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EVALUATING TOTAL METABOLIC TUMOR VOLUME (TMTV) ON PET/CT AS A DETERMINANT FOR PERSONALIZED RADIATION DOSE OPTIMIZATION IN HODGKIN LYMPHOMA PATIENTS

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ABSTRACT

Objective: To assess baseline total metabolic tumour volume (TMTV) measured by ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) in patients with Hodgkin lymphoma (HL) undergoing radiotherapy and to explore its associations with disease characteristics, radiotherapy factors and treatment response and to determine an exploratory baseline TMTV cut-off for predicting non-complete response to radiotherapy in patients.

Material and Methods: This prospective observational cohort study included 80 histopathologically confirmed HL patients treated at the Institute of Nuclear Medicine and Oncology Lahore. Pre-radiotherapy TMTV and PET/CT baseline characteristics were obtained. Non-parametric tests, analysis of variance and Pearson correlation were used to assess associations. Discrimination between complete and non-complete response was assessed using receiver operating characteristic (ROC) analysis.

Results: Mean baseline TMTV was 137.6±108.8 cm³ (range, 18.0–580.9). TMTV differed significantly across Ann Arbor stages ($H=50.173$, $p<0.001$), bulky disease ($U=1508.000$, $p<0.001$), B-symptom status ($U=1100.500$, $p<0.001$), and lesion distribution ($H=7.887$, $p=0.019$). TMTV correlated positively with radiation dose ($r=0.562$, $p<0.001$) and number of fractions ($r=0.562$, $p<0.001$), but not radiation technique ($H=3.682$, $p=0.451$). There was a difference between the response groups in terms of TMTV ($F=4.442$, $p=0.006$). Forty-four patients (55.0%) achieved complete response. Baseline TMTV was negatively correlated with percentage reduction in TMTV ($r=-0.354$, $p=0.001$). ROC analysis yielded AUC 0.674 (95% CI, 0.556–0.792; $p=0.004$); an exploratory cutoff of 161.25 cm³ had 50.0% sensitivity and 77.3% specificity.

Conclusion: Baseline TMTV was associated with disease burden, radiotherapy prescription, and treatment response. The exploratory cutoff needs to be validated before clinical use, but TMTV can be used in conjunction with the conventional parameters in HL radiotherapy planning.

KEYWORDS: Hodgkin lymphoma; total metabolic tumor volume; ^{18}F-FDG PET/CT; radiotherapy; treatment response; metabolic tumor burden.

INTRODUCTION

Hodgkin lymphoma (HL) is a highly curable lymphoid malignancy, but there is clinical heterogeneity in disease burden and treatment response (Ansell, 2018). ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) plays a pivotal role in the staging and response assessment of Hodgkin lymphoma (HL) due to its metabolic information as well as anatomic imaging (Kanoun et al., 2018). Total metabolic tumor volume (TMTV) is the sum of the volumes of all metabolically active lesions and may contain information in addition to single-lesion parameters like maximum standardized uptake value (SUV-max) (Meignan et al., 2021; Milgrom et al., 2021).

Baseline TMTV has been associated with disease stage and clinical outcomes in HL. Research conducted among pediatric and adolescent patients has reported a correlation between higher TMTV and worse response and survival in early and advanced disease, and the optimal TMTV thresholds have been different depending on patient population and segmentation method. There are no universally accepted thresholds and variations in PET acquisition and segmentation are significant obstacles to clinical use (Boellaard et al., 2024; Walker et al., 2015; Yousefirizi et al., 2024).

The use of radiotherapy for HL is becoming more personalized based on the distribution of the disease, response to treatment, target anatomy, and the need to spare normal tissues (Kröger et al., 2025; Mikhaeel et al., 2019; Pepper et al., 2023; Specht et al., 2014). In keeping with the trend toward imaging-directed, personalized management of lymphoma, quantitative PET-derived tumor burden may be used to supplement conventional clinical and anatomic parameters during treatment planning (Barrington & Johnson, 2017). There is, however, limited evidence directly linking baseline TMTV to radiotherapy dose, fractionation, technique and treatment response, especially in local clinical settings.

This study thus assessed baseline TMTV in patients with HL treated with radiotherapy using ^{18}F-FDG PET/CT. The aims were to explore the relationship between baseline TMTV and disease characteristics, radiotherapy-related factors, and treatment response, and to determine an exploratory threshold for TMTV to differentiate complete from non-complete treatment response. We hypothesized that higher baseline TMTV would be correlated with higher disease burden, higher prescribed radiation dose, and poorer treatment response.

MATERIAL AND METHODS

Study design and setting

A prospective observational cohort study was carried out at the Institute of Nuclear Medicine and Oncology Lahore (INMOL). The study was conducted on 80 patients for a period of 4 months after institutional and ethical approval. Consecutive non-probability sampling was used.

Sample size

The minimum sample size was determined by the standard formula for estimating a single proportion, $n=Z^2p(1-p)/d^2$, with a 95% confidence level ($Z=1.96$), an anticipated proportion of 0.50, and a margin of error of 11%, which resulted in a minimum sample size of 80 patients.

Participants

Patients of either sex with histopathologically confirmed HL who were planned to receive radiotherapy and had an interpretable baseline PET/CT performed before radiotherapy were eligible. PET/CT images needed to be appropriate for TMTV calculation with dedicated analysis software. Patients were excluded if they had received radiotherapy prior to the baseline PET/CT, had poor quality or incomplete PET/CT images that prevented TMTV measurement, had another concurrent malignancy that would affect the interpretation of the PET/CT, did not complete planned radiotherapy or were lost prior to response assessment, or had uncontrolled medical conditions that would interfere with treatment or imaging.

Ethics

All participants gave written informed consent. Study codes were used to ensure patient confidentiality. Participants were told that there were no extra PET/CT scans, radiation or medical procedures involved in the study other than routine clinical care, and that they could withdraw from the study without impacting their treatment.

PET/CT assessment

Baseline ^{18}F-FDG PET/CT was conducted as part of routine clinical assessment, staging, restaging or treatment planning as clinically judged. Imaging was done on Siemens Biograph Vision 600 PET/CT with 64-slice CT, and GE Discovery STE PET/CT with 16-slice CT (Siemens Healthineers, 2020). PET and the corresponding CT images were examined simultaneously. FDG-avid lymphoma lesions were detected without physiologic uptake and without other non-tumor activity, and when necessary, anatomic CT information was used to characterize the lesions. The metabolic volumes of individual lesions were measured using dedicated PET/CT analysis software and summed to obtain patient-level TMTV. The PET/CT variables collected were number of FDG-avid lesions, SUV-max, SUV-mean (if available), lesion distribution, nodal/extra-nodal involvement, bulky disease, and TMTV.

Radiotherapy and response assessment

The study did not change the radiotherapy treatment. Varian Clinac iX and Varian Halcyon linear accelerators were used for treatment. The following treatment variables were recorded: total dose, number of fractions, radiation energy, and technique. Follow-up assessment was typically carried out 6–8 weeks after radiotherapy, as per institutional practice and availability. Response was defined as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) by clinical assessment and PET/CT. Post-treatment TMTV was recorded and compared to baseline TMTV. In the primary response analysis, CR was compared with non-complete response (PR, SD, or PD).

Statistical analysis

IBM SPSS Statistics (version 25.0) was used for coding and analysis of data. Demographic, clinical, PET/CT and treatment variables were analysed using descriptive statistics. Analysis of variance (ANOVA) was used to compare differences in baseline TMTV among the two or more response or disease categories when parametric assumptions were met; non-parametric alternatives were used when appropriate. Significant ANOVA results were followed by Post-hoc Tukey significant difference testing. Non-normally distributed comparisons were made using Kruskal-Wallis and Mann-Whitney U tests. Pearson correlation was used to evaluate the relationships between baseline TMTV, radiation dose, number of fractions, and percentage reduction in TMTV. The level of statistical significance was $p \leq 0.05$. Discrimination of baseline TMTV between complete and non-complete response was assessed by receiver

operating characteristic (ROC) analysis, and an exploratory cutoff was derived and assessed within the same cohort, without an independent validation set.

RESULTS

Patient and disease characteristics

Eighty patients with histopathologically confirmed HL were included in the study. The largest age group was 25–44 years (47, 58.8%), followed by 15–24 years (21, 26.3%); 5 patients (6.3%) were aged 0–14 years, 5 (6.3%) were aged 45–59 years, and 2 (2.5%) were aged 60–74 years. There were 43 females (53.8%) and 37 males (46.3%). Forty-six patients (57.5%) had nodal disease, 21 (26.3%) had mixed nodal and extra-nodal disease, and 13 (16.3%) had isolated extra-nodal disease. The most common histological type was nodular sclerosis (51, 63.7%), followed by mixed cellularity (16, 20.0%), nodular lymphocyte-predominant HL (6, 7.5%), lymphocyte-rich HL (5, 6.3%), and lymphocyte-depleted HL (2, 2.5%).

Ann Arbor stage II was most common (34, 42.5%), followed by stage III (23, 28.7%), stage IV (18, 22.5%), and stage I (5, 6.3%). Bulky disease was present in 45 patients (56.3%) and B symptoms were reported in 51 (63.7%) as shown in Table 1.

Table 1. Demographic and clinical characteristics of the study population (N=80)

Characteristic	n (%)
Age group, years	
0–14	5 (6.3)
15–24	21 (26.3)
25–44	47 (58.8)
45–59	5 (6.3)
60–74	2 (2.5)
Sex	
Female	43 (53.8)
Male	37 (46.3)
Lesion distribution	
Nodal	46 (57.5)
Mixed nodal/extra-nodal	21 (26.3)
Extra-nodal	13 (16.3)
Histological subtype	
Nodular sclerosis	51 (63.7)
Mixed cellularity	16 (20.0)
Nodular lymphocyte-predominant HL	6 (7.5)
Lymphocyte-rich HL	5 (6.3)
Lymphocyte-depleted HL	2 (2.5)
Ann Arbor stage	
I	5 (6.3)
II	34 (42.5)
III	23 (28.7)
IV	18 (22.5)
Bulky disease	45 (56.3)

Characteristic	n (%)
B symptoms	51 (63.7)

Baseline PET/CT and radiotherapy characteristics

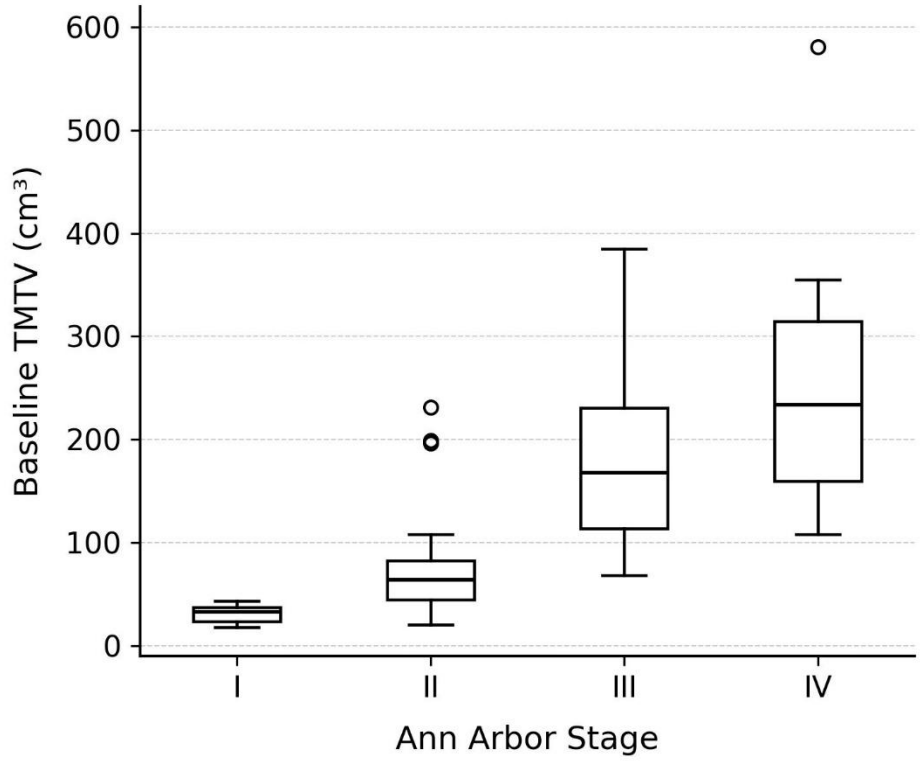
The mean number of FDG-avid lesions was 10.0±8.1 (range, 1–37). Mean SUV-max was 15.9±4.6 (range, 6.0–30.4), and mean SUV-mean was 7.2±2.2 (range, 2.7–15.5). Mean baseline TMTV was 137.6±108.8 cm³, with a range of 18.0–580.9 cm³.

Radiotherapy doses were 20 Gy in 15 patients (18.8%), 24 Gy in 14 (17.5%), 26 Gy in 10 (12.5%), 30 Gy in 30 (37.5%), 34 Gy in 5 (6.3%), and 36 Gy in 6 (7.5%). Fractionation schedules included 10 fractions in 15 patients (18.8%), 12 in 14 (17.5%), 13 in 10 (12.5%), 15 in 30 (37.5%), 17 in 5 (6.3%), and 18 in 6 (7.5%); every schedule corresponded to 2 Gy per fraction.

Association of TMTV with disease characteristics

Baseline TMTV was significantly different between Ann Arbor stages (Kruskal-Wallis H=50.173, df=3, $p<0.001$). Pairwise comparisons using Bonferroni correction revealed significant differences between stages I and III ($p<0.001$), I and IV ($p<0.001$), II and III ($p<0.001$), and II and IV ($p<0.001$); however, differences between I and II ($p=0.791$) and III and IV ($p=1.000$) were not significant (Figure 1).

Figure 1. Distribution of baseline total metabolic tumor volume (TMTV) across Ann Arbor stages I–IV in patients with Hodgkin lymphoma. Box-and-whisker plots show median, interquartile range, and range.



There was also a significant difference between TMTV and bulky disease (Mann-Whitney U=1508.000, $p<0.001$) and B-symptom status (U=1100.500, $p<0.001$). There was a significant difference between the categories of lesion distribution (Kruskal-Wallis H=7.887, df=2, $p=0.019$) across all categories (Figure 2, 3). The difference between nodal and mixed disease was significant (adjusted $p=0.018$), while the difference between nodal and extra-nodal disease and between extra-nodal and mixed disease was not significant (adjusted $p=0.599$ and 1.000, respectively).

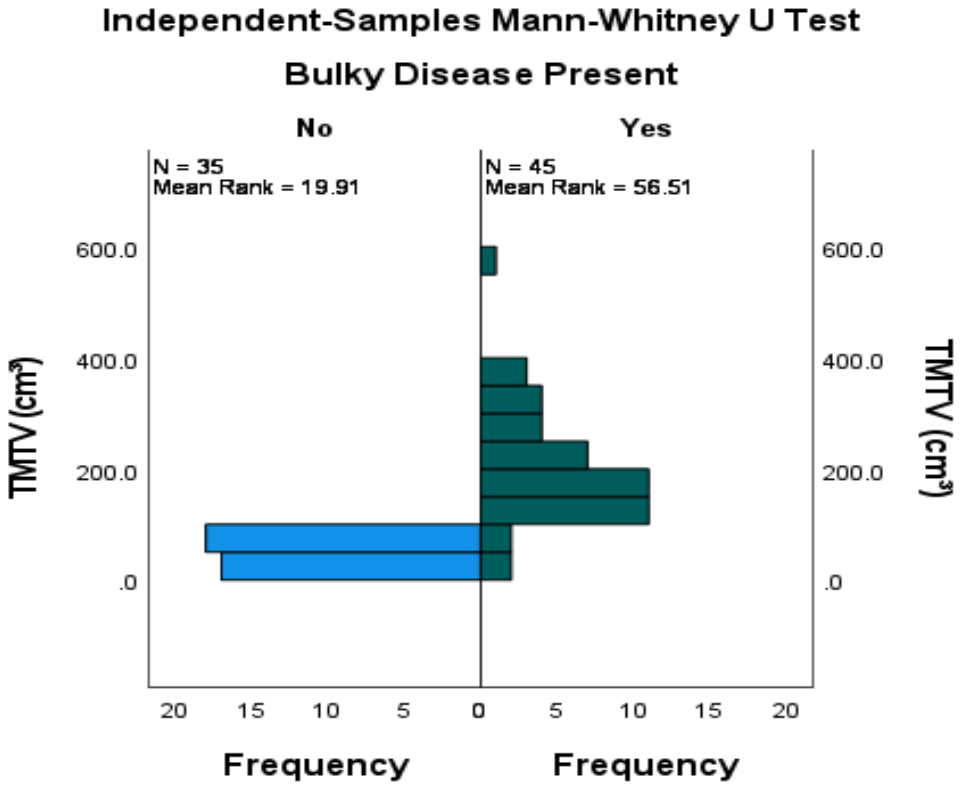


Figure 2. Mann–Whitney U Test Showing the Distribution of TMTV by Bulky Disease Status.

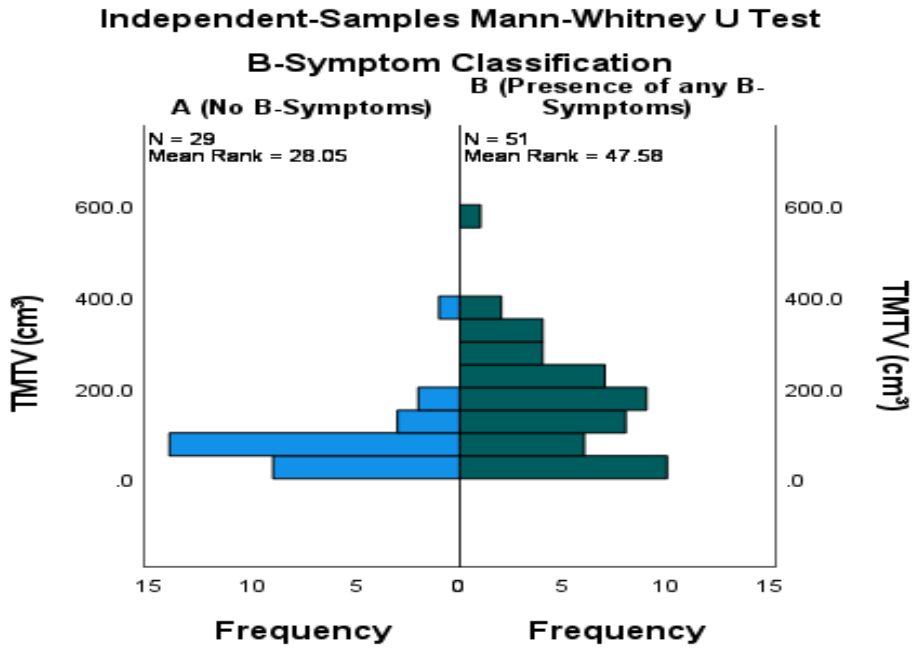


Figure 3. Mann–Whitney U Test Showing the Distribution of TMTV by B symptom Status.

Association with radiotherapy factors

Baseline TMTV was moderately correlated with prescribed radiation dose ($r=0.562$, $p<0.001$) and with number of fractions ($r=0.562$, $p<0.001$); since all fractionation schedules in this cohort were fixed at 2 Gy per fraction, the dose and the number of fractions were collinear, hence the same correlation coefficient. However, there was no significant difference between the radiation technique groups for baseline TMTV (Kruskal-Wallis $H=3.682$, $df=4$, $p=0.451$) as shown in Table 2.

Table 2. Principal associations between baseline TMTV and clinical, radiotherapy, and response variables

Variable	Statistical result	p-value
Ann Arbor stage	H=50.173	<0.001
Bulky disease	U=1508.000	<0.001
B symptoms	U=1100.500	<0.001
Lesion distribution	H=7.887	0.019
Radiation dose	r=0.562	<0.001
Number of fractions	r=0.562	<0.001
Radiation technique	H=3.682	0.451
Response category	F(3,76)=4.442	0.006
Percentage reduction in TMTV	r=−0.354	0.001
ROC: CR vs non-CR	AUC=0.674 (95% CI, 0.556–0.792)	0.004

Treatment response

The baseline TMTV was significantly different across the four response categories (ANOVA $F(3,76)=4.442$, $p=0.006$). The Tukey test revealed that there was a significant difference between CR and SD (mean difference, −100.89 cm^3; $p=0.017$), with higher baseline TMTV in the SD group. There were no other statistically significant pairwise comparisons of baseline TMTV: CR versus PR ($p=0.582$), CR versus PD ($p=0.065$), PR versus SD ($p=0.358$), PR versus PD ($p=0.460$), and SD versus PD ($p=1.000$).

Forty-four patients (55.0%) achieved CR, while 36 (45.0%) had PR, SD, or PD. Baseline TMTV was negatively correlated with percentage reduction in TMTV ($r=-0.354$, $p=0.001$), indicating that greater baseline TMTV was associated with a smaller percentage reduction as shown in Table 3.

Table 3. Post-hoc Tukey HSD test for the Realationship between Baseline TMTV and Radiotherapy Response.

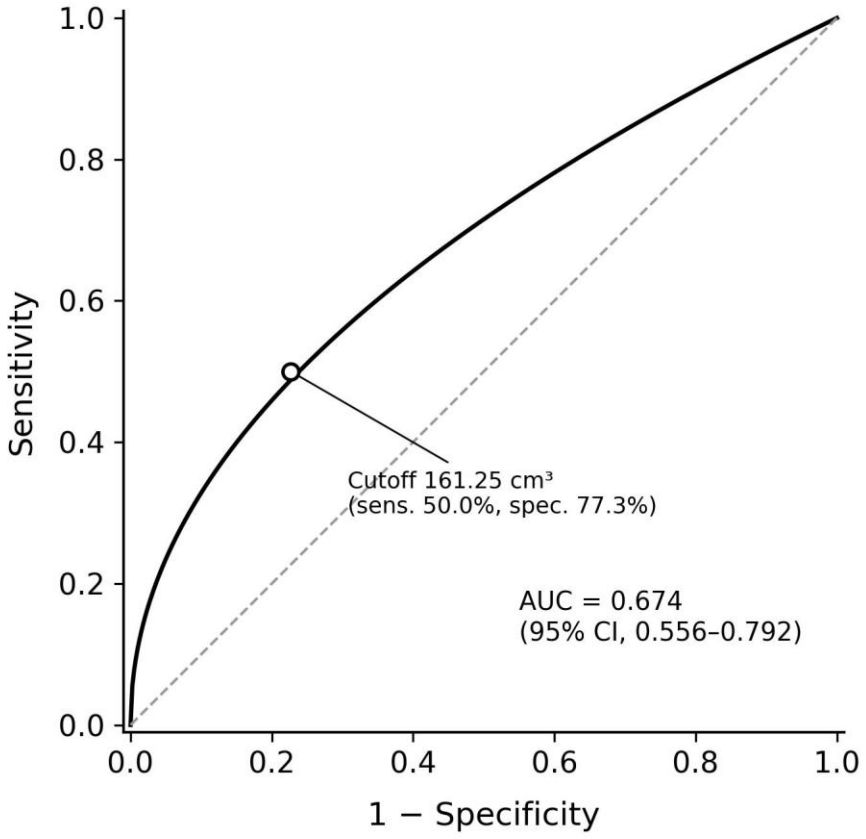
Multiple Comparisons					
Tukey HSD					
Dependent Variable	Response Category of Patients	Response Category of Patients	Mean Difference (I-J)	Std. Error	Sig.
TMTV (cm^3)	Complete Response	Partial Response	-37.2346	29.2312	.582
		Stable Disease	-100.8856*	33.3357	.017
		Progressive Disease	-104.8666	41.6526	.065
	Partial Response	Complete Response	37.2346	29.2312	.582
		Stable Disease	-63.6510	38.5937	.358
		Progressive Disease	-67.6319	45.9689	.460
	Stable Disease	Complete Response	100.8856*	33.3357	.017
		Partial Response	63.6510	38.5937	.358
		Progressive Disease	-3.9810	48.6821	1.000
	Progressive Disease	Complete Response	104.8666	41.6526	.065
		Partial Response	67.6319	45.9689	.460
		Stable Disease	3.9810	48.6821	1.000
% Reduction in TMTV	Complete Response	Partial Response	25.8222*	2.3412	.000
		Stable Disease	65.5962*	2.6699	.000

		Progressive Disease	104.9903*	3.3360	.000
	Partial Response	Complete Response	-25.8222*	2.3412	.000
		Stable Disease	39.7740*	3.0910	.000
		Progressive Disease	79.1681*	3.6817	.000
	Stable Disease	Complete Response	-65.5962*	2.6699	.000
		Partial Response	-39.7740*	3.0910	.000
		Progressive Disease	39.3940*	3.8990	.000
	Progressive Disease	Complete Response	-104.9903*	3.3360	.000
		Partial Response	-79.1681*	3.6817	.000
		Stable Disease	-39.3940*	3.8990	.000
*. The mean difference is significant at the 0.05 level.					

ROC analysis

ROC analysis for the distinction of CR from non-complete response yielded an area under the curve (AUC) of 0.674 (95% confidence interval (CI) 0.556–0.792; p=0.004) (Figure 4).

Figure 4. Receiver operating characteristic (ROC) curve of baseline total metabolic tumor volume to discriminate between complete and non-complete treatment response.



The exploratory cutoff value of 161.25 cm³ resulted in a sensitivity of 50.0%, specificity of 77.3%, and a Youden index of 0.273.

DISCUSSION

In this prospective observational study, baseline metabolic tumor burden (MTB) was found to be significantly different between 80 patients with HL and was statistically significantly associated with several clinical characteristics, radiotherapy parameters, and treatment-response measures. The mean baseline TMTV was 137.6 cm³, with a wide range of 18.0–580.9 cm³. This variation suggests significant disease burden heterogeneity in terms of metabolic activity among patients (Meignan et al., 2021; Milgrom et al., 2021).

Most of the cohort was young, with 58.8% aged 25-44 years and 26.3% aged 15-24 years. The most common histological type was nodular sclerosis (63.7%) and 53.8% of the participants were female. These findings represent this one-institution cohort. The predominance of females is in contrast with a Pakistani series of 658 patients that observed a male-to-female ratio of 3.3:1 (Siddiqui et al., 2006). Variation between cohorts may be due to differences in referral patterns, population structure, histology, and study design.

Over half of the patients had advanced disease (stage III–IV), bulky disease or B symptoms. Baseline TMTV was significantly correlated with Ann Arbor stage, and there were significant differences between early and advanced stage groups, but not between stage I and stage II or stage III and stage IV groups after adjustment. The present analysis was observational and did not assess survival endpoints, and this supports previous observations that TMTV reflects overall disease burden and is associated with clinical disease extent, but should be considered as complementary to, not a replacement for, established staging systems (Cottereau et al., 2018; Pinochet et al., 2021).

However, TMTV should be regarded as complementary to, rather than a replacement for, established staging systems because the present analysis was observational and did not evaluate survival endpoints.

The significant association between TMTV and bulky disease is clinically coherent because both variables reflect disease burden, although they quantify it differently. Conventional bulky disease is based on anatomic dimensions, whereas TMTV incorporates metabolically active lesions across the body (Meignan et al., 2021; Song et al., 2013). The present study cannot establish a biological mechanism or causality for these associations.

TMTV differed significantly among nodal, extra-nodal, and mixed lesion-distribution groups, with the significant pairwise difference occurring between nodal and mixed disease. This is compatible with the ability of PET/CT to capture metabolically active disease across multiple anatomic sites (Barrington et al., 2014).

An important finding was the moderate positive correlation between baseline TMTV and prescribed radiation dose ($r=0.562$) and between TMTV and number of fractions ($r=0.562$); as noted above, this equality reflects the fixed 2 Gy-per-fraction prescription used throughout the cohort rather than two independent associations. These results show that, within this cohort, patients with greater baseline TMTV tended to receive higher prescribed doses and more fractions. They do not demonstrate that TMTV determined treatment prescriptions, because radiotherapy decisions are influenced by stage, treatment response, target location, anatomy, treatment intent, and institutional protocols. Current lymphoma radiotherapy guidance emphasizes individualized target definition and treatment planning using clinical and imaging information (Mikhaeel et al., 2019; Specht et al., 2014). Thus, TMTV may be considered a candidate complementary measure for future treatment-planning research, but the present data do not establish a TMTV-based dose prescription strategy.

Baseline TMTV was not significantly associated with radiation technique. This may reflect the fact that technique selection is driven largely by target geometry, adjacent organs at risk, treatment resources, and institutional practice. The finding suggests that TMTV and delivery technique represent different aspects of radiotherapy planning.

Baseline TMTV was significantly associated with overall radiotherapy response. The post-hoc analysis identified a significant difference between complete response and stable disease, with lower baseline TMTV in the complete-response group. However, other pairwise comparisons were not significant. Therefore, the overall ANOVA finding should not be interpreted as evidence that TMTV separates every response category. Forty-four patients achieved CR and 36 had PR, SD, or PD. The negative correlation between baseline TMTV and percentage reduction in TMTV was statistically significant but modest ($r=-0.354$), indicating that patients with greater baseline burden tended to have smaller proportional reductions.

The ROC analysis provided an AUC of 0.674 (95% CI, 0.556–0.792), indicating that baseline TMTV had statistically significant but moderate discrimination between complete and non-complete response in this cohort. The exploratory threshold of 161.25 cm^3 had 50.0% sensitivity and 77.3% specificity. The modest sensitivity is important for clinical interpretation. TMTV thresholds vary across studies because of differences in segmentation, scanners, acquisition procedures, populations, and treatment regimens (Boellaard et al., 2015; Boellaard et al., 2024; Chauvie et al., 2021; Mettler et al., 2019; Milgrom et al., 2019; van Heek et al., 2022). Accordingly, 161.25 cm^3 should be regarded as hypothesis-generating rather than a validated clinical cutoff.

The present study has several limitations. First, the sample size was small and obtained from a single institution, limiting precision and generalizability. Second, PET/CT examinations were performed on two scanner platforms, and available documentation does not provide sufficient detail to confirm whether acquisition and reconstruction parameters were fully harmonized between them. Third, the study was observational; therefore, associations between TMTV, radiotherapy prescriptions, and response cannot establish causality. Fourth, treatment response assessment and post-treatment TMTV were dependent on clinical follow-up and imaging availability. Finally, the exploratory cutoff was derived and evaluated within the same cohort, which can overestimate discriminatory performance and requires external validation.

CONCLUSION

Baseline TMTV measured by ^{18}F-FDG PET/CT was significantly associated with Ann Arbor stage, bulky disease, B symptoms, lesion distribution, prescribed radiation dose, number of fractions, and treatment response in this cohort of

patients with HL. Higher baseline TMTV was also associated with a smaller percentage reduction in TMTV after treatment. Baseline TMTV demonstrated moderate discrimination between complete and incomplete response, with an exploratory cutoff of 161.25 cm^3. These findings support further evaluation of TMTV as a quantitative biomarker that may complement conventional clinical and imaging parameters in HL. Larger multicenter studies using standardized PET/CT acquisition and TMTV segmentation, predefined treatment protocols, and independent validation cohorts are needed before TMTV thresholds can be incorporated into routine radiotherapy decision-making.

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CONFLICTS OF INTEREST
There are no potential conflicts of interest to declare.

DATA AVAILABILITY
The data are available from corresponding author upon reasonable request.

AUTHOR CONTRIBUTIONS
All authors contributed to study conception and design, data acquisition, analysis and interpretation, drafting and critical revision of the manuscript, and approved the final version submitted. All authors are accountable for all aspects of the work.

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