

The correlation between interim imaging results and disease prognosis of patients with Hodgkin and diffuse large B cell lymphoma: single center experience

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Abstract

Objective: This study aims to explore the relationship between interim imaging outcomes and disease prognosis in patients diagnosed with Hodgkin lymphoma (HL) and diffuse large B-cell lymphoma (DLBCL).

Method: A total of 157 patients were retrospectively analyzed, comprising 90 with DLBCL and 67 with HL, who received follow-up at our institution. Interim and baseline PET/CT scans (I-PET/CT) from 121 patients were independently interpreted by two nuclear medicine specialists, blinded to clinical data. Additionally, 53 patients underwent both initial and interim contrast-enhanced computed tomography (I-CT), which was independently reviewed by two radiologists under blinded conditions.

Results: Interim PET/CT findings were analyzed in relation to post-treatment outcomes to determine the predictive performance of the imaging modality. The positive predictive value (PPV) and negative predictive value (NPV) were calculated separately for HL and DLBCL. In HL cases, I-PET/CT demonstrated a PPV of 36% and an NPV of 95.4%, while in DLBCL, the respective values were 61.9% and 93.1%. Notably, among patients assessed with both PET/CT and I-CT, 2 individuals in the DLBCL group exhibited negative I-CT results despite positive I-PET/CT findings. Conversely, 3 HL patients showed positive I-CT findings despite negative I-PET/CT.

Conclusion: PET/CT provided a substantial advantage in evaluating therapeutic response over conventional CT, reducing the risk of overtreatment in early-stage disease and undertreatment in more advanced stages. Interim PET/CT negativity was found to be a strong indicator of favorable progression-free survival outcomes, potentially guiding clinicians toward more individualized and less intensive treatment strategies. Nevertheless, confirmation of these findings through prospective randomized trials remains essential.

Keywords: Lymphoma, interim assessment, PET/CT

INTRODUCTION

Lymphomas constitute a major category of hematologic cancers globally, originating from lymphoid cells at

different stages of maturation and presenting with diverse morphological, immunophenotypic, and clinical characteristics (1). They are traditionally classified into

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Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL), with diffuse large B-cell lymphoma (DLBCL) being the most frequent NHL subtype, comprising approximately 30–40% of all cases (2).

With recent advances in systemic therapies, many forms of lymphoma have transitioned from uniformly fatal diseases to largely curable conditions. Consequently, current therapeutic strategies emphasize not only maximizing treatment efficacy but also minimizing associated toxicities. This paradigm shift has driven increased attention toward early prognostic tools that support individualized, response-guided treatment decisions (3,4). Among these tools, interim imaging modalities hold promise in identifying patients at elevated risk for treatment failure during the course of therapy.

Fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) has become integral in the diagnostic and management pathways for lymphoma. It surpasses conventional computed tomography (CT) in detecting both nodal and extranodal disease and is more effective in distinguishing active tumor from post-therapy fibrosis or necrosis (5). Over the past two decades, FDG PET/CT has evolved from a staging modality to an essential tool for early response assessment and outcome prediction—particularly for FDG-avid subtypes like HL and DLBCL.

Multiple studies have underscored the prognostic utility of interim PET/CT (I-PET/CT) in estimating progression-free survival (PFS) and overall survival (OS). In a large multicenter analysis, Eertink et al. compared assessment criteria such as the Deauville score (DS) and changes in maximum standardized uptake values (Δ SUVmax), highlighting the importance of standardized metabolic response evaluations (6). Similarly, Duarte and colleagues demonstrated that combining visual scoring with semiquantitative analysis significantly enhanced risk stratification and helped identify patients with exceptionally poor prognosis (7). Kitajima et al. also reported that I-PET/CT positivity in DLBCL patients receiving R-CHOP chemotherapy correlated with lower two-year PFS, though they advised caution against using I-PET/CT findings as the sole basis for altering therapy (8).

Concurrently, artificial intelligence (AI) and deep learning techniques have increasingly been applied to PET/CT imaging to enhance consistency and predictive accuracy. Metrics such as total metabolic tumor volume (TMTV) and lesion dissemination have shown potential in improving individualized prognostic models and informing personalized treatment strategies.

Despite these advancements, the clinical integration of I-PET/CT in DLBCL remains under exploration. While response-adapted approaches are more established in HL, the need to

balance therapeutic escalation and toxicity in DLBCL limits its broader applicability.

In light of these considerations, our study aimed to investigate the association between interim imaging responses and clinical outcomes. Through the use of multiple imaging assessment tools, we sought to identify patients who might benefit from intensified or adjusted treatment regimens.

METHOD

This retrospective analysis encompassed 90 patients diagnosed with DLBCL and 67 patients with HL, all of who had been monitored at the department of hematology in a tertiary care center. Clinical data were retrieved from the medical archives of the same institution.

The inclusion criteria for the study were as follows: patients aged ≥ 18 years who had available imaging data from pre-treatment, interim (following 2 to 4 cycles of therapy), and post-treatment time points.

Written informed consent was obtained from both patients and their legal guardians or relatives. Diagnosis and histological subtypes were classified in accordance with the World Health Organization guidelines (2). Staging was based on the Ann Arbor classification system (2).

HL patients were divided into early-stage favorable, early-stage unfavorable, and advanced-stage disease, and the advanced-stage cohort was further stratified using the International Prognostic Score (IPS) into $IPS \leq 3$ and $IPS > 3$ according to IPS-7 criteria (9). For DLBCL patients, Ann Arbor staging was applied and risk categorization was conducted using the International Prognostic Index (IPI), resulting in three risk groups: low-risk (IPI 0–1), intermediate-risk (IPI 2–3), and high-risk (IPI 4–5) (10).

Collected data included demographic characteristics, disease subtype and stage, interim and final imaging findings, and survival outcomes such as PFS and OS. OS was defined as the time from initiation of treatment to the last follow-up date, whereas PFS was calculated from the treatment start date to the first occurrence of disease progression, relapse, or death due to lymphoma.

A total of 121 patients underwent both baseline and I-PET/CT; scans were interpreted independently by two nuclear medicine physicians under blinded conditions. Quantitative analysis involved measuring SUVmax using regions of interest (ROIs), accompanied by visual scoring. Treatment response was classified using the Deauville five-point scale, with scores ≤ 3 considered negative. Patients were thus categorized as I-PET/CT positive or negative. PPV and NPV values were determined separately for HL and DLBCL based on interim PET/CT status and post-treatment clinical outcomes. No artificial intelligence-based imaging software or automated

segmentation tools were used in this study; all PET/CT images were interpreted visually and semi-quantitatively by experienced nuclear medicine physicians.

Additionally, patients were grouped into four response categories using the Lugano PET/CT-based response criteria as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD).

Contrast-enhanced CT (I-CT) was performed both before and during treatment in 53 patients. These scans were independently reviewed by two radiologists, also blinded to clinical data. Five target lesions per patient—commonly including the spleen and liver—were selected for bidimensional measurement at baseline and interim imaging.

Anatomical response evaluation on contrast-enhanced CT was performed using both Response Evaluation Criteria in Solid Tumors (RECIST 1.1) and Lugano CT-based classification, focusing on changes in the longest axial diameter of target lesions.

Patients were assigned to CR, PR, SD, or PD categories based on anatomical response. End-of-treatment evaluations were conducted using a combination of imaging reports and clinical follow-up records.

The agreement between interim PET/CT-based Lugano responses and CT-based responses (via both RECIST 1.1 and Lugano criteria) was analyzed using kappa statistics. Kappa analysis was also used to compare interim imaging findings with final treatment outcomes to assess the relative diagnostic utility of I-PET/CT and I-CT.

Statistical analyses were conducted using SPSS version 22.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were computed for all variables. Survival analyses were carried out using Kaplan–Meier estimates, and intergroup comparisons were evaluated using the log-rank test. A p-value less than 0.05 was considered statistically significant.

Interpretation of kappa agreement strength was as follows:
0.00–0.20: no agreement,
0.21–0.40: minimal agreement,
0.41–0.60: weak agreement,
0.61–0.80: moderate agreement,
0.81–1.00: strong agreement.

RESULTS

A total of 157 patients, monitored at the hematology department of a tertiary care center prior to the cutoff date of June 1, 2018, were enrolled in this study. Demographic information and survival outcomes are detailed in Table 1. When analyzed by diagnosis, patients with HL exhibited a 90% survival rate over a 99-month observation period. In contrast, those with DLBCL demonstrated an 83.7% survival rate during the same timeframe. This difference was statistically significant

in favor of HL ($p = 0.028$) (Figure 1).

Table 1. Patient demographics and clinical data

	HL	DLBCL
Age, years (median-range)	34.02 (16-76)	55.97 (18-82)
Female/Male	33/34	41/49
Progression free survival, months (Median-Range)	48 (6-99)	40 (2-94)
Overall survival, months (Median-Range)	56 (4-99)	35 (1-96)

HL: Hodgkin lymphoma, DLBCL: Diffuse large B-cell lymphoma

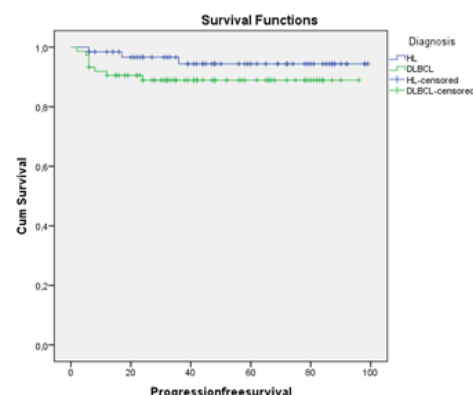


Figure 1. Kaplan–Meier Curves for Progression-Free Survival by Lymphoma Subtype (HL vs. DLBCL)

Among DLBCL patients who underwent both PET/CT and I-CT, 2 out of 8 showed negative I-CT results despite positive findings on I-PET/CT. Conversely, in the HL group, 3 of 9 patients had positive I-CT results while their I-PET/CT scans were negative.

When kappa statistics were applied to assess agreement across imaging modalities in the full cohort, no substantial concordance was observed between I-PET/CT-based Lugano classifications and those derived from I-CT using either Lugano or RECIST 1.1 criteria ($\kappa=0.073$ and $\kappa=0.023$, respectively). In contrast, a stronger level of agreement was identified between I-PET/CT responses and final treatment outcomes ($\kappa=0.434$), compared to the lower agreement observed with both Lugano-based I-CT ($\kappa=0.047$) and RECIST 1.1 ($\kappa=0.071$).

The diagnostic performance of I-PET/CT was further evaluated by calculating PPV and NPV based on post-treatment disease status. In HL patients, PPV and NPV were 36% and 95.4%, respectively; in the DLBCL group, these values were 61.9% and 93.1%. Regarding long-term outcomes, the seven-year PFS was 54% among HL patients with positive I-PET/CT findings and 83% among those with negative scans. For DLBCL patients, PFS rates were 20% and 79% in I-PET/CT positive and negative groups, respectively. A summary of these

findings is provided in Table 2.

Table 2. Correlation between I-PET/CT predictive values and progression-free survival

	Number of Patients	Stage	PPV	NPV	7 years PFS (+)	7 years PFS (-)
HL	55	I-IV	36%	95.4%	54%	83%
DLBCL	66	I-IV	61.9%	93.18%	20%	79%

I-PET / CT: interim positron emission tomography/computed tomography, HL: Hodgkin Lymphoma, DLBCL: diffuse large B-cell lymphoma, PPV: positive predictive value, NPV: negative predictive value, PFS: progression free survival

Further subgroup analyses of HL patients, stratified by risk groups, are presented in Tables 3 and 4, including corresponding PPV and NPV values. Similar data for DLBCL patients are detailed in Tables 5 and 6.

Table 3. Characteristics of Hodgkin lymphoma patients

		Number of patients
Histologic subtypes	NSHL	36
	MCHL	10
	LRHL	5
	LDHL	NA
	NLPHL	16
Stage and risk assessment	Early-stage favorable disease	11
	Early-stage unfavorable disease	21
	Advanced stage disease IPS≤3	29
	Advanced stage disease IPS>3	6
Interim PET/CT Deauville score	1	31
	2	4
	3	9
	4	5
	5	6

NSHL: nodular sclerosis Hodgkin lymphoma, MCHL: mixed cellularity Hodgkin lymphoma, LRHL: lymphocyte-rich Hodgkin lymphoma, LDHL: lymphocyte-depleted Hodgkin lymphoma, NLPHL: nodular lymphocyte-predominant Hodgkin lymphoma

Table 4. Hodgkin lymphoma patients, I-PET/CT PPV and NPV according to risk groups

Risk group	Number of patients	PPV	NPV
Early-stage, favorable	11	NA	100%
Early-stage, unfavorable	17	50%	100%
Advanced stage IPS ≤ 3	22	40%	88%
Advanced stage IPS > 3	5	50%	100%

I-PET / CT: interim positron emission tomography/computed tomography, PPV: positive predictive value, NPV: Negative predictive value, IPS: international prognostic score

Table 5. Characteristics of DLBCL patients

		Number of patients
Stage	I	7
	II	16
	III	16
	IV	51
Risk assessment	Low risk (IPI 0-1)	27
	Moderate risk (IPI 2-3)	38
	High risk (IPI 4-5)	25
I-PET/CT Deauville score	1	29
	2	7
	3	8
	4	8
	5	13
	X	1

DLBCL: diffuse large B-cell lymphoma, I-PET / CT: interim positron emission tomography/computed tomography, IPI: international prognostic index

DISCUSSION

HL accounts for nearly 10% of all lymphoid malignancies and represents approximately 0.6% of all newly diagnosed cancer cases globally. In the United States, annual estimates suggest around 8,260 new cases and 1,070 deaths, while in Europe the incidence rate is approximately 2.4 per 100,000 individuals (11,12). Thanks to therapeutic advancements, HL is now considered a largely curable disease, with global cure rates approaching 75%. However, late complications associated with treatment have become a major cause of long-term morbidity and mortality. Hence, current therapeutic strategies emphasize both curative intent and reduction of long-

term toxicity.

DLBCL, representing about 25% of all NHL, remains the most prevalent subtype in this category (13–15). The incidence of DLBCL is estimated at roughly 7 per 100,000 in the US and UK, and 4.92 per 100,000 in Europe (12,13,16). While standard immunochemotherapy (e.g., R-CHOP) achieves long-term remission in approximately 60% of patients (17), early identification of poor responders remains critical for optimizing clinical outcomes. Incorporating prognostic tools into early treatment phases can help improve patient stratification and reduce unnecessary toxicity.

The incorporation of 18F-FDG PET/CT into lymphoma care has markedly improved staging accuracy and response monitoring, outperforming older imaging techniques such as CT and gallium scans. Persistent FDG uptake post-therapy serves as a reliable indicator of active disease rather than post-treatment inflammation (18). Thus, PET/CT has become a cornerstone in both the initial assessment and longitudinal follow-up of lymphoma patients.

Despite its broad availability and cost-effectiveness, conventional CT has several drawbacks. It lacks sensitivity for small or extranodal lesions (19) and cannot reliably distinguish viable disease from fibrosis or necrosis following treatment, which may lead to false assessments (5,20).

In the present study, we observed notable discrepancies between CT-based and PET/CT-based assessments at the interim stage. In the DLBCL group, CT failed to detect positive responses in two cases that were PET-positive, whereas in the HL group, three CT-positive patients had negative I-PET/CT scans. These mismatches underscore the metabolic limitations of anatomical imaging.

The superior prognostic performance of PET/CT has been consistently supported in previous research. For instance, one study revealed stage migration in 8% of lymphoma cases when PET/CT replaced CT in staging (21). In early-stage HL treated with ABVD, I-PET/CT has demonstrated strong negative predictive value (NPV), though positive predictive value (PPV) tends to be the modest in advanced disease (22–25). Furthermore, I-PET/CT has outperformed traditional indices like the IPS in forecasting survival (22,26,27).

In our HL subgroup, I-PET/CT yielded a PPV of 36% and an NPV of 95.4%, with seven-year progression-free survival (PFS) rates of 54% and 83% for PET-positive and PET-negative patients, respectively. These results align with a meta-analysis by Terasawa et al., which demonstrated substantial PFS differences between PET-2–positive and PET-2–negative patients in advanced HL (24).

In DLBCL, while earlier studies emphasized a strong association between I-PET/CT and clinical outcomes (28–31), more

recent reports have shown mixed results (32–34). For example, Mamot et al. reported two-year event-free survival rates of 76% for PET-negative and 41% for PET-positive patients (35). Our findings were consistent, with PPV and NPV values of 61.9% and 93.1%, and seven-year PFS rates of 20% and 79% for PET-positive and PET-negative individuals, respectively. Kong et al. also proposed a prognostic index integrating age ≥ 60 years, stage III/IV, non-GCB subtype, and positive I-PET/CT to enhance risk stratification (36).

To improve predictive accuracy, the GELA group advocated for the inclusion of Δ SUVmax, suggesting that a $\geq 66\%$ reduction was more reliable than visual assessment alone (31,37–39). Our findings support those of Duarte et al., who demonstrated that combining Δ SUVmax with the Deauville score improved prognostic accuracy (7). Zhao and colleagues added that changes in Δ SUVmax(LLR), total metabolic tumor volume (Δ TMTV), and total lesion glycolysis (Δ TLG) were significantly associated with poorer outcomes [40]. Although our study did not incorporate advanced quantitative or AI-assisted PET metrics such as TMTV, TLG, Δ SUVmax or lesion-based SUV ratios, these parameters are increasingly recognized for providing a more comprehensive assessment of metabolic tumor burden and reducing interobserver variability through semi-automated and AI-supported segmentation.

Recent evidence also questions the sufficiency of visual analysis alone. Studies by Ferrari and Li showed that lesion-to-liver SUV ratio (LLR) provides better specificity than Deauville scores (41,42). Gao et al. further identified interim lesion-to-liver maximum standardized uptake value ratio (RLL) and bone marrow involvement as predictors of incomplete metabolic remission, reinforcing the utility of quantitative imaging parameters (43). In this context, interim RLL has been used as a quantitative parameter expressing the ratio between the maximum SUV of residual lesions and liver uptake. Incorporating these emerging metabolic biomarkers alongside visual Deauville scoring may enhance prognostic precision, particularly in patients with heterogeneous disease biology or ambiguous interim PET findings.

Moreover, spatial dissemination indices such as SDmax, particularly when used with TMTV, have been shown to enhance baseline prognostic modeling in DLBCL (44). The integration of AI tools into imaging workflows is also promising. Capobianco et al. showed that PET-assisted reporting systems (PARS) offered TMTV estimates on par with expert evaluations and were predictive of survival outcomes (45). Similarly, Veziroğlu et al. demonstrated that AI-driven segmentation significantly reduced interobserver variability and improved the reproducibility of PET analyses (46). Thus, quantitative and AI-assisted PET tools may complement conventional interim PET/CT interpretation and support more individualized es-

calation or de-escalation strategies in future treatment algorithms.

Collectively, these technological innovations support a personalized oncology approach in which imaging biomarkers guide early therapeutic decisions. Despite its limitations, our study confirms the utility of I-PET/CT in prognosticating both HL and DLBCL and supports its incorporation into risk-adapted treatment protocols.

Limitations of the Study

Several limitations of this study should be considered. First, the retrospective design introduces a potential for selection bias and restricts causal inference. Second, as a single-center analysis with relatively small subgroups—particularly those undergoing both interim CT and PET/CT—the findings may not be widely generalizable. Third, the lack of simultaneous imaging for all patients could have compromised the strength of the modality comparisons. Additionally, key quantitative PET/CT parameters such as Δ SUVmax and TMTV were not available for every patient, potentially limiting the precision of response evaluations. Lastly, although long-term outcomes such as seven-year PFS were assessed, incomplete follow-up data in some cases may have introduced attrition bias. Future prospective, multicenter trials with standardized imaging protocols are essential to validate and expand upon these findings.

CONCLUSION

Interim PET/CT demonstrated superior prognostic performance compared to contrast-enhanced CT in both HL and DLBCL. PET negativity was strongly associated with favorable PFS, supporting its role in guiding response-adapted treatment strategies. While PET-positive results may indicate higher risk, treatment escalation based solely on positivity should be approached cautiously. Therefore, future prospective research integrating TMTV, TLG, Δ SUVmax, and automated or AI-assisted PET quantification may offer additional prognostic value beyond visual interim evaluation alone.

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Ethical Declaration: Ethical permission was obtained from the Dokuz Eylül University, Non-interventional Research Ethics Committee for this study number 2018/11-19 at 03.05.2018, and Helsinki Declaration rules were followed to conduct this study.

Authorship Contribution: Concept: GHÖ, EE, Design: GHÖ, EE, Supervising: GHÖ, ÖÖ, MS, Data collection and entry: EE, AŞ, AA, HAÖ, Analysis and interpretation: EE, AŞ Literature search: EE Writing: EE, AŞ, GHÖ, Critical review: GHÖ

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