

# Does Interim PET Scan After 2 Cycles of ABVD Predict Outcome in Hodgkin Lymphoma? Real-World Evidence

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**PURPOSE** Escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) improves overall survival (OS) in patients with Hodgkin lymphoma (HL) relative to ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) therapy. However, the associated higher cost and toxicity discourage clinicians from prescribing it. Identifying high-risk patients and administering escalated BEACOPP remains an effective strategy. We assessed the significance of interim positron emission tomography (iPET) scan after 2 cycles (iPET2) in identifying this high-risk subset.

**PATIENTS AND METHODS** This cohort study used secondary data from 12 tertiary care centers in South India gathered over 10 years (2008-2018). OS, event-free survival (EFS), determinants of EFS, and complete response (CR) in iPET2 were assessed.

**RESULTS** The study included 409 patients with HL (mean age, 34.5 years; male/female ratio, 1.4:1). The median duration of follow-up was 2.8 years. Of 409 patients, 63% underwent PET-based staging and 37% underwent computerized tomography (CT) staging. Stage IV (28.9%) and bone involvement (9.2%) were seen more often with PET than with CT staging (9.2% and 2%, respectively). Among 171 patients with iPET2 results, 24% did not achieve CR, and no factors were significantly associated. The 5-year EFS and OS rates of the entire cohort were 78% and 97%, respectively. The 5-year EFS and OS rates of patients with CR on iPET2 were 90% and 99%, respectively, whereas these were 65% and 100%, respectively, for patients not achieving CR. On univariable analysis, sex, stage, and iPET2 response significantly predicted inferior EFS. On multivariate analysis, only iPET2 response significantly predicted EFS ( $P < .000$ ).

**CONCLUSION** Our study supports the use of PET for staging and iPET2 for response assessment. Non-achievement of CR on iPET2 indicates unfavorable outcome, and such patients may benefit from more intensive treatment.

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## INTRODUCTION

Hodgkin lymphoma (HL) accounts for approximately 10% of all lymphomas, with excellent long-term cure rates.<sup>1</sup> The ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) combination yields a complete response (CR) rate of 75% and an overall survival (OS) rate of 73% and has been considered a standard regimen for several decades.<sup>2,3</sup> However, ABVD fails to result in remission in 20% to 30% of patients with HL, who then require salvage chemotherapy and transplantation. Intensive regimens like dose-escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; [EB]) have shown better cure rates versus ABVD but are rarely used because of increased treatment-related mortality and morbidity.<sup>4,6</sup> Therefore, it is important to identify patients with high risk of unfavorable

outcome and treat them with intense regimens such as EB is important.

International Prognostic Score (IPS7) and modified scoring system (IPS3) are used for prognostication, but they do not demarcate risk groups sufficiently to justify deviation from standard ABVD therapy.<sup>7-10</sup> More recently, an interim positron emission tomography (iPET)/computed tomography (CT) scan performed after 2 cycles of ABVD therapy (iPET2) was reported to be a better prognosticator than IPS.<sup>11,12</sup>

In India, younger age, male preponderance, and increased frequency of mixed cellularity are the major features of the disease.<sup>13-21</sup> This study was conducted to provide real-world evidence of the role of iPET2 in the management of HL and analyze various factors predicting its outcome.

## ASSOCIATED CONTENT

### Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

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## CONTEXT

### Key Objective

Although dose-escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; EB) improves outcome in Hodgkin lymphoma (HL), it is not widely used because of cost and toxicity. Identifying high-risk patients and treating them with EB should be the norm. We evaluated the efficacy of positron emission tomography (PET) scanning in identifying this high-risk subset in a real-world setting.

### Knowledge Generated

Four of every 6 patients were staged with PET, and we noticed more stage IV disease and skeletal involvement with PET than with computed tomography–based staging. The 5-year event-free and overall survival rates of the entire cohort were 78% and 97%, respectively. Patients with positive interim PET after 2 cycles of first-line therapy (iPET2) had a 5-time increased risk of unfavorable outcome than iPET2-negative patients. International Prognostic Score–based risk showed no correlation with survival.

### Relevance

PET for patients with HL for both staging and response assessment at 2 months is recommended. Not achieving complete remission on iPET2 indicates poor prognosis, and such patients may benefit from treatment intensification.

## PATIENTS AND METHODS

### Study Design

This was a cohort study involving secondary data.

### Setting

**Study sites.** The study was conducted in 12 private tertiary care centers across 3 states in South India (Tamil Nadu, Andhra Pradesh, and Karnataka; Appendix Table A1). Patients either paid out of pocket or were covered under the state-funded or private health insurance schemes.

**Routine diagnosis and management of HL.** All patients required histopathologic diagnosis with excisional nodal, core needle, or bone marrow biopsy. Morphologic evaluation and classification of the patients were performed using the revised European-American lymphoma classification.<sup>22</sup>

The workup included documentation of presenting complaints, including B symptoms (unexplained fever, > 10% weight loss, and/or drenching night sweats), physical examination, and investigation reports (Appendix; Appendix Table A2). Stage was assigned based on the Ann Arbor staging system with Cotswolds modifications and determined using clinical examination and CT and/or PET scan.<sup>23</sup> Early-stage prognostic grouping included stages I, IIA, IX, and IIX, and advanced-stage grouping included stages IB, IIB, III, and IV. Treatment strategy was in accordance with National Comprehensive Cancer Network guidelines.<sup>24</sup>

All patients received chemotherapy in a daycare facility as outpatients. ABVD was delivered as per the original schedule,<sup>2</sup> EB according to the HD-9 study,<sup>25</sup> and BEACOPP-14 as per the RATHL study.<sup>26</sup> Interim response assessment was performed using PET or CT imaging after 2 or 4 cycles based on clinician opinion and institutional policy. iPET2 was performed 2 to 3 days before the third

cycle of chemotherapy. Repeat PET or CT imaging was performed at the end of treatment. PET images were interpreted by an experienced nuclear medicine physician at the particular center, and no second review or central review was performed in our study. CT and PET scan reporting was based on the Lugano recommendation for response assessment, and PET images were scored according to the 5-point Deauville score.<sup>11,12</sup>

CR based on PET imaging was defined as a Deauville score of 1, 2, and 3 on interim scans and a score of 1 or 2 at the end-of-treatment scan. On the basis of CT scan findings, CR was defined as complete disappearance of all clinical and radiologic evidence of disease; partial response (PR) was defined as a 50% reduction in tumor area (the product of the 2 longest diameters) but less than that in a CR. Appearance of a new lesion or a 50% increase in an existing lesion was considered progressive disease (PD). All other responses were considered stable disease.<sup>11,12</sup> Patients who did not achieve CR after 2 cycles of ABVD, had bulky disease at presentation, had early-stage disease, and had residual disease at the end of treatment were considered for consolidation radiotherapy (RT). After completing treatment, patients were observed as per the institution policy.

**HL electronic database.** A list of all newly registered patients with HL was prepared from patient case records, outpatient department files, and investigation reports. This was captured in an electronic database using online Google forms in all 12 tertiary care centers. A check for missing data was conducted every month, and the database was updated after referring to the paper-based records.

### Study Population

The study population included all patients diagnosed with and initiating treatment for HL between January 1, 2008,

**TABLE 1.** Profile of Patients With HL Treated in 12 Tertiary Care Centers Across South India (2008-2018; N = 409)

Characteristic	No.	%
Year of recruitment		
2008-2011	104	25.4
2012-2018	305	74.6
Age, years		
0-14	45	11.0
15-44	250	61.1
45-64	85	20.8
≥ 65	29	7.1
Sex		
Male	264	64.5
Female	145	35.5
B symptoms	191	46.6
Nodal site		
Supradiaphragmatic	191	46.7
Infradiaphragmatic	36	8.8
Both	182	44.5
Bulky disease (nodal size > 10 cm)	78	19.1
No. of nodal sites		
< 3	8	2.0
≥ 3	225	55.0
Missing	176	43.0
Histopathology		
Nodular sclerosis	91	22.2
Mixed cellularity	89	21.0
Lymphocyte rich	46	11.2
Lymphocyte depleted	4	1.0
Unclassified	179	43.7
ESR, mm/hr		
< 30	65	15.9
30-50	70	17.1
> 50	87	21.3
Not done	185	45.2
Missing	2	0.5
Albumin < 4 g/dL	160	39.1
Total WBC count > 15,000/mm <sup>3</sup>	48	11.7
Absolute lymphocyte count < 600/mm <sup>3</sup>	9	2.2
Hemoglobin < 10.5 g/dL	162	39.6
Mediastinal involvement	174	42.5
Bulky mediastinum	38	9.3
Splenic involvement	55	13.4
Extra lymphatic involvement	117	28.6
Bone involvement	27	6.6
Bone marrow involvement	23	5.6

Abbreviations: ESR, erythrocyte sedimentation rate; HL, Hodgkin lymphoma.

**TABLE 2.** Staging, Prognostic Grouping, and Risk Stratification of Patients With HL Treated in 12 Tertiary Care Centers Across South India (2008-2018; N = 409)

Characteristic	No.	%
Stage		
I	53	13.0
II	121	29.6
III	133	32.5
IV	102	24.9
Early-stage disease <sup>a</sup>	120	29.3
Favorable <sup>b</sup>	5/120	4.2
Unfavorable <sup>b</sup>	56/120	46.6
Undefined	59/120	49.2
Advanced-stage disease <sup>c</sup>	289	70.6
Low risk (0-2)	179/289	61.9
High risk (≥ 3)	110/289	38.1

Abbreviation: HL, Hodgkin lymphoma.

<sup>a</sup>IA, IIA, IX, and IIX.

<sup>b</sup>Categorized into favorable and unfavorable based on the presence of ≥ 1 of the following factors: extranodal disease, bulky mediastinal mass > 10 cm, erythrocyte sedimentation rate > 50, ≥ 3 disease sites, and age ≥ 50 years.

<sup>c</sup>Low and high risk based on International Prognostic Score.

and October 31, 2018. They were observed on record until December 31, 2018 (date of censoring). Patients with nodular lymphocyte-predominant HL were excluded from the study.

### Data Variables and Sources

Variables extracted from the electronic database included name of treating center, patient ID, age, stage, sex, B symptoms, site of lymphadenopathy, albumin level, erythrocyte sedimentation rate, IPS, histology, extranodal sites, WBC count, absolute lymphocyte count, mediastinal involvement, interim and end-of-treatment response, treatment modifications with iPET2, and outcome (alive and in remission, relapse, death, or lost to follow-up). Date of diagnosis, treatment initiation of ABVD, iPET, and outcome or censoring (whichever was earlier) were also collected.

An event (unfavorable outcome) was defined as relapse after previous CR, progression after documenting PR or PD on CT scan assessments during treatment, or death resulting from any cause or treatment failure, whichever occurred first. Not achieving CR on the last date of follow-up was considered treatment failure. If a patient had a relapse followed by loss to follow-up or death, the outcome was documented as relapse. Loss to follow-up was defined as missing 2 scheduled visits to the center and not responding to telephonic reminders. The date of last visit to the center was considered 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. The primary end point was event-free survival (EFS), which was calculated from the date of diagnosis to the date of occurrence of the event. The secondary end point was OS, defined as time from diagnosis until death resulting from any cause or censored at the date of last information of the patient being alive.

### Data Analysis

Data were analyzed using STATA (version 12.1; STATA, College Station, TX). Incidence rates of events per 100 person-years of follow-up were calculated. The 2- and 5-year EFS and 2- and 5-year OS rates were calculated. Crude and adjusted hazard ratios were calculated using Cox proportional hazards regression to determine the risk factors for events. Among those undergoing iPET2, factors associated with not attaining CR were assessed using log binomial regression.

The regression models included age, sex, and variables with a crude *P* value < .2 (stage, iPET2 response, B symptoms). Bone, spleen, extralymphatic involvement, and site of lymphadenopathy were used to determine stage. Therefore, we considered stage over these variables in the regression model. Prognostic grouping was based on stage and B symptoms, which were therefore included instead of prognostic grouping.<sup>27</sup>

### Ethics

Ethics approval was obtained from the Dr GVN Ethics Committee of the Dr GVN Cancer Institute (Tiruchirappalli, India; dated July 30, 2018) and the Ethics Advisory Group (EAG) of the International Union Against Tuberculosis and Lung Disease (Paris, France; EAG No. 29/18; dated June 11, 2018). Because the study involved 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 study initiation.

## RESULTS

### Baseline Characteristics

The baseline characteristics and staging profiles of 409 patients are summarized in Table 1. The mean age was 34.5 years (standard deviation, 17.8 years), and the male/female ratio was 1.4:1. B symptoms were seen in 198 (48.4%) and bulky disease in 78 patients (19.1%). The most common histopathologic subtype was nodular sclerosis (*n* = 91; 22.2%). Of 409 patients with HL, 102 (24.9%) received treatment under a state government-supported health insurance scheme, and the rest (75.1%) paid either out of pocket or through private health insurance schemes.

### Prognostic Grouping and Treatment Profile

Stage, prognostic grouping, risk stratification, and treatment profile details are summarized in Tables 2 and 3 and Figure 1. Of 409 patients with HL, 259 (63.3%) underwent PET-based and 150 (36.7%) underwent CT-based initial staging evaluation. Stage IV (28.9%) and bone involvement (9.2%) were more often seen with PET-based staging than with CT-based staging (9.2% and 2%, respectively; data not shown). Per prognostic grouping, 120 patients (29.3%) had early-stage and 289 (70.6%) had advanced-stage disease.

A median of 6 cycles of chemotherapy was administered to patients with both early- (range, 2-8 cycles) and advanced-stage disease (range, 4-8 cycles). Combined-modality treatment was administered to 52 patients (43.3%) with early-stage disease and 50 (17.3%) with advanced-stage disease. Of the 52 patients with early-stage disease, 5 received 20 Gy of involved-site RT (ISRT) along with 2 ABVD cycles, and the remaining patients received 30 Gy of ISRT as a partial combined-modality treatment. The patients with advanced HL received 30 to 36 Gy of ISRT; the indications were bulky disease (*n* = 28), iPET2-positive sites (slow responders; *n* = 5), residual disease at the end of treatment (*n* = 14), and consolidation treatment of an extranodal site (*n* = 3).

### Response Assessment

The results of interim and end-of-treatment response assessments after the end of first-line therapy are summarized in Table 4. Interim response assessment was performed

**TABLE 3.** Treatment Profile of Patients With HL Treated in 12 Tertiary Care Centers Across South India (2008-2018)

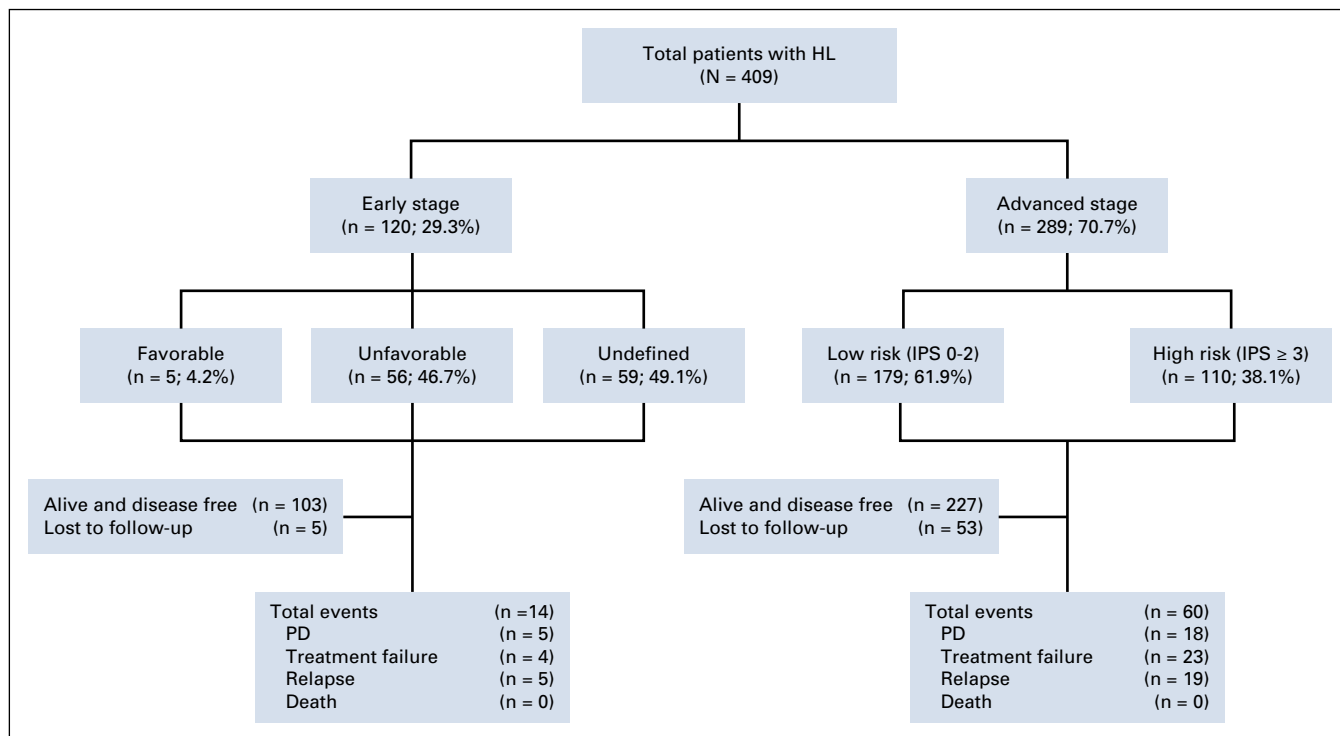
Characteristic	Total (N = 409)		Early Stage (n = 12)		Advanced Stage (n = 289)	
	No.	%	No.	%	No.	%
Treatment regimen						
ABVD	385	94.1	115	95.8	270	93.4
Escalated BEACOPP	2	0.5	—	—	2	0.01
Other <sup>a</sup>	22	5.3	5	4.1	17	5.8
No. of ABVD cycles						
2	—	—	6	5.2	—	—
3-4	—	—	44	38.3	—	—
5-6	—	—	59	51.3	—	—
Other <sup>b</sup>	—	—	6	5.2	—	—
6	—	—	—	—	153	56.7
7-8	—	—	—	—	53	19.6
Other <sup>c</sup>	—	—	—	—	64	23.7
Combined-modality treatment	102	24.9	52	43.3	50	17.3

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; HL, Hodgkin lymphoma.

<sup>a</sup>Including AVD (doxorubicin, vinblastine, and dacarbazine), COPP (cyclophosphamide, vincristine, procarbazine, and prednisone) protocol, hybrid regimen, and definitive radiotherapy.

<sup>b</sup>> Six cycles.

<sup>c</sup>< Six cycles.



**FIG 1.** Flowchart depicting the outcome of all patients with Hodgkin lymphoma (HL) treated in 12 tertiary care centers across South India (2008-2018; N = 409). IPS, International Prognostic Score; PD, progressive disease.

for 408 patients: 280 were PET based and 128 were CT based. Among patients with an interim PET scan, 171 underwent their scans after 2 cycles and 109 after 4 cycles. One patient missed the interim assessment and directly underwent the end-of-treatment assessment. CR rates at interim and end-of-treatment assessments were 72.9% and 75.3% with PET and 39% and 73.5% with CT imaging, respectively. On follow-up of patients achieving CR with interim PET scan ( $n = 204$ ), 186 (91.1%) were alive and disease free, 12 (5.8%) had a relapse, 2 had PD, and 4 were receiving treatment. Among patients achieving CR on interim CT scan ( $n = 50$ ), 44 (90%) were alive and disease free, 5 (10%) had a relapse, and 1 was receiving treatment. Of the 93 patients not achieving CR (based on either PET or CT) at the end of first-line therapy, 66 achieved CR at a later date with further salvage therapy.

#### iPET2 Response Assessment and Treatment Modification

Among the 409 patients, 171 (41.8%) underwent iPET2. Figure 2 shows the outcome of all patients who underwent the iPET2 scan. Of these 171 patients, 130 (76%) achieved CR and 41 (24%) did not. None of the baseline factors significantly predicted iPET2 response (data not shown). On follow-up of patients achieving CR ( $n = 130$ ) on iPET2, 118 (90.7%) were alive and disease free, 7 (5.3%) had a relapse, 2 had PD, and 3 were receiving treatment. Among patients not achieving CR ( $n = 41$ ), 28 (68.2%) were alive and disease free, 8 (19.5%) experienced

treatment failure, 3 (7.3%) had PD, 1 had a relapse, and 1 was receiving treatment.

Among patients not achieving CR ( $n = 41$ ), dose escalation was administered to 4 patients, of whom 3 received BEACOPP-14 and 1 received EB. Of these 4 patients, 3 achieved CR and 1 had PR status at the end of treatment; on the last follow-up, 2 continued to remain in CR, 1 experienced a relapse, and 1 had PD. Of 130 patients with CR on iPET2, dose de-escalation to AVD was performed for 8 patients (6.1%), of whom 5 achieved CR, 1 experienced a relapse, and 2 were receiving treatment.

#### Toxicity

The most common acute toxicity was grade IV febrile neutropenia, seen in 22 patients (5.7%) receiving ABVD, 3 patients receiving EB (100%), 3 receiving BEACOPP-14 (100%), and 1 receiving COPP (100%). Bleomycin toxicity was seen in 21 patients (5.1%), of whom 19 required hospitalization and 1 died. Four patients with HL developed doxorubicin-related cardiotoxicity with no documented death. Dose modification because of treatment toxicity was required in 28 patients (7.2%) receiving ABVD, 3 receiving EB (100%), 1 receiving BEACOPP-14 (33.3%), and 1 receiving COPP (100%).

#### Survival

Of the total 1,154 person-years of follow-up, 74 events were documented, translating to an incidence rate of 6.4 (95% CI, 5.1 to 8.1) per 100 person-years of follow-up. Of the 74



**TABLE 4.** Response Assessment of All Patients With HL Treated in 12 Tertiary Care Centers Across South India (2008-2018)

Response	Total	CR		PR <sup>a</sup>		SD <sup>a</sup>		PD <sup>a</sup>	
	No.	No.	%	No.	%	No.	%	No.	%
IR									
Total	408 <sup>b</sup>	254	62.2	120	29.4	16	3.9	18	4.4
PET based	280	204	72.8	63	22.4	3	0.01	10	12.3
CT based	128	50	39.0	57	44.5	13	10.1	8	0.06
EOT									
Total	399	306	75.3	50	12.3	18	5.4	25	6.9
PET based	199	159	79.9	19	9.5	6	3.01	15	7.5
CT based	200	147	73.5	31	15.5	12	6.0	10	5.0

Abbreviations: CR, complete response; CT, computed tomography; EOT, end of treatment; HL, Hodgkin lymphoma; IR, interim response; PET, positron emission tomography; PD, progressive disease; PR, partial response; SD, stable disease.

<sup>a</sup>Of the 93 patients not achieving CR at the end of first-line treatment, 66 achieved CR at a later date with salvage chemotherapy.

<sup>b</sup>One patient missed interim assessment and directly underwent EOT assessment.

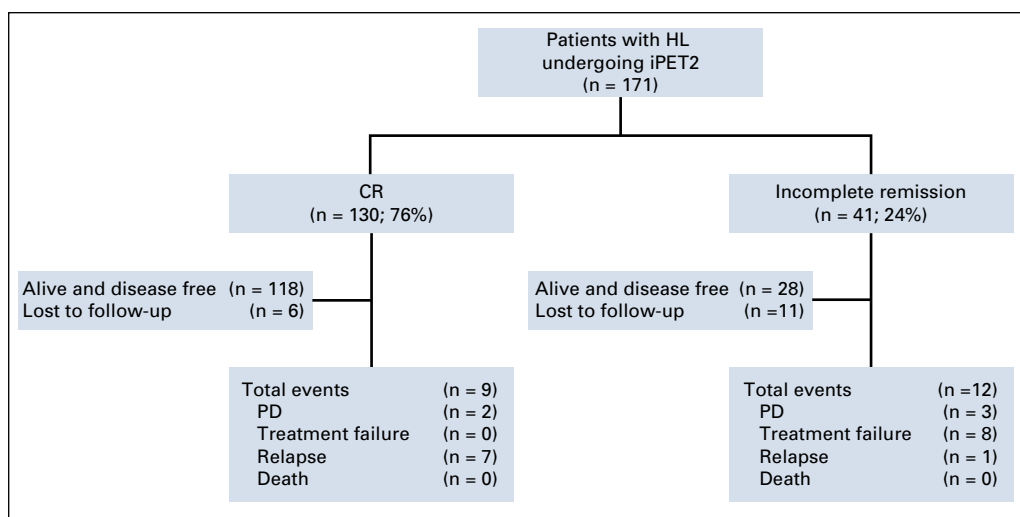
events, 27 were treatment failure, 24 were relapse, and 23 were PD. Seven deaths were documented, of which 4 resulted from PD, 2 from relapse, and 1 from relapse with bleomycin toxicity.

The median duration of follow-up was 2.8 years (interquartile range, 0.75-4.25 years), and the 2- and 5-year EFS rates for the entire cohort were 82% (95% CI, 78% to 86%) and 78% (95% CI, 73% to 83%), respectively. The 2- and 5-year OS rates for the entire cohort were 98% (95% CI, 96% to 99%) and 97% (95% CI, 94% to 99%), respectively. Both 2- and 5-year EFS rates of patients with CR on iPET2 were 90% (95% CI, 84% to 95%), whereas these were 65% (95% CI, 46% to 79%) for patients not achieving CR. The OS rate of patients with CR on iPET2 was 99% (95% CI, 91% to 100%) at 2 and 5 years, and no death was reported among patients not achieving CR.

Table 5 summarizes the unadjusted and adjusted associations of factors with EFS and OS. The survival curves stratified by the associated factors are shown in Figure 3. On univariable analysis, sex, stage, and iPET2 response significantly predicted inferior EFS. On multivariable analysis, only response on iPET2 scan significantly predicted EFS ( $P < .000$ ).

## DISCUSSION

This study is the largest multicenter study to our knowledge from India that provides insights into the demographic profile, management, and outcome of patients with HL and the role of iPET2 as a predictor of EFS. A high proportion of patients had advanced-stage disease at presentation, and approximately three-fourths had EFS for 5 years after diagnosis. The iPET2 scan results were a strong predictor of



**FIG 2.** Flowchart depicting the outcome of patients with Hodgkin lymphoma (HL) undergoing interim positron emission tomography scan after 2 cycles of first-line therapy (iPET2) treated in 12 tertiary care centers across South India (2008-2018; n = 171). CR, complete response; PD, progressive disease.

**TABLE 5.** Association of Factors With EFS and OS in Patients With HL Treated in 12 Tertiary Care Centers Across South India (2008-2018)

Parameter	EFS				OS			
	Unadjusted		Adjusted		Unadjusted		Adjusted	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Stage								
I	0.19 (0.045 to 0.83)	.027	0.97 (0.18 to 5.18)	.974	0.70 (0.50 to 0.98)	.038	0.73 (0.50 to 1.08)	.112
II	0.94 (0.50 to 1.76)	.849	1.61 (0.47 to 5.49)	.444	0.83 (0.64 to 1.09)	.184	0.87 (0.63 to 1.20)	.386
III	1.43 (0.80 to 2.54)	.223	2.35 (0.74 to 7.40)	.146	0.92 (0.71 to 1.20)	.545	0.95 (0.70 to 1.28)	.726
IV	Reference				Reference		Reference	
IPI7								
< 3	0.86 (0.54 to 1.37)	.531	NA		0.97 (0.80 to 1.19)	.792	NA	
≥ 3	Reference				Reference			
IPI3								
0-1	0.87 (0.51 to 1.46)	.587	NA		0.86 (0.68 to 1.08)	.190	0.95 (0.71 to 1.27)	.719
2-3	Reference				Reference			
Age, years								
0-14	0.43 (0.15 to 1.21)	.110	0.25 (0.04 to 1.77)	.165	1.51 (0.93 to 2.44)	.097	NA	
15-45	0.43 (0.21 to 0.90)	.024	0.23 (0.06 to 0.93)	.039	1.14 (0.76 to 1.70)	.538	NA	
45-60	0.83 (0.38 to 1.80)	.636	0.48 (0.11 to 2.19)	.343	1.14 (0.74 to 1.77)	.548	NA	
> 60	Reference				Reference		Reference	
Sex								
Male	Reference				Reference		Reference	
Female	0.51 (0.30 to 2.88)	.016	1.07 (0.39 to 2.96)	.892	0.87 (0.71 to 1.06)	.167	0.88 (0.71 to 1.08)	.213
B symptoms								
Absent	0.63 (0.39 to 1.01)	.05	0.72 (0.29 to 1.81)	.485	0.88 (0.72 to 1.07)	.206	NA	
Present	Reference				Reference		Reference	
iPET2								
CR	Reference				Reference			
No CR	5.13 (2.16 to 12.20)	.000	6.23 (2.45 to 15.83)	.000	0.81 (0.57 to 1.15)	.234	NA	

Abbreviations: CR, complete response; EFS, event-free survival; HL, Hodgkin lymphoma; HR, hazard ratio; iPET2, interim positron emission tomography scan after 2 cycles of first-line therapy; IPI, International Prognostic Index; NA, not applicable; OS, overall survival.

survival. One key limitation was that only two-fifths of the patients underwent iPET2 scans.

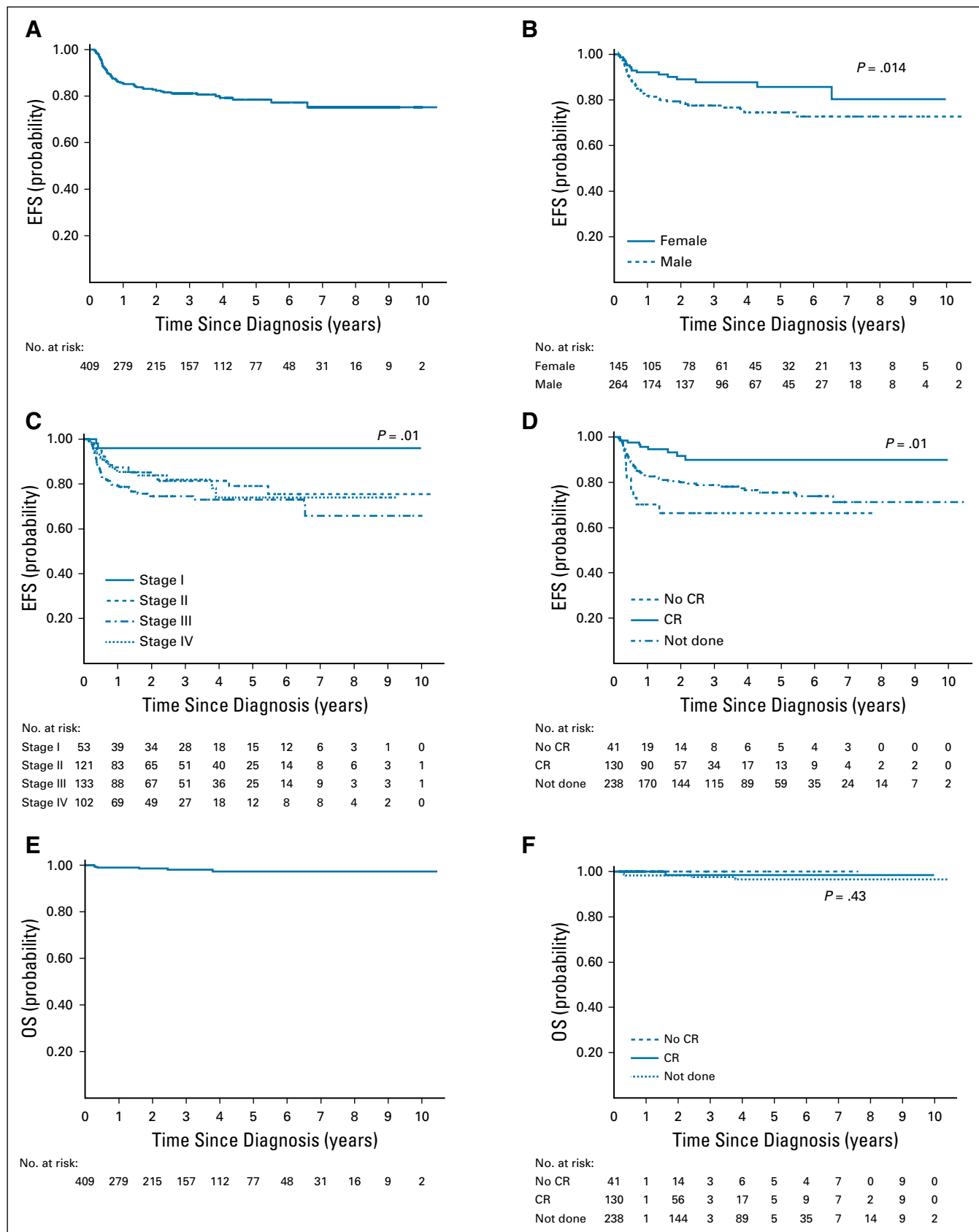
Prior studies from India presented similar results with regard to age distribution, male/female ratio, and proportion of patients with advanced-stage disease on presentation.<sup>13-21</sup> The possible reasons for advanced-stage presentations are delay in diagnosis, which can be explained by late referral from primary care physicians, high incidence of tuberculosis leading to misdiagnosis, lack of financial assistance, and poor access to health care facilities. The high proportion of men may be because of women not seeking appropriate treatment.

By histopathologic subtype, both nodular sclerosis and mixed cellularity had nearly equal distribution, with no clear dominant pattern. Most studies from developed nations indicate nodular sclerosis is the most common subtype.<sup>3,27</sup> In India, some studies showed mixed cellularity as the most

common HL subtype, whereas others reported nodular sclerosis.<sup>28-31</sup>

A combined-modality approach was used in 43% patients with early-stage and 17% with advanced-stage HL. Despite recent studies showing superior efficacy of the combined-modality approach over chemotherapy alone in early-stage HL, 67% of our early-stage patients did not receive RT.<sup>32-35</sup> This may be because of concern among practitioners regarding the long-term effects of RT. Omission of RT did not affect outcome in our study, because most of our patients with early-stage disease received 6 ABVD cycles instead of the standard 4 cycles. Similar findings on additional chemotherapy cycles negating the benefit of RT have been reported.<sup>36,37</sup>

Four of every 6 patients were evaluated with PET, and we observed a higher incidence of stage IV disease and skeletal involvement in PET-based staging than in CT-based staging. Similar findings have been reported in



**FIG 3.** (A-D) Event-free survival (EFS) and (E-F) overall survival (OS) of patients with Hodgkin lymphoma treated in 12 tertiary care centers across South India (2008-2018), (A, E) overall and (B-D, F) stratified by factors significantly predicting survival (N = 409): (B) sex, (C) stage, and (D, E) interim positron emission tomography scan after 2 cycles of first-line therapy (iPET2). CR, complete response.



other studies, where incorporation of PET resulted in stage changes in approximately 20% of patients, and half of these patients may require aggressive management.<sup>38-40</sup>

Two-fifths of patients underwent iPET2, of whom 24% did not achieve CR. Similar results with iPET2 scans have been reported in the literature, and an Indian study of patients with advanced HL reported 16% not achieving CR with iPET2.<sup>37,40,41</sup> In our study, the reasons for not intensifying treatment in most patients despite not achieving CR on iPET2 could have been high cost, clinician choice, lack of supporting health care facilities, noncoverage under state insurance schemes, and patient preference. Similarly, de-escalation after CR on iPET2 was seen in few patients. Because of the lack of evidence supporting de-escalation, most clinicians preferred removing bleomycin only for patients at high risk of bleomycin toxicity, and all patients treated before 2016 had received bleomycin irrespective of iPET2 results.<sup>26</sup> In our study, the CR rate at the end of treatment was 75.3%, 5-year EFS rate was 78%, and 5-year OS rate was 97%. The better EFS rate compared with CR rate at the end of treatment can be explained by the practice of continuing first-line treatment with salvage

chemotherapy followed by autologous transplantation in patients not achieving CR at the end of 6 ABVD cycles. Our 5-year EFS rate is comparable to those in other studies.<sup>42-45</sup>

Male sex, stage III disease, and iPET2 positivity predicted poor EFS. IPS-based risk classification (IPS7 and IPS3) into high- and low-risk groups did not show a significant difference in survival. Given similar results from recent studies, the significance of IPS as a predictor of outcome and its ability to risk stratify HL in the current timeframe is questionable.<sup>7,8</sup>

According to our results, we recommend performing PET for all patients with HL for both staging and response assessment at 2 months. We recommend using PET results after 2 cycles as a predictor of survival. Not achieving CR on iPET2 indicates poor prognosis, and such patients may benefit from more intensive treatment programs. Similarly, de-escalation could be considered in case of CR. The real-world effectiveness of this strategy needs to be assessed in future studies, especially in developing countries like India, where the cost and toxicity of EB keep clinicians from using it as first-line therapy.

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## APPENDIX

Details of clinical workup on diagnosis of Hodgkin lymphoma:

1. Physical examination should be careful and complete
  - a. Each involved site and lymph node regions are measured and noted
  - b. The size of liver/spleen in centimeters below costal margin
  - c. Baseline pubertal status
2. Mandatory laboratory investigations
  - a. Complete blood counts and differential leukocyte counts
  - b. Lactate dehydrogenase, liver function tests, and serum creatinine
  - c. Computed tomography (CT) chest and whole abdomen are mandatory
  - d. Adequate bilateral bone marrow biopsy should be performed in patients with stage III or IV disease or B symptoms and if upfront positron emission tomography (PET)/CT is not done
  - e. HIV, hepatitis B surface antigen, and hepatitis C virus status should be determined

Optional investigations:

1. Upfront PET/CT scan is highly recommended
2. Bone scan: indicated in case of bone pain and elevated alkaline phosphatase; not needed if PET scan has been done
3. Any node with longest transverse diameter > 1.5 cm at the time of diagnosis should be considered compatible with lymphomatous involvement in the absence of a compelling alternative etiology, such as infection. This includes supraclavicular, infraclavicular, epitrochlear, brachial, preauricular, and popliteal nodes. Cervical, axillary, inguinal, and mesenteric lymph nodes may reach a diameter of 2 cm before being considered involved with lymphoma if reactive hyperplasia is considered possible. If there is doubt about

a particular site of disease noted by CT or physical examination, and PET scan is feasible for the patient, PET avidity can be used to determine whether a site is involved. If involvement of a site will change the patient's risk group or significantly alter the radiation therapy field, biopsy should be considered to document or exclude involvement.

4. Any focal mass lesion of a visceral organ (eg, liver, spleen, kidney) is considered lymphomatous in the absence of reasonable alternative explanation (eg, cyst, hemangioma, abscess), unless too small to characterize. Lesions too small to characterize are indeterminate unless follow-up studies allow characterization or tissue sampling is performed. Hepatosplenomegaly is not considered involvement of the organs with lymphoma but can instead result from cytokine production.
5. A measurable lesion by CT is a lesion that can be accurately measured in 2 orthogonal dimensions. Nonmeasurable assessable lesions include permeative bone lesions, malignant ascites, malignant effusions, lymphangitic spread, and lesions too small to accurately measure in 2 dimensions by CT. Measurable lesions up to a maximum of 6 lesions in total, representative of all involved organs, will be measured as target lesions at baseline and observed for response. Target lesions will be selected on the basis of size (eg, largest lesions) and suitability for accurate repeated measurements by imaging or clinical examination. Size is to be recorded using metric notation. Lesion size is expressed as the product of the perpendicular diameters (PPDs) and serves as a surrogate measurement of area with dimensions of square centimeters. The PPD is obtained by multiplying the longest diameter of the lesion by the maximal diameter perpendicular to the longest diameter. The sum of the PPDs is obtained by adding the PPDs of all measurable lesions.
6. All nonmeasurable assessable lesions should be recorded and noted at follow-up.

**TABLE A1.** Details of 12 Private Tertiary Care Centers Across South India (2008-2018)

Hospital	Location	No. of Beds	New Patients per Year	Patient Distribution (%)	
				Government Free Schemes	Private Insurance or Out of Pocket
Dr GVN Cancer Institute	Trichy	130	3,000	85	15
MMHRC	Madurai	800	6,000	75	25
Vydehi Institute of Medical Science	Bengaluru		5,000	80	20
Kumaran Hospital	Chennai	100	1,000	—	100
Apollo Hospital	Bengaluru	250	1,000	—	100
Manglore Institute of Oncology	Mangaluru	122	1,110	75	25
Manipal Hospital	Vijayawada	240	3,000	15	85
Columbia Asia, Yeshwanthpur	Bengaluru	160	2,000	—	100
Columbia Asia, Whitefield	Bengaluru	160	500	—	100
HCG Center	Hubli	45	2,000	30	70
Kovai Medical Center and Hospital	Coimbatore	750	4,000	80	20
Kasturba Medical College	Manipal	820	5,500	80	20

Abbreviation: MMHRC, Meenakshi Mission Hospital and Research Center.

**TABLE A2.** Patient Evaluation Medical Record

Investigation	At Diagnosis	At Early Response Assessment	At Completion of Therapy	Follow-Up
CBC with differential	M			
Serum creatinine	M			
LFT	M			
ESR	M			
LDH	M			
HIV/HBsAg/HCV	M			
USG testis				
CT chest, whole abdomen	M (if iPET2 not done)	M (if iPET2 not done)	M (if CR not documented)	Document clinical relapse
Biopsy <sup>a</sup>	M			All relapses require biopsy; highly recommended
Immunohistochemistry	M			Highly recommended
Echocardiogram	M		Highly recommended	M (cardiotoxicity suspected)
PFT and SpO <sub>2</sub> <sup>b</sup>	M		Highly recommended	M (lung toxicity suspected)
Diffusion lung capacity for carbon monoxide	Highly recommended	Highly recommended		HR (lung toxicity suspected)
PET CT scan/CT scan	Highly recommended	Highly recommended	Highly recommended (if CR, recommended)	
BMA and BMBx <sup>c</sup>		M (if positive upfront)		

Abbreviations: BMA, bone marrow aspirate; BMBx, bone marrow biopsy; CBC, complete blood count; CR, complete response; CT, computed tomography; ESR, erythrocyte sedimentation rate; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; iPET2, interim positron emission tomography scan after 2 cycles of first-line therapy; LFT, liver function test; LDH, lactate dehydrogenase; M, mandatory; PET, positron emission tomography; PFT, pulmonary function test; SpO<sub>2</sub>, peripheral oxygen saturation; USG, ultrasound.

<sup>a</sup>Excisional biopsy/core needle biopsy and fine-needle aspiration cytology not enough for diagnosis.

<sup>b</sup>PFT if feasible in children age > 7 years; SpO<sub>2</sub> for all.

<sup>c</sup>Only if stage III or IV or B symptoms and if PET CT not done.