

Role of ¹⁸F-FDG PET/CT Metabolic Parameters in Treatment Response Evaluation and Prognostic Assessment of Hodgkin Lymphoma: A Retrospective Analysis

Hodgkin Lenfoma Tedavi Yanıtının Değerlendirilmesi ve Prognostik Değerlendirmesinde ¹⁸F-FDG PET/CT Metabolik Parametrelerinin Rolü: Retrospektif Bir Analiz

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Abstract

Objective: This study aimed to evaluate the predictive value of volumetric metabolic parameters and their longitudinal changes from ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT) for progression-free survival (PFS) and overall survival (OS) in Hodgkin lymphoma (HL).

Materials and Methods: Metabolic tumor volume (MTV), total lesion glycolysis (TLG), and maximum standardized uptake value (SUVmax) were calculated from the baseline, interim, and post-treatment PET/CT scans of 63 adult patients with HL. Delta (Δ) parameters representing percentage changes were computed. Cox regression and Kaplan-Meier analyses were performed. Receiver operating characteristic curve analysis was applied to determine optimal cut-offs for baseline parameters; median dichotomization was used for delta metrics.

Results: Pre-treatment MTV1 was significantly higher in patients with progression (650.98 \pm 751.34 vs. 354.15 \pm 306.72 cm³, p=0.048) and non-survivors (916.91 \pm 1040.12 vs. 369.44 \pm 310.39 cm³, p=0.024). Interim and post-treatment parameters showed similar associations (p \leq 0.02 for all). Cox regression confirmed MTV1 and TLG1 as significant predictors for both PFS and OS (p \leq 0.027). Notably, long-interval metabolic changes (Δ MTV₁₋₃, Δ TLG₁₋₃, Δ SUVmax₁₋₃) demonstrated strong prognostic significance (p \leq 0.007 for all), with Δ SUVmax₁₋₃ independently predicting PFS (hazard ratio: 0.30, 95% confidence interval: 0.12-0.76; p=0.011). Optimal baseline MTV1 cut-offs were 232 cm³ for PFS and 308 cm³ for OS.

Öz

Amaç: Bu çalışma, ¹⁸F-florodeoksiglukoz pozitron emisyon tomografisi/bilgisayarlı tomografiden (PET/BT) elde edilen volumetrik metabolik parametrelerin ve bunların uzunlamasına değişikliklerinin Hodgkin lenfomada (HL) progresyonsuz sağkalım (PFS) ve genel sağkalım (OS) için öngörü değerini değerlendirmeyi amaçlamıştır.

Gereç ve Yöntemler: Altmış üç yetişkin HL hastasının başlangıç, ara ve tedavi sonrası PET/BT taramalarından metabolik tümör hacmi (MTV), total lezyon glikolizi (TLG) ve maksimum standardize tutulum değeri (SUVmaks) hesaplandı. Yüzde değişiklikleri temsil eden delta (Δ) parametreleri hesaplandı. Cox regresyon ve Kaplan-Meier analizleri yapıldı. Başlangıç parametreleri için alıcı işletim karakteristiği eğrisi analizi; delta metrikleri için medyan dikotomizasyonu kullanıldı.

Bulgular: Tedavi öncesi MTV1, progresyon yaşayan hastalarda (650,98 \pm 751,34'e karşı 354,15 \pm 306,72 cm³, p=0,048) ve hayatta kalmayan hastalarda (916,91 \pm 1040,12'ye karşı 369,44 \pm 310,39 cm³, p=0,024) anlamlı derecede yüksekti. Ara ve tedavi sonrası parametreler benzer ilişkiler gösterdi (tümü p \leq 0,02). Cox regresyon, MTV1 ve TLG1'in hem PFS hem de OS için anlamlı öngörücüler olduğunu doğruladı (p \leq 0,027). Özellikle, uzun aralıklı metabolik değişiklikler (Δ MTV₁₋₃, Δ TLG₁₋₃, Δ SUVmax₁₋₃) güçlü prognostik önem gösterdi (tümü p \leq 0,007), Δ SUVmaks₁₋₃ bağımsız olarak PFS'yi öngördü (risk oranı: 0,30, %95 güven aralığı: 0,12-0,76; p=0,011). Optimal başlangıç MTV1 kesim değerleri PFS için 232 cm³ ve OS için 308 cm³ idi.

Sonuç: Başlangıç volumetrik parametreler ve uzun aralıklı metabolik değişiklikler HL'de güçlü prognostik belirteçlerdir. Δ SUVmax₁₋₃, başlangıç ölçümlerinin ötesinde ek risk sınıflandırması sağlar ve dinamik PET metriklerinin klinik uygulamaya entegrasyonunu destekler.



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Abstract

Conclusion: Baseline volumetric parameters and long-interval metabolic changes are powerful prognostic markers in HL. $\Delta\text{SUV}_{\text{max}_{1-3}}$ provides additional risk stratification beyond baseline measurements, supporting the integration of dynamic PET metrics into clinical practice.

Keywords: Hodgkin lymphoma, Positron emission tomography, Metabolic tumor volume, Total lesion glycolysis, Prognosis, $\Delta\text{SUV}_{\text{max}}$, ΔMTV , ΔTLG

Öz

Anahtar Sözcükler: Hodgkin lenfoma, Pozitron emisyon tomografisi, Metabolik tümör hacmi, Total lezyon glikolizi, Prognoz, $\Delta\text{SUV}_{\text{maks}}$, ΔMTV , ΔTLG

Introduction

Hodgkin lymphoma (HL) is a significant hematological malignancy with an estimated 83,000 new cases and 23,000 deaths worldwide in 2022, showing a particularly notable incidence in young adults [1]. Accounting for approximately 10% of all lymphomas, HL originates from germinal center B-cells [2]. While modern treatment strategies achieve high cure rates, especially in early-stage disease (73%-85%), a significant proportion of patients develop primary refractory disease (5%-10%) or relapse (10%-30%), leading to worsened prognosis [3]. Therefore, identifying reliable prognostic factors is crucial for optimizing treatment strategies and accurately stratifying patients into risk groups.

Tumor burden has long been considered one of the most powerful prognostic parameters in HL [4]. It reflects not only the extent of the disease but also its biological aggressiveness. ^{18}F -fluorodeoxyglucose (^{18}F -FDG) positron emission tomography/computed tomography (PET/CT) offers a unique opportunity to quantitatively measure this burden [5,6]. Metabolic parameters derived from FDG PET/CT, such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG), allow the simultaneous evaluation of the functionally active volume and metabolic activity of the tumor.

Numerous studies in recent years have demonstrated that baseline MTV and TLG are independent prognostic factors in HL [7,8], and a recent review further confirmed this finding [9]. Their roles in predicting treatment response have also been shown [10]. Furthermore, new metrics that include not only volumetric parameters but also tumor dissemination (e.g., $\text{tMTV}/\text{D}_{\text{max}}\text{Vox}$) have been reported to have prognostic value [11].

However, the prognostic value of these metabolic parameters at different time points during treatment, especially interim and post-treatment, and their interrelationships have not yet been fully elucidated. Recent studies in the pediatric population particularly emphasize the critical role of quantitative data obtained from interim PET in predicting survival [12,13]. This suggests that a similar dynamic might exist in adult patients, warranting further investigation.

Therefore, the aim of this study was to retrospectively investigate the predictive power of MTV and TLG values obtained from pre-treatment, interim, and post-treatment FDG-PET/CT scans for progression-free survival (PFS) and overall survival (OS) in adult patients with HL.

Materials and Methods

Study Design and Patient Population

This retrospective study was conducted in the Pamukkale University Medical Faculty's Department of Hematology and was approved by the Pamukkale University Non-interventional Clinical Research Ethics Committee (date: 24.11.2020, decision no: 22). We identified 118 patients diagnosed with HL between January 2012 and January 2020 from the nuclear medicine archives. After a detailed review of the hospital information systems, 63 adult patients aged >18 years who met the inclusion criteria were enrolled. The inclusion criteria were histopathologically confirmed HL and available baseline, interim, and post-treatment PET/CT scans. Patients with a history of autoimmune disease, secondary malignancy, or incomplete imaging data were excluded. To minimize false-positive FDG uptake, patients with active infection or elevated inflammatory markers at the time of PET/CT were excluded after clinical and laboratory evaluation. Clinical, laboratory, and follow-up data, including progression and survival status, were collected from patient records.

^{18}F -FDG PET/CT Imaging Protocol

All PET/CT scans were performed with a Gemini TF TOF PET/CT scanner (Philips, Cleveland, OH, USA). Patients were required to fast for at least 4 hours, with serum glucose levels between 70 and 200 mg/dL. An intravenous injection of 0.09-0.12 mCi/kg (250-400 MBq) of ^{18}F -FDG was administered. Whole-body imaging was performed approximately 60 minutes after the injection. Low-dose CT (50-120 mAs, 90-140 kVp, 5-mm slice thickness) was used for attenuation correction and anatomical localization, without intravenous contrast. PET images were reconstructed using a three-dimensional ordered subset expectation maximization algorithm (33 subsets, 3 iterations) with time-of-flight correction.

Image Analysis and Volumetric Parameters

Images were analyzed with a Philips Fusion Viewer workstation by two experienced nuclear medicine physicians. For each lesion, a three-dimensional volume of interest was drawn. The MTV was automatically calculated by the workstation, delineating all spatially connected voxels within a threshold of 40% of the maximum standardized uptake value (SUVmax). Total MTV (tMTV) for each patient was defined as the sum of MTVs from all individual lesions. TLG was calculated by multiplying the MTV of each lesion by its mean SUV. Global TLG was taken as the sum of all individual TLGs. Response assessment was performed using the 5-point Deauville scale. Volumetric parameters were calculated from baseline (pre-treatment: MTV1, etc.), interim (after 2-4 cycles of chemotherapy: MTV2, etc.), and post-treatment (MTV3, etc.) PET/CT scans.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics 22.0 (IBM Corp., Armonk, NY, USA). Continuous variables were compared using the Student t-test or Mann-Whitney U test based on normality as assessed by the Shapiro-Wilk test. Categorical variables were compared using the chi-square or Fisher exact test. Kaplan-Meier analysis with the log-rank test was used to evaluate OS and PFS. Cox regression analysis was performed to identify independent prognostic factors. Receiver operating characteristic (ROC) curve analysis was used to determine optimal cut-off values for MTV and TLG to predict outcomes. Values of $p < 0.05$ were considered statistically significant.

Results

Patient Characteristics and Outcomes

A total of 63 patients (41 male, 65.1%; 22 female, 34.9%) were included in the final analysis. The median age was 32 years (range: 18-78), and the median follow-up was 75 months (range: 11-118). During the follow-up period, 18 patients (28.6%) experienced disease progression and 8 patients (12.7%) died. The most common histological subtype was nodular sclerosis (49.2%), followed by mixed cellularity (34.9%). At baseline, 57 patients (90.5%) had advanced-stage disease (Ann Arbor Stage \geq III or Stage II with \geq 3 nodal sites). Detailed patient characteristics are summarized in Table 1. The OS curve for all patients is shown in Figure 1.

Association of Volumetric Parameters with Progression

At baseline, patients who later experienced progression had a significantly higher mean tMTV1 compared to non-progressing patients ($650.98 \pm 751.34 \text{ cm}^3$ vs. $354.15 \pm 306.72 \text{ cm}^3$; $p=0.048$). A significant difference was not observed for baseline SUVmax1 or TLG1. At the interim PET scan, patients with progression

had significantly higher mean tMTV2, SUVmax2, and tTLG2 values ($p=0.01$, $p=0.017$, and $p=0.012$, respectively). Similarly, at the post-treatment PET scan, all volumetric parameters (tMTV3, SUVmax3, tTLG3) were significantly higher in the group with progression ($p < 0.001$ for all). In addition to the absolute metabolic values, the dynamic changes in MTV, TLG, and SUVmax between baseline, interim, and post-treatment PET/CT scans demonstrated a strong association with disease progression. Patients who experienced progression had a significantly higher

Table 1. Demographic and clinical characteristics of study patients.

Characteristic	Value (n=63)
Age, years, mean \pm SD	36.44 \pm 16.05
Sex, n (%)	
Male	41 (65.1)
Female	22 (34.9)
Laboratory findings, mean \pm SD	
LDH, U/L	248.75 \pm 109.97
Hemoglobin, g/dL	12.3 \pm 2.53
WBC count, $\times 10^9/L$	9.45 \pm 5.72
Lymphocyte count/ μL	1650.38 \pm 886.11
Albumin, g/dL	4.06 \pm 0.68
CRP, mg/L	4.92 \pm 6.42
ESR, mm/h	45.22 \pm 30.97
Follow-up data, mean \pm SD	
Progression-free survival, months	59.29 \pm 37.09
Overall survival, months	72.38 \pm 28.81

SD: Standard deviation; LDH: lactate dehydrogenase; WBC: white blood cell; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.

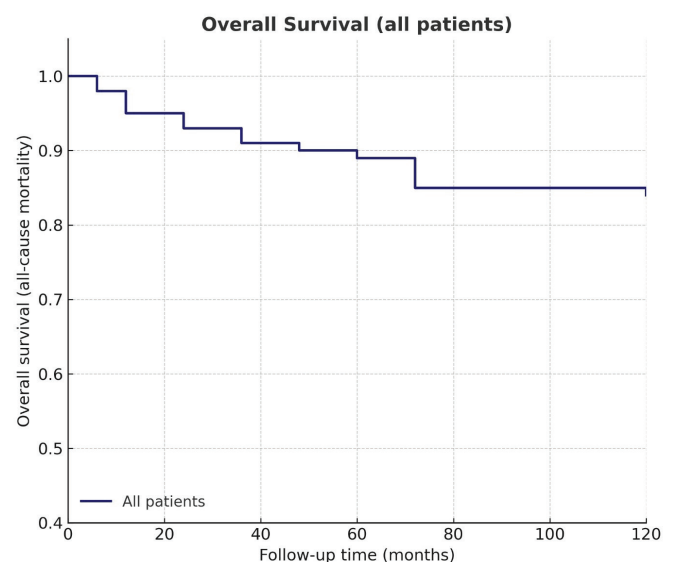


Figure 1. Kaplan-Meier curve showing overall survival of all patients during follow-up.

initial metabolic tumor burden, with markedly elevated MTV1 values at baseline. Although SUVmax1 did not differ significantly between the groups, both MTV1 and TLG1 tended to be higher in the group with progression, reflecting a more aggressive metabolic phenotype at presentation.

At the interim PET scan, patients with progression had substantially higher MTV2, SUVmax2, and TLG2 values, indicating inadequate early metabolic response to chemotherapy ($p < 0.02$ for all). These findings highlight the importance of early metabolic assessment and suggest that insufficient reduction in volumetric or glycolytic activity during early treatment may serve as an early indicator of treatment resistance.

Post-treatment PET parameters demonstrated the clearest separation between the groups. MTV3, SUVmax3, and TLG3 were all significantly higher in patients with progression ($p = 0.001$ for all), underscoring the prognostic importance of residual metabolic activity after completion of therapy. Persistent volumetric or metabolic activity at the end of treatment strongly correlated with poor clinical outcomes.

Analysis of percentage changes revealed that patients with progression experienced significantly smaller metabolic reductions from baseline to interim imaging for all parameters (ΔMTV_{1-2} , ΔTLG_{1-2} , $\Delta SUVmax_{1-2}$). Moreover, reductions from baseline to post-treatment PET (ΔMTV_{1-3} , ΔTLG_{1-3} , $\Delta SUVmax_{1-3}$) also differed markedly between the two groups, with the progression group demonstrating substantially less decline or, in some cases, paradoxical increases. These findings collectively indicate that both the magnitude and the trajectory of metabolic change across the course of treatment are strongly associated with treatment outcomes.

These results are detailed in Table 2. The OS curves for patients with and without disease progression are presented in Figure 2 and the PFS curve for all patients is shown in Figure 3.

Association of Volumetric Parameters with Overall Survival

Patients who died during follow-up had significantly higher baseline MTV1 ($916.91 \pm 1040.12 \text{ cm}^3$ vs. $369.44 \pm 310.39 \text{ cm}^3$; $p = 0.024$) and TLG1 (2275.56 ± 2132.41 vs. 941.95 ± 823.81 ; $p = 0.039$) compared to survivors. At the post-treatment scan, MTV3, SUVmax3, and TLG3 were also significantly higher in

Table 2. Comparison of pre-treatment, interim, and post-treatment PET/CT metabolic parameters between patients with and without disease progression.

Parameter	Total (n=63)	No progression (n=45)	Progression (n=18)	p
Pre-treatment parameters				
MTV1, cm ³	438.96±489.71	354.15±306.72	650.98±751.34	0.048*
SUVmax1	8.77±3.78	8.72±4.31	8.87±2.0	0.361
TLG1	1111.3±1142.29	915.14±829.25	1601.7±1619.41	0.08
Interim parameters				
MTV2, cm ³	4.7±11.1	2.2±6.4	10.9±16.9	0.01*
SUVmax2	1.2±2.55	0.7±1.73	2.47±3.69	0.017*
TLG2	9.6±25.3	4.3±12.0	23.0±41.2	0.012*
Post-treatment parameters				
MTV3, cm ³	26.4±89.1	1.3±3.8	89.0±151.9	0.001*
SUVmax3	1.76±2.95	0.6±1.47	4.69±3.68	0.001*
TLG3	58.48±208.77	2.74±7.58	197.82±360.58	0.001*
Percent change parameters (Δ)				
ΔMTV ₁₋₂ , %	-95.20±22.77	-94.36±26.78	-97.29±5.37	0.033*
ΔMTV ₂₋₃ , %	158.46±583.16	-66.19±56.09	355.03±763.44	0.300
ΔMTV ₁₋₃ , %	-89.63±41.62	-97.12±10.46	-70.91±74.26	0.000*
ΔTLG ₁₋₂ , %	-93.16±38.12	-91.87±44.78	-96.37±9.69	0.035*
ΔTLG ₂₋₃ , %	476.15±1583.78	-65.33±63.94	949.94±2112.69	0.300
ΔTLG ₁₋₃ , %	-93.99±16.41	-97.12±10.18	-86.15±24.96	0.000*
ΔSUVmax ₁₋₂ , %	-82.28±41.25	-86.31±39.70	-72.21±44.45	0.027*
ΔSUVmax ₂₋₃ , %	-30.33±99.66	-65.87±49.91	0.77±123.94	0.360
ΔSUVmax ₁₋₃ , %	-77.56±37.79	-90.99±22.57	-43.97±47.11	0.000*

*: Statistically significant ($p < 0.05$), Mann-Whitney U test. Data are presented as mean ± standard deviation. PET/CT: Positron emission tomography/computed tomography; MTV: metabolic tumor volume; SUVmax: maximum standardized uptake value; TLG: total lesion glycolysis.

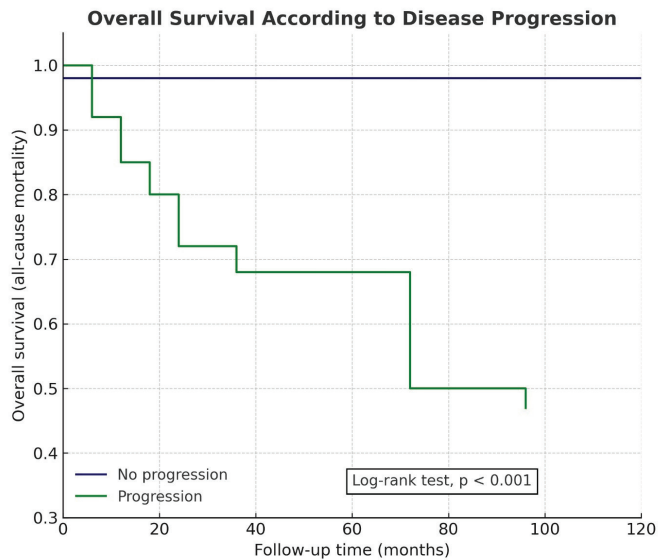


Figure 2. Kaplan-Meier curves for overall survival according to disease progression status. Patients with progression had significantly worse overall survival compared to those without progression (log-rank test, $p < 0.001$).

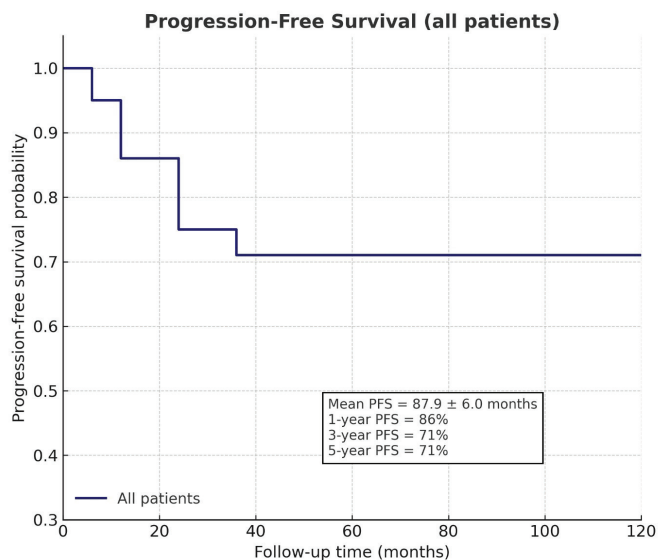


Figure 3. Kaplan-Meier curve showing progression-free survival (PFS) for all patients. The mean PFS was 87.9 ± 6.0 months. Estimated 1-, 3-, and 5-year PFS rates were 86%, 71%, and 71%, respectively.

non-survivors ($p < 0.001$, $p = 0.002$, and $p < 0.001$, respectively). These results are detailed in Table 3. Patients who died during follow-up had markedly higher metabolic tumor burden at baseline compared to survivors. Both MTV1 and TLG1 were significantly elevated in non-survivors ($p = 0.024$ and $p = 0.039$, respectively), suggesting that extensive disease burden and high glycolytic activity at diagnosis are strongly associated with poorer OS. In contrast, baseline SUVmax1 did not differ significantly, indicating that volumetric and glycolytic tumor

metrics are more prognostically relevant for OS than single-voxel intensity measurements.

The interim PET/CT parameters of MTV2, SUVmax2, and TLG2 did not provide meaningful prognostic discrimination between survivors and non-survivors. This may be partly explained by the absence of early deaths in this cohort. Additionally, the relatively low lesion-to-background FDG uptake observed on interim PET scans may hinder optimal volumetric quantification, thereby reducing the accuracy and discriminatory capacity of interim metabolic parameters.

Post-treatment PET findings demonstrated the strongest association with mortality. Non-survivors had substantially higher MTV3, SUVmax3, and TLG3 values ($p \leq 0.002$ for all), indicating that persistent metabolic activity following the completion of therapy is a powerful predictor of poor survival outcomes. These results emphasize that the metabolic quality of the end-of-treatment response is critical for long-term prognosis.

Regarding percentage changes, most Δ parameters did not significantly differ between groups; however, ΔMTV_{1-3} , ΔTLG_{1-3} , and $\Delta\text{SUVmax}_{1-3}$ were significantly less favorable in non-survivors. These patients experienced either insufficient reductions or even paradoxical increases in metabolic activity, underscoring the prognostic relevance of long-term metabolic dynamics across treatment.

Collectively, these findings indicate that both the initial metabolic tumor load and the residual metabolic disease after treatment are strong predictors of OS, whereas interim measurements showed limited prognostic value in this sample.

Prognostic Value and Cut-Off Analysis

Univariate Cox regression analysis confirmed that baseline MTV1 and TLG1 were significant predictors for both PFS ($p = 0.002$ for both) and OS ($p = 0.027$ and $p = 0.018$, respectively). Post-treatment parameters (MTV3, SUVmax3, TLG3) also showed strong prognostic significance for both outcomes. Using ROC analysis, an optimal baseline tMTV1 cut-off value of 232 cm^3 was identified for predicting progression (area under the curve: 0.660, $p = 0.048$). The ROC curve for MTV1 in predicting mortality is shown in Figure 4. Kaplan-Meier analysis showed that patients with a baseline MTV1 of $\geq 232 \text{ cm}^3$ had significantly shorter PFS (log-rank $p = 0.048$). For OS, the optimal MTV1 cut-off was 308 cm^3 , which also significantly stratified patients (log-rank $p = 0.024$). The OS curves according to pre-treatment MTV1 values are presented in Figure 5 and PFS curves are presented in Figure 6.

In Kaplan-Meier analyses, dynamic metabolic parameters were dichotomized using median delta values. Both ΔTLG_{1-3} and

Table 3. Comparison of pre-treatment, interim, and post-treatment PET/CT metabolic parameters between surviving and deceased patients.

Parameter	Total (n=63)	Alive (n=55)	Deceased (n=8)	p
Pre-treatment parameters				
MTV1, cm ³	438.96±489.71	369.44±310.39	916.91±1040.12	0.024*
SUVmax1	8.77±3.78	8.72±3.94	9.09±2.6	0.457
TLG1	1111.3±1142.29	941.95 ± 823.81	2275.56±2132.41	0.039*
Interim parameters				
MTV2, cm ³	4.68±11.11	4.2±9.7	7.8±18.8	0.399
SUVmax2	1.2±2.55	1.19±2.64	1.32±1.92	0.481
TLG2	9.64±25.27	9.7±25.7	9.1±23.5	0.464
Post-treatment parameters				
MTV3, cm ³	26.38±89.08	13.7±61.2	113.9±177.2	0.001*
SUVmax3	1.76±2.95	1.3±2.51	4.97±3.89	0.002*
TLG3	58.48±208.77	34.24±169.45	225.13±357.99	0.001*
Percent change parameters (Δ)				
ΔMTV ₁₋₂ , %	-95.20±22.77	-94.64±24.33	-98.98±2.29	0.507
ΔMTV ₂₋₃ , %	158.46±583.16	195.14±647.05	11.73±193.52	0.704
ΔMTV ₁₋₃ , %	-89.63±41.62	-89.66±44.47	-89.39±9.42	0.007*
ΔTLG ₁₋₂ , %	-93.16±38.12	-92.22±40.76	-99.60±0.90	0.580
ΔTLG ₂₋₃ , %	476.15±1583.78	577.40±1766.51	71.14±296.43	0.704
ΔTLG ₁₋₃ , %	-93.99±16.41	-94.80±16.68	-88.43±14.07	0.005*
ΔSUVmax ₁₋₂ , %	-82.28±41.25	-81.50±43.68	-87.65±17.84	0.543
ΔSUVmax ₂₋₃ , %	-30.33±99.66	-24.23±106.40	-54.74±78.39	0.704
ΔSUVmax ₁₋₃ , %	-77.56±37.79	-83.61±30.77	-35.90±55.46	0.003*

*: Statistically significant (p<0.05), Mann-Whitney U test. Data are presented as mean ± standard deviation. PET/CT: Positron emission tomography/computed tomography; MTV: metabolic tumor volume; SUVmax: maximum standardized uptake value; TLG: total lesion glycolysis.

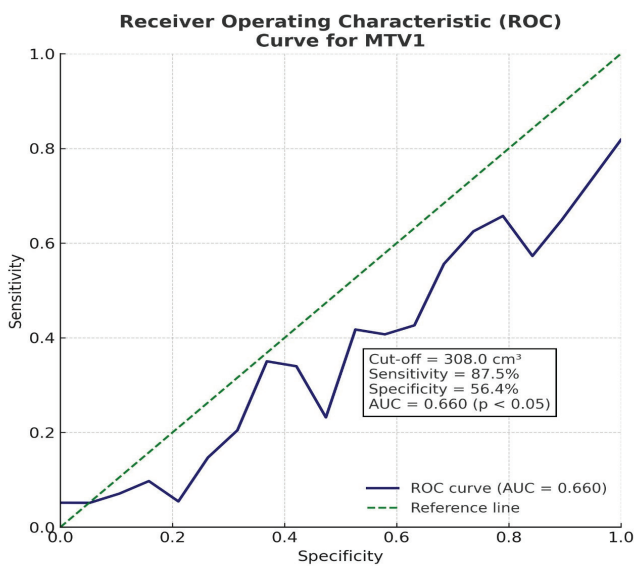


Figure 4. Receiver operating characteristic curve for pre-treatment metabolic tumor volume (MTV1) in predicting mortality. The optimal cut-off value was 308.0 cm³, yielding sensitivity of 87.5% and specificity of 56.4%, with an area under the curve (AUC) of 0.660 (p<0.05). The diagonal line represents the reference line (random classifier).

ΔSUVmax₁₋₃ had a median of -100%, resulting in two distinct groups: patients achieving complete metabolic resolution (Δ ≤ -100%), classified as the favorable-response group, and those with incomplete metabolic decline (Δ > -100%), categorized as poor responders. The refined Kaplan-Meier panel (Figure 7) demonstrated a clear prognostic gradient based on the extent of long-interval metabolic change. For PFS, both ΔTLG₁₋₃ and ΔSUVmax₁₋₃ showed significant curve separation, indicating that insufficient metabolic reduction was associated with markedly poorer outcomes (log-rank p<0.05). The prognostic value of ΔSUVmax₁₋₃ for PFS was further confirmed in the Cox proportional hazards model, where favorable responders exhibited a ~70% reduction in the risk of progression or death (hazard ratio: 0.30, 95% confidence interval: 0.12-0.76; p=0.011). For OS, ΔSUVmax₁₋₃ showed a similar but non-significant trend; the lack of statistical significance is likely attributable to the limited number of death events (n=8). Overall, these findings suggest that long-interval metabolic dynamics, spanning the entire treatment course, provide stronger prognostic discrimination than early or interim metrics alone.

Discussion

In this study, we investigated the prognostic value of MTV and TLG measured by ¹⁸F-FDG PET/CT at pre-treatment, interim, and post-treatment stages in patients with HL. Our primary finding is that baseline MTV1 is a strong and independent predictor for both PFS and OS. The MTV1 cut-off values determined by ROC analysis (232 cm³ for PFS and 308 cm³ for OS) significantly stratified patients into different risk groups at baseline.

This result is consistent with the prevailing view in the literature. Numerous studies have shown that high baseline MTV is associated with poor prognosis [7,8,14]. A recent review by Pellegrino Feres et al. [9] further reinforced this evidence. Our

findings not only confirm this general consensus in our own patient cohort but also provide specific, validated cut-off values, bringing these variables closer to clinical application. The 225 cm³ cut-off value identified by Kanoun et al. [7] is remarkably close to our finding of 232 cm³ for PFS, supporting the external validity of our results.

In a cohort of 179 patients, Pinochet et al. [15] reported 5-year PFS and OS rates of 70% and 87%, respectively, with the MTV cut-off of ≥ 217 cm³ being associated with significantly worse 5-year PFS (64% vs. 77%) compared to patients with lower MTV. The prospective RATHL trial [16] further strengthened this evidence by demonstrating the prognostic significance of

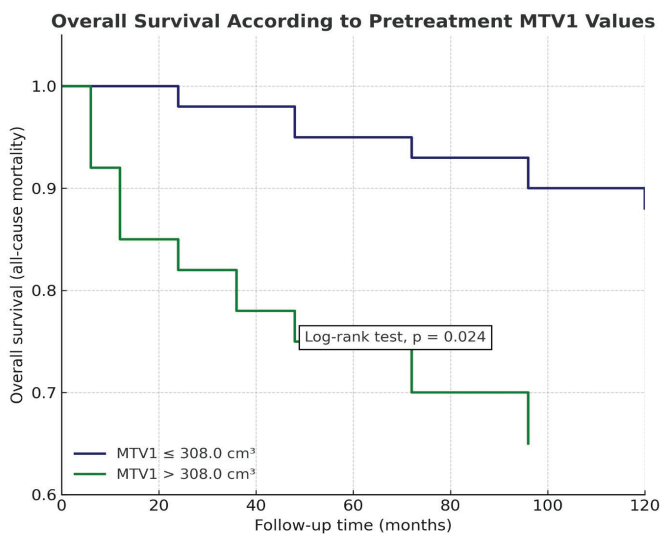


Figure 5. Kaplan-Meier curves for overall survival according to pre-treatment metabolic tumor volume (MTV1) values. Patients with MTV1 of >308.0 cm³ had significantly worse overall survival compared to those with MTV1 of ≤ 308.0 cm³ (log-rank test, $p=0.024$).

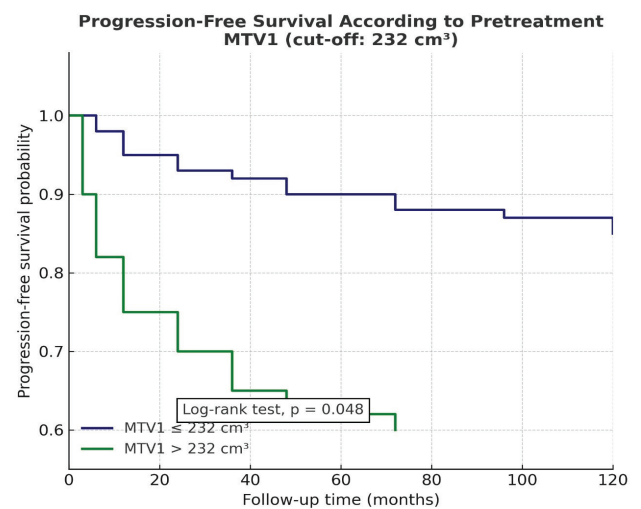


Figure 6. Kaplan-Meier curves for progression-free survival (PFS) according to pre-treatment metabolic tumor volume (MTV1) cut-off value of 232 cm³. Patients with MTV1 of >232 cm³ had significantly worse PFS compared to those with MTV1 of ≤ 232 cm³ (log-rank test, $p=0.048$).

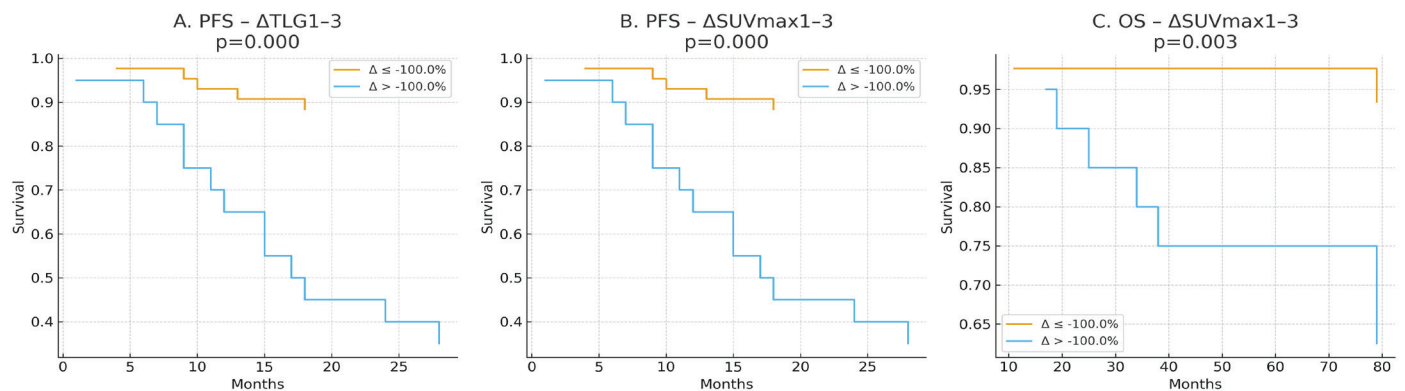


Figure 7. Kaplan-Meier curves for significant delta parameters. (A) Progression-free survival (PFS) stratified by the change in total lesion glycolysis from pre-treatment to post-treatment scan (ΔTLG_{1-3}); (B) PFS stratified by the change in maximum standardized uptake value from pre-treatment to post-treatment scan ($\Delta SUV_{max_{1-3}}$); (C) overall survival (OS) stratified by $\Delta SUV_{max_{1-3}}$. Median thresholds were -100.0% for ΔTLG_{1-3} and -100.0% for $\Delta SUV_{max_{1-3}}$. Patients with Δ values above the median exhibited significantly worse survival outcomes.

baseline PET parameters in 1214 patients with advanced-stage HL, thereby reinforcing the clinical utility of metabolic imaging parameters in risk stratification. Consistent with these findings, the H10 trial [17] involving 258 patients showed that high MTV was significantly associated with shorter PFS and OS (5-year PFS: 71% vs. 92.5%; 5-year OS: 83% vs. 98%). Additionally, Song et al. [8] demonstrated that elevated MTV correlated with poor PFS and OS in 127 patients, while Akhtari et al. [18] confirmed that baseline MTV serves as a reliable prognostic indicator for PFS and OS in patients with early-stage HL. Collectively, these findings offer a strong consensus that baseline MTV represents a robust prognostic indicator in HL across different stages and patient populations.

One of the most significant contributions of our study to the literature is its comprehensive analysis of three different time points during the treatment process, including baseline, interim, and post-treatment scans. Our findings indicate that not only the initial tumor burden but also the dynamics of treatment response are crucial determinants of prognosis. Specifically, the strong association of high MTV3 and TLG3 values observed in post-treatment PET/CT with both progression and death ($p < 0.001$) underscores the critical importance of the quality of metabolic response at the end of treatment for long-term outcomes. This suggests that quantitative volumetric analyses may be valuable in managing post-treatment residual masses, in addition to qualitative Deauville scores.

Our interim PET findings are also noteworthy. Patients who experienced progression had significantly higher MTV2 and TLG2 values measured on interim PET. This result parallels recent studies that emphasized the prognostic importance of interim PET parameters, particularly in the pediatric HL population [12,13]. Our confirmation of this in the adult population suggests that the significance of interim PET might extend beyond merely being “positive” or “negative” to “how positive” it is. However, the fact that interim PET parameters did not emerge as independent risk factors for PFS in Cox regression analysis might suggest that their prognostic power could be less dominant compared to baseline and post-treatment measurements, or that our patient number was insufficient to detect this effect. There are limited studies evaluating interim PET and post-treatment PET metabolic parameters in HL.

An additional strength of our study is the evaluation of percentage change (Δ) parameters across all three PET/CT time points, providing a dynamic perspective on metabolic response. While early Δ values (baseline to interim) did not show significant prognostic separation in our cohort, this finding was likely influenced by the absence of early deaths and the relatively low lesion-to-background FDG uptake on interim PET, which may limit precise volumetric quantification and reduce the discriminatory capacity of early metabolic markers. In contrast,

long-interval metabolic changes, particularly ΔMTV_{1-3} , ΔTLG_{1-3} , and $\Delta SUVmax_{1-3}$, were clearly associated with both progression and mortality, suggesting that sustained metabolic behavior throughout treatment may better capture cumulative disease resistance than static measurements alone.

Previous studies evaluating ΔMTV , ΔTLG , or $\Delta SUVmax$ in HL have reported variable prognostic significance across different patient populations and treatment settings. In pediatric populations, both Hussien et al. [19] and Kartal et al. [20] demonstrated that early metabolic changes between baseline and interim PET could predict outcomes. In adult HL patients, findings regarding early metabolic changes have been heterogeneous: Pinczés et al. [21] found that $\Delta SUVmax$ of $>88\%$ after 2 cycles was associated with longer PFS and that combining $\Delta SUVmax$ with the Deauville score further stratified patients. In contrast, Santos et al. [22] reported that among 234 patients with positive interim PET, only $\Delta SUVmax$ of $\geq 68.8\%$ was significant for PFS (hazard ratio: 0.31), while ΔMTV and ΔTLG did not reach significance. Similarly, Kovaleva et al. [23] found that $\Delta SUVmax$ of $<72\%$ was independently associated with inferior PFS (hazard ratio: 5.1), while ΔTLG and $\Delta TMTV$ achieved only univariate significance. However, Albano et al. [24] showed that longitudinal metabolic changes were independent prognostic factors for both PFS and OS in elderly HL patients. These discrepant findings, particularly regarding ΔMTV and ΔTLG , may reflect differences in patient populations, treatment regimens, and the timing of metabolic assessment. Notably, most prior studies have focused primarily on early changes (baseline to interim) or have been limited to two time points, and the HD18 trial [25] demonstrated that while baseline MTV failed to predict outcomes, metabolic response assessment remained prognostically relevant.

In contrast, our study extends this concept by incorporating three sequential PET time points in adult HL patients, demonstrating for the first time that late metabolic dynamics (i.e., changes from baseline to the end of treatment) hold independent prognostic significance for both PFS and OS beyond early metabolic response. This approach addresses the observation that interim PET changes alone may have limited or inconsistent prognostic value, while end-of-treatment metabolic assessment provides more robust outcome prediction. In particular, our finding that ΔMTV_{1-3} , ΔTLG_{1-3} , and $\Delta SUVmax_{1-3}$ all had independent prognostic significance suggests that cumulative metabolic changes over the entire treatment course may provide superior prognostic discrimination compared to early interval assessments. These results suggest that longitudinal changes in metabolic tumor burden over the entire treatment course may serve as an additional prognostic marker and may justify further evaluation in larger, prospective adult HL cohorts.

An important methodological observation from our analysis is that both ΔTLG_{1-3} and $\Delta SUVmax_{1-3}$ had a median value of -100% ,

indicating that more than half of the patients achieved complete metabolic normalization by the end of therapy. Thus, the long-interval delta parameters essentially function as a surrogate for distinguishing patients with complete metabolic response from those with residual metabolic activity. This may explain why Δ_{1-3} metrics demonstrated markedly stronger prognostic performance compared to early interim changes (Δ_{1-2}), as end-of-treatment metabolic status is biologically more relevant for long-term outcomes. These findings also align with the hypothesis that insufficient metabolic clearance rather than early partial response alone captures cumulative treatment resistance and residual disease biology. Therefore, the prognostic strength of long-interval delta parameters in our study likely reflects the clinical significance of achieving a true complete metabolic response, supporting the growing emphasis on end-of-treatment PET as the most powerful PET-based prognostic determinant in adult HL.

Another important methodological point concerns the selection of cut-off thresholds for dynamic metabolic parameters. Although ROC-derived cut-offs are frequently used for baseline PET metrics, they are less suitable for percentage-change-based delta parameters such as ΔMTV_{1-3} , ΔTLG_{1-3} , and $\Delta\text{SUVmax}_{1-3}$. Delta parameters are normalized, ratio-based metrics (i.e., $[\text{final} - \text{baseline}]/\text{baseline} \times 100$) that eliminate information about absolute baseline tumor burden. For example, an 80% reduction in a small tumor ($10 \rightarrow 2 \text{ cm}^3$) yields the same delta value as an 80% reduction in a large tumor ($500 \rightarrow 100 \text{ cm}^3$) despite markedly different residual disease volumes. ROC analysis is designed for original measurement scales, not normalized metrics, making thresholds biologically uninterpretable. Additionally, these Δ metrics exhibit a pronounced ceiling effect (median: -100% in our cohort), and limited survival events would produce unstable, overfitted thresholds. ROC methods are also time-independent and cannot capture three-time-point dynamics. Therefore, we adopted median dichotomization as a robust, assumption-free strategy, consistent with prior PET prognostic studies.

Methodological differences in the literature pose the greatest challenge in comparing results. Specifically, variations in MTV calculation segmentation methods (e.g., 41% SUVmax threshold, fixed 2.5 SUV threshold) and heterogeneity in patient populations (e.g., stage, age, treatment regimens) explain why reported cut-off values differ across studies [26]. In a series of 30 patients, Tseng et al. [27] found that pre-treatment MTV was not associated with prognosis. The use of a higher SUVmax threshold (>50%) in that study for MTV and TLG calculations may have led to an underestimation of tumor volumes. In our study, the use of the 40% SUVmax threshold, which has been validated in phantom studies, provided a methodologically sound basis [28]. However, as suggested by Aksu et al. [11], evaluating new metrics that include not only volumetric parameters but also

tumor dissemination (e.g., tMTV/Dmax) in future studies could further improve prognostic modeling.

Study Limitations

Our study has several limitations. First, its retrospective design and single-center nature may have led to potential selection bias. Second, our relatively small sample size of 63 patients might have limited statistical power, especially in subgroup analyses. A further limitation is that ROC-based cut-off determination was not applied to Δ parameters due to their normalized, ratio-based nature and heavily skewed distribution (median: -100%). As detailed in this study, ROC analysis is methodologically inappropriate for percentage-change metrics and limited survival events ($n=8$ deaths, $n=18$ progressions) would yield unstable thresholds. Therefore, median dichotomization was adopted as a robust, reproducible strategy for these dynamic parameters. Despite these limitations, the long median follow-up period of our study (75 months) and its comprehensive coverage of three different time points during treatment are significant strengths.

Conclusion

Both baseline metabolic tumor burden and long-interval metabolic changes demonstrated strong prognostic value in HL. Baseline MTV effectively stratified patient risk, while deep metabolic responses, and particularly reductions in $\Delta\text{SUVmax}_{1-3}$, were associated with significantly improved progression-free outcomes. These results highlight the complementary role of dynamic PET metrics and support their integration into future risk-adapted management strategies. Prospective multicenter validation of our findings will accelerate the integration of this valuable parameter into routine clinical practice.

Ethics

Ethics Committee Approval: Pamukkale University Non-interventional Clinical Research Ethics Committee (date: 24.11.2020, decision no: 22).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: N.G.; Concept: H.U., A.G.; Design: H.U.; Data Collection or Processing: H.U., N.G., F.S.Ş., T.Ş., D.Y.; Analysis or Interpretation: H.U., A.G., N.G., N.Ş.T., F.S.Ş., T.Ş., D.Y.; Literature Search: H.U.; Writing: H.U., A.G.

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