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Original Research Article

Clinical outcomes of interim positron emission tomography-computed tomography scan-guided response-adaptive therapy in advanced Hodgkin's lymphoma: a tertiary cancer centre experience from South India

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ABSTRACT

Background: Hodgkin's lymphoma (HL) is a highly curable malignancy, but some patients fail standard ABVD chemotherapy, requiring intensified treatment. Interim positron emission tomography-computed tomography scan (iPET-CT) using the Deauville scoring system allows response-adapted therapy, enabling de-escalation to AVD in good responders and escalation to dose-escalated BEACOPP (EB) in poor responders. This study evaluates iPET-guided therapy outcomes in HL patients at a tertiary care center in South India.
Methods: A retrospective study of 69 HL patients (aged 12-65 years) treated over 5 years was conducted. After two ABVD cycles, iPET-2 scans guided treatment: PET-negative patients (Deauville 1-3) received four additional AVD cycles, while PET-positive patients (Deauville 4-5) received four EB cycles. The primary endpoint was event-free survival (EFS); secondary endpoints included overall survival (OS), toxicities, and quality of life. Statistical analyses included Kaplan-Meier survival analysis and Cox regression.
Results: The cohort (median age: 38 years, 87% male) had predominantly advanced-stage disease (73.9%) and systemic B symptoms (81.2%). iPET identified 16% as PET-positive. Median OS was 73 months (95% CI: 67.77-78.23), and median EFS was 30 months (95% CI: 28.64-31.36). PET-negative patients showed significantly better 2-year EFS (81%) compared to PET-positive patients (50%; $p<0.05$). Toxicities were higher in the EB group, with grade 3-4 neutropenia in 85% of cycles.
Conclusions: iPET-CT-guided therapy effectively stratifies HL patients, improving outcomes in PET-positive poor responders while avoiding overtreatment in PET-negative patients. Despite higher toxicities, escalated BEACOPP was feasible and safe, highlighting the potential of response-adapted strategies in resource-limited settings.

Keywords: HL, iPET-CT, Response-adapted therapy, EFS

INTRODUCTION

Hodgkin lymphoma (HL) is a unique lymphoid malignancy, characterized by its high curability, particularly in the modern era of combination chemotherapy and advanced imaging techniques. Despite accounting for only 10% of all lymphomas globally, HL remains a focus of oncologic research due to its distinct biology and treatment responsiveness.[1,2] Combination chemotherapy using ABVD (doxorubicin, bleomycin,

vinblastine, and dacarbazine) has been the cornerstone of therapy for decades, providing cure rates of approximately 75% and an OS rate of 73% in advanced HL.[2,3] However, approximately 20-30% of patients fail to achieve complete remission or experience relapse, necessitating alternative treatment strategies.[3,4] This subset of patients poses a clinical challenge, emphasizing the need for effective prognostic tools to guide treatment intensification.

The introduction of dose-escalated BEACOPP (EB), a more intensive regimen, has been shown to improve cure rates to 85-87%, compared to ABVD.[4,5] Nevertheless, the higher treatment-related mortality and morbidity associated with BEACOPP limit its widespread use.[6] Furthermore, most patients with advanced HL achieve remission with ABVD alone, making routine use of BEACOPP an overtreatment for the majority.[7,8] Therefore, identifying patients with a poor prognosis early in the treatment course is critical to balance the benefits of aggressive therapy against its potential toxicity.

Historically, the international prognostic score (IPS) and its modified variants have been used to stratify risk in advanced HL. The IPS, developed in the 1990s, integrates seven clinical and laboratory parameters, including age, stage, and serum albumin, to predict outcomes.[9] Despite its utility, the IPS has limitations in accurately identifying patients who would benefit from treatment intensification. In the modern treatment era, these scoring systems often fail to capture the nuanced differences in outcomes, as advances in therapy have narrowed survival gaps between risk groups.[10]

iPET, performed after two cycles of chemotherapy, has emerged as a superior prognostic tool, offering dynamic and individualized risk stratification. Unlike IPS, which is based on static baseline factors, iPET assesses early treatment response, a critical determinant of long-term outcomes.[11] Multiple studies have demonstrated that iPET positivity is associated with significantly lower progression-free survival (PFS) and OS compared to iPET negativity.[11,12] For instance, a landmark study reported three-year PFS rates of 94% in iPET-negative patients versus only 28% in iPET-positive patients.[13]This ability to distinguish poor responders has made iPET-guided therapy a cornerstone of personalized treatment approaches in HL.

The adoption of the Deauville five-point scoring system has standardized the interpretation of iPET scans, facilitating consistent prognostication and decision-making.[14,15]A Deauville score of 1-3 is considered negative, indicating adequate response to initial therapy, while a score of 4-5 is deemed positive, reflecting inadequate response and a higher likelihood of treatment failure.[15] Based on iPET results, response-adapted therapy allows for treatment intensification in poor responders, potentially improving their outcomes. Studies have shown that escalated BEACOPP, when used in iPET-positive patients, can overcome early resistance and achieve durable remissions.[16]

Despite widespread adoption of iPET-guided therapy in high-income countries, data from developing nations like India remain scarce. Most centers in India continue to rely on ABVD as primary regimen, with outcomes comparable to those reported in the West.[7] However, the increasing availability of PET-CT in India provides an opportunity to integrate response-adapted approaches, potentially improving outcomes in resource-limited settings.

In India, HL primarily affects young adults, often presenting with advanced-stage disease and systemic symptoms. While ABVD remains the standard of care, the subset of patients who fail to achieve remission continues to face poor outcomes. iPET-guided therapy represents a promising strategy to address this unmet need by identifying patients at high risk of treatment failure and tailoring their management accordingly. However, limited data exist on the long-term outcomes of response-adapted therapy in Indian populations.[17] Furthermore, the impact of escalated BEACOPP in poor responders, including its safety, tolerability, and effect on quality of life, remains underexplored.

This study aims to address these gaps by evaluating the outcomes of iPET-guided response-adapted therapy in advanced HL at a tertiary cancer center in South India. The primary objective is to assess EFS and OS in this high-risk cohort. Secondary objectives include evaluating treatment-related toxicities, prognostic factors, and the safety and tolerability of escalated BEACOPP. Additionally, the study seeks to provide insights into the quality of life of patients undergoing intensive therapy, a crucial consideration in managing a predominantly young patient population.

The findings of this study have the potential to inform clinical practice in India and other resource-limited settings. By demonstrating the utility of iPET in stratifying risk and guiding therapy, the study can support the adoption of personalized treatment approaches in advanced HL. Moreover, understanding the outcomes of escalated BEACOPP in Indian patients will provide valuable insights into its feasibility and effectiveness in real-world settings. This is particularly important given the unique challenges of managing HL in developing countries, including late-stage presentations, comorbidities, and limited access to advanced supportive care.

METHODS

Study design and setting

This retrospective study was conducted at a tertiary care cancer centre in South India government Royapettah hospital affiliated to government Kilpauk medical college, evaluating outcomes of iPET-based response-adapted

therapy in patients with advanced HL. The study covered five years period and followed up for 2 years from January 2017 till December 2022 according to institutional protocols.

Eligibility criteria

Patients aged 12-65 years with histologically and immunohistochemically confirmed HL were included if they had normal organ function and a Karnofsky performance status of ≥70% or an ECOG performance status of <3. Patients were excluded if they could not tolerate the recommended chemotherapy, had systemic comorbidities such as congestive cardiac failure or chronic kidney disease, or were HIV, HBV, or HCV positive. Pregnant women were also excluded.

Pretreatment evaluation

All patients underwent a comprehensive clinical and diagnostic assessment before initiating therapy. This included a detailed history, physical examination, and laboratory investigations such as complete blood count, renal and liver function tests, viral markers, serum lactate dehydrogenase, and erythrocyte sedimentation rate. Imaging studies, including whole-body PET-CT scans, were used for staging, and baseline cardiac assessments with ECG and 2D echocardiography were performed to ensure eligibility for anthracycline-based chemotherapy. Histopathology and immunohistochemistry were essential for confirming the diagnosis.

Treatment protocol

Eligible patients received two cycles of ABVD chemotherapy, followed by an iPET-2 for response assessment using the Deauville five-point scoring system. Patients with negative iPET-2 results (Deauville scores 1-3) continued with four additional cycles of AVD, completing six cycles in total. Patients with positive iPET-2 results (Deauville scores 4-5) were switched to four cycles of dose-escalated BEACOPP (EB), resulting in a total of two cycles of ABVD followed by 4 cycles of EB.[5]

At the end of therapy, all patients underwent a final PET-CT scan to evaluate treatment response. Patients with persistent positive findings (lymph node size ≥2 cm and Deauville score ≥4) underwent biopsy whenever feasible, or they were monitored with imaging at 3-6-month intervals and biopsied if findings persisted or progressed. Radiation therapy was delivered to sites of bulky disease unless the PET-CT findings showed complete resolution (Deauville score 1).[14,15]

Follow-up

Patients were followed regularly to monitor disease progression, recurrence, or treatment-related toxicities. Follow-up visits were scheduled every three months for the first two years and every six months thereafter. Clinical assessments and imaging studies were performed as required during these visits.

Response evaluation

The Deauville five-point scoring system was used to evaluate response to therapy. A score of 1 indicated no uptake, 2 indicated slight uptake below or equal to the mediastinum, 3 indicated uptake above the mediastinum but below or equal to the liver, 4 indicated moderately higher uptake than the liver, and 5 indicated markedly increased uptake or new lesions.

Endpoints

The primary endpoint of the study was EFS, defined as the time from treatment initiation to disease progression, relapse, or death from any cause. Secondary endpoints included OS, treatment-related toxicities, the safety and tolerability of dose-escalated BEACOPP, and quality of life during and after treatment.

Statistical analysis

Data were entered into Microsoft excel and analyzed using SPSS version 21 software. Qualitative data were presented as proportions, and quantitative data were summarized as means and standard deviations. Graphical representations such as bar charts and pie diagrams were used for visualization. Statistical comparisons of continuous variables were performed using Student's t-tests and ANOVA, while chi-square tests were applied for categorical variables. Survival analysis was conducted using the log-rank test, and Cox regression analysis was used to identify independent prognostic factors. A $p<0.05$ was considered statistically significant.

RESULTS

The study cohort predominantly consisted of middle-aged individuals, with a median age of 38 years (IQR: 29-48). The majority were male (87%), with females accounting for 13%. Advanced disease stages were common, with 43.5% of patients in stage III, 30.4% in stage IV, and 26.1% in stage IIB. Performance status (PS) was predominantly 2 (56.5%), while the remainder had a PS of 1 (43.5%). Systemic B symptoms were highly prevalent, affecting 81.2% of patients, and bulky disease was observed in 36.2%. Anemia was present in 58.0% of the cohort, and hypoalbuminemia was frequent, affecting 65.2%. While total lymphocyte count was normal in 58.0% of patients, 42.0% had elevated levels, and only 5.8% exhibited a low lymphocyte percentage (Table 1).

The IPS demonstrated a significant proportion of high-risk patients, with 58.0% scoring 0-3 and 42.0% scoring 4-7. Most patients (81.2%) were treated with ABVD regimens, while 18.8% received dose-escalated BEACOPP (eBEACOPP). About 24.6% required salvage therapy with regimens including ICE (13.0%), GDP (5.8%), and

GEMOX (5.8%). Mortality during follow-up was 26.1%, with 73.9% of patients alive at the time of the last analysis. These findings highlight a population characterized by advanced disease, systemic symptoms, and high-risk prognostic factors but achieving promising survival outcomes with appropriate treatment (Table 1).

The analysis of survival outcomes revealed important distinctions based on clinical factors. Patients with bulky disease had longer survival times compared to those without. The mean survival time for patients with bulky disease was 31.37 months (95% CI: 29.21-33.53), and the median was 33 months (95% CI: 30.75-35.25). Conversely, patients without bulky disease exhibited a mean survival time of 27.92 months (95% CI: 26.82-29.03) and a median of 28 months (95% CI: 26.59-29.41), suggesting potential benefits of tailored treatments for this subgroup (Table 2).

Table 1: Baseline clinical characteristics and treatment details of the cohort.

Variables	Category	N (%)
Age (in years)	Median (IQR)	38.0 (29.0-48.0)
Gender	Male	60 (87.0)
	Female	9 (13.0)
Stage	IIB	18 (26.1)
	III	30 (43.5)
	IV	21 (30.4)
Performance status (PS)	PS 1	30 (43.5)
	PS 2	39 (56.5)
B symptoms	Absent	13 (18.8)
	Present	56 (81.2)
Bulky disease	No	44 (63.8)
	Yes	25 (36.2)
Haemoglobin (Hb)	Low	40 (58.0)
	Normal	29 (42.0)
Total lymphocyte count (TLC)	High	29 (42.0)
	Normal	40 (58.0)
Lymphocyte (%)	Low	4 (5.8)
	Normal	65 (94.2)
Albumin (ALB)	Low	45 (65.2)
	Normal	24 (34.8)
IPS	0-3	40 (58.0)
	4-7	29 (42.0)
ABVD/AVD treatment	No	13 (18.8)
	Yes	56 (81.2)
eBEACOPP treatment	No	56 (81.2)
	Yes	13 (18.8)
Salvage treatment	None	52 (75.4)
	ICE	9 (13.0)
	GDP	4 (5.8)
	GEMOX	4 (5.8)

Table 2: Survival outcomes stratified by key clinical factors.

Factors	Group	Mean survival time (Months)	Std. error (Mean)	95% CI (Mean)	Median survival time (Months)	Std. error (Median)	95% CI (Median)
Bulky disease	Absent	27.92	0.56	26.82-29.03	28	0.72	26.59-29.41
	Present	31.37	1.1	29.21-33.53	33	1.15	30.75-35.25
	Overall	28.8	0.54	27.74-29.85	30	0.69	28.64-31.36
B symptoms	Absent	28.25	1	26.29-30.21	27	0.69	25.64-28.36
	Present	28.96	0.64	27.72-30.21	30	0.38	29.26-30.74
	Overall	28.8	0.54	27.74-29.85	30	0.69	28.64-31.36
IPS (Recode)	0-3 (IPS 1)	28.37	0.65	27.09-29.65	28	1.18	25.69-30.31
	4-7 (IPS 2)	29.68	0.94	27.84-31.51	31	0.44	30.15-31.85
	Overall	28.8	0.54	27.74-29.85	30	0.69	28.64-31.36

For patients with B symptoms, survival outcomes were relatively similar across groups. Patients without B symptoms had a mean survival time of 28.25 months (95% CI: 26.29-30.21) and a median of 27 months (95% CI: 25.64-28.36). Those with B symptoms had slightly better outcomes, with a mean survival time of 28.96 months (95% CI: 27.72-30.21) and a median of 30 months (95% CI: 29.26-30.74). These findings suggest that B symptoms do not significantly impair survival and might even be associated with slightly improved outcomes, potentially due to differences in treatment response or disease biology.

Analysis of IPS categories revealed an unexpected trend where patients with higher scores (IPS 2: 4-7) exhibited better survival than those with lower scores (IPS 1: 0-3). Patients in the IPS 2 category had a mean survival time of 29.68 months (95% CI: 27.84-31.51) and a median of 31 months (95% CI: 30.15-31.85). In contrast, patients in the IPS 1 group demonstrated a mean survival time of 28.37 months (95% CI: 27.09-29.65) and a median of 28 months (95% CI: 25.69-30.31) (Figure 1).

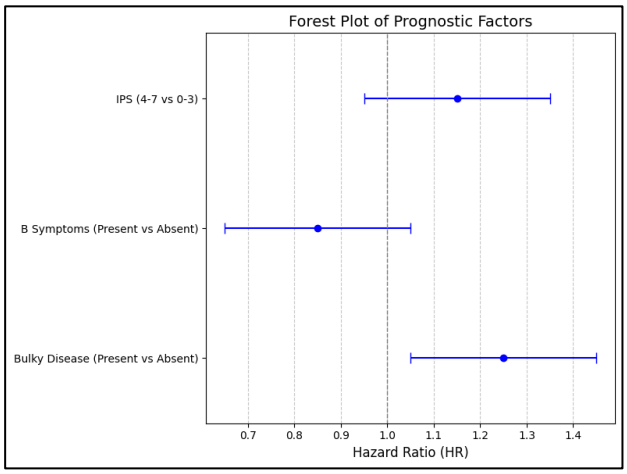

Figure 1: Forest plot of hazard ratios for key prognostic factors in HL.

Overall, the cohort's mean survival time across all groups was 28.80 months (95% CI: 27.74-29.85), with a median survival time of 30 months (95% CI: 28.64-31.36). Kaplan-Meier survival analysis revealed a significant difference between OS and EFS. The median OS was 73 months (95% CI: 67.77-78.23), indicating that 50% of patients survived for at least this duration. However, the median EFS was substantially shorter at 30 months (95% CI: 28.64-31.36), reflecting a higher burden of disease progression or relapse. By 36 months, the cumulative OS was 70.1%, while EFS dropped to 36.7%, underscoring the challenge of maintaining disease-free intervals despite prolonged survival. At 60 months, OS remained at 54.5%, but EFS decreased to just 2.3% (Figure 2).

These findings demonstrate the effectiveness of current treatment strategies in achieving long-term survival in advanced HL. However, the disparity between OS and EFS highlights the need for novel approaches to delay disease progression and improve quality of life for patients with poor initial responses.

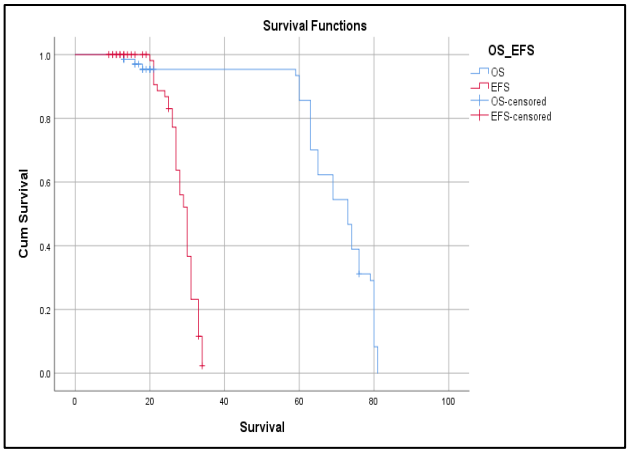

Figure 2: Kaplan-Meier survival curve showing the EFS and OS of the entire cohort.

DISCUSSION

This study evaluated survival outcomes and clinical characteristics in a high-risk cohort of patients with advanced HL. The population was predominantly male (87.0%) with a median age of 38 years, reflecting a typical demographic distribution of advanced HL cases. The majority of patients presented with stage III (43.5%) or stage IV (30.4%) disease, and systemic B symptoms were prevalent (81.2%), emphasizing the advanced and aggressive nature of the disease in this cohort. Despite these unfavorable prognostic factors, the survival outcomes were encouraging, demonstrating the efficacy of current treatment strategies.

Demographics and clinical presentation

The high proportion of stage III and IV patients and the frequent presence of bulky disease (36.2%) and systemic symptoms are consistent with the disease's presentation in advanced stages, as previously reported in the literature.[17,18] Hypoalbuminemia (65.2%) and anemia (58.0%) further underscore the poor baseline condition of many patients. These characteristics align with previous findings that low albumin and hemoglobin levels are common adverse prognostic markers in HL.[9] The IPS, with 42.0% of patients scoring 4-7, indicates that a substantial portion of the cohort was at high risk for poor outcomes.

Treatment modalities

Treatment primarily consisted of ABVD/AVD regimens (81.2%), which remain the gold standard for advanced HL due to their balance of efficacy and manageable toxicity.[19]A smaller proportion (18.8%) received escalated BEACOPP (eBEACOPP), reflecting its use in select high-risk patients despite the associated increased toxicity.[20]

Remarkably, although all patients had positive iPET scans, only 24.6% required salvage therapy. This suggests that the frontline treatment protocols were highly effective in achieving disease control, even in this challenging population. The most common salvage regimen was ICE (13.0%), consistent with its established role in relapsed/refractory HL management.[21]

Survival outcomes

The Kaplan-Meier survival analysis demonstrated a median OS of 73 months, highlighting favorable long-term outcomes for most patients. However, EFS was markedly shorter, with a median of 30 months. This discrepancy reflects a common challenge in advanced HL, where disease recurrence or treatment-related complications occur well before mortality. By 36 months, cumulative OS was 70.1%, compared to only 36.7% for EFS, indicating that while most patients survived, a significant proportion faced disease progression or relapse within the first three years. This trend aligns with prior studies emphasizing the critical need for effective salvage therapies in achieving durable remissions.[8]

Interestingly, bulky disease was associated with longer survival times, with a mean survival time of 31.37 months and a median of 33 months compared to 27.92 months and 28 months, respectively, in those without bulky disease. This finding contradicts traditional views of bulky disease as a poor prognostic factor.[22] However, it may reflect the impact of aggressive management strategies tailored to this subgroup, resulting in improved outcomes.

The presence of B symptoms did not significantly impair survival. Patients with B symptoms had a mean survival time of 28.96 months and a median of 30 months, slightly better than those without B symptoms (mean: 28.25 months; median: 27 months). This result suggests that systemic symptoms, while indicative of advanced disease, do not independently predict worse survival outcomes when effective treatments are applied.[23]

The analysis of IPS showed an unexpected trend where patients with higher scores (4-7) exhibited better survival outcomes than those with lower scores (0-3). Patients with IPS 2 had a mean survival time of 29.68 months and a median of 31 months, compared to 28.37 months and 28 months, respectively, for IPS 1 patients. While counterintuitive, this finding could be influenced by small sample sizes or the use of intensified treatments in high-risk patients, potentially improving their outcomes. Similar anomalies have been noted in smaller cohorts, where treatment modifications based on risk stratification alter expected survival patterns.[10,24]

Clinical implications

The results underscore the effectiveness of current treatment protocols in managing advanced HL, even in high-risk patients. The promising survival outcomes, despite a challenging disease profile, highlight the importance of tailored therapy based on interim PET scans, IPS, and disease characteristics such as bulky disease. The relatively low requirement for salvage therapy further emphasizes the success of frontline regimens in achieving initial disease control. However, the significant disparity between OS and EFS points to the need for novel strategies aimed at delaying relapse and prolonging disease-free intervals. Emerging approaches such as checkpoint inhibitors and targeted therapies may hold promise in addressing these challenges.[25,26]

Limitations

While the findings are encouraging, the study has limitations that must be acknowledged. The sample size is relatively small, particularly in subgroup analyses such as IPS categories, which may limit the generalizability of the results. Additionally, the study's retrospective nature may introduce selection bias, particularly in treatment allocation (e.g., eBEACOPP vs. ABVD/AVD). Prospective studies with larger, more diverse cohorts are needed to validate these findings and refine risk stratification and treatment approaches.

CONCLUSION

This study highlights the complexity of managing advanced HL, characterized by high-risk features such as systemic symptoms, hypoalbuminemia, and advanced-stage disease. Despite these challenges, the cohort achieved promising survival outcomes, demonstrating the efficacy of contemporary treatment strategies. The findings emphasize the need for continued refinement of risk-adapted therapies, with a focus on minimizing relapse rates and extending EFS. Future research should explore the integration of novel agents into frontline and salvage regimens, guided by biomarkers and interim imaging, to further improve outcomes for this high-risk population.

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