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ORIGINAL ARTICLE

Consolidative proton therapy after chemotherapy for patients with Hodgkin lymphoma

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Background: We investigated early outcomes for patients receiving chemotherapy followed by consolidative proton therapy (PT) for the treatment of Hodgkin lymphoma (HL).

Patients and methods: From June 2008 through August 2015, 138 patients with HL enrolled on either IRB-approved outcomes tracking protocols or registry studies received consolidative PT. Patients were excluded due to relapsed or refractory disease. Involved-site radiotherapy field designs were used for all patients. Pediatric patients received a median dose of 21 Gy(RBE) [range 15–36 Gy(RBE)]; adult patients received a median dose of 30.6 Gy(RBE) [range, 20–45 Gy(RBE)]. Patients receiving PT were young (median age, 20 years; range 6–57). Overall, 42% were pediatric (≤18 years) and 93% were under the age of 40 years. Thirty-eight percent of patients were male and 62% female. Stage distribution included 73% with I/II and 27% with III/IV disease. Patients predominantly had mediastinal involvement (96%) and bulky disease (57%), whereas 37% had B symptoms. The median follow-up was 32 months (range, 5–92 months).

Results: The 3-year relapse-free survival rate was 92% for all patients; it was 96% for adults and 87% for pediatric patients ($P = 0.18$). When evaluated by positron emission tomography/computed tomography scan response at the end of chemotherapy, patients with a partial response had worse 3-year progression-free survival compared with other patients (78% versus 94%; $P = 0.0034$). No grade 3 radiation-related toxicities have occurred to date.

Conclusion: Consolidative PT following standard chemotherapy in HL is primarily used in young patients with mediastinal and bulky disease. Early relapse-free survival rates are similar to those reported with photon radiation treatment, and no early grade 3 toxicities have been observed. Continued follow-up to assess late effects is critical.

Key words: Hodgkin lymphoma, radiotherapy, proton therapy, chemotherapy

Introduction

Combination chemotherapy and radiation therapy provides the best relapse-free survival among patients with Hodgkin lymphoma (HL) [1, 2]. Unfortunately, survivors of HL are at high risk of developing late side-effects with ~50% of survivors developing a grade 3 or higher toxicity within 30 years of treatment [3]. These late side-effects are mostly due to cardiovascular complications and secondary malignancies.

A well-established linear relationship has been observed between radiation dose to most organs and subsequent toxicity. By reducing the dose, treatment volumes, or a combination of both, radiation oncologists can modify their radiation treatment to reduce late effects while maintaining the best chances of cure. Indeed, field reduction from the larger mantle field to the smaller involved-field radiation therapy (IFRT) was associated with reduced secondary breast cancer risk [4]. More recently, lower prescription radiation doses and additional field reductions with involved-node radiation therapy and involved-site radiation therapy (ISRT) have been implemented to further reduce late toxicity.

Another important approach in the reduction of radiation morbidity is the use of more conformal radiation techniques, such as intensity-modulated radiation therapy (IMRT) and proton therapy (PT). These treatments are included in the National Comprehensive Cancer Network (NCCN) guidelines for HL and non-HL and are allowed to be used on current International collaborative HL studies [Children's Oncology Group (COG) study AHOD 1331 (NCT02166463) and Euronet-PHL-C2 (NCT02684708)].

Yet these newer treatments, which can help reduce the radiation dose to different organs, are more expensive and not widely available. Furthermore, concerns have been raised regarding the potential increased risk of relapse due to the steeper dose gradient.

Utilizing prospective academic and community registry data, we report current patterns-of-care and early outcomes among patients with HL receiving PT.

Patients and methods

Patients diagnosed with HL and treated with chemotherapy followed by consolidative PT between June 2008 and August 2015 were prospectively enrolled on one of the following institutional review board-approved protocols: the University of Florida outcomes tracking protocol ($n = 39$), the University of Pennsylvania Adult or Pediatric proton registry ($n = 54$), or the Proton Collaborative Group (PCG) registry ($n = 45$). Patients were excluded if they had refractory or relapsed HL, if they received PT as a boost following photon radiation, or if they had composite HL/non-HL.

Baseline patient, disease, and treatment characteristics are included in Table 1. As erythrocyte sedimentation rate and all sites of involvement were not routinely reported, risk group stratification included favorable early-stage (stage IA or IIA non-bulky), unfavorable early-stage (stage I or II with either B symptoms or bulky disease), or advanced stage (stage IIB bulky and all stage III and IV patients) disease. Positron emission tomography (PET)/computed tomography (CT) imaging to assess chemotherapy response was available for most patients (94%); however, standard reporting was not carried out across institutions. For the purpose of this study, a complete response (CR) by PET/CT scan was considered if the report stated a complete metabolic response or a Deauville 1, 2, or 3 score, while a partial response by PET/CT scan was considered if the report stated an incomplete or partial metabolic response or a Deauville 4 or 5 score at the end of chemotherapy. Immobilization and simulation techniques varied across patients and institutions. In general, motion management was carried out using four-dimensional CT planning with the creation of an internal target volume as an expansion of the clinical target volumes. Some patients underwent the deep inspiration breath-hold technique for motion management.

PT was delivered using ISRT [5] or similar fields based on modern radiation treatment planning concepts of omission of uninvolved nodes and volumetric target delineation including INRT, with the addition of a boost to high-risk sites based on the physicians' discretion [6, 7]. The median dose was 21 Gy(RBE) for pediatric patients [range 15–36 Gy(RBE)] and 30.6 Gy(RBE) for adult patients [range 20–45 Gy(RBE)] and was delivered with either passive-scatter ($n = 64$), uniform-scanning ($n = 57$), or pencil-beam scanning ($n = 17$) techniques [8]. Twenty-one patients treated with a mediastinal proton field matched to a photon neck plan at the University of Pennsylvania were included.

At each weekly on-treatment and follow-up visit, patients were assessed for radiation toxicity and disease progression using the Common Terminology Criteria for Adverse Events, version 4, in addition to a physical examination and periodic imaging. The median follow-up was 32 months (range 5–92 months). The Kaplan-Meier method was used to

Table 1. Patient, disease, and treatment characteristics ($N = 138$)[a]

Characteristic	No. of patients	%
Sex		
Male	53	38.4
Female	85	61.6
Age (years)		
5–10	6	4.3
11–18	53	38.4
19–30	50	36.2
31–40	20	14.5
>40	9	6.5
Stage		
I	7	5.1
II	93	67.4
III	21	15.2
IV	17	12.3
B symptoms		
Yes	51	37.0
No	86	62.3
Unknown	1	0.7
Bulky disease		
Yes	78	57.4
No	58	42.0
Unknown	2	0.7
Mediastinal		
Yes	132	95.7
No	6	4.3
Risk		
Favorable (I/II A, non-bulky)	41	29.7
Unfavorable (I/II with B or bulky)	39	28.2
High (I/II B bulky, III, or IV)	58	42.0
Chemotherapy		
ABVDx2–3	9	6.5
ABVDx4	34	24.6
ABVDx5–6	32	22.5
ABVE-PCx3–4	39	28.3
ABVE-PCx5	7	5.1
ABVE-PCx4 + (DECA or IV)	6	4.3
Other	11	8.0
PET/CT response to chemotherapy		
Complete response	115	83.3%
Partial response	15	10.9%
Not clearly defined	8	5.8%
Proton dose Gy (RBE)		
15–25.9	62	44.9
26–30.9	58	42.0
31–36.9	14	10.1
37–45	4	2.9

[a]Median age for the cohort was 20 years (range 6–57 years). Pediatric patients received a median dose of 21 Gy(RBE) [range 15–36 Gy(RBE)]; adult patients received a median dose of 30.6 Gy(RBE) [range 20–45 Gy(RBE)].
ABVD, adriamycin, bleomycin, vinblastine, dacarbazine; ABVE-PC, adriamycin, bleomycin, vincristine sulfate, etoposide, prednisone, cyclophosphamide; DECA, dexamethasone, etoposide, cisplatin, and cytarabine; IE, ifosfamide, etoposide.

assess relapse-free survival from the time of diagnosis and log-rank test for univariate analysis.

Results

Patient-, disease-, and treatment-related characteristics are listed in Table 1. The median age for the cohort was 20 years (range 6–57 years); 42% and 93% were under 19 years old (pediatric) and under 40 years old adolescent/young adult (AYA), respectively. Most patients in the cohort were female (62%). Stage distribution included 73% of patients with I/II and 27% with III/IV. Patients predominantly had mediastinal involvement (96%) and bulky disease (57%), while 37% had B symptoms. Risk-group stratification as previously described included 30% favorable early-stage, 28% unfavorable early-stage disease, and 42% advanced-stage.

Pediatric patients were typically treated with ABVE-PC (adriamycin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide)-based chemotherapy (84%) with three to four cycles ($n = 37$), five cycles ($n = 7$), two additional cycles of DECA (dexamethasone, etoposide, cisplatin, cytarabine), or IV (ifosfamide, vinorelbine) ($n = 5$). Most adult patients (90%) received ABVD (adriamycin, bleomycin, vinblastine, dacarbazine) chemotherapy for two to three cycles ($n = 7$), four cycles ($n = 33$), or five to six cycles ($n = 32$). Response to chemotherapy by PET/CT scan included 115 patients with a complete response, 15 patients with a partial response (PR), and 8 patients with an unknown response. Dose escalation for PR at the physician's discretion was done for 10 of the patients, including doses up to 30–36 Gy for four patients ≤19 year old for whom the standard dose is 21 Gy, and to 36–45 Gy for six adult patients. The remaining patients who did not receive dose escalation were 3 ≤19 years old treated to 21 Gy and two adults treated to 30 Gy.

The 3-year relapse-free survival rate was 92% (Figure 1A) and by age group it was 96% for adults and 87% ($P = 0.18$) for pediatric patients (Figure 1B). According to risk group stratification, the 3-year relapse-free survival rates for favorable early-stage, unfavorable early-stage, and advanced-stage disease were: 97%, 88%, and 92% ($P = 0.33$), and by age group they were 97%, 93%, and 96% ($P = 0.64$) for adult patients and 100%, 83%, and 87% ($P = 0.64$) for pediatric patients (Figure 1C and D). When relapse-free survival was evaluated by PET/CT response to chemotherapy, patients who experienced a PR had a statistically significant higher risk of relapse compared with the patients who experienced a complete or unknown response to treatment (3-year relapse-free survival, 78% versus 94%; $P = 0.0034$; Figure 1E).

Ten recurrences developed, including six in-field, one in-field and out-of-field, and three out-of-field in immediately adjacent nodal regions. Six of the seven recurrences (86%) with an in-field component developed in pediatric patients treated to <30 Gy(RBE), including two with a PR treated to 21 Gy. All in-field recurrences occurred in the middle of the radiation field. There were no marginal recurrences at the edge of the proton field that could be attributed to proton range uncertainties. The three out-of-field recurrences developed immediately inferiorly or superior to the ISRT-defined PTV, including in two patients without prechemotherapy PET/CT imaging previously described [9].

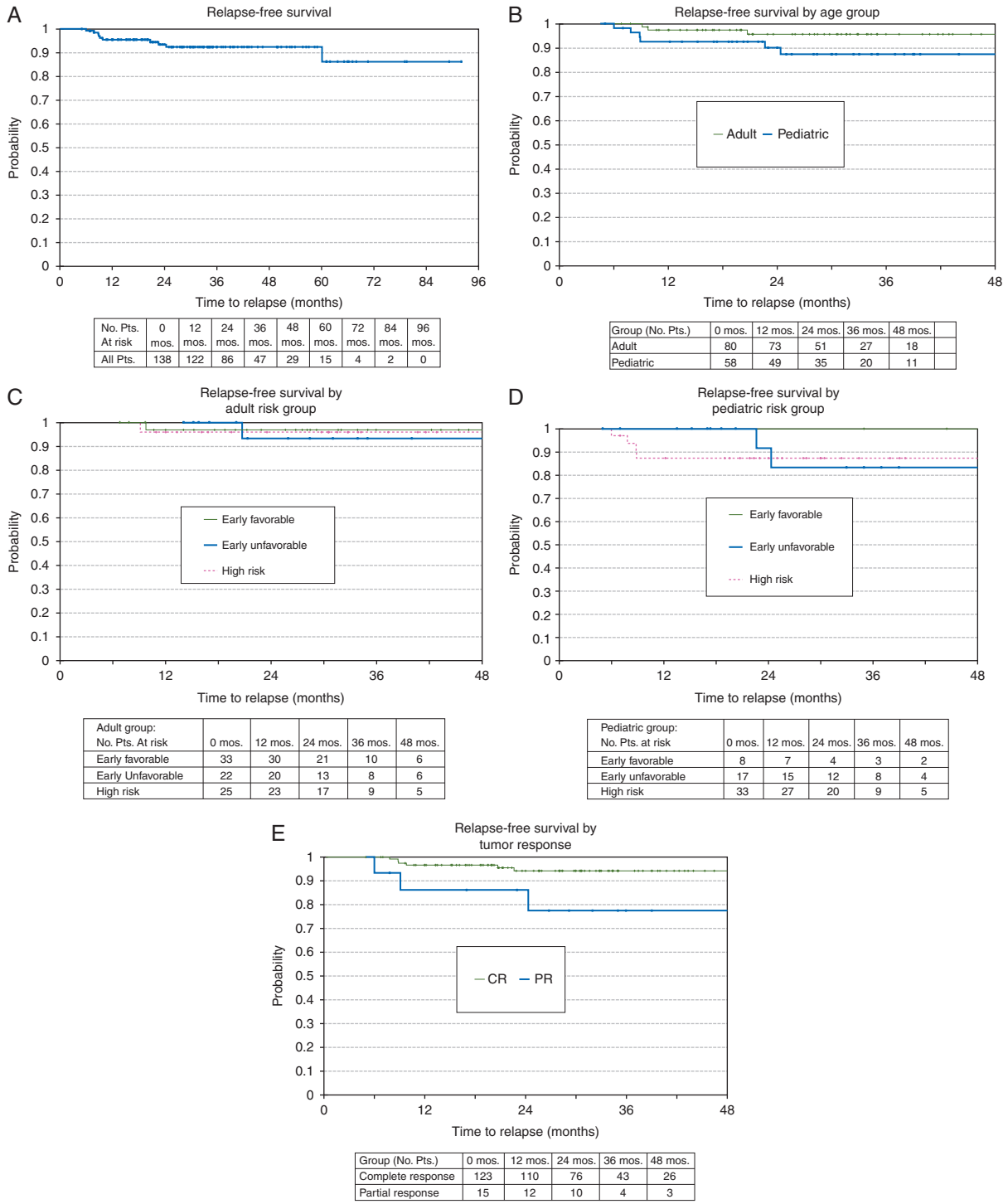
No grade 3 toxicities were observed during follow-up among the patients in our cohort. Grade 1 and 2 toxicities are reported in Table 2 and separated by institution. No clinically meaningful pneumonitis was reported in the cohort.

Discussion

The present study is the first proton outcomes study to merge data from three separate IRB-approved registry studies and demonstrates the feasibility and benefits of collaborating to attain a meaningful number of patients with HL managed with PT. Collaboration among proton centers has been encouraged by the American Society for Radiation Oncology (ASTRO) in their Model Policy on PT in order to facilitate evidence development for using proton therapy. Furthermore, the importance of this collaborative effort is even more impressive based on a recent National Cancer Database (NCDB) study that reported on radiation techniques utilized for patients with HL; only 40 patients were treated with PT, which was considered too small a number to report outcomes [10].

In the present study, most patients who received PT for HL as part of first-line therapy were those with the highest risk of developing late toxicities, including younger patients with longer life expectancies in survivorship, female patients with a higher risk of developing a second cancer because of the breast cancer risk, and patients with bulky mediastinal disease adjacent to the lung, heart, and breasts. Although difficult to compare due to differences in data collection between studies, the results contrast with findings from a patterns-of-care analysis from the NCDB, which evaluated the use of three-dimensional (3D) conformal radiation therapy (CRT) and IMRT [10]. IMRT was predominantly used among older patients (>40 years old, 55%), males (59%), and those with head-and-neck involvement compared with patients with mediastinal disease (38% versus 13%, respectively) [10]. Compared with IMRT, 3D-CRT was more commonly delivered to females (48% versus 41%), patients stage III/IV disease (15% versus 8%), and to the mediastinum/chest (30% versus 13%). The difference in patterns of care may be due to the concern of a low-dose radiation bath from IMRT, which can increase the risk of second cancers in younger female patients with mediastinal disease or, alternatively, increased insurance coverage for head and neck sites for salivary gland sparing [11].

The predominant use of PT for mediastinal involvement is not surprising considering the thirteen published dosimetric studies, including a prospective clinical trial, evaluating the use of PT in HL. These studies have demonstrated the potential dose reduction to the heart, lung, breast, and esophagus among patients with mediastinal disease compared with either CRT or IMRT [12–15] and the consistent reduction in integral dose (whole-body radiation exposure) by 40%–50% with PT [13]. Although, the magnitude of benefit in some patients might be low for the difference in dose to the organs, the integral dose (whole body exposure) is always substantially reduced in all patients (40%–50%). Consequently, when following the ALARA (as low as reasonably achievable) principle, PT would be the treatment of choice, especially in young adult, adolescent, and pediatric patients. Data have emerged over the last two decades that a radiation dose–response relationship exists between mean doses to the heart and coronary heart disease [16] and



No. Pts. At risk	0 mos.	12 mos.	24 mos.	36 mos.	48 mos.	60 mos.	72 mos.	84 mos.	96 mos.
All Pts.	138	122	86	47	29	15	4	2	0

Group (No. Pts.)	0 mos.	12 mos.	24 mos.	36 mos.	48 mos.
Adult	80	73	51	27	18
Pediatric	58	49	35	20	11

Adult group: No. Pts. At risk	0 mos.	12 mos.	24 mos.	36 mos.	48 mos.
Early favorable	33	30	21	10	6
Early Unfavorable	22	20	13	8	6
High risk	25	23	17	9	5

Pediatric group: No. Pts. at risk	0 mos.	12 mos.	24 mos.	36 mos.	48 mos.
Early favorable	8	7	4	3	2
Early unfavorable	17	15	12	8	4
High risk	33	27	20	9	5

Group (No. Pts.)	0 mos.	12 mos.	24 mos.	36 mos.	48 mos.
Complete response	123	110	76	43	26
Partial response	15	12	10	4	3

Figure 1. Relapse-free survival curves for the entire cohort (A), by age group stratification (B) and by risk group stratification for (C) adults and (D) pediatrics patients and according to favorable early-stage (Fav), unfavorable early-stage (Inter), and advanced-stage (High) disease. (E) Relapse-free survival rates by positron emission tomography/computed tomography response to chemotherapy. CR, complete response; PR, partial response.

valvular disease [17] in survivors of HL. Furthermore, similar associations of radiation dose to the lungs, breast, and body and risk of lung cancer, breast cancer, and sarcomas have been demonstrated [18]. Although these rates are expected to fall, owing to smaller radiation treatment fields and lower prescription doses, PT has the potential to further reduce these risks. Importantly, these dose reductions are expected to lower the risk of second cancers and cardiovascular complications, which translates into an overall survival advantage with PT over volumetric arc therapy or 3D CRT [19].

Although these results are preliminary, they represent excellent 3-year outcomes, especially considering most patients (70%) had unfavorable early-stage or advanced-stage disease. Despite the

Table 2. Grade 1 and 2 toxicity reporting according to institution

	UF ($n = 39$)		PCG ($n = 45$)		UP ($n = 54$)	
Toxicity	**Grade1**	**Grade 2**	**Grade 1**	**Grade 2**	**Grade 1**	**Grade 2**
Anorexia	5	1	2	2	9	1
Anxiety/depression/agitation	14	1			5	0
Constipation			1	0	11	0
Cough	27	1	11	0	15	1
Diarrhea			1	0	2	0
Dry Mouth	17	1	1	0	9	0
Dyspepsia			2	2	9	0
Dyspnea	19	0			11	0
Esophagitis	21	7	14	8	13	10
Fatigue	27	4	11	1	30	2
Hoarseness			11	0	5	0
Hypothyroidism	0	3				
Mucositis					2	0
Nausea	13	3	3	0	13	1
Pain	18	1	4	0		
Performance status	7	1				
Pulmonary (fibrosis/pneumonitis/effusion)	6	0			0	0
Radiation dermatitis	33	2	34	3	28	3
Vomiting	6	2			2	0

PCG, Proton Collaborative Group; UF, University of Florida; UP, University of Pennsylvania.

adverse risk factors in our cohort of PT patients (i.e. risk group, PET/CT response, bulky disease, and B symptoms), our results compare favorably to the only three published clinical outcomes studies of IMRT for Hodgkin lymphoma, which altogether comprise 140 patients treated with IMRT [20–22]. A post-chemotherapy partial response on PET/CT was associated with inferior outcomes, notwithstanding consolidation with PT. Finally, although the worse relapse free-survival was among these partial responders, many remained in remission following PT and avoided salvage regimens and stem cell transplant, and their associated toxicities.

The predominant pattern of failure in this study was in-field recurrences after lower doses of radiation [<30 Gy(RBE)]. Similar patterns of recurrence have been reported by the Children's Oncology Group for pediatric HL treated to 21 Gy, in which >85% of relapses occurred with an in-field component [23]. Importantly, neither marginal relapses attributed to the dramatic dose fall-off observed with PT nor end-of-range uncertainty was observed, confirming the effectiveness of PT in consolidation after chemotherapy in HL. In this study, marginal relapses were more likely owing to inadequate radiation field design, which has been reported in radiation quality assessments in clinical trials [24]. Although modern radiation fields utilizing ISRT concepts were used in the study, we could not evaluate the quality of target volumes (since they were either too big or too small) for most patients because of the lack of baseline PET/CT imaging data, which is a limitation of the study.

No acute grade 3 toxicities were observed during follow-up among the patients in our cohort. This finding is not surprising given the rarity of acute grade 3 radiation-related toxicities with the relatively low dose of radiation used in HL. While grade 2 esophagitis is to be expected, the lack of any grade 2 pneumonitis was surprising given the 7% rate of grade 3 pneumonitis (using the RTOG scale) reported by investigators at MD Anderson Cancer Center (Houston, TX) among mediastinal lymphoma patients receiving IMRT [25]. Their group determined that the strongest predictor for pneumonitis was >55% of the lung receiving 5 Gy or more (V5); thus, the absence of a low-dose proton bath may mitigate the risk of clinically meaningful pneumonitis. Overall, the lack of clinically significant toxicity in this proton cohort is encouraging.

No late grade 3 toxicities developed in the cohort, which is unsurprising given the decades of follow-up needed to observe significant late toxicities, such as cardiac morbidity and secondary cancers. Although the present study is unable to provide evidence for reducing late toxicity from treatment, investigators at Massachusetts General Hospital (MGH; Boston, MA) reported on development of second cancers after PT [26]. In their study, patients treated at MGH with PT were matched to similar patients from the Surveillance, Epidemiology, and End Results (SEER) registry treated with photon radiation. Compared with patients treated with photons, there was a 50% reduction in second cancers among those treated with PT at MGH (HR 0.52; 95% CI 0.32–0.85; $P = 0.009$). This finding suggests that the reduction in integral dose allowed by PT translates into a clinically meaningful difference in second cancer reduction.

The present study is subject to the weaknesses of any observational study. Treatment techniques, including chemotherapy regimen, PT technique, and motion management strategies were not standardized across the cohort; nevertheless, such heterogeneity

can also be considered a strength as it makes the study more pragmatic and demonstrates the feasibility of delivering PT safely and effectively across different institutions, including community and academic hospitals. A strength of the present collaboration was our ability to extract additional relevant data, such as post-chemotherapy PET/CT response, bulky disease, and patterns of relapse, with respect to radiation treatment field, which cannot be done with other larger cancer registries (SEER, NCDB).

In conclusion, PT is predominantly used in patients with HL that are at greatest risk of developing late toxicity, including young patients, female patients, and those with mediastinal involvement. Early results with PT demonstrate excellent relapse-free survival with a favorable acute toxicity profile including very low rates of pneumonitis. These results are encouraging and support continued treatment of patients with HL with PT in a registry setting, which permits long-term follow-up and potential confirmation of decreased late toxicity.

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Disclosure

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