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Irradiating Residual Disease to 30 Gy with Proton Therapy in Pediatric Mediastinal Hodgkin Lymphoma

Bradford S. Hoppe, MD, MPH[1]; Raymond B. Mailhot Vega MD, MPH[2]; Nancy P. Mendenhall, MD[2]; Eric S. Sandler, MD[3]; William B. Slayton, MD[4]; Howard Katzenstein, MD[3]; Michael J. Joyce, MD[3]; Zuofeng Li, DSc[2]; and Stella Flampouri, PhD[5]

[1]Department of Radiation Oncology, Mayo Clinic, Jacksonville, FL, USA
[2]Department of Radiation Oncology, University of Florida, Jacksonville, FL, USA
[3]Division of Pediatric Hematology and Oncology, Department of Pediatrics, Nemours Children's Specialty Care, Jacksonville, FL, USA
[4]Department of Pediatric Hematology/Oncology, University of Florida, Gainesville, FL, USA
[5]Department of Radiation Oncology, Emory University, Atlanta, GA, USA

Abstract

Background: Local relapse is a predominant form of recurrence among pediatric patients with Hodgkin lymphoma (PHL). Although PHL radiotherapy doses have been approximately 20 Gy, adults with Hodgkin lymphoma receiving 30 to 36 Gy experience fewer in-field relapses. We investigated the dosimetric effect of such a dose escalation to the organs at risk (OARs).

Materials and Methods: Ten patients with PHL treated with proton therapy to 21 Gy involved-site radiation therapy ($ISRT_{21Gy}$) were replanned to deliver 30 Gy by treating the ISRT to 30 Gy ($ISRT_{30Gy}$), delivering 21 Gy to the ISRT plus a 9-Gy boost to postchemotherapy residual volume ($rISRT_{boost}$), and delivering 30 Gy to the residual ISRT target only ($rISRT_{30Gy}$). Radiation doses to the OARs were compared.

Results: The $ISRT_{30Gy}$ escalated the dose to the target by 42% but also to the OARs. The $rISRT_{boost}$ escalated the residual target dose by 42%, and the OAR dose by only 17% to 26%. The $rISRT_{30Gy}$ escalated the residual target dose by 42% but reduced the OAR dose by 25% to 46%.

Conclusion: Boosting the postchemotherapy residual target dose to 30Gy can allow for dose escalation with a slight OAR dose increase. Treating the residual disease for the full 30Gy, however, would reduce the OAR dose significantly compared with $ISRT_{21Gy}$. Studies should evaluate these strategies to improve outcomes and minimize the late effects.

Keywords: Hodgkin lymphoma; dose escalation; pediatric lymphoma; organs at risk

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Corresponding Author:
Bradford S. Hoppe, MD, MPH
Mayo Clinic Radiation Oncology
4500 San Pablo Rd S
Jacksonville, FL 32224, USA
Phone: +1 (904) 953-2000
hoppe.bradford@mayo.edu

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Introduction

In the 1970s, the first protocols of chemotherapy with consolidative low-dose involved-field radiotherapy in pediatric Hodgkin lymphoma (PHL) were developed to reduce the potential long-term complications of full-dose, definitive radiotherapy, especially as it affected bone growth [1]. During the past half century, PHL protocols have encouraged enrollment of older patients; use of newer systemic therapy combinations—including targeted agents and immunotherapy—and use of smaller radiotherapy fields, such as

involved-site radiotherapy (ISRT); or no radiotherapy. When radiotherapy has been used, the standard dose has remained between 21 and 25.5 Gy [2, 3].

Response-adaptive trials in PHL have identified rapidly responding patients for whom radiotherapy may not provide a meaningful benefit when weighed against its potential late effects [2, 3]. However, those trials also identify patients who do not respond well to chemotherapy and may benefit from more-aggressive systemic therapies and higher radiotherapy doses. Studying the pattern of relapse can be helpful in determining whether relapse rates can be improved with additional radiation (which manages local relapses) or systemic therapy (which manages distant relapses). In the largest intermediate-risk PHL study conducted, Children's Oncology Group study AHOD0031), the 4-year, event-free survival was 85% and, among the relapses, 88% occurred in field after 21 Gy [4]. Importantly, despite similar rates of overall relapse, the in-field relapse rate was twice as high as that seen in adult patients with intermediate-risk Hodgkin lymphoma (HL) who received 30 to 36 Gy and relapsed out of field [5].

Because of concerns about the late effects from radiotherapy, oncologists hesitate to increase the radiotherapy dose in any protocol. However, if a higher radiation dose could be delivered without an increase to the dose to the organs at risk (OARs), oncologists might consider allowing higher doses. Recent studies have demonstrated excellent outcomes with smaller involved-node radiotherapy and ISRT fields [6]. Therefore, the next logical step is to evaluate even smaller radiation therapy (RT) treatment fields, such as the postchemotherapy anatomic disease volume [7].

The present study evaluated the potential implication to the OARs of escalating the postchemotherapy radiation dose in PHL patients to 30 Gy compared with 21 Gy, either by increasing the prescription dose or through a boost field to the gross residual disease.

Materials and Methods

After institutional review board approval and with informed consent, 10 PHL patients with mediastinal involvement enrolled in an institutional prospective study and treated with consolidative ISRT were selected for this planning study.

All patients had ISRT field volumes developed following International Lymphoma Radiation Oncology Group guidelines and were planned to receive 21 Gy at 1.5 Gy/fraction [6]. The ISRT target volumes included residual anatomic disease seen at the time of computed tomography (CT) simulation of $>$1 cm gross tumor volume ($GTV_{residual}$) in dimension. The ISRT clinical target volume (CTV_{ISRT}) included the $GTV_{residual}$ and locations of previously involved lymph nodes seen during staging positron emission tomography (PET)/CT scan with a margin to account for differences in positioning between the fusion of the PET/CT staging scan and the CT simulation. An ISRT internal target volume (ITV_{ISRT}) was developed from the 4-dimensional CT simulation and a planning target volume $(PTV)_{ISRT}$ margin of 7 mm added to the ITV. For the purposes of the study, the $GTV_{residual}$ was expanded per the internal $GTV_{residual}$. The $ITV_{residual}$ was the internal $GTV_{residual}$ without further expansion; the $PTV_{residual}$ included a 5-mm margin for the residual ISRT (rISRT) (**Figure 1A** and **1B**).

Three additional RT treatment plans were retrospectively developed for each patient. Plan 1 treated the ISRT to 21 Gy ($ISRT_{21Gy}$). Plan 2 treated the ISRT to 30 Gy ($ISRT_{30Gy}$). Plan 3 treated the ISRT to 21 Gy with a 9-Gy boost delivered to the rISRT ($rISRT_{boost}$). Finally, Plan 4 treated the rISRT only to 30 Gy ($rISRT_{30Gy}$).

Radiation treatment plans were developed with passive-scatter proton therapy techniques designed using Eclipse software (Eclipse Foundation, Ottawa, ON Canada), as previously described [8]. In short, the 3-dimensional conformal proton plans were designed to treat $ISRT_{21Gy}$ and $rISRT_{boost}$ with a robustness of 2.5% range uncertainties and setup errors of 5 mm. For the cases resulting in a range margin smaller than the PTV margin, no effort was made to cover the PTV along individual beams. Laterally, custom-made collimators shaped the individual proton beams to the PTV with a margin for the penumbra. Range compensators were smeared to allow target coverage under tissue and density variations on the proton beam paths. All plans were designed and calculated on the average 4-dimensional CT image. Depending on the size and complexity of the targets, 1 to 3 proton fields were used per plan. The proton beams with the shortest path in healthy tissue were favored. Plan priority was set to the target coverage. The OAR importance was set to the heart, breast (female), and lung. Plan 2 was a scaled-up version of plan 1 from 21 to 30 Gy radiobiological equivalents (GyRBE). Plan 3 included plan 1 as the initial setup and an additional boost plan. Plan 4 was the boost plan scaled up from 9 to 30 GyRBE. All plans were normalized to cover 99% of the ISRT volumes with the prescribed dose and maintain the coverage on inhale and end of exhale during the 4-dimensional phases. Moreover, 95% of the PTV was covered by $\geq$95% of the prescribed dose.

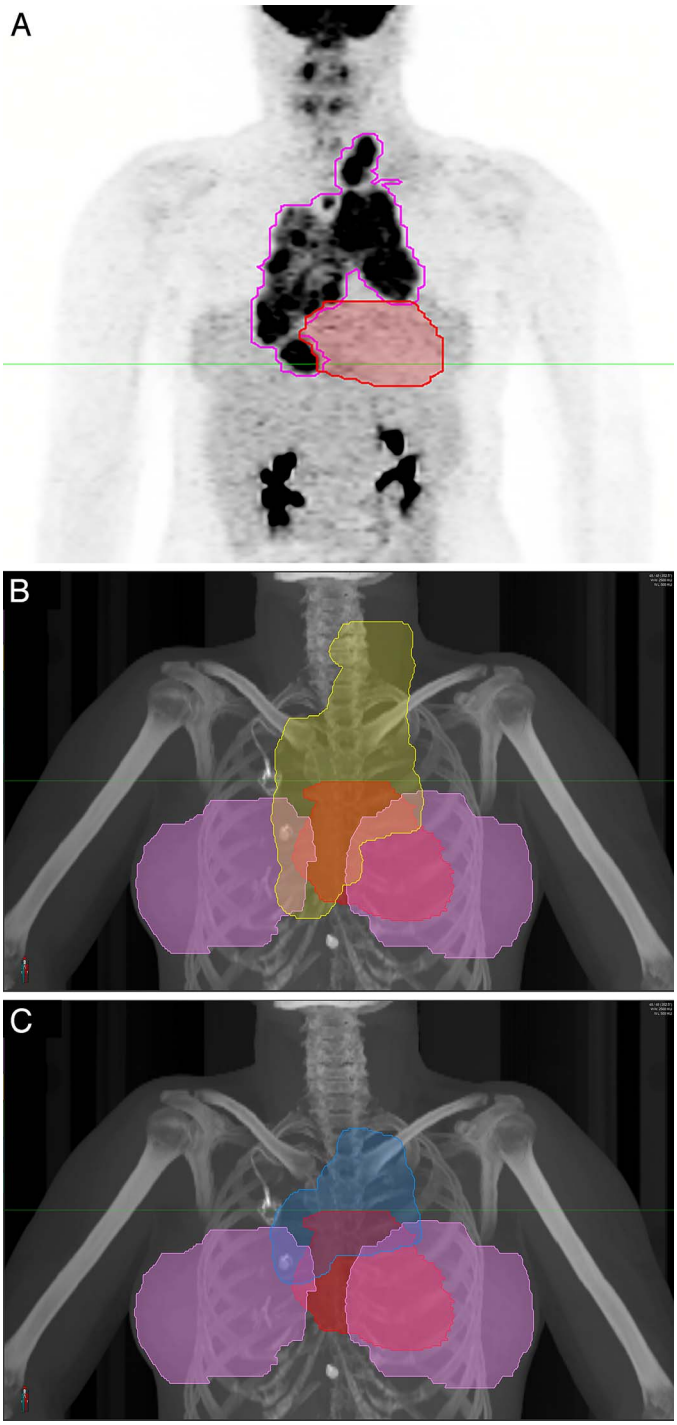

Figure 1. (A) Prechemotherapy positron emission tomography/computed tomography scan of a pediatric patient with Hodgkin lymphoma, outlined in pink, and the heart outlined in red. (B) Digitally reconstructed radiograph of the involved-site radiotherapy target volume (yellow), the breasts (pink), and the heart (red). (C) Digitally reconstructed radiograph of the residual involved-site radiotherapy target volume (blue), the breasts (pink), and the heart (red).

Excel software (Microsoft Corporation, Richmond, WA) was used for basic statistical calculations. Doses to each OAR were recorded, and relative dose differences were calculated between each plan.

Results

We found that treating patients with ISRT to 30 Gy, rather than 21 Gy, increased the relative dose to the target and the thoracic OARs by 42% for $ISRT_{30Gy}$. The mean heart dose was, on average, 8.5 Gy with $ISRT_{21Gy}$ and increased by 3.6 Gy with $ISRT_{30Gy}$. However, the mean heart dose only increased by 15% when the $rISRT_{boost}$ was used, and dropped by 46% for the

Table. Mean dose to organs at risk (OARs) by plan and relative does change to OARs by plan compared with standard 21-Gy involved-site radiation therapy ($ISRT_{21Gy}$).

	$ISRT_{21Gy}$		$ISRT_{30Gy}$		$rISRT_{boost}$		$rISRT_{30Gy}$	
OAR	Mean dose, median (range), Gy	Relative dose change, Gy	Mean dose, median (range), Gy	Relative dose change, Gy	Mean dose, median (range), Gy	Relative dose change, Gy	Mean dose, median (range), Gy	Relative dose change, Gy
Heart	8.5 (4.4-13.2)	1.00	12.1 (6.3-18.9)	0.43	9.8 (4.9-15.2)	0.17	4.6 (0.4-11.2)	−0.42
LAD	14.9 (0.3-23)	1.00	21.25 (0.4-33)	0.43	16.9 (0.3-30.9)	0.17	3.15 (0-28.9)	−0.46
Lungs	6.75 (4.5-8.2)	1.00	9.65 (6.4-11.8)	0.43	8.15 (5.4-10.6)	0.26	4.8 (2.5-7.4)	−0.25
Breast	4.4 (1.3-10.2)	1.00	6.3 (1.9-14.6)	0.43	5.5 (1.6-13.4)	0.25	3 (0.9-9.1)	−0.30
Body[a]	55.0 (43.5-98)	1.00	78.7 (61.2-139.7)	0.43	68.9 (51.7-125.2)	0.23	40.4 (18.7-95.2)	−0.29

[a]Joules.

Abbreviations: $ISRT_{21Gy}$, ISRT to a total radiotherapy dose of 21 Gy; $ISRT_{30Gy}$, ISRT to 30 Gy; rISRT, residual-disease ISRT; LAD, left anterior descending artery.

$rISRT_{30Gy}$ plan. The corresponding doses to the various thoracic OARs among the 4 different treatment plans are shown in the **Table**.

Discussion

Consolidative radiotherapy has been shown to improve overall survival over chemotherapy alone for patients with pediatric Hodgkin lymphoma [18]. Although higher doses of RT have been avoided in PHL to limit late effects, the greatest concern is OAR dose. Mean heart and lung doses of 10 and 12 Gy [9, 10], respectively, are considered reasonably tolerable, whereas doses of 18 to 20 Gy to the bone can stunt growth [11]. Our results demonstrate that higher RT doses to the target can be delivered while reducing the dose to the OARs with a smaller target volume, as with the $rISRT_{30Gy}$ plan.

Identifying the ideal radiation dose is important to achieving the best chance of local control and relapse-free survival. In the adult population, randomized controlled studies have demonstrated that, although 20 Gy is sufficient for favorable early stage adult HL after 2 cycles of Adriamycin (doxorubicin), bleomycin, vinblastine, and dacarbazine (ABVD), patients with unfavorable early stage adult HL required doses of 30 Gy with 4 cycles of ABVD [12, 13]. Conversely, radiotherapy dose has not, to our knowledge, been studied in the PHL population, leaving us to ponder the results of the Children's Oncology Group study AHOD 0031, wherein after IFRT to 21 Gy, the primary site of relapse (>90%) occurred within the radiotherapy site [4]. These findings left the authors to suggest that 21 Gy may be insufficient for controlling disease and that higher doses (ie, 30 Gy in adults), may be necessary to control poorly responding disease. The present study describes ways of safely escalating this radiation dose.

We expect patients to relapse within the postchemotherapy volume. Limited data, however, are available to support that theory. Postchemotherapy residual disease volumes have been treated in other protocols (NCT01868451, NCT01920932), including the GHSG H15 study [14], which reported excellent outcomes in adults. Field reductions or boost fields have been used in numerous protocols during the past 30 years, but only a randomized phase 3 study can answer whether these target volumes provide similar levels of control to more standard ISRT volumes. Unfortunately, such a study is not feasible in this rare disease for which the focus is on exploring targeted therapies and immunotherapies. For RT to remain relevant in future PHL studies, a smaller RT volume must be adopted and evaluated just as ISRT/involved-node radiotherapy was adopted 10 years ago alongside new RT technologies, such as intensity-modulated radiation therapy, proton therapy, and the breath-hold technique [15–18]. Understanding relapse patterns within these new field designs will help us understand whether target volumes have become too small and whether the doses we use are appropriate. We may find that treating even smaller fields is feasible [19].

Although the present study cannot define which patients benefit most from RT, the appropriate RT field size, or the appropriate total dose in the treatment of adult PHL, it does report 2 important findings: first, an additional 9-Gy boost to residual postchemotherapy disease can be added to a standard 21-Gy ISRT plan with minimal increase in the radiation dose to the OARs; second, by treating only the postchemotherapy volume to 30 Gy, we can reduce the dose to the OARs in a clinically meaningful way compared with 21 Gy of ISRT.

ADDITIONAL INFORMATION AND DECLARATIONS

Conflicts of Interest: Bradford S. Hoppe, MD, MPH, and Nancy P. Mendenhall, MD, are Associate Editor and Editor-in-Chief of the *International Journal of Particle Therapy*, respectively. In addition, Dr Hoppe is a scientific consultant for Merck & Co, Inc, and Bristol-Myers Squibb. Raymond B. Mailhot Vega, MD, MPH, has received a travel grant from IBA.
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