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Role of Interim PET Scan after 2 Cycles of ABVD in Pediatric Hodgkin Lymphoma: Retrospective Multicenter Study from South India

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Abstract

Introduction Most Indian centers use Adriamycin/Bleomycin/Vinblastine/Dacarbazine (ABVD) chemotherapy for pediatric Hodgkin lymphoma (pHL). To reduce the late toxicity, robust predictive markers are needed to risk stratify pHL patients, thereby limiting the number of chemotherapy cycles and omitting radiation for low-risk and intensifying treatment for high-risk children.

Objective This study was conducted to analyze the outcome of pHL patients treated with ABVD and various factors predicting the outcome.

Materials and Methods This retrospective study analyzed the outcome of 113 consecutive pHL children treated with ABVD chemotherapy from 11 tertiary care centers in South India from 2009 to 2019.

Results The median duration of follow-up was 2.73 years. The median age was 13 years. B symptoms are seen in 50.5% patients, bulky disease in 23%, and stage IV in 28.3%. Of 113 pHL, 69% had a positron emission tomography (PET) and 31% had computed tomography (CT)-based staging. Stage IV (37.1%) and extranodal involvement (31.2%) were seen more often with PET than with CT staging (8.5 and 2.8%, respectively). Among 64 patients with interim PET scan after two cycles (iPET2), 20.3% did not achieve complete remission (CR) and no factors were significantly associated. The 4-year event-free survival (EFS) rate of the entire cohort was 86%. The 4-year EFS

Keywords
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- pediatric Hodgkin lymphoma
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rate was 93% for patients with CR in iPET2 and 52% for patients not achieving CR. The only independent predictor of low EFS was iPET2 response ($p < 0.05$).

Conclusion Our study confirms the prognostic role of PET scan staging and response assessment. Not achieving CR on the iPET2 scan indicates poor prognosis and warrants clinical trial enrollment for a better outcome.

Introduction

The cure rate of pediatric Hodgkin lymphoma (pHL) with combined multiagent-chemotherapy and radiation has steadily improved over the years.[1-12] The primary aim of combined modality treatment in pHL is to strike a balance between cure and late toxicity. Consequently, efforts have focused on risk-based and response-based strategies. The German society of Pediatric Oncology and Hematology-Hodgkin diseases 95 trial showed radiation therapy (RT) could be safely omitted in low-risk pHL.[13] The European pediatric and adolescent HL network evaluated the omission of RT in all patients with adequate positron emission tomography (PET)-based response to two cycles of Oncovin/Etoposide/Prednisone/Adriamycin (OEPA). The interim results of this study suggested the feasibility of eliminating RT in patients with an adequate response. The use of OEPA/COPDAC in pHL patients decreases the total cumulative dose of alkylators and anthracyclines, but the long-term toxicity associated with etoposide, procarbazine, and radiation needs consideration.[14]

In a resource-limited setting, factors like management cost, treatment abandonment, availability of pediatric oncologist, and lack of transplant centers play a key role in the outcome. As the number of relapsed pHL undergoing salvage chemotherapy and the transplant is low, most of the centers in India aim for a high cure rate with low relapses and continue to use Adriamycin/Bleomycin/Vinblastine/Dacarbazine (ABVD) chemotherapy.[15-19] To reduce the late toxicity and limit to the number of chemotherapy cycles, we need to identify robust predictive markers that risk stratifies pHL patients into low-risk and high-risk categories.

Although the International Prognostic Score (IPS) is widely used for prognostication of HL, it includes certain predictors that are not applicable to the pediatric/adolescent population.[20-23] Role of Childhood Hodgkin International Prognostic Score (CHIP) is limited to intermediate-risk pHL patients and there is a paucity of data regarding the prognostic role of CHIP in pHL patients treated with ABVD.[24,25]

The present data on the role of iPET2 scan in pHL patients are conflicting and require further prospective trials.[26-30] In comparison with adult HL patients, the studies on interim PET scan after two cycles (iPET2) response adapted treatment modification in children are sparse.[26,31-34]

This study was conducted to ascertain the outcomes of children with HL treated with ABVD chemotherapy and to analyze various factors predicting the outcome.

Materials and Methods

Study Design

Ours was a retrospective study with secondary data collection.

Patient Eligibility

One hundred and thirteen consecutive HL patients, younger than or equal to 18 years of age, and started on the ABVD chemotherapy regimen were included. Patients who were diagnosed, but refused treatment, were excluded. Patients diagnosed as nodular lymphocytes preponderance HL were excluded.

Study Period and Study Sites

We collected the data of all consecutive, previously untreated pHL patients from February 1, 2009 to January 31, 2019. The study was conducted in 11 private tertiary care centers involving nine cities across three states in South India (Appendix A).

Diagnosis and Management of pHL

All patients required histopathological diagnosis using excisional nodal or core needle or bone marrow biopsy. Morphologic evaluation and classification of the patients were done by the revised World Health Organization (WHO) Classification of Tumours of Hematopoietic and Lymphoid Tissues.[35]

The workup included documentation of presenting complaints including B symptoms (unexplained fevers, more than 10% weight loss and/or drenching night sweats), physical examination, and investigation reports. The stage was assigned based on The Ann Arbor staging system with Cotswolds modifications and decided using clinical examination, computed tomography (CT), and/or PET scan.[36] Early-stage prognostic grouping included stage I_A, II_A, I_X, II_X, and advanced stage included stage I_B, II_B, III, and IV. Early-stage pHL patients were further categorized into favorable and unfavorable based on the presence of one or more risk factors. The risk factors were extranodal disease, bulky mediastinum, erythrocyte sedimentation rate (ESR) more than 50 mm/h, and three or more nodal site involvement.

The chemotherapy regimens used to treat the patients during the study period were ABVD. The risk stratification, number of cycles of chemotherapy, the timing of response assessment, the addition of involved-field radiotherapy (IFRT), and the IFRT dose were individualized based on the

decision of the treating institution multidisciplinary tumor board. Patients with early-stage disease (stages I and II) and advanced-stage disease (stages III and IV) were scheduled for a minimum of four and six cycles of chemotherapy respectively. The response was assessed clinically after each cycle and radiologically after completion of two cycles for early-stage and after two or four cycles of chemotherapy for advanced-stage pHL patients. Few patients had the radiologic assessment of response after completing six cycles. It was the practice during the period of study in some treating centers to restrict to two cycles of chemotherapy along with IFRT for early-stage—favorable pHL patients and to give two additional cycles of chemotherapy after documentation of radiologic complete remission (CR) for a maximum of six cycles for early-stage and eight cycles in advanced-stage pHL patients.

ABVD was delivered as per the original schedule.[37,38] Interim response assessment was done after two cycles for early-stage and two or four cycles for the advanced stage. Radiology reporting of the interim CT scans was based on Lugano recommendation for response assessment and PET images according to the five-point Deauville score.[39,40] Deauville score of one, two, or three were considered as negative/(CR) in interim scans, while a score of one and two was considered negative/CR at end of treatment scans. Repeat imaging (PET or CT) was done after the completion of additional chemotherapy cycles.

Patients who failed to achieve CR after two cycles of ABVD, bulky disease at presentation, early-stage patients, and residual disease at the end of treatment were considered for consolidation radiotherapy. In patients who initially had bulky disease, early-stage patients received IFRT with a total dose of between 20 and 30 Gy, and in patients with residual disease, IFRT was administered to the site at a dose that was between 30 and 36 Gy. IFRT was administered in a daily fraction of 1.8 to 2 Gy and was given 5 days of the week.

After completing treatment, patients were followed up clinically and investigations were performed only if there were clinical signs or symptoms.

HL Electronic Database

As a routine, a list of all newly registered patients with HL was prepared based on the information collected using a data collection form (Appendix B) from patient case records, outpatient department files, and investigation reports. This was retrospectively captured into an electronic database using online Google forms in all the 11 tertiary care centers.

Data Variables and Source of Data

Variables extracted from the pHL electronic database were the name of the treating center, patient ID, age, stage, sex, B symptoms, site of lymphadenopathy, albumin, ESR, histology, extranodal sites, mediastinal involvement, interim and end of treatment response, treatment toxicity, treatment modifications, and outcome (alive and in remission, relapse, death, loss to follow-up). CHIP score was calculated using four variables (fever, hypoalbuminemia, mediastinal involvement, and stage IV). Dates of diagnosis, treatment initiation of ABVD, iPET scan, and outcome or censoring (whichever was earlier) were also collected. The loss to follow-up was defined as "missing two scheduled visits to the center and not responding to telephonic reminders." The last center visit was considered as the date of loss to follow-up. Patients who were lost to follow-up were censored and not considered for analysis after the date of loss to follow-up.

Data Analysis

Data were analyzed using STATA (version 12.1, copyright 1985–2011 StataCorp LP USA, serial number: 30120504773). Frequency, proportion, mean (standard deviation [SD]), median (interquartile range [IQR]) were used.

Our primary objective was to measure the event-free survival (EFS)and overall survival (OS) at 2 years and 5 years. Any relapse, death, or treatment failure was considered as an "event" (unfavorable outcome). Not achieving CR at the end of treatment with ABVD chemotherapy was considered a treatment failure. Since only one death was documented, OS was not calculated. All patients were censored at the date of lost to follow-up, or May 31, 2019, whichever was earlier. EFS was estimated using the Kaplan–Meier method, and variables were compared using the log-rank test. p-values< 0.05 were considered significant. Crude hazard ratios were calculated using Cox proportional hazard regression to determine the risk factors for events. Factors predicting outcome and nonachievement of CR in an iPET2 scan were assessed using log-binomial regression.

Ethics

Ethics approval was obtained from Dr. GVN Ethics Committee, Dr. GVN cancer institute, Tiruchirappalli, India (Protocol No. PHL/07/2018 dated July 30, 2018) (Appendix C). As the study involved the review of patient records (secondary data), a waiver for informed consent was sought and approved by the ethics committees. Administrative approval was obtained from collaborative institutions before starting the study and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Results

One hundred and thirteen patients with pHL were identified during the 10 years. The median age was 13 years (SD: 4.96) and 83 of 113 pHL patients (73.5%) were male. The most common histopathology was mixed cellularity (32.8%) (►**Table 1**).

Baseline Imaging Characteristics

Of 113 pHL, 78 (69.1%) patients had PET scan and 35 (30.9%) had CT scans as baseline investigation. Stage IV disease was seen in 29 (37.1%) of 78 pHL patients with a baseline PET evaluation and three (8.5%) of 35 pHL patients with a baseline CT scan evaluation. Extranodal sites were seen in 29 (37.1%) of 78 pHL patients with baseline PET scan evaluation and one (2.8%) of 35 pHL patients with baseline CT scan evaluation (►**Table 2**).

Table 1 Profile of pHL patients treated in 11 tertiary care centers across South India (2009–2019)

Characteristics	*n* (%)
Total	**113 (100.0)**
Demographic	
Age (in y)	
≤ 5	17 (15.1)
06–12	37 (32.7)
13–18	59 (52.2)
Sex	
Male	83 (73.5)
Female	30 (26.5)
Clinical	
B-symptoms	57 (50.5)
Bulky disease (nodal size > 6 cm)	26 (23.0)
Number of nodal sites	
<3	11 (9.7)
≥3	102 (90.3)
Laboratory	
Histopathology	
Nodular sclerosis	19 (16.8)
Mixed cellularity	37 (32.8)
Lymphocyte rich	13 (11.6)
Lymphocyte depleted	1 (0.8)
Unclassified	43 (38.0)
ESR (mm/h)	
<30	25 (22.2)
30–50	14 (12.4)
>50	24 (21.2)
Not done	45 (39.8)
Missing data	5 (4.4)
Albumin <35 gm/dL	35 (40.0)
Staging investigation results	
Mediastinal involvement	49 (43.4)
Bulky mediastinum	11 (9.7)
CHIP score	
Low risk (0–1)	60 (53.1)
High risk (2,3,4)	53 (46.9)

Abbreviations: CHIP score, Childhood Hodgkin International Prognostic score; ESR, erythrocyte sedimentation rate; pHL, pediatric Hodgkin lymphoma.

Prognostic Grouping and Treatment's Profile

Stage I was seen in 13 (11.5%) pHL patients and stage IV in 32 (28.3%) patients (►**Table 2**). Of 113 patients, 104 patients completed treatment, six patients abandoned treatment, and three had a change of treatment protocol due to progressive disease. The early-stage based on prognostic grouping was seen in 34 (30.0%) and advanced stage in 79 (69.9%) patients (►**Table 3**).

Early-Stage Disease

Of 34 early-stage pHL patients, six (17.6%) were in favorable and 28 (82.4%) were in unfavorable prognostic group (►**Table 3**). The median number of cycles of ABVD chemotherapy in early-stage pHL patients was four cycles (range: 2, 8). Three of the six favorable prognostic group early-stage pHL patients received two cycles along with IFRT treatment. Fifteen (44.1%) early-stage patients received four cycles, of which six underwent combined modality treatment (►**Table 4**).

Table 2 Staging outcomes based on the baseline imaging used for initial evaluation of pHL patients treated in 11 primary centers across South India (2009–2019)

Parameters	Total *n* (%)	PET based *n* (%)	CT based *n* (%)
Total	**113 (100)**	**78 (100)**	**35 (100)**
Stage			
Stage I	13 (11.5)	12 (15.4)	1 (2.8)
Stage II	38 (33.6)	21 (27.0)	17 (48.5)
Stage III	30 (26.6)	16 (20.5)	14 (40.0)
Stage IV	32 (28.3)	29 (37.1)	3 (8.5)
Extranodal involvement			
Spleen	12 (10.6)	12 (15.4)	–
Bone	14 (12.3)	14 (17.9)	–
Others[a]	7 (6.2)	6 (7.7)	1 (2.8)
Mediastinum involvement	49 (43.4)	34 (43.6)	15 (42.8)
Bulky sites involvement	26 (23.0)	16 (20.5)	10 (28.5)

Abbreviations: CT, computed tomography; PET, positron emission tomography; pHL, pediatric Hodgkin lymphoma.
[a]Lung—5, liver—1, skin—1 (1 case had both lung and spleen involvement, 1 case had both lung and skin involvement, and 1 case had bone and spleen).

Table 3 Staging and prognostic grouping of pHL patients treated in 11 tertiary care centers across South India (2009–2019)

Characteristics	*n* (%)
Stage	
I	13 (11.5)
II	38 (33.6)
III	30 (26.6)
IV	32 (28.3)
Early stage[a]	34 (30.0)
Favorable[b]	6/34 (17.6)
Unfavorable[b]	28/34 (82.4)
Advanced stage[c]	79 (70.0)

Abbreviation: pHL, pediatric Hodgkin lymphoma.
[a]IA, IIA, IX, and IIX.
[b]Categorized into favorable and unfavorable based on the presence of ≥ 1 of the following factors: Extranodal disease, bulky mediastinum, ESR > 50 mm/h, 2 or more the 2 nodal site involvement.
[c]IB, IIB, III, and IV.

Advanced Stage

Of 79 advanced-stage pHL patients, 42 (53.1%) received six cycles and 28 (35.4%) received eight cycles ABVD chemotherapy (►**Table 4**). The median number of cycles was six (range: 2, 8). Nine advanced pHL patients discontinued ABVD treatment. Among nine patients, five patients are alive and disease-free, two patients are alive with the disease on metronomic treatment, one patient died due to progressive disease, and one patient with the progressive disease was rescued with salvage chemotherapy followed by transplant. Radiotherapy was given to 15 (18.9%) out of 79 advanced pHL patients, of which six cases received RT for partial remission status in the interim scan, six cases for the bulky site at initial presentation, and three cases for the residual disease at the end of treatment.

Response Assessment

Results of the interim and end of treatment assessment are depicted in ►**Table 5**. CR at interim and end of treatment assessment was 79.4% (*n* = 69) and 87.7% (*n* = 57) with PET and 46.1 (*n* = 12) and 77.5% (*n* = 31) with CT-based imaging, respectively. Nearly 92.0% completed treatment and 85.0% achieved CR at the end of treatment.

iPET2 Response Assessment

Among 113 patients, 64 (56.6%) patients underwent iPET2 scan. ►**Fig. 1** depicts the outcome of pHL children with iPET2 scans. Of the 64 children with iPET2 scan, 51(79.7%) patients achieved CR, and 13(20.3%) failed to achieve CR.

Five of 64 patients with iPET2 scan discontinued treatment. Among those five patients, four are alive and disease-free and one patient had treatment failure. Of the four patients who are alive and disease-free, three patients had CR in iPET2 scan and one had progressive disease in iPET2 requiring salvage chemotherapy and transplant. The patient who had treatment failure did not achieve CR in the iPET2 scan.

Toxicity

The most common acute toxicity was grade IV febrile neutropenia seen in eight patients. There were no cases with anthracycline cardiotoxicity, bleomycin-induced lung toxicity, and second malignancy.

Event Free Survival

Of the total 337.86 person-years of follow-up, 17 events were documented giving an incidence rate of five (confidence interval [CI]: 3.1–8.1) per 100 person-years follow-up. Of 17 events, four had treatment failure, seven relapsed, and six had progressive disease. One patient with a progressive disease died. ►**Fig. 2** shows the outcome of the entire cohort.

Table 4 Treatment profile of pHL patients treated in 11 tertiary care centers across South India (2009–2019)

Characteristics *n* (%)	Total *n* (%)	Early stage *n* (%)	Advanced stage
Total	113 (100)	34 (100)	79 (100)
Number of ABVD cycles			
2 ABVD	–	3 (8.8)	–
4 ABVD	–	15 (44.1)	9 (11.3)
6 ABVD	–	15 (44.1)	42 (53.1)
8 ABVD	–	1 (3.0)	28 (35.4)
Combined modality treatment	24 (21.2)	9 (26.5)	15 (18.9)

Abbreviations: ABVD, Adriamycin/Bleomycin/Vinblastine/Dacarbazine; pHL, pediatric Hodgkin lymphoma.

Table 5 Response assessment of pHL patients treated in 11 tertiary care centers across South India (2009–2019)

Response	Total	CR *n* (%)	PR[a] *n* (%)	SD[a] *n* (%)	PD[a] *n* (%)
IR response					
Total	113	81 (71.7)	28 (24.8)	1 (0.8)	3 (2.7)
PET based	87	69 (79.4)	17 (19.5)	–	1 (1.1)
CT based	26	12 (46.1)	11 (42.4)	1 (3.8)	2 (7.7)
EOT response					
Total	105[b]	88 (83.8)	11 (10.5)	2 (1.9)	4 (3.8)
PET based	65	57 (87.7)	6 (9.2)	–	2 (3.1)
CT based	40	31 (77.5)	5 (12.5)	2 (5.0)	2 (5.0)

Abbreviations: CR, complete remission; CT, computed tomography; EOT, end of treatment; IR, interim response; PD, progressive disease; PET, positron emission tomography; pHL, pediatric Hodgkin lymphoma; PR, partial remission; SD, stable disease.
[a]Number in the parentheses denotes row percentage.
[b]Eight patients missed end of treatment assessment.

The median duration of follow-up was 2.73 years (IQR: 3.32 years) and the 2- and 4-year EFS of the entire cohort were 86.0 and 81.0%, respectively (►**Fig. 3**). For early-stage pHL patients, 2- and 4-year EFS rates were 90.0 and 83.0%, while for advanced-stage pHL patients, these were 85.0 and 80.0%, respectively. The 2- and 4-year EFS rates for iPET2 positive patients were 67.0 and 52.0%, while for iPET2 negative patients these were 93.0 and 93.0%, respectively. Of all the factors analyzed, the only independent predictor of low EFS was iPET2 response (►**Table 6**). The survival curves stratified by iPET2 responses are depicted in ►**Fig. 4**. When compared with patients with CR on iPET2, patients with incomplete remission (hazard ratio: 5.30 95.0% [CI]: 1.25–22.38) had significantly lower survival. None of the baseline factors predicted the response in iPET2 scans (data not shown).

Discussion

Our study documents the role of an iPET2 scan in pHL patients and the largest multicenter study from South India to provide insight into demographic profiles, treatment, and outcome of pHL patients. The main limitation of our study is its retrospective nature and only three-fifths of the entire cohort underwent an iPET2 scan for response assessment. Since formal testing for chemotherapy-related late effects was not done at the study sites, treatment-related late toxicity could not be captured in our study.

The baseline disease characteristics showed a lower median age at presentation, male preponderance, mixed cellularity as commonest histological presentation, increased proportion with B symptoms, and advanced stage at presentation. Similar findings were reported in previous studies from India.[15-19,41,42]

In our study, one-half of patients had B symptoms, a quarter of patients presented with bulky disease, and two-third was diagnosed with advanced-stage disease. Similar findings were reported in other Indian studies.[16,19,35,36,41,43-46]

Three-fourth of the patients underwent PET scan as an initial staging investigation and one-fourth had CT scan. We noticed more stage IV and extranodal involvement with PET-based imaging. Increased sensitivity and specificity of PET scan in comparison to CT scan-based staging are well reported in the literature.[28,47-50] However, considering the extensive patient preparation, long examination time, increased cost, and limited availability of PET scan, it is very important to identify the impact of PET-based upstaging on the treatment protocol and long-term outcome.

Treatment offered to our patients was heterogeneous due to the evolution of pHL management over the years and the multicentric nature of our study. Nearly 92.0% of the study

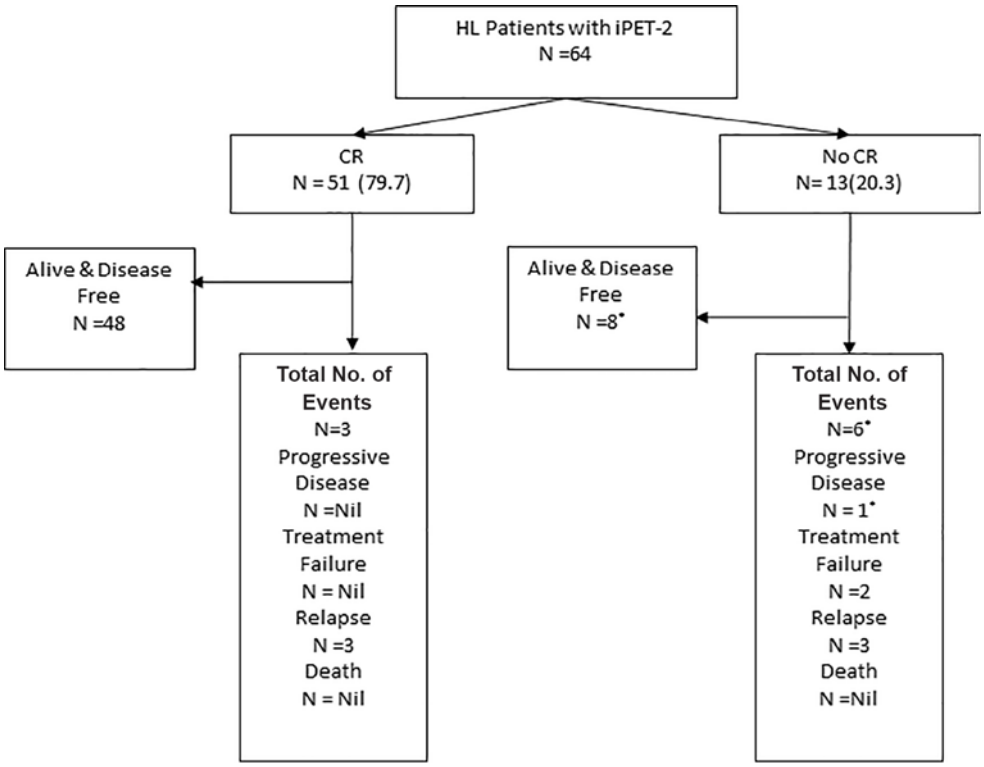

Fig. 1 Flowchart depicting the outcome of pHL patients with iPET2 scan treated in 11 primary centers across South India (2009–2019).
Abbreviations: CHIP, Childhood Hodgkin International Prognostic; pHL, pediatric Hodgkin lymphoma; iPET2, interim PET scan after two cycles; CR, complete response. *One patient with progressive disease in iPET2 underwent salvage chemotherapy and transplant following which he is alive and disease free.

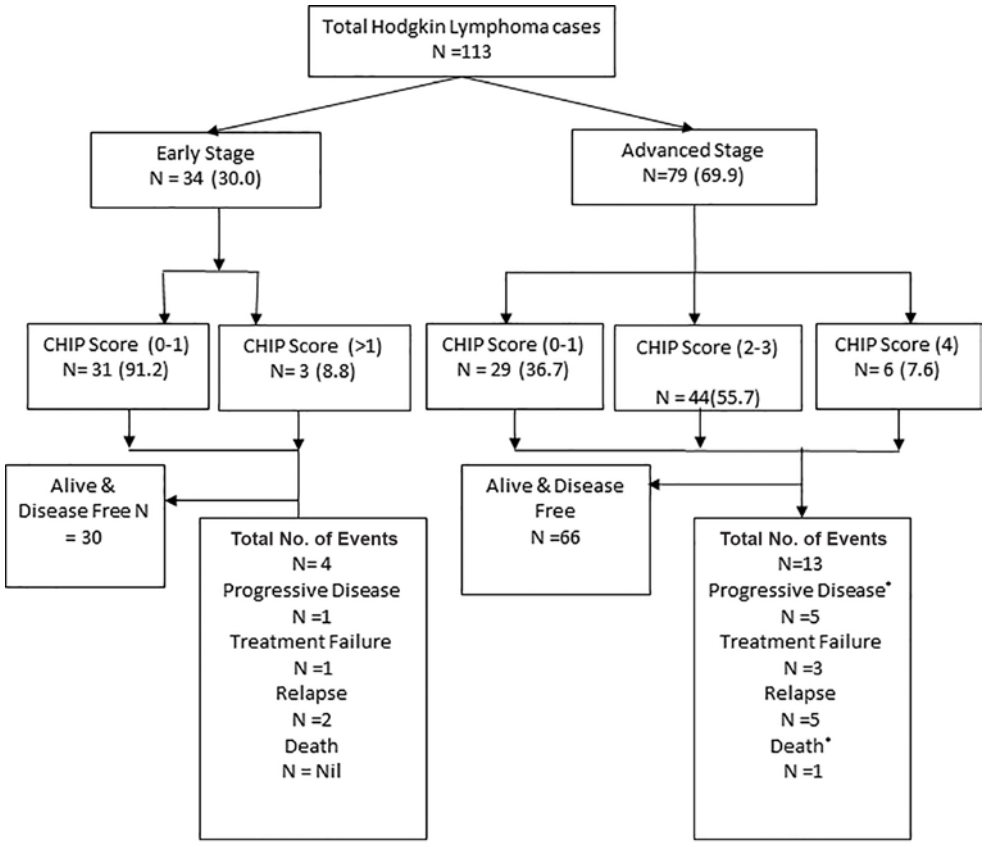

Fig. 2 Flowchart depicting the outcome of all pHL patients treated in 11 primary centers across South India (2009–2019).
Abbreviation: pHL, pediatric Hodgkin lymphoma. *One patient died due to progressive disease, so the event is taken as a progressive disease for analysis.

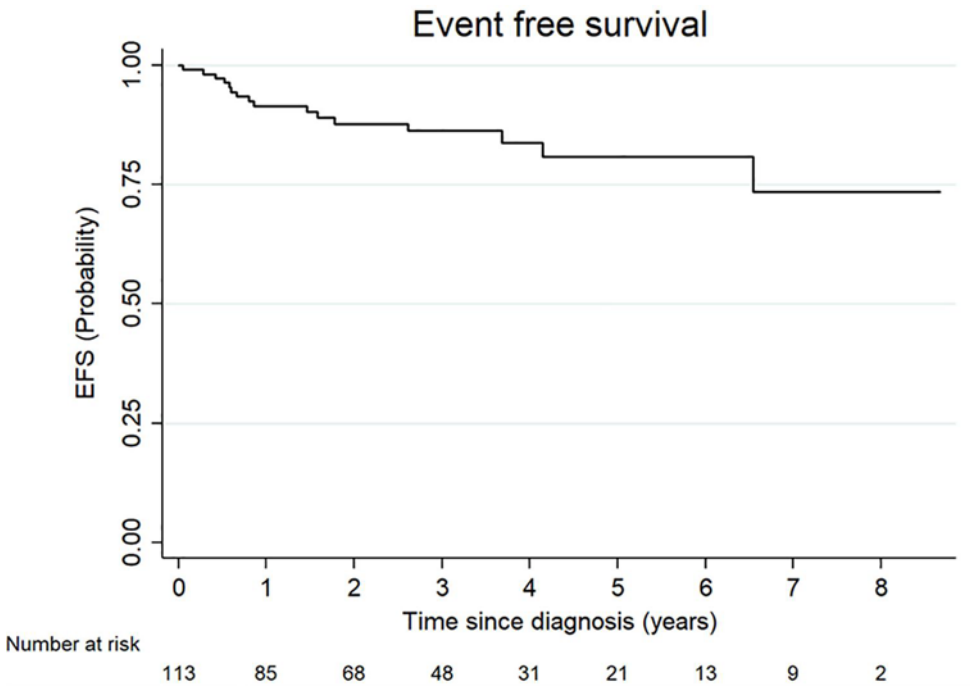

Fig. 3 Event-free survival of pHL patients treated in 11 primary centers across South India (2009–2019): (*n* = 113). pHL, pediatric Hodgkin lymphoma.

Table 6 Association of factors (unadjusted analysis) with event-free survival of pHL patients treated in 11 tertiary care centers across South India (2009–2019)

Parameters		Hazard ratio	CI	*p*-Value
Sex	Male	Reference		
	Female	1.154	0.403–3.308	0.790
B-symptoms	Absent	0.619	0.233–1.644	0.336
	Present	Reference		
Stage	I	0.676	0.075–6.078	0.727
	II	0.993	0.266–3.702	0.992
	III	1.604	0.467–5.507	0.453
	IV	Reference		
Bulky mediastinum	Yes	Reference		
	No	0.776	0.273–2.209	0.635
Extranodal present	Yes	Reference		
	No	1.077	0.347–3.343	0.898
Mediastinum involvement	Yes	Reference		
	No	0.999	0.385–2.596	0.999
HB <10.5 gm/dL	Yes	Reference		
	No	1.214	0.440–3.351	0.708
CHIP score	Low risk	1.627	0.590–4.486	0.347
	High risk	Reference		
iPET-2	No CR	5.305	1.258–22.38	0.023
	CR	Reference		
Radiation	Given	0.831	0.086–8.004	0.831
	Not given	Reference		

Abbreviations: CHIP score, Childhood Hodgkin International Prognostic score; CI, confidence interval; CR, complete response; iPET2, interim PET scan after two cycles; NS, not significant; pHL, pediatric Hodgkin lymphoma.

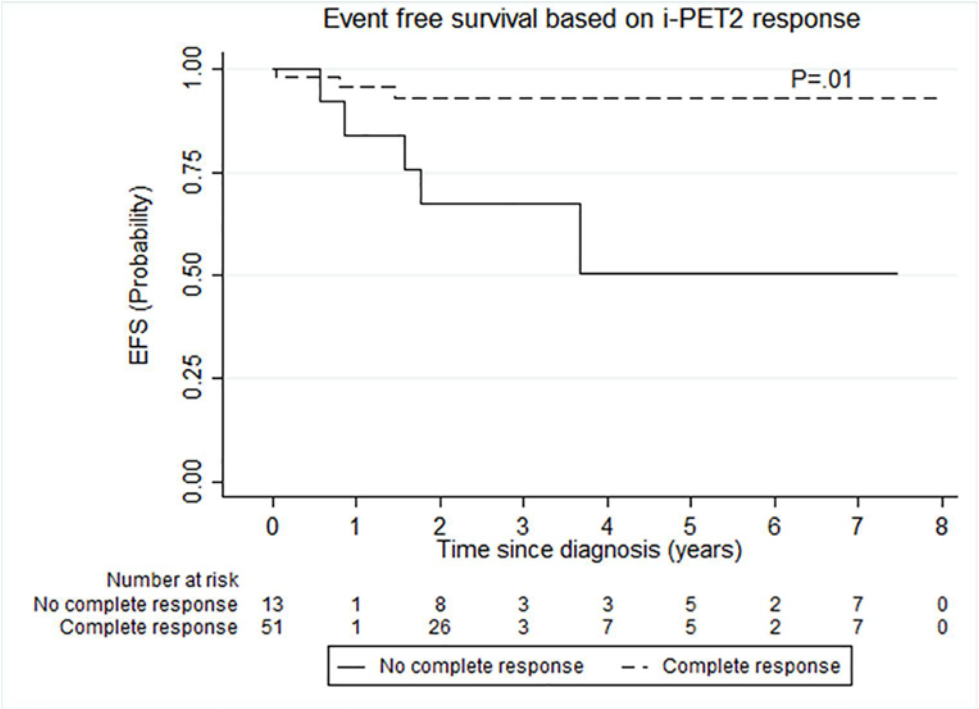

Fig. 4 Event-free survival of pHL patients treated in 11 primary centers across South India (2009–2019): Stratified by interim positron emission tomography scan after two cycles of first-line therapy (iPET2). iPET2, interim positron emission tomography 2; pHL, pediatric Hodgkin lymphoma.

population completed treatment and 83.8% achieved CR at the end of treatment. Similar CR rates with ABVD were reported from other centers.[29,41,42] A combined modality approach was used in one-fourth of early-stage patients and one-fifth of advanced-stage patients. The primary aim of combined modality treatment in pHL is to strike a balance between cure and late toxicity. In a resource-limited setting, factors like management cost, treatment abandonment, availability of a pediatric oncologist, and lack of transplant centers play a key role in the outcome. As the number of relapsed pHL undergoing salvage chemotherapy and transplant is low, most of the Indian centers aim for the high cure rate with low relapses and continue to use ABVD chemotherapy.[41,42] In our study, one out of the 17 patients with adverse outcome was rescued using salvage chemotherapy and transplant.

Three-fifths of our patients underwent iPET2 scan, of which 20.3% did not achieve CR. Several studies have reported an iPET2 positive rate between 7.6 and 33.3%. In our study, none of the patients underwent treatment modification based on the iPET2 response. In comparison with adult HL patients, the studies on iPET2 response adapted treatment modification in pHL are sparse.[26,31-34]

In our study, patients not achieving CR in the iPET2 scan had five times increased risk of an adverse outcome when compared with patients achieving CR. Results from several studies on the role of iPET scan in the management of pHL are varied and conflicting. A prospective Indian study of the 57 pHL patients by Bakhshi et al from India has suggested posttreatment PET scan rather iPET scan to be a predictor of outcome in pHL patients.[27] The study concluded iPET2 imaging to have low sensitivity with no significant impact on EFS and OS. However, the study showed iPET2 imaging to have higher specificity for predicting relapse (91.4%) than CT imaging(40.3%) ($p < 0.0001$).[25] A retrospective Indian study of 49 pHL patients on ABVD chemotherapy by Totadri et al has demonstrated the possibility of omitting radiation in patients who achieve metabolic remission on iPET2 scan.[51] A study by Furth et al on iPET2 response assessment demonstrated excellent negative predictive value but a poor positive predictive value (PPV) for relapse.[28] Another study by Ilivitzki et al showed a higher PPV for the same.[30] Few retrospective studies have shown high sensitivity of iPET assessment.[27,29,31] Interim analysis from Euronet-HD showed the feasibility of eliminating RT for patients achieving CR in iPET2 scan after two cycles of OEPA. However, long-term outcome of Euronet-HD study is awaited.[14] Above-mentioned studies were limited by the small number of subjects, short follow-up, retrospective nature, and lack of uniform assessment criteria.[27-29,52,53] Prospective large randomized study to assess the role of treatment intensification for pHL patients not achieving CR in iPET2 imaging is the need of the hour.

Children's Oncology Group has identified CHIP score as an effective marker for predicting outcome in pHL patients.[24] In our study, there is no difference in outcome for CHIP score-based low-risk and high-risk subgroups. A similar finding was reported by Khedr et al from Cairo, Egypt.[25] Probably, the role of CHIP score in pHL patients treated with ABVD chemotherapy needs further evaluation.

Our study confirms the prognostic value PET scan for all children with pHL for staging and response assessment. Not

achieving CR on the iPET2 scan indicates poor prognosis and warrants clinical trial enrollment for a better outcome.

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Local investigators had the responsibility of collecting the data and entering into the database. Preexisting local resources were used to collect the required information. Hence, no funding was required for this research project

Conflict of Interest
None.

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