Advances in Radiation Oncology (2023) 8, 101090

advances in radiation oncology

www.advancesradonc.org

Scientific Article

Proton Radiation Therapy After Chemotherapy in the Management of Aggressive Mediastinal Non-Hodgkin Lymphomas: A Particle Therapy Cooperative Group Lymphoma Subcommittee Collaboration

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Received 15 April 2022; accepted 19 September 2022

Abstract

Purpose: Combined modality therapy with multiagent chemotherapy and radiation therapy is a standard treatment option for aggressive mediastinal non-Hodgkin lymphomas (AMNHLs); however, concerns regarding acute and late radiation toxicities have fueled an effort to use systemic therapy alone. The use of proton therapy (PT) is a promising treatment option, but there are still limited data regarding clinical outcomes with this treatment modality. In this Particle Therapy Cooperative Group lymphoma subcommittee collaboration, we report outcomes of patients with AMNHL treated with pencil-beam scanning PT or double-scatter PT after chemotherapy.

Methods and Materials: This was a multi-institutional retrospective observational cohort study of patients with AMNHL treated with PT following chemotherapy between 2011 and 2021. Progression-free survival (PFS), local recurrence−free survival (LRFS), and overall survival (OS) rates were estimated with the Kaplan-Meier method. PT toxicity was graded by the Common Terminology Criteria for Adverse Events version 5.0. A 2-tailed paired *t* test was used for dosimetric comparisons.

Results: Twenty-nine patients were identified. With a median follow-up time of 4.2 years (range, 0.2-8.9 years), the estimated 5-year PFS for all patients was 93%, 5-year LRFS was 96%, and estimated 5-year OS was 87%. Maximum acute grade 1 (G1) toxicities occurred in 18 patients, and 7 patients had maximum G2 toxicities. No G3+ radiation-related toxicities were observed. Average mean lung dose and lung V20 Gy were lower for patients treated with pencil-beam scanning PT compared with double-scatter PT ($P = .016$ and .006, respectively), while patients with lower mediastinal disease had higher doses for all evaluated dosimetric heart parameters.

Sources of support: This work had no specific funding.

Disclosures: 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.

Research data are stored in an institutional repository and may be shared upon reasonable request to the corresponding author.

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https://doi.org/10.1016/j.adro.2022.101090

Conclusions: PT after chemotherapy for patients with AMNHL resulted in excellent outcomes with respect to 5-year PFS, LRFS, and OS without high-grade toxicities. Future work with larger sample sizes is warranted to further elucidate the role of PT in the treatment of AMNHL.

Introduction

Aggressive mediastinal non-Hodgkin lymphomas (AMNHLs), including primary mediastinal large B-cell lymphomas and mediastinal diffuse large B-cell lymphomas (DLBCL), encompass a group of highly curable tumors associated with favorable long-term outcomes.[1,2] Standard treatment options for AMNHLs have historically included multiagent chemotherapy such as R-CHOP (rituximab, cyclophosphamide, vincristine, prednisone) followed by radiation therapy (RT).[3-8] However, concerns over acute and late radiation toxicities have fueled an effort to treat with more intensive systemic therapy regimens alone such as dose-adjusted etoposide, doxorubicin, and cyclophosphamide with vincristine, prednisone, and rituximab.[9-11] At the same time, novel RT techniques have also allowed for possible reductions in acute and long-term toxicities.[12,13] Thus, different treatment options are currently available for AMNHLs, but there is still no consensus on the optimal treatment approach and whether RT can be safely omitted in this population.

Proton therapy (PT) is a promising treatment option for AMNHLs after systemic therapy. Given the intrinsic dosimetric differences between photon- and proton-based approaches, PT can be designed to deliver radiation to high-risk areas with reduced entrance doses and no measurable exit doses, thus reducing the risk of damage to organs at risk (OARs).[14,15] With better sparing of OARs, such as the heart and lungs, the risk of both short- and long-term complications are theoretically decreased. Dosimetric studies comparing PT to conventional 3-dimensional conformal PT in patients with mediastinal Hodgkin lymphomas have overwhelmingly demonstrated significantly reduced radiation doses to critical OARs.[12,15-17] Currently, there are limited data regarding the use of PT after chemotherapy in the treatment of AMNHLs. Similarly, there are few data comparing the 2 different possible PT treatment approaches for AMNHLs—double-scattered PT (DSPT) or pencil-beam scanning PT (PBSPT). In this Particle Therapy Cooperative Group lymphoma subcommittee collaborative report, we describe outcomes, toxicities, and dosimetric comparisons for patients with AMNHLs treated with either DSPT or PBSPT after chemotherapy.

Methods and Materials

Patients

A retrospective observational cohort study was performed that included patients with AMNHL (either primary mediastinal large B-cell lymphomas or mediastinal DLBCL) treated between 2011 and 2021 at the University of Pennsylvania and at the University of Florida. Patients were enrolled on either tracking protocols or registry studies that were approved by institutional review boards at each institution. Electronic medical records were reviewed for patients who received PT after first-line chemotherapy for AMNHL. The following baseline patient and disease characteristics were recorded for each patient: age at diagnosis, sex, stage, tumor grade, extranodal involvement, presence of B-symptoms, presence of bulky disease (defined as ≥7.5 cm), presence of gene rearrangements of MYC and BCL-2/6 (ie, double-hit), maximum diameter of disease, disease status (no evidence of disease vs recurred), date of last follow-up, and survival status. The following treatment characteristics were recorded for each patient: chemotherapy regimen, chemotherapy duration, PT technique, PT total dose, PT fractions, PT duration, motion management (deep inspiration breath-hold [DIBH] vs use of a 4-dimensional computed tomography [4DCT] scan and an internal target volume [ITV]), and acute radiation toxicities. Dosimetric values included were mean lung dose (MLD), lung V5 Gy (%), lung V20 Gy (%), mean heart dose (MHD), heart V5 Gy (%), heart V20 Gy (%), left and right mean breast dose, and left and right V4 Gy (%).

Upper mediastinum was defined as disease extending above the inferior aspect of the left pulmonary artery, middle mediastinal as disease extending below the inferior aspect of the left pulmonary artery to inferior aspect of aortic valve, and lower mediastinum as disease extending below the level of the aortic valve as previously described.[18] The use of PBSPT or DSPT was determined at the discretion of the treating physician and was affected by the available resources at the time of treatment. Response to treatment was graded as complete response (CR), partial response (PR), stable disease, or progressive disease (PD) as defined by Deauville score[19] or Response Evaluation Criteria in Solid Tumors (RECIST).[20]

Statistical analysis

Follow-up time was defined as time from start of PT to event or last follow-up. Local recurrence was defined as recurrence within the radiated field. Disease progression included both in-field and out-of-field progression. Progression-free survival (PFS), local recurrence–free survival (LRFS) and overall survival (OS) rates were

estimated with the Kaplan-Meier method from start of PT to event or last follow-up. PT toxicity was graded by Common Terminology Criteria for Adverse Events version 5.0, with acute toxicity defined as onset of symptoms during or within 3 months of completing PT. A 2-tailed, paired *t* test was used to compare dosimetric outcomes. A $P < .05$ was considered statistically significant. All statistical analyses were conducted using Stata 16.1 (StataCorp, College Station, TX).

Results

A total of 29 patients met the inclusion criteria; baseline patient and treatment characteristics are listed in Table 1. A slight majority of patients treated were male (52%), with a median age at diagnosis of 36.1 years (range, 21.9-74.0 years). Fifteen patients had mediastinal DLBCL, while 14 patients had PMBCL. The majority of patients had earlier-stage disease, with stage distribution including 11 stage I (38%), 13 stage II (45%), 3 stage III (10%), and 2 stage IV (7%). Nearly all had bulky disease at presentation. All patients received first-line chemotherapy before PT with either R-CHOP (23 patients) or BV-R-CHP (brentuximab vedotin, rituximab, cyclophosphamide, doxorubicin, prednisone) (6 patients) as part of a research protocol.[21] With regards to PT treatment details, median PT dose was 30.6 Gy (range, 30-39.6 Gy). DSPT was used in 18 patients while PBSPT was used in 11 patients. DIBH was used in 11 of 29 patients, with the remainder undergoing 4DCT for motion management. The majority of patients had involvement of the upper (29/29, 100%) and middle (28/29, 97%) mediastinum. In contrast, the lower mediastinum was only involved in approximately half of the patients (15/29, 52%).

With a median follow-up time of 4.2 years (range, 0.2-8.9 years), the estimated 5-year PFS for all patients was 93%, estimated 5-year LRFS was 96%, and the estimated 5-year OS was 87% (Fig. 1). Following chemotherapy and before PT, 25 patients (86%) had a metabolic CR (11 patients Deauville 1, 10 Deauville 2, and 4 Deauville 3); all of the patients with Deauville 1 to 3 response after chemotherapy also had a CR after PT and never relapsed. One patient had a PR (Deauville 4) following chemotherapy and achieved a CR after PT. Another patient had PD (Deauville 5) after chemotherapy, but then had a CR after PT. In total, 27 patients had a metabolic CR after PT, and none of these patients experienced a relapse or died.

Overall, 2 patients had disease progression after PT. Of these 2 patients, 1 had stage III PMBCL with a PR (Deauville 4) after 6 cycles of BV-R-CHP. This patient was then treated with DSPT to a total dose of 39.6 Gy in 22 fractions but had an in-field failure within the irradiated anterior mediastinal mass 4 months after finishing PT. He was treated with salvage CD19-targeting chimeric antigen receptor T-cell therapy and pembrolizumab but unfortunately died of disease progression 3 years after finishing PT. The other patient had stage IV mediastinal DLBCL with PD (Deauville 5) after 6 cycles of R-CHOP. This patient was then treated with DSPT to a total dose of 30.6 Gy in 17 fractions but had an out-of-field failure in

Table 1 Baseline patient and treatment characteristics

Characteristics	Patients
Age at diagnosis (y), median (range)	36.1 (21.9-74.8)
Follow-up (mo), median (range)	49.8 (2.3-107.2)
Sex	
Male	15 (52%)
Female	14 (48%)
Diagnosis	
PMBCL	14 (48%)
Mediastinal DLBCL	15 (52%)
Stage	
I	11 (38%)
II	13 (45%)
III	3 (10%)
IV	2 (7%)
B symptoms	13 (45%)
Bulky disease (>7.5 cm)	27 (93%)
Extranodal involvement	8 (28%)
Double hit	2 (7%)
Mediastinal involvement	
Upper	29 (100%)
Middle	28 (97%)
Lower	15 (52%)
Chemotherapy	
R-CHOP	23 (79%)
R-CHOP cycles, median (range)	6 (4-6)
R-CHP-BV	6 (21%)
R-CHP-BV cycles, median	6*
Radiation therapy	
Dose (Gy), median (range)	30.6 (30-39.6)
PBSPT	11 (38%)
DSPT	18 (62%)
DIBH	11 (38%)

Abbreviations: DIBH = deep inspiration breath-hold; DLBCL = diffuse large B-cell lymphomas; DSPT = double-scattered proton therapy; PBSPT = pencil-beam scanning proton therapy; PMBCL = primary mediastinal large B-cell lymphomas; R-CHOP = rituximab, cyclophosphamide, vincristine, prednisone; R-CHP-BV = rituximab, cyclophosphamide, doxorubicin, prednisone, brentuximab vedotin.
Data are presented as n (%) unless otherwise indicated.
* All patients received 6 cycles of R-CHP-BV.

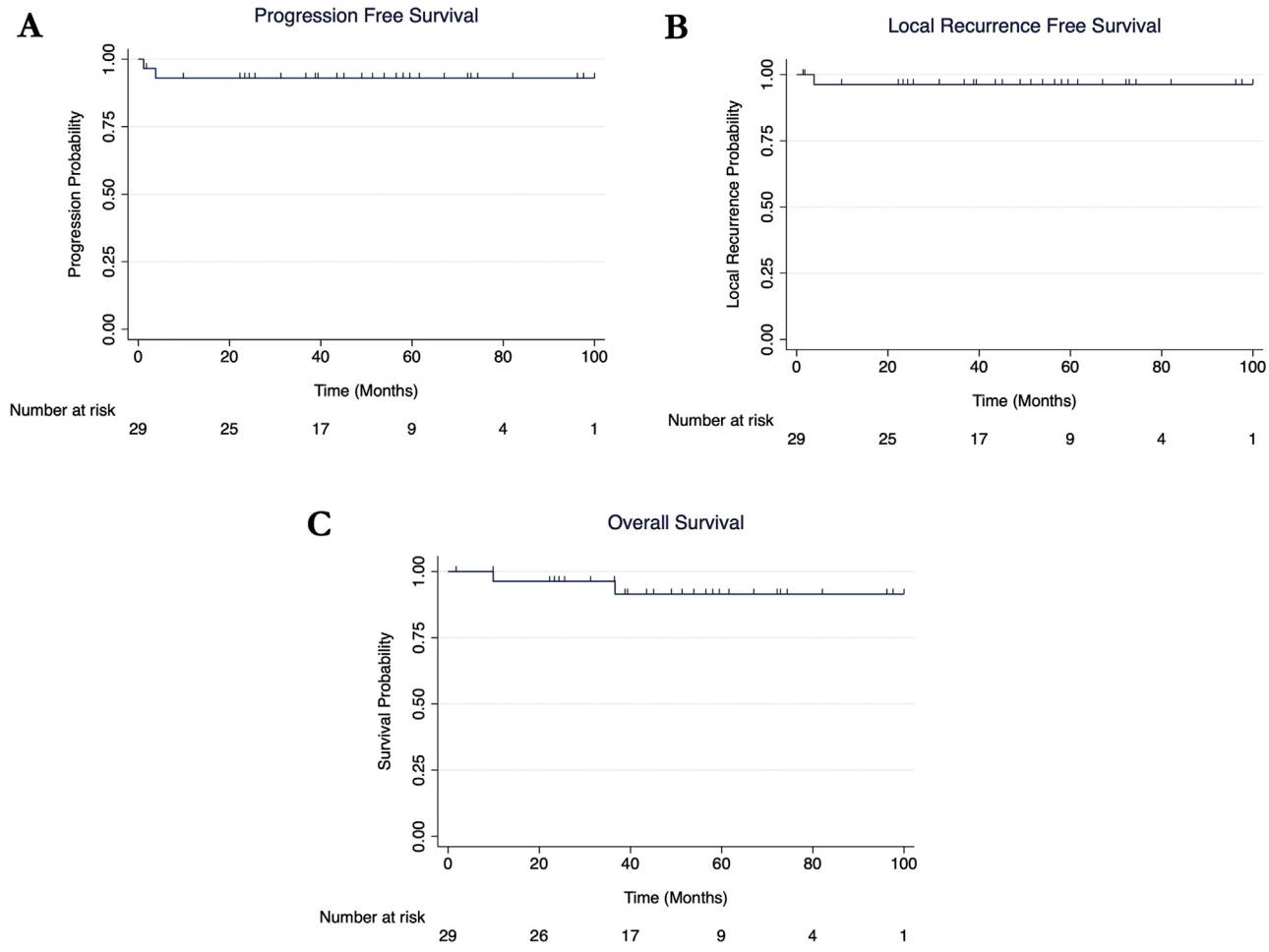

Figure 1 Progression-free survival (A), local recurrence–free survival (B), and overall survival (C) for patients with aggressive mediastinal non-Hodgkin lymphoma treated with proton therapy after chemotherapy.

the hilum and infradiaphragmatic region 1 month after finishing PT; he died of disease progression 11 months after finishing PT.

Maximum acute grade 1 (G1) toxicities occurred in 18 patients, while 7 patients had maximum G2 toxicities. The most common reported G1 acute toxicity, radiation dermatitis, was reported by 18 patients (10 patients treated with DSPT and 8 with PBSPT), and the most common reported G2 toxicity, esophagitis, was reported by 3 patients (Table 2). No G3+ radiation-related toxicities were observed. Of note, no G2+ radiation pneumonitis was present in the cohort. All cumulative acute PT toxicities are listed in Table 2.

Dosimetric values for all patients included in the cohort are listed in Table 3. Average MLD and lung V20 Gy were lower for patients treated with PBSPT compared with DSPT (Table 4, Fig. 2A). Patients with lower mediastinal disease involvement had higher doses for all dosimetric heart parameters compared with patients with upper and middle mediastinal disease involvement (Table 4, Fig. 2B). There were nonstatistically significant reductions in all examined dosimetric parameters in

Table 2 Cumulative acute toxicities reported after proton therapy

Acute toxicity	Patients, n (%)
Grade 1	
Radiation dermatitis	18 (62%)
Fatigue	14 (48%)
Esophagitis	10 (34%)
Dyspepsia	5 (17%)
Hoarseness	5 (17%)
Cough	5 (17%)
Radiation pneumonitis	1 (3%)
Grade 2	
Esophagitis	3 (10%)
Dermatitis	2 (7%)
Anorexia	1 (3%)
Hoarseness	1 (3%)

Other grade 1 toxicities included 4 patients with anorexia, 3 with dyspnea, 3 with constipation, and 2 with diarrhea.

Table 3 Dosimetric values for all patients

Dosimetric parameter	Dosimetric value, median (range)
MLD (Gy)	6.3 (2.4-16.8)
Lung V5 Gy (%)	28 (12-50)
Lung V20 Gy (%)	14 (4-39)
MHD (Gy)	9.9 (0.01-16.9)
Heart V5 Gy (%)	40 (0-62)
Heart V20 Gy (%)	27 (0-52)
Left MBD (Gy)*	1.8 (0.5-4.1)
Left breast V4 Gy (%)*	8.8 (2.4-17.4)
Right MBD (Gy)*	1.0 (0.2-3.5)
Right breast V4 Gy (%)*	4.9 (1.4-15.6)

Abbreviations: MBD = mean breast dose; MHD = mean heart dose; MLD = mean lung dose.
* Data from the 12 female patients with breast dosimetric data available.

patients treated with DIBH compared with those treated in free breathing (4DCT with an ITV expansion). Interestingly, lung parameters were affected more than the heart with DIBH, with associated *P* values trending toward significance (Table 4).

Discussion

In this Particle Therapy Cooperative Group lymphoma subcommittee collaborative retrospective study, we describe the outcomes of 29 patients with AMNHL treated with PT after receiving chemotherapy with either R-CHOP or BV-R-CHP. PT resulted in excellent outcomes with respect to 5-year PFS (93%), 5-year LRFS (96%), and 5-year OS (87%). Only 2 patients in the cohort had disease progression which both occurred <6 months after finishing PT. The remaining patients showed durable responses with no relapses with a median follow-up of 4.2 years. Importantly, PT was well tolerated with no acute high-grade (≥G3) toxicities reported. The absence of significant radiation pneumonitis in our study is consistent with prior studies which have reported favorable rates of pneumonitis in patients with mediastinal lymphomas treated with PT.[13,22]

Table 4 Dosimetric comparisons

Average dosimetric parameters	PBSPT	DSPT	*P* value
MLD (Gy)	4.7 ± 1.8	7.7 ± 3.5	.016*
Lung V5 Gy (%)	23.6 ± 9.1	31.9 ± 12.3	.063
Lung V20 Gy (%)	10.5 ± 4.7	19.5 ± 9.1	.006*
MHD (Gy)	10.1 ± 4.7	9.9 ± 5.4	.915
Heart V5 Gy (%)	39.9 ± 16.5	33.9 ± 18.2	.377
Heart V20 Gy (%)	28.2 ± 14.2	25.5 ± 15.5	.646
	Lower mediastinum involvement	**No lower mediastinum involvement**	
MLD (Gy)	6.9 ± 3.7	5.7 ± 1.9	.385
Lung V5 Gy (%)	30.1 ± 13.3	25.8 ± 6.9	.366
Lung V20 Gy (%)	16.8 ± 9.9	14.7 ± 5.7	.565
MHD (Gy)	12.2 ± 3.9	4.8 ± 3.3	.001*
Heart V5 Gy (%)	42.8 ± 14.7	21.3 ± 14.1	.001*
Heart V20 Gy (%)	32.5 ± 12.5	13.3 ± 10.7	.001*
	DIBH	**4DCT**	
MLD (Gy)	5.2 ± 1.8	7.4 ± 3.7	.086
Lung V5 Gy (%)	24.2 ± 7.8	31.6 ± 13.0	.099
Lung V20 Gy (%)	12.3 ± 4.6	18.4 ± 10.0	.066
MHD (Gy)	9.2 ± 5.1	10.4 ± 5.1	.544
Heart V5 Gy (%)	34.4 ± 16.2	37.2 ± 18.6	.687
Heart V20 Gy (%)	24.8 ± 14.5	27.6 ± 15.3	.629

Abbreviations: 4DCT = 4-dimensional computed tomography; DIBH = deep inspiration breath-hold; DSPT = double-scattered proton therapy; MHD = mean heart dose; MLD = mean lung dose; PBSPT = pencil-beam scanning proton therapy.
Values are reported as averages with corresponding standard deviations.
* $P < .05$.

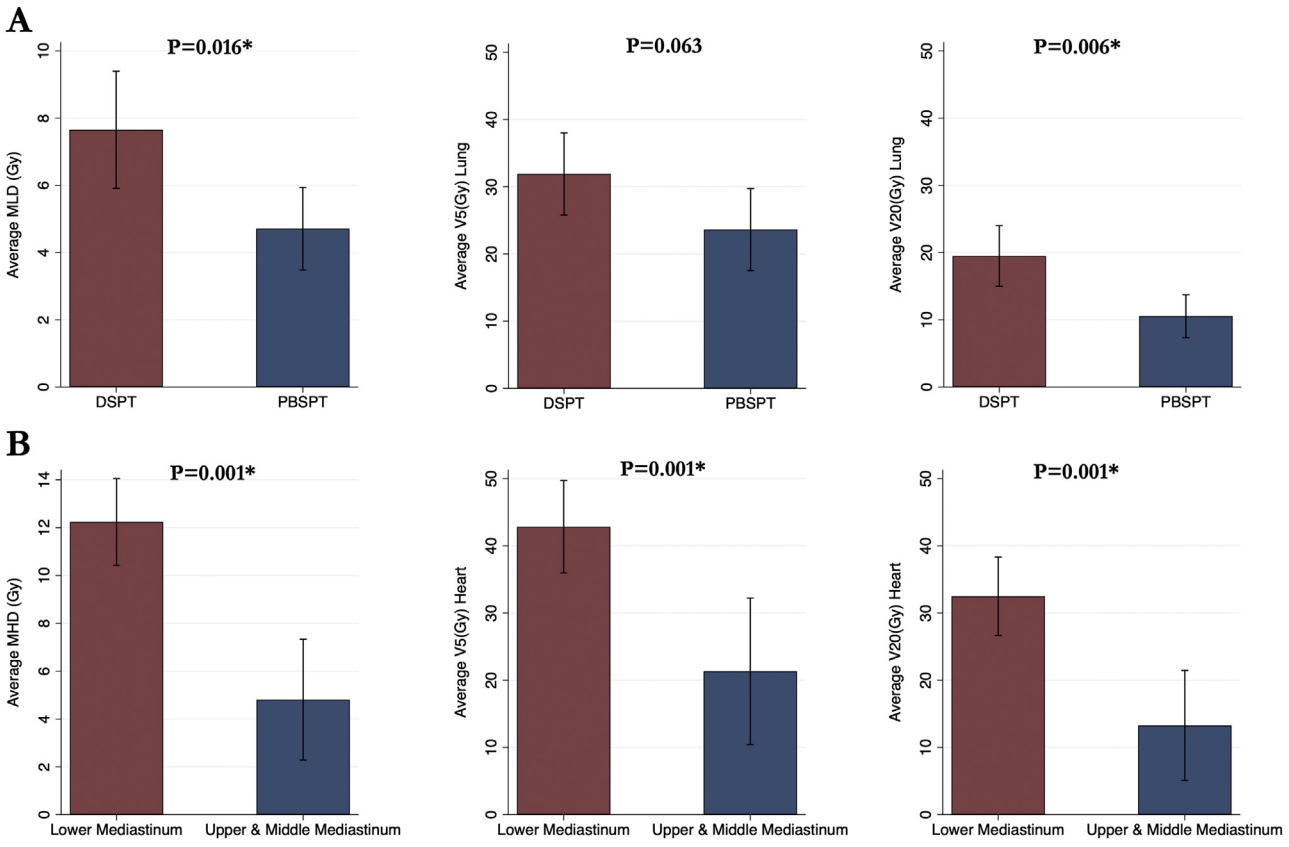

Figure 2 Dosimetric comparisons for patients with aggressive mediastinal non-Hodgkin lymphoma treated with double-scattered proton therapy (DSPT) compared with pencil-beam scanning proton therapy (PBSPT) (A) and patients with lower mediastinal disease involvement compared with upper and middle disease involvement (B). Values are shown as averages with error bars displaying the corresponding 95% confidence intervals. *$P < .05$. *Abbreviations:* MHD = mean heart dose; MLD = mean lung dose.

Although PT for Hodgkin lymphoma is becoming increasingly accepted,[16,23] only a few studies have described the use of PT for patients with AMNHL. Tseng et al described the use of PT in patients with relapsed/refractory mediastinal lymphoma, some of whom had AMNHL,[13] but only a handful of studies have described the use of PT following chemotherapy in this population. König et al evaluated the use of PBSPT following chemotherapy in 20 patients with mediastinal lymphomas (11 patients with AMNHL and 9 patients with Hodgkin lymphoma).[24] Although outcomes were not separately reported for the patients with AMNHL, they reported overall favorable 2-year local and distant PFS (95.5% and 95%, respectively), no high-grade toxicities, and dosimetric advantages with the use of PT across their entire cohort.[24] Similarly, Sachsman et al reported early favorable outcomes with no relapses and no high-grade toxicities in 3 patients with AMNHL treated with PT after chemotherapy.[25] Our findings are essentially consistent with these studies; however, to our knowledge, this study includes the largest number of patients with AMNHL treated with PT following chemotherapy (29 patients). The multi-institutional experiences over a decade reflects the evolution of PT, including the shift from DSPT to PBSPT and the addition of DIBH.

Dosimetric improvements with PT have been previously described in patients with mediastinal lymphomas.[23,24,26] In our study, the dosimetric values for the reported median MLD and median mean breast dose (both left and right) were consistent with ideal doses based on guidelines published by the International Lymphoma Radiation Oncology Group.[27] On the other hand, the reported median MHD was greater than the ideal MHD dose listed by the guidelines. This could be explained by the fact that about a half of our patients (52%) had lower mediastinal disease involvement, which we found to be associated with higher radiation doses to the heart (Table 4 and Fig. 2A, 2B). In fact, the average MHD (4.8 Gy) for patients without lower mediastinal disease involvement was consistent with the ideal MHD recommendation from the International Lymphoma Radiation Oncology Group (<5 Gy).

Compared with DSPT, we found that PBSPT yielded lower radiation doses to the lung (MLD and V20 Gy). As opposed to DSPT, PBSPT has the ability to conform to a target 3-dimensionally and can achieve both proximal

and distal dose conformality.[28,29] A representative proton radiation plan of a patient treated with PBSPT is shown in Fig. E1. Compared with DSPT, PBSPT has the potential to lead to better sparing of OARs,[30] which is consistent with our findings in reductions of lung dosages. Although skin toxicity rates were not clearly different in our study, PBSPT also has a potential for less radiation dermatitis due to its proximal conformality. Availability and techniques for motion management have previously limited the use of PBSPT in the thorax, but advancements in this technique and rigorous quality assurance as previously described[31] could allow for its increased utilization, especially as more proton centers evolve to PBSPT-only capability.

Another technique investigated in this study was the use of DIBH compared with free breathing (4DCT with an ITV expansion). DIBH is an advanced strategy that can minimize respiratory-induced motion and can theoretically improve pulmonary and cardiac dosimetry.[32,33] DIBH has been shown to improve the sparing of OARs in different types of cancers including thoracic tumors.[34] Even though our comparisons in dosimetric values between patients treated with DIBH versus free breathing did not reach significance, the magnitude of all the average dosimetric parameters for heart and lung were lower for the patients in which the DIBH technique was used. Furthermore, the use of DIBH was associated with an absolute average MLD reduction of 30% and MHD reduction of 11% compared with free breathing, which could lead to a clinically significant benefit, especially in patients with favorable outcomes where long-term complications become more worrisome. Though the literature is still limited with regards to the combination of PT with DIBH in the treatment of AMNHL, previous studies in mediastinal lymphomas have suggested this combination could result in superior lung sparing compared with other combinations such as PT with free breathing or photon-based radiation with DIBH or free breathing.[35,36] Our practice has been to routinely use DIBH with PT, especially when cardiophrenic disease is not a target.[37]

Besides having a small sample size, this study has several additional limitations. First, this was a retrospective study so our analysis regarding outcomes, toxicity, and dosimetric comparisons are essentially descriptive. These patients were highly selected based on referral patterns, available resources, and insurance authorization. Due to our limited sample size, we lacked the statistical power required to perform subgroup analyses by mediastinal location or perform dosimetric comparisons for breast doses. Similarly, due to our limited follow-up time, we were not able to report on longer-term complications such as the development of secondary malignancies or cardiac toxicity, which are some of the main concerns regarding the use of radiation in this population.[12,38] Previous reports have suggested that the use of PT could lead to lower secondary malignancy risk compared with photon-based radiation.[39-41] For example, in a national cohort study, Xiang et al found that the relative risk of secondary cancers was lower for patients treated with PT compared with intensity modulated radiotherapy.[41] However, long-term follow-up of the surviving patients in this and other cohorts will be essential to monitor for the development of late toxicities and secondary malignancies in patients with AMNHL.

Conclusion

Although there has been a recent interest in treating patients with AMNHL with dose-escalated chemotherapies that omit radiation, the optimal treatment strategy is still unknown. Currently, several guidelines continue to support the need for radiation in select patients.[8,42,43] For the patients who require radiation after chemotherapy, the use of PT is a promising approach as it can lead to better OAR sparing and can result in favorable outcomes as seen in this study. Furthermore, optimizing the delivery of radiation by using PBSPT and DIBH could further widen the therapeutic window.[44] Despite the limitations, this study fills a void in the literature. While cure rates of AMNHL may not surpass Hodgkin lymphoma, the excellent clinical outcomes in this and other series highlight the need for the utmost care in radiating patients with AMNHL. Larger sample sizes and longer follow-up times are still needed to determine and characterize the benefits of PT for both Hodgkin lymphoma and AMNHL, but ultimately there is a strong rationale to consider PT for AMNHL.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.adro.2022.101090.

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