entire Cohort.

Parameter	Comparison	Hazard Ratio	95% Confidence Interval		P-value
Year of Diagnosis	≤1970 vs 1996-2009	0.671	0.317	1.423	0.2981
	1971-1985 vs 1996-2009	0.841	0.570	1.241	0.3833
	1986-1995 vs 1996-2009	1.186	0.765	1.841	0.4457
Stage	Early unfavorable vs Early favorable	0.809	0.572	1.145	0.2316
	Advanced vs Early favorable	0.466	0.235	0.926	0.0293
No. of Radiation Courses	≥3 vs 1-2	1.889	1.258	2.837	0.0022
Radiation Dose	30.1-36 vs ≤30	2.027	1.145	3.587	0.0153
	36.1-60 vs ≤30	1.525	0.902	2.580	0.1152

Also contrary to expectations, the cumulative incidence rate of SM was higher among more recently treated patients: the 20-year cumulative incidence of SM for patients treated < 1970, 1971–1986, 1986–1995 and 1996–2009 were 11.1%, 11.9%, 17% and 21.8%, respectively (Fig. 2A). Using the year 1996 (when 3D conformal radiation was introduced) as cutoff, the 20-year cumulative incidence of SM for patients treated 1996 or earlier and 1997–2009 were 13.8% and 21.4%, respectively.

Exploratory analysis

In our analysis of the entire dataset, the paradoxical finding of **lower** SM risks in patients who received cobalt radiation or total nodal irradiation, and the **higher** cumulative incidence of SM in more recently treated patients can be attributed to the high rate of early deaths in patients from an earlier era, with many did not surviving long enough to develop a SM. Indeed, in patients treated prior to 1970, 64.3% died without experiencing a SM, and this steadily decreased over time to 45%, 22.6% and 16.5% in patients treated during 1971–1985, 1986–1995 and 1996–2006, respectively. Similarly, the lower SM risk among early-unfavorable and advanced-stage patients can be explained by their lower likelihood of long-term survival to face SM risks. As such, we further conducted an exploratory analysis, excluding patients treated
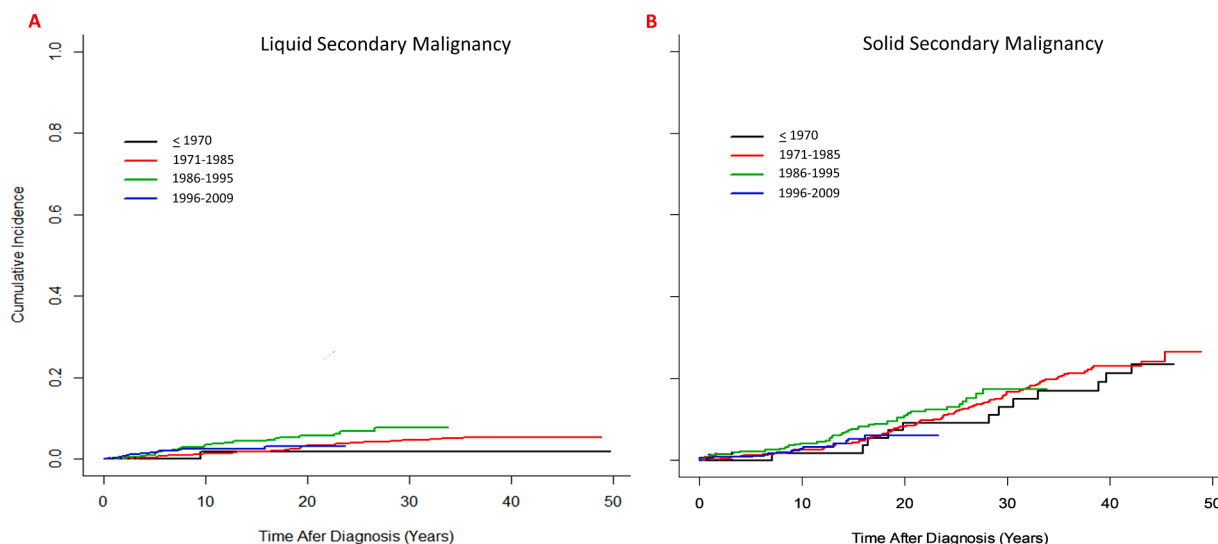

Fig. 1. Cumulative incidence of solid and liquid secondary malignancies after treatment of Hodgkin's lymphoma stratified by treatment era (A) Liquid/hematologic cancers (B) Solid tumors.
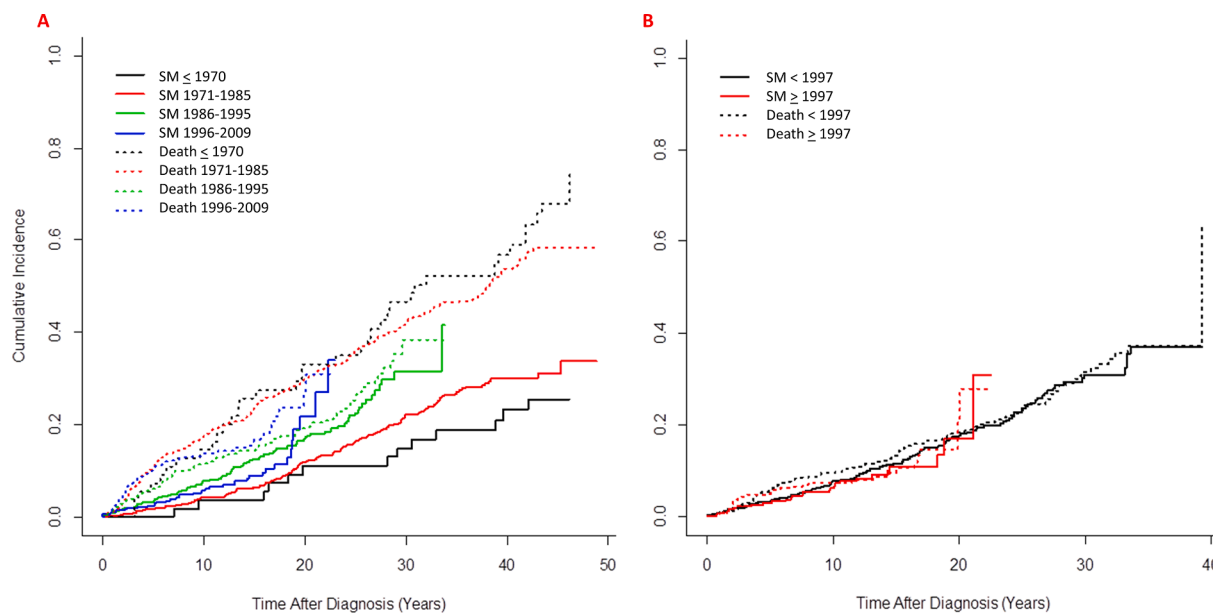
Fig. 2. Cumulative incidence of secondary malignancies and death after treatment of Hodgkin's lymphoma stratified by treatment era (A) Entire cohort (B) Exploratory analysis excluding patients treated before 1980 and those with early unfavorable/advanced-stage disease.

prior to 1980 (when more than half of patients died without experiencing a SM; also, when the transition from cobalt to linac-based radiation started), and those who had early unfavorable or advanced-stage disease. Of note, despite the exclusion of patients treated from the very early era, in this new cohort of 818 patients with early-favorable HL treated after 1980, there was still a significant proportion of patients who received cobalt radiation (23%), EFRT (67.8%), and a radiation dose of >30 Gy (91.7%). At a median follow up of 15.4 years (range 0.08–39.5 years) among 597 living patients at the last contact, 135 (16.5%) developed a SM. By focusing on this selected cohort, the 20-year cumulative incidence of SM for patients treated from 1980 to 1996 and 1997–2009 were 17.7% and 17.1%, respectively (Fig. 2B). On multivariable analysis (Table 3), in contrast to the full cohort, there was a non-significant trend of a lower SM risk in more recently treated patients (HR, 0.716, p = 0.17). In addition age >40 (HR, 2.09, p = 0.01), ≥3 radiation courses (HR, 3.3, p = 0.007), radiation dose of >30 Gy (HR 2.45, p = 0.029), and history of relapse (HR, 1.92, p = 0.014) were significantly associated with a higher SM risk.

Types of second malignancies

For the entire cohort of 1,544 patients, of the 290 patients who developed a SM, 66 (4.3%) had hematologic malignancies and 195

Table 3
Multivariate analysis of 818 patients with early, favorable HL Treated after 1980.

Parameter	Comparison	Hazard Ratio	95% Confidence Interval		P-Value
Year of Diagnosis	>1996 vs 1:≤1996	0.716	0.446	1.151	0.1678
Age	>20-40 vs ≤20	0.956	0.551	1.658	0.8729
	>40 vs ≤20	2.094	1.190	3.684	0.0103
No. of Radiation Courses	≥3 vs 1-2	3.302	1.653	6.600	0.0007
Radiation Dose	30.1-36 vs 1:≤30	2.452	1.097	5.480	0.0288
	36.1-60 vs 1:≤30	1.572	0.724	3.417	0.2531
Relapsed Disease	Yes vs No	1.919	1.140	3.229	0.0142

(12.6%) had solid tumors. The median time to the development of hematologic malignancies was 7.4 years, and 13.8 years for solid tumors.

When restricting the analysis to the 818 patients with early-favorable HL treated after 1980, 135 patients developed a SM, including 32 hematologic malignancies and 84 solid tumors. Types of malignancies are detailed in a supplementary Table 4. In patients treated from 1980 to 1996, the 10-, 15-year and 20-year cumulative incidence of solid tumors were 4.9%, 7.7% and 11.7%, while for patients treated after 1996, the corresponding cumulative incidence were 3.6%, 6.5%, and 6.5%, respectively (HR, 0.57; p = 0.0651) (Fig. 3).
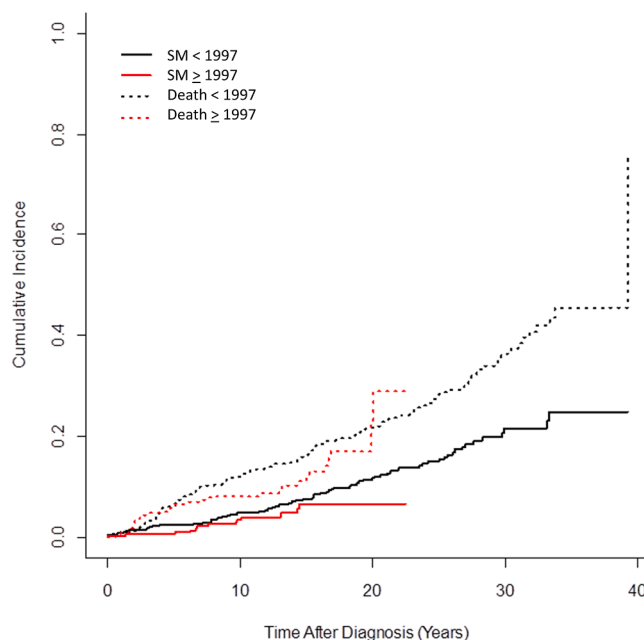

Fig. 3. Cumulative incidence of solid tumor and death after treatment of Hodgkin's lymphoma stratified by treatment era in the exploratory cohort of patients.

Discussion

In this large single-institutional analysis of HL patients treated over a 50-year period, when the entire cohort of patients were included, we found paradoxically that treatment in the more recent era is associated with a significantly increased SM risk. This peculiar finding is likely due to the fact that in the early era, HL therapeutic options available were highly limited, with ineffective and toxic systemic therapy, and crude and primitive radiation treatment delivery. In addition, during that time period, proper supportive care in managing life-threatening acute side effects such as myelosuppression and infections were also not yet available. It is therefore no surprise that a low SM malignancy risk was observed in these earlier treated patients, since many did not survive long enough to experience a therapy-related late effect. Over time, as more effective HL management and supportive care became available, with reduced early mortality from HL or from acute/subacute treatment toxicity, the number of person-years at risk increases. As such, even if there is a reduction in the absolute hazard of SM, the observed cumulative incidence of SM will increase. In fact, this observed increase is a reflection of the growing success of HL therapy over the decades.

Others have evaluated the relationship between the time period of HL therapy and SM risks. Hodgson et al, using the SEER database, found no evidence that patients treated after 1984 had a lower risk of solid cancers than those who were treated from 1970 to 1984 [17]. Schaapveld et al., [18] reporting on SM risks among HL patients treated in the Netherlands over a 40-year period, similarly found that the cumulative incidence of solid cancers, breast cancer and gastrointestinal cancer did not differ significantly according the treatment periods of 1965–1976, 1977–1988, 1989–2000. In our study, which included patients treated prior to 1960 and spanned a 50-year period, we in fact found a significantly higher risk of SM in patients treated in more recent time period. These findings underscore the challenges of comparing the risk of an event that has a long latency and that does not occur linearly over time, such as solid tumor development, among groups with significant disparity in early mortality rates. This limitation is especially pronounced when the study cohort spans over many decades, such that there is an even more pronounced discrepancy in early death rates according to calendar-year of treatment, or among patients who received historical versus modern therapy. Other limitations that may skew the findings include differences in length of follow-up, level of awareness of late effects, and late effect screening practice and detection of patients from different treatment era.

We attempted to attenuate the effect of the disproportionately high number of early deaths in the earliest cohort of patients, as well as the high early HL-related deaths in patients with unfavorable or advanced-stage disease, by limiting our analysis to patients with early-stage favorable disease treated after 1980, when cobalt therapy was beginning to be replaced by linac-based radiation therapy. When restricting the analysis to this patient cohort, there is a reversal in the trend of SM by calendar year, notably for the risk of solid tumors. When comparing patients treated from 1980 to 1996 versus after 1996 (the year 1996 as a cut-off, an important turning point in radiation practice, when radiation therapy transitioned from 2-dimensional to 3-dimensional-based planning and delivery, and when EFRT was replaced by IFRT), after adjusting for available disease and treatment factors, we found that patients treated after 1996 had an estimated 43% lower risk of solid tumor, the most common type of SM that is largely attributed to radiation.

We also found that in both the entire cohort and in the exploratory analysis, higher radiation doses, a history of relapse and multiple therapeutic courses were significantly associated with increased SM risk. These findings are consistent with prior published results [19–23]. Further radiation dose de-escalation after complete metabolic response to chemotherapy, as supported by available data [7,24–26], is expected to further reduce the SM risk. In addition, the results highlight the importance of maximizing upfront disease control. Several randomized trials have failed to show the non-inferiority of chemotherapy alone in early-stage HL, even with interim and end-of-chemotherapy complete metabolic response [26–28], unless intensive chemotherapy such as escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (eBEACOPP) is used [29]. The omission of radiotherapy in early-stage HL patients therefore needs to be carefully weighed against the toxicities associated with more intensive salvage therapies for relapsed disease.

In the last 10 to 15 years, we have witnessed another watershed in radiation approach for HL. Involved-node radiation therapy (INRT) [6], first introduced 15 years ago, and subsequently involved-site radiation therapy (ISRT) [30,31], to accommodate for differences in patient positioning between diagnostic scans and radiation therapy, have since replaced IFRT. With INRT/ISRT, the radiation treatment volume is tailored to individual cases and is significantly more limited compared to IFRT. Over the past decade, modern high-precision radiotherapy techniques, such as intensity-modulated radiotherapy (IMRT) [32,33] and proton therapy [34], allow targeting radiation doses precisely to the shape of tumors. Daily image guidance with image-guided radiation therapy (IGRT) allows further reduction in treatment volume by reducing uncertainty [35]. In addition, simple maneuvers such as breath-hold and inclined board have been shown to significantly reduce doses to critical organs-at-risk including heart, lungs and breasts outside of the radiation field [36–40].

Radiation therapy for HL has evolved from a one-size-fit-all approach to a highly personalized form of therapy, with close attention to minimizing doses to surrounding normal organs while maintaining target coverage. Volumetric dose data of critical structures including heart and cardiac substructures, lungs, breasts, thyroid, salivary glands, and esophagus are now routinely tracked as part of ISRT for HL. With longer follow up time, the data will allow us to directly correlate doses to specific organs with any late complications, instead of using such surrogates as calendar-year of treatment in assessing the effect of therapeutic changes on late complications. The results will further guide HL treatment decisions, enhance risk assessment and advance HL survivorship care.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2022.04.011.

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