Curative Treatment of Pediatric Hodgkin Lymphoma With Doxorubicin, Bleomycin, Vinblastine, and Dacarbazine and Consolidation Radiotherapy: A Systematic Review and Suggested Recommendations

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ABSTRACT

PURPOSE Doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) chemotherapy is used commonly for pediatric Hodgkin lymphoma (pHL) in low- and middle-income countries. The role of radiotherapy (RT) after ABVD in pHL is uncertain.

MATERIALS AND METHODS We conducted a systematic review to explore the use of ABVD with or without RT in pHL. Key clinical questions included the number of cycles of ABVD, indications for and dose of RT, and outcomes by risk group. A search was performed in PubMed. Articles reporting survival outcomes by risk group were included.

RESULTS Of 97 articles identified in the literature search, nine met inclusion criteria. Chemotherapy consisted of four to six cycles in limited disease and mostly six cycles in advanced disease. Three studies used RT for all patients within a specified risk group. Six studies dictated an adapted RT approach, with 3%-43% of the patients receiving RT for bulky adenopathy, slow early response (SER), and/or incomplete response. Radiation doses ranged between 20 and 36 Gy. The progression-free survival and overall survival at 4-10 years ranged from 84% to 100% and 93%-100% in limited disease and 50%-84.4% and 75%-95.3% in advanced disease, respectively. Studies did not directly assess the impact of certain chemotherapy or RT strategies. Recommendations were made after reviewing outcomes with particular approaches.

CONCLUSION Four cycles of ABVD are recommended for limited disease, and six cycles of ABVD are recommended for advanced disease. In both limited and advanced diseases, RT is recommended with a dose of 20-21 Gy only to sites of bulky and/or SER, with a boost of up to 36 Gy to sites of incomplete response. This approach could spare radiation for at least half of the patients with limited disease and one third of advanced disease.

ACCOMPANYING CONTENT

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INTRODUCTION

Hodgkin lymphoma (HL) represents the most common cancer in adolescents and is associated with cure rates above 90%.[1] Pediatric oncology cooperative groups have focused on optimizing patient treatment to maintain high levels of cure while minimizing the risk of late effects[2] (Data Supplement, Figs S1-S3).

Many centers outside Europe and North America use doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) because of drug availability, outpatient administration, and minimal acute toxicities. However, there are established risks of late pulmonary and cardiovascular toxicities.

The National Comprehensive Cancer Center (NCCN) has launched guidelines regarding therapy for pediatric HL (pHL). Version 2.2023 specifies radiotherapy (RT) indications according to protocol-specific chemotherapy (Children's Oncology Group [COG] trials, HRHL13, or EuroNet-PHL-C1). ABVD is listed as an alternative regimen given its long-standing history although childhood cancer cooperative groups in the United States and Europe have not published results for ABVD use for pHL, the era of risk-based approaches. NCCN advises to refer to adult HL guidelines

CONTEXT

Key Objective

What is the role of radiotherapy (RT) after doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) chemotherapy in pediatric Hodgkin lymphoma (pHL) in low- and middle-income countries (LMICs)?

Knowledge Generated

Recommendations were generated by an Expert Panel answering specific questions regarding the number of chemotherapy cycles, RT indications, and appropriate doses. The heterogeneity of studies was highlighted. Radiation was recommended to slow early responding sites and bulk.

Relevance

In the absence of prospective randomized data evaluating outcomes of pHL treated with ABVD, we offer these recommendations, most applicable in LMICs with differential access to imaging modalities and limited access to novel and/or salvage therapies. There is still an urgent need for more prospective trials, hopefully collaborations across LMICs, that help to illustrate the precise indications of RT and optimal radiation doses and techniques.

when using ABVD chemotherapy, where there are specific RT indications according to clinical stage, early response, and preference of treatment modality (chemotherapy alone or combined modality with radiation).[3,4] This recommendation follows results of phase three randomized trials (Table 1); however; these adult trials only included adolescent patients age between 15 and 18 years. Furthermore, the radiation dose recommended in adult HL after complete response (CR) is 20-36 Gy,[4] with 36 Gy being notably higher compared with doses from pediatric cooperative group studies.

Given the prevalence of ABVD usage in low- and middle-income countries (LMICs), with differential access to imaging modalities and RT, and the lack of trials that investigated the role of RT after this chemotherapy in pHL, we sought to evaluate the literature to describe outcomes and provide recommendations.

MATERIALS AND METHODS

A search was performed in the PubMed database on the utilization of ABVD in pHL, from its inception to August 2022, following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines.[5] Search items were (ABVD) AND (Hodgkin lymphoma) AND (Radiation OR Radiotherapy) AND (childhood OR pediatric). Titles and abstracts were independently screened by two reviewers. Only English articles of pediatric patients with HL treated with ABVD with or without RT as first-line management were included. Publications that did not report progression-free survival (PFS) (event-free survival [EFS], failure from treatment-free survival, or other similar outcomes) by risk group or by stage group were excluded. Full-text article review, selection, and risk of bias assessment were performed by a third reviewer. Data from selected articles were collected and arranged by study design, patient age range, number of patients, risk or stage group, number of ABVD cycles, response assessment with computed tomography (CT) and/or positron emission tomography (PET), RT strategy, and survival outcomes. RT volumes, doses, and techniques were detailed when specified. Extracted data validation and recommendations were conducted by all the authors.

While COG and Euronet use three risk groups (low, intermediate, and high), the authors chose to dichotomize groups as most included articles categorized patients as limited or advanced disease. Low- and intermediate-risk (IR) diseases in studies describing three risk groups were analyzed within the limited disease group. Each study had their own criteria for risk stratification. Two sets of bias assessments were conducted, using methodologies used by the Pediatric Normal Tissue Effects in Clinic Consortium and the International Guideline Harmonization Group.[6,7] Using the results of the systematic review, we sought to evaluate five specific questions:

1. Outcomes of four versus six cycles of ABVD for limited disease
2. Indications for RT in limited disease
3. Outcomes of four versus six versus eight cycles of ABVD for advanced disease
4. Indications for RT in advanced disease
5. The appropriate dose for RT

Recommendation strength was provided by consensus review of the authors, with quality of recommendation framed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria.[8]

RESULTS

The search identified 97 studies. After review, 12 met inclusion criteria, and three were excluded because they did not detail survival outcomes with respect to any risk group

TABLE 1. Randomized Phase Three Trials That Evaluated the RT Impact in Adult Patients With HL Treated With ABVD

Trial	Patients' Age, Years	Clinical Stages	Initial Therapy	Randomized RT Arms	5-Year PFS, %	5-Year OS, %
GHSG HD10[30]	16-75	I-II favorable	ABVD X4	IFRT 30 Gy	93.9	96.9
			ABVD X4	IFRT 20 Gy	93.2	97.3
			ABVD X2	IFRT 30 Gy	90.8	90.8
			ABVD X2	IFRT 20 Gy	91.6	91.6
GHSG HD11[31]	16-75	I-II unfavorable	ABVD X4	IFRT 30 Gy	94.3	87.2
			ABVD X4	IFRT 20 Gy	93.8[a]	82.1
			BEACOPP X4	IFRT 30 Gy	94.6	87.9
			BEACOPP X4	IFRT 20 Gy	95.1	87
RAPID[32]	16-75	IA and IIA nonbulky	ABVD X3 → PET−	IFRT 30 Gy	94.6[b]	97.1[b]
				No RT	90.8[a,b]	99[b]
EORTC/LYSA/FIL H10[33]	15-70	I-II favorable	ABVD X2 → PET−	ABVD X1 + INRT	99	100
				ABVD X2 → no RT	87.1[a]	99.6
		I-II unfavorable	ABVD X2 → PET−	ABVD X2 + INRT	92.1	96.7
				ABVD X4 → no RT	89.6[a]	98.3
GHSG HD16[34]	18-75	I-II favorable	ABVD X2 → PET−	IFRT 20 Gy	93.4	98.1
				No RT	86.1[a]	98.4
GITIL/FIL HD0607[35]	18-60	IIB-IV bulky	ABVD X2 → PET− → ABVD X4 → PET−	IFRT 30.6 Gy to bulky	92[c]	99[c]
				No RT	90[c]	98[c]
FIL HD0801[36]	18-70	IIB-IV bulky	ABVD X2 → PET− → ABVD X4 → PET−	RT 30 Gy to bulky	83.5[d]	
				No RT	85.2[d]	

NOTE. All arms within a trial had statistically equivalent outcomes except that noninferiority could not be demonstrated.
Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; HL, Hodgkin lymphoma; IFRT, involved-field RT; INRT, involved-node RT; OS, overall survival; PET−, negative positron emission tomography; PFS, progression-free survival; RT, radiation therapy; X, cycle.
[a]Noninferiority could not be demonstrated.
[b]3-year PFS and OS.
[c]6-year PFS and OS.
[d]2-year PFS and OS.

(Fig 1). Bias assessments were conducted with the nine included studies demonstrating low risk of bias (Data Supplement, Tables S1 and S2).[9-20]

Limited Disease Pediatric Hodgkin Lymphoma

Seven studies were analyzed for this group (Table 2).[9-14,20] The majority of the patient population included those with stage I and IIA disease,[9-12,20] but IIB and IIIA were included in two studies, and IVA in one study as part of the IR category.[13,14] Zubizarreta et al[13] excluded stage I and II diseases with bulky mediastinum from their limited disease classification.

In all studies, chemotherapy consisted of between four and six cycles of ABVD. Response assessment was heterogeneous in terms of timing and method across studies and also within each of some of the studies: for example, CT, PET, or PET-CT was used in three studies.[11,12,20]

Regarding RT utilization in the publications evaluating limited disease, two studies recommended its use for all patients.[9,10] Five studies adapted indications according to bulky adenopathy or response to chemotherapy: two if bulky or slow early response (SER) were determined by CT, PET, or PET-CT after two to three cycles,[11,20] one if there was residual disease at the end of chemotherapy (CT with or without gallium scan),[13] one if SER (PET-CT) or residual disease,[14] and one if residual disease (CT or PET) in children younger than 16 or 18 years and also if SER (CT or PET) in adolescents and young adults age between 16 and 25 years.[12] In these five studies in which an adapted radiation approach was pursued, ultimately 2.7%-38.8% underwent irradiation.[11-14,20]

Five studies specified that involved-field RT (IFRT) was used,[10-14] whereas two did not specify the radiation volume technique.[9,20] Only one of the five studies with an adapted radiation approach specified that RT volume included only bulky and SER sites.[20] RT doses ranged between 20 and 36 Gy, with high doses recommended as boost for residual disease at competition of chemotherapy. The reported long-term PFS ranged from 84% to 100% with the overall survival (OS) between 93% and 100%, estimated at 4-10 years across studies.

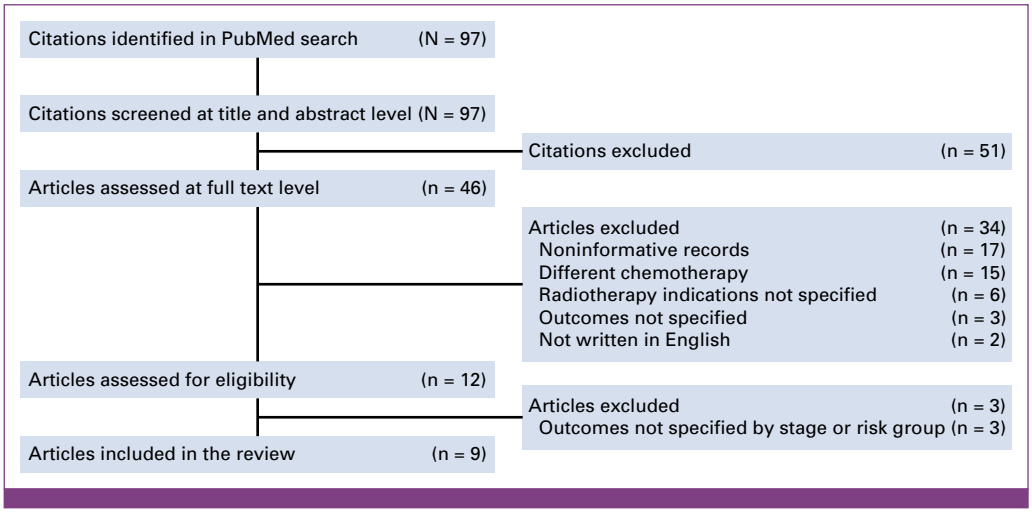

FIG 1. PRIMSA flow diagram with the results of systematic review.

Advanced Disease Pediatric Hodgkin Lymphoma

Seven studies were analyzed in this group (Table 3).[10-15,19] The patient populations included were heterogeneous: two studies included stage IIB-IV disease,[15,19] another two, stage III-IV disease,[10,11] and one only stage IIIB and IVB[14] disease; two studies included stage I-II disease with bulk in this high-risk (HR) or advanced category.[12,13]

Chemotherapy consisted of six cycles of ABVD for all identified except in the study by Sherief et al,[10] in which patients with stage IIIA2 (infradiaphragmatic disease beyond retroperitoneal and splenic nodes) and IV disease received eight cycles and no radiation. Response assessment was heterogeneous in terms of timing and method.

RT approaches were different among almost all the studies. Sherief et al[10] reported IFRT only for stage IIIA1 disease after six cycles of ABVD, but as mentioned above, not for patients with stage IIIA2-IV disease. Zubizarreta et al[13] indicated consolidation IFRT in all patients with advanced disease. Five studies used an adapted RT strategy: one only if bulky,[15] two only if bulky or SER (CT, PET, or PET-CT),[11,19] one only if SER (PET-CT) or residual,[14] and one only if residual (CT or PET).[12] Between 18% and 43.4% of patients received RT in the five studies where an adapted approach was followed.[11,12,14,15,19] Six studies reported usage of IFRT.[10-15] Three of the five studies using adapted RT provided clear specifications: irradiated volumes were limited to bulky sites,[15] bulky and SER sites,[19] or residual disease.[12] Conversely, radiation volume included all initial involved sites in the study by Zubizarreta et al[13] and in patients with stage IIIA1 disease from the study by Sherief et al.[10] Radiation doses ranged between 20 and 25 Gy for consolidation and up to 36 Gy for residual disease.

Regarding 5- and 10-year PFS, outcomes were considerably wide-ranging, from 50% to 84.4%, whereas the 5- and 10-year OS ranged between 75% and 95.3%.

DISCUSSION

This systematic review aimed to evaluate reported outcomes of ABVD and consolidation RT in pHL. The RT role in pHL has been investigated after other chemotherapy regimens and, as mentioned before, in adult HL after ABVD.

According to COG and EuroNet-PHL-C1 protocols, RT may be restricted to cases of bulky, SER, or residual in conjunction with multidrug intensive chemotherapy for the intermediate-risk and HR groups (Data Supplement, Figs S1-S3).[1,21-28] Moreover, although RT had traditionally been delivered to all sites of initial involvement, RT limited to the initial bulky, SER, or residual sites (assessed by PET) is recommended in HR pHL by COG Trials[24,27] and just to sites of inadequate early response by the Pediatric Hodgkin Consortium.[29]

As opposed to pediatric trials, RT after ABVD in the adult population has been thoroughly investigated as a primary study end point in prospective randomized trials (Table 1).[30-36]

In children and adolescents, some prospective randomized trials have investigated the role of RT based on risk group and response, with varying results, but none within the context of an ABVD regimen (Table 4).[23,37-39] Although results from adult trials with ABVD could be extrapolated to the pediatric population, some studies have reported different behavior and response to therapies between pediatric and adult patients with HL, particularly regarding the effectiveness of RT.[40,41] A randomized trial from Tata Memorial Hospital assessed the need of consolidative RT in patients with stage I-IV disease achieving clinicoradiologic CR after six cycles of ABVD; they found better 8-year PFS and OS with RT, particularly in patients younger than 15 years, where the PFS was 97% and 53%, $P = .02$, respectively, with and

TABLE 2. Studies of LR and IR or Limited pHL Treated With ABVD With or Without RT

Study	Type	Patient(s) Age, Years	Clinical Stage	No. of Patient(s)	Chemotherapy	Response Assessment	RT Strategy	Irradiated Patient(s), %	5-Year PFS, %	5-Year OS, %
Oberlin 1992 FSPO[9]	Randomized multicentric	≤18	IA and IIA	132	ABVD X4	CT	RT 20 Gy, 40 Gy if <PR	All	90[a]	
					ABVD/MOPP X4				87[a]	
Sherief 2015 Egypt[10]	Retrospective two centers	≤18	I-II	28	ABVD X4-6	NS	IFRT 21 Gy, 35 Gy boost to residual	All	100	100
Jain 2016 New Delhi[11]	Retrospective single center	≤18	I-II	114	ABVD X4-6	CT or PET	IFRT 20-36 Gy only if bulky or SER	32.4	93.9	97.2
Marr 2017 British Columbia[12]	Retrospective population registry	<25	I-IIA nonbulky	78	ABVD X4-6	CT or PET	IFRT 35 Gy only if SER or residual in AYA	24	90	100
							IFRT 21 Gy only if residual in pediatric		93	100
Zubizarreta 2017 Buenos Aires[13]	Prospective single center	<17	LR: I-IIA without bulky mediastinum nor any risk factor[b]	49	ABVD X4	CT with or without gallium scan	IFRT 21 Gy only if residual, 35 Gy boost to residual	22.4	88[c]	100[c]
			IR: I-IIA without bulky mediastinum but at least one risk factor; IIB and III without bulky mediastinum	49	ABVD X6				84[c]	93[c]
Ingley 2000 British Columbia[14]	Retrospective single center	≤18	LR: IA and IIA nonbulky	5	ABVD X4	PET-CT	IFRT only if SER or residual	2.7	100	100
			IR: IA and IIA bulky; IB, IIB, IIIA, and IVA	32	ABVD X4-6				94	100
Mahajan 2021 InPOG-HL-15-01[20]	Prospective multicentric	≤18	I-IIA	134	ABVD X4	CT or PET-CT	RT 21 Gy only if bulk or SER	38.7 (48% eligible per protocol)	95.5	97.7

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; ABVD/MOPP, ABVD, mechlorethamine, vincristine, procarbazine, and prednisone; AYA, adolescents and young adults; CT, computed tomography; FSPO, French Society of Pediatric Oncology; IFRT, involved-field RT; InPOG, Indian Pediatric Oncology Group; IR, intermediate risk; LR, low risk; NS, not specified; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival; pHL, pediatric Hodgkin lymphoma; RT, radiation therapy; SER, slow early response; X, cycle.

[a]4-year PFS.

[b]Risk factor: hilar adenopathy, ≥4 nodal sites, or nonmediastinal bulky.

[c]10-year PFS and OS.

TABLE 3. Studies of HR or Advanced pHL Treated With ABVD With or Without RT

Study	Type	Patient(s) Age, Years	Clinical Stage	No. of Patient(s)	Chemotherapy	Response Assessment	RT Strategy	Irradiated Patient(s), %	5-Year PFS, %	5-Year OS, %
Sherief 2015 Egypt[10]	Retrospective two centers	≤18	III-IV	33	IIIA1 ABVD X6, IIIA2-IV ABVD X8	NS	IIIA1 IFRT 21 Gy, 35 Gy boost to residual, IIIA2-IV no RT	IIIA1 all; IIA2-IV none	72.7	93.9
Jain 2016 New Delhi[11]	Retrospective single center	≤18	III-IV	53	ABVD X6	CT or PET	IFRT 20-36 Gy only if bulky or SER	26.4	63.7	94.3
Bhethanabhotla 2017 New Delhi[15]	Retrospective multicentric	≤18	IIB-IV	186	ABVD X6	CT or PET-CT	IFRT 25 Gy only if bulky	40.3	84.4	95.3
Marr 2017 British Columbia[12]	Retrospective population registry	<25	I-IIA bulky; IIB-IV	131	ABVD X6	CT or PET	IFRT 21-35 Gy only to residual	18	80	95
Zubizarreta 2017 Buenos Aires[13]	Prospective single center	<17	HR: I-III with bulky mediastinum, IV	67	ABVD X6	CT with or without gallium scan	IFRT 21 Gy, 35 Gy boost to residual	All	82[a]	85[a]
Ingley 2020 British Columbia[14]	Retrospective single center	≤18	HR: IIIB and IVB	8	ABVD X6	PET-CT	IFRT only if SER or residual	37.5	50	75
Jain 2022 InPOG-HL-15-01[19]	Prospective multicentric	≤18	IIB-IV	262	ABVD X6	CT or PET-CT	RT 21 Gy only if bulky or SER	42.4 (63.7% eligible per protocol)	81.8	90.8

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; CT, computed tomography; HR, high risk; IFRT, involved-field RT; InPOG, Indian Pediatric Oncology Group; NS, not specified; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival; pHL, pediatric Hodgkin lymphoma; PR, partial response; RT, radiation therapy; SER, slow early response.

[a]10-year PFS and OS.

without radiation, in comparison with outcomes in patients 15 years and older, where the PFS was 85% and 83%, $P = .18$; this trial did not specify outcomes by risk groups or stage groups for patients younger than 15 years and was not included in the primary review.[42] Synthesis of RT efficacy nor meta-analysis was conducted as all trials were observational with RT indications protocolled. Similarly, there was heterogeneity for the classification of risk group, precluding meta-analysis to provide estimates for the benefit of RT.

To our knowledge, this is the first systematic review assessing RT utilization in pHL after ABVD chemotherapy. Key recommendations are summarized in Table 5. Based on the observational nature of all studies included, the quality of the studies and the strength of the recommendations are low using GRADE criteria.[8]

Most patients with limited disease were treated with a range of four to six cycles of ABVD.[9-14,20] Strategies implementing adaptive RT with four cycles yielded PFS estimates >90%. Based on the added toxicity of extra systemic therapy, we recommend four cycles of ABVD for limited-stage disease.

Of the seven included studies, two described radiation given to all patients; the other five studies limited radiation to cases of bulky, SER, and/or residual. The only study with a PFS of < 90% (at 10 years) was published by Zubizarreta et al,[13] where only patients with residual disease determined by CT with or without gallium scan received RT.

With these data, we recommend an adaptive radiation strategy in patients with limited disease who receive four cycles of ABVD, limiting RT to cases of bulky disease, SER (CT or PET-CT), and/or residual disease. With this approach, more than half of the patients could spare radiation.[11-14,20] A larger proportion of patients may avoid RT if PET-CT is used for assessment, as observed in some studies,[11,20] because a lower proportion of SERs can be expected using response criteria by PET than with CT.

None of the studies included in the advanced risk group analysis used four cycles. In fact, six cycles + RT/adapted RT were used in all but one study.[10-15,19] Based on the cumulative anthracycline dose of 350 mg/m^2 and suboptimal PFS reported for eight cycles, our recommendation is for six cycles of ABVD.

In the study by Sherief et al,[10] patients with stage IIIA2-IV pHL were treated with eight cycles of ABVD without radiation and the 5-year PFS was 72.7%. In the study by Zubizarreta et al,[13] a prospective single-center study, all patients with HR pHL received IFRT, with a 10-year PFS of 82%; however, this high-risk category included stage I-II disease with bulky mediastinum. The other five studies used an adaptive RT approach: Bhethanabhotla et al[15] reported a 5-year PFS of 84.4% with radiation only if bulky in stage IIB-IV disease; however, a subanalysis revealed that patients with adverse characteristics like stage IV, lymphopenia, leukocytosis, and B symptoms had a worse prognosis of 75% PFS with two of these characteristics and 14% with three or four. The study by Ingley et al[14] included only stage IIIB and IVB disease for their high-risk category classification, prescribing IFRT only if SER (PET-CT) or residual, with a 5-year PFS of 50%. Marr et al[12] reported a 5-year PFS of 80%, with radiation only to residual disease (CT or PET), but this study included stage I-IIA disease bulky in the definition of advanced disease; in fact, a subanalysis of outcomes in the high-risk category according to the COG definition (IIIB and IVB) revealed a PFS of 69%.

Up to this point, it seems that advanced pHL treated with six cycles of ABVD and RT adapted only to bulky or SER sites (but not both) is associated with a HR of progression, when considering the reported 3- and 5-year EFS ranging from 79.1% to 97.4% for patients with HR pHL treated within the AHOD0831, AHOD1331, HLHRL13, and EuroNet-PHL-C1 trials.[21,24,27,29]

Two studies described an adaptive RT approach to both bulky and SER sites (CT, PET, or PET-CT), both by Jain et al[11]: the first one is a retrospective report of 53 patients with stage III-IV pHL with a 5-year PFS of 63.7%; the second, a multicentric prospective trial, Indian Pediatric Oncology Group (InPOG)-15-01, described 262 patients with stage IIB-IV pHL and a 5-year PFS of 81.8%. In InPOG-15-01, 63.7% of the patients had an indication of RT according to the protocol, but only 42.4% received it. Notably, those who had an indication but did not receive RT had a significantly higher number of events compared with those who did receive it, 46.4% versus 9%, $P < .001$; radiation was the only factor associated with improved PFS on multivariable analysis.[19]

Based on these data, we recommend an adaptive RT strategy to bulky, SER (CT or PET-CT), and/or residual disease after six cycles of ABVD for advanced-risk disease. This strategy results in acceptable disease control with sparing up-front radiation in at least one third of the patients.[11,19]

Using PET-CT instead of just CT for early response assessment (ERA) would increase the proportion of patients that spare radiation as a reduced number of SER cases would be expected.[19] For instance, in the retrospective study by Jain et al, only 11.9% of the patients with PET at ERA received radiation in comparison with 36.8% of the patients without it. Similarly, in the InPOG-15-01 trial, the rate of satisfactory response at ERA was higher when estimated with PET than with CT, 87.9% versus 77.7% in early stages and 77.5% versus 59.8% for advanced stages ($P < .003$).[11,19,20]

Moreover, it remains to be investigated whether PET-CT utilization for interim assessment could also allow radiation sparing in pediatric patients treated with six cycles of ABVD with bulky disease and rapid early response (RER). Avoiding

TABLE 4. Prospective Randomized Trials That Evaluated the RT Impact in pHL

Trial	Patient(s) Age, Years	Clinical Stages	Initial Therapy	Response Assessment	Randomized RT Arms	5-Year PFS, %	5-Year OS, %
POG 8725[37]	<21	IIB, IIIA2, IIIB, and IV	MOPP-ABVD X8 → CR	PE, radiograph, CT, gallium scan, and/or biopsy	TNI or sub-TNI 21 Gy	80	87
					No RT	90	96
CCG 5942[38]	<21	CG1: I and IIA without any risk factor (hilar adenopathy, ≥4 nodal sites, bulky)	COPP/ABV X4 → CR	CT and gallium scan	IFRT 21 Gy	100[a,b]	
					No RT	89.1[b]	
		CG2: I and IIA with at least one risk factor, IIB and III	COPP/ABV X6 → CR		IFRT 21 Gy	84[b]	
					No RT	78[b]	
		CG3: IV	AraCVP16-COPP/ABV-CHOP X6 → CR		IFRT 21 Gy	88.5[b]	
					No RT	79.9[b]	
AHOD 0031[23]	<22	IR: IA bulky, IIA bulky, IB, IAE, IIB, IIAE, IIIA, and IVA	ABVE-PC X2 → RER → ABVE-PC X2 → CR	CT + gallium scan or PET	IFRT 21 Gy	87.9[c]	98.8[c]
					No RT	84.3[c]	98.8[c]

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; ABVE-PC, doxorubicin, bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide; AraCVP16-COPP-CHOP, cytarabine, etoposide, cyclophosphamide, vincristine, procarbazine, prednisone, doxorubicin, bleomycin, and vinblastine; CG, clinical group; COPP/ABV, cyclophosphamide, vincristine, procarbazine, prednisone, doxorubicin, bleomycin, and vinblastine; CR, complete response; CT, computed tomography; IFRT, involved-field RT; IR, intermediate risk; MOPP-ABVD, mechlorethamine, vincristine, procarbazine, and prednisone, ABVD; OS, overall survival; PE, physical examination; PET, positron emission tomography; PFS, progression-free survival; pHL, pediatric Hodgkin lymphoma; RER, rapid early response; RT, radiation therapy; TNI, total nodal irradiation.

[a]Statistically significant reduction in relapse.

[b]10-year PFS and OS.

[c]4-year PFS and OS.

TABLE 5. Summary of Key Recommendations

Question	Recommendation	Supporting Level of Evidence/Strength of Recommendation
Outcomes of 4 *v* 6 cycles for limited disease	Four cycles of ABVD are recommended	Low
Indications for radiotherapy for limited disease	Adapted radiation is recommended, limiting radiotherapy to cases of bulky, SER, and/or residual disease[a]	Low
Outcomes of 4 *v* 6 *v* 8 cycles for advance disease	Six cycles of ABVD are recommended	Low
Indications for radiotherapy for advanced disease	Adapted radiation is recommended, limiting radiotherapy to cases of bulky, SER, and/or residual disease[a]	Low
The appropriate dose for radiotherapy	A dose of 20-21 Gy can be used with a boost to 36 Gy to residual disease, at 1.5-2 Gy per daily fraction, both for limited and advanced diseases	Low

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; CT, computed tomography; PET, positron emission tomography; SER, slow early response.

[a]Imaging modalities for response assessment and response criteria should be explored in prospective studies. In settings with limited access to PET, response assessment with CT only will result in a lower percentage of patients sparing radiotherapy.

RT in this context could have a critical impact on late cardiopulmonary toxicity for patients with initial mediastinal bulky disease who receive higher cumulative doses of doxorubicin and bleomycin[43]; such a strategy would also follow the same criteria for radiation dictated in EuroNet-PHL-C1 and HRHL13 trials.[21,28,29]

Radiation doses across studies ranged mostly between 20 and 36 Gy, five of the nine studies indicated the upper end of this range only for residual disease, but none of the studies specified on local control according to dose, so the dose-outcome association was not explored.[6-10] In accordance with the majority of studies reviewed, a dose of 20-21 Gy is recommended, with a boost to 36 Gy to residual disease, at 1.5-2 Gy per daily fraction, both for limited and advanced diseases.[10,11,13,19,20]

Regarding the RT technique and volumes, most of the studies reported on using IFRT; however, we recommend replacing it by involved-site RT as it will allow for reduction of irradiated tissue.[1,19,20,44]

There are several limitations in this review. There is a possibility of missing articles despite the strategic search as the search was limited to articles on PubMed owing to the location and access of the authors; relevant additional articles might have been included if search was extended to other databases, if search terms were used in more ways, or if non-English articles were considered. There is a risk of publication bias. Only one of the studies included was randomly assigned, and five were retrospective. Comparisons between included studies are hindered since study populations were heterogeneous in terms of included population, criteria for stage groups and risk classification, and modalities and criteria for response assessment; these heterogeneities were considered main obstacles for a meta-analysis. In addition, as mentioned above, many RT technical aspects were not detailed.

The presented recommendations represent authors' points of view after reviewing the studies, favoring less intense therapies in terms of number of chemotherapy cycles and RT indications/doses, that yielded acceptable PFS. PFS, instead of OS, was considered for recommendation formulation because access to salvage therapies like autologous stem-cell transplant for relapse/refractory HL can be considerably limited in LMICs.[45]

A comparison with prospective randomized trials of adapted RT in adults with HL treated with ABVD could not be done because these trials only randomly assigned patients with RER, or bulky and RER, to receive either no further treatment or radiation.[32-36] Articles of adapted RT included in this review reported outcomes of all patients within a stage or risk group without specifying outcomes for the patients who were spared radiation because of a RER. Three articles do include outcomes of patients comparing EFS between those who did and did not receive RT (Data Supplement, Table S3). An important limitation with respect to both the reviewed articles and access is the availability of CT and PET-CT. Particularly for settings using ABVD with only CT for diagnostic, interim, and end of therapy imaging, understanding how best to de-escalate RT while maintaining excellent outcomes requires an understanding of the efficacy of CT (rather than PET-CT as used in contemporary adult trials) for relapse prediction and patient selection. As noted above, RT rates would be higher for locales with access only to CT.

In the absence of prospective randomized data evaluating outcomes of pediatric patients with HL receiving ABVD, we offer these recommendations, most applicable in LMICs with differential access to imaging modalities and limited access to novel therapies. There is an urgent need for more prospective trials, hopefully collaborations across LMICs, that help to illustrate precise indications of RT for patients with pHL treated with ABVD and optimal radiation doses and techniques.

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