Correlation between PET-CT parameters and treatment response in lymphoma patients

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Declarations:

Ethics approval and consent to participate:

This study had approval from the Institutional Review Board of Mansoura Faculty of Medicine on January 2021.
Written informed consent was obtained from all patients.

Consent for publication:

A written consent to publish this information was obtained from study participants.

Availability of data and materials:

Due to privacy regulations, the clinical data collected in this study are not deposited in a public registry, but the data can be made available via a request to the corresponding author.

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The authors declare that they have no competing interests, and no relationships with any companies, whose products or services may be related to the subject matter of the article.

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Abstract

Background

Accurate radiologic assessment of treatment response in lymphoma patients is important to evaluate the effectiveness of treatment. The value of PET-CT for post-treatment prognosis prediction has been recently investigated. The aim of this study is to highlight the correlation between PET-CT quantitative parameters and treatment response in lymphoma patients.

Results

Among the included 61 patients, post-treatment SUV, MTV, and TLG were significantly lower in a responsive group (CR group) than the non-responsive group (PR and PD groups). Values of quantitative PET/CT parameters were significantly lower in the responsive group.

Conclusions

This study suggests that interim and end-of-treatment PET-CT quantitative parameters (SUV max, MTV and TLG) are significantly correlated with treatment response in patients with lymphoma.

Key words

Lymphoma

PET-CT

SUV max

MTV

TLG

Background

Lymphoma comprises heterogeneous malignancies that arise from the clonal proliferation of lymphocytes. It represents approximately 5% of malignancies. Overall survival is estimated to be 72%.(Jamil & Mukkamalla, 2022).Once diagnosed, accurate assessment of initial disease status is important for planning treatment and determining prognosis.(Yoo, 2022)

Currently, staging and treatment response evaluation for lymphoma has been standardized into the Lugano classification. Lugano classification incorporates positron emission tomography (PET) into the existing response criteria using Deauville scoring system, and response assessment using FDG-PET/CT has been proven to predict the prognosis in various lymphoma subtypes effectively.(Ricard et al., 2023)

However, one of the drawbacks of Deauville scale is the overlap between partial response and progressive disease when given the same scores 4 and 5 depending on the SUV max of the most active lesion. (Jensen et al., 2022)

The aim of this study is to highlight the diagnostic and prognostic values of interim and end-of-treatment PET-CT quantitative metabolic volumetric parameters in the evaluation of lymphoma patients with higher diagnostic confidence.

Methods

Patients

This retrospective study was conducted between January 2021 and January 2023. Sixty one patients with biopsy-proven lymphoma (including both HL and NHL) performed interim (after the first 3 chemotherapy cycles) and post-therapy (6–8 weeks after the end of chemotherapy) PET/CT imaging studies. The study was performed after approval of the international research board, Faculty of Medicine. Consent was taken from all patients. Both sexes were included with no age predilection. Patients with atopic chronic liver or renal disease or bad general condition were excluded. Patients who underwent recent surgical intervention or received radiotherapy were also excluded.

Patient preparation

Procedure time was at interim and 6–8 weeks after the end of the chemotherapy. Patients fasted for 6 h before the examination but with good hydration. Exercise was avoided minimum for 4 h

before the scan. Pre-scanning blood glucose level estimation (below 200 mg/dl) was done, and insertion of an intravenous cannula was performed.

Technique of 18F-FDG PET/CT scan

A radioactive tracer (18F-FDG) was injected intravenously with a dose of 0.06–0.08 mCi/kg. All patients were kept in a warm room, asked to rest and void just before imaging. Scanning by hybrid PET/CT scanner (GE Discovery IQ 5 rings) was performed 60 min after injection. The patient was positioned supine on the table. Initial single-phase contrast-enhanced helical CT (optima 540 16 slice) was performed following an injection of 125 ml of a low osmolarity iodinated contrast medium (Optiray 350) at a rate of 4 ml/s by using power injector (Discovery IQ, GE Medical System, USA). CT scanning (from the head to mid-thigh) was obtained using 110 mA, 110 kV, 0.5 s tube rotation time, and 3.3 mm section thickness. After CT scanning, PET scan covering the same field of view was obtained immediately. Six- to seven-bed positions were planned in three-dimensional acquisition mode for scanning the entire patient with 3–5 min acquisition at each position. Images were transferred to the workstation (Advantage Window 4.7) to be reconstructed and displayed in axial, coronal, and sagittal planes. Fused images were obtained.

Image analysis

Images were analyzed by two experienced radiologists. Analysis of CT images was done by visual inspection for the selection of target lesions. Then MTV and TLG were calculated for each lesion. The total MTV and TLG were calculated by adding the measurements of each lesion (semi-automated method). TLG was the end result of SUV average multiplied by MTV. This was applied for each PET/CT study.

Statistical analysis

All statistical analyses were performed in Statistical Package for Social Science (SPSS) version 27 for windows (IBM SPSS Inc, Chicago, IL, USA). Data were tested for normal distribution using Shapiro Walk test, parametric quantitive data were expressed as mean and standard deviation while non-parametric quantitive data were expressed as median (range). Qualitative data were represented as frequencies and relative percentages. The study sample was analyzed by summarizing the patients age by mean and standard deviation. Sex and subtypes of lymphoma were summarized by number and percentage. Response to the treatment of the study sample was categorized into three group; complete response (CMR), partial response (PMR), and progressive disease (PMD) and every group was summarized also by number and percentage.

Comparison between HL and NHL regarding the metabolic measures after the 1st and 2nd cycle of treatment (SUV max, MTV, and TLG) was done using Mann-Whitney U test. Wilcoxon Signed Rank test was used to compare the median of metabolic measures (SUV, MTV, and TLG) after the 1st and 2nd cycles of treatment at the HL group and NHL group.

Results

61 patients were included in the study with a mean age of 54.3 ± 15.7 years and median age of 45 years (range 18-72 years), including 57.4% men (35/61) and 42.6% (26/60). From the study population, 52.5% have NHL [(32/61) 16 men and 16 women] and 47.5% have HL [(29/61) 19 men and 10 women]. (Table 1 and 2)

Characteristic	All Patients (N=61)
Age Range	18-72
Median	45
Mean ±SD	45.3±15.7
Gender	
Male	35(57.4%)
Female	26(42.6%)

Table 1. Study population characteristics at the time of lymphoma diagnosis

Type of lymphoma	Male	Female
NHL	16 (45.7%)	16(61.5%)
HL	19(54.3%)	10(38.5%)
Total	**35**	**26**

Table 2. Frequency of NHL and HL distribution according to patients' gender

The study patients (n=61) were classified according to the treatment response into three groups in both HL and NHL. In HL group (29/61) the percentage and number as following; CMR 24.1% (7/29), PMR 41.1% (12/29), and PMD 34.5% (10/29) and in NHL groups (32/61); CMR 28.1% (9/32), PMR 25% (8/29), and PMD 46.9% (15/32). Although higher number of patients with NHL had complete remission (9 vs 7) and more patients had a progressive disease (15 vs 10) than patients with HL, the difference was of no statistical significance (p>0.05).

There was no statistically significant difference between the two groups regarding the metabolic measures (SUV, MTV, and TLG), p > 0.05 after the 1st 3 cycles and after the 2nd 3 cycles of the treatment. (Tables 3 and 4)

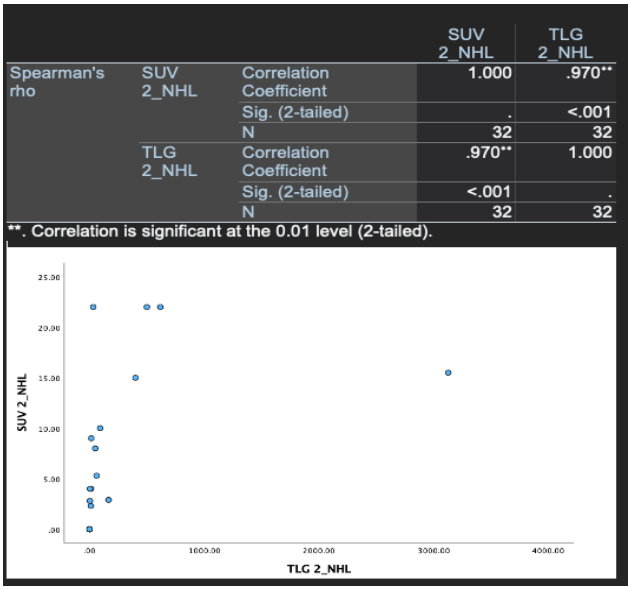
Groups / Variables	NHL group (n= 32)	HL group (n=29)	Mann- Whitney U test	P-value
SUV1				
Minimum	0	0		
Maximum	29	30	444.5	>.05
Median	6	7		
MTV1				
Minimum	0	0		
Maximum	380	544	463.5	>.05

Groups / Variables	NHL group (n= 32)	HL group (n=29)	Mann- Whitney U test	P-value
SUV2 Minimum Maximum Median	 0.0 22 0.0	 0 24 3.3	401	>.05
MTV2 Minimum Maximum Median	 0.0 512 0.0	 0 216 10	364.5	>.05
TLG2 Minimum Maximum Median	 0.0 3127 0.0	 0 1027 16	372.5	>.05
Median	16.3	19		
TLG1 Minimum Maximum Median	 0 4905 59	 0 2617 80	437.5	>.05

Table 3. Comparison between NHL and HL regarding metabolic measures after the 1st 3 treatment cycle using Mann Whitney U test

Table 4. Comparison between NHL and HL regarding metabolic measures after the 2nd 3 treatment cycle using Mann Whitney U test

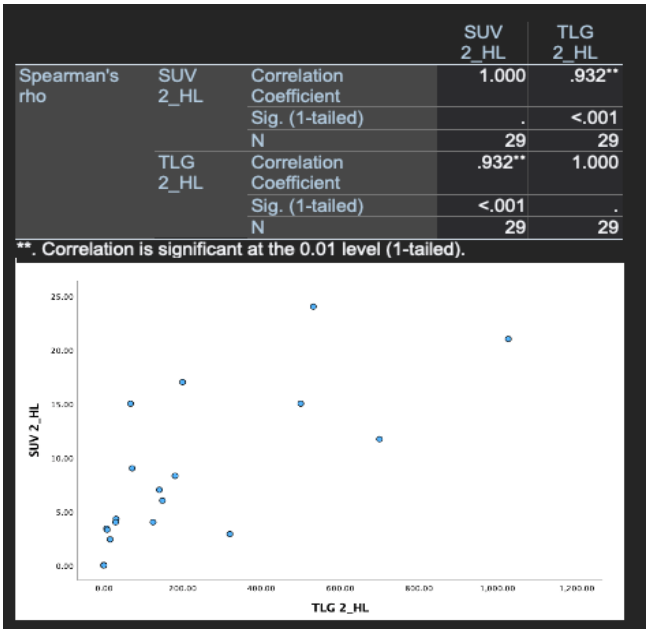
Interestingly, there were a statistically significant very high positive correlations between SUV2 and TLG2 in both HL and NHL group. The correlation coefficient and p-value were (0.93, $p < 0.001$) for HL group and (0.97, $p < 0.001$) for NHL group. (Fig. 1 and 2).



			SUV 2_NHL	TLG 2_NHL
Spearman's rho	SUV 2_NHL	Correlation Coefficient	1.000	.970**
		Sig. (2-tailed)	.	<.001
		N	32	32
	TLG 2_NHL	Correlation Coefficient	.970**	1.000
		Sig. (2-tailed)	<.001	.
		N	32	32

**. Correlation is significant at the 0.01 level (2-tailed).

Fig. 1 Graph correlation between SUV2 and TLG2 in NHL group; very high positive correlation between the SUV2 and TLG2 in HL group (0.97, p <0.001)



			SUV 2_HL	TLG 2_HL
Spearman's rho	SUV 2_HL	Correlation Coefficient	1.000	.932**
		Sig. (1-tailed)	.	<.001
		N	29	29
	TLG 2_HL	Correlation Coefficient	.932**	1.000
		Sig. (1-tailed)	<.001	.
		N	29	29

**. Correlation is significant at the 0.01 level (1-tailed).

Fig. 2 Graph correlation between SUV2 and TLG2 in HL group; very high positive correlation between the SUV2 and TLG2 in HL group (0.93, p <0.001)

The three outcomes of our study (CMR, PMR, and PMD) were compared by Independent variable in Kruskal-Wallis test. There was a statistically significant difference in the median of SUV2 (P = 0.002), TLG2 (P = 0.007), MTV2 (P = 0.017) with higher values of these metabolic measures in PMD and PMR than CMR.

This test result indicated the significance of these metabolic measures in assessment and predicting the disease outcomes. The pairwise comparison subtest of the Kruskal-Wallis test found significant differences between (CMR-PMD, P = 0.002) and (CR-PR, P = 0.04) using SUV2 but only significant difference between (CMR-PMD, P = 0.005) using TLG2 and (CMR-PMD, P = 0.01) using MTV2. The pairwise comparison made the SUV2 values superior to the TLG2 and MTV2 in differentiation the different disease outcome at least in our small sample study. (Fig.3)

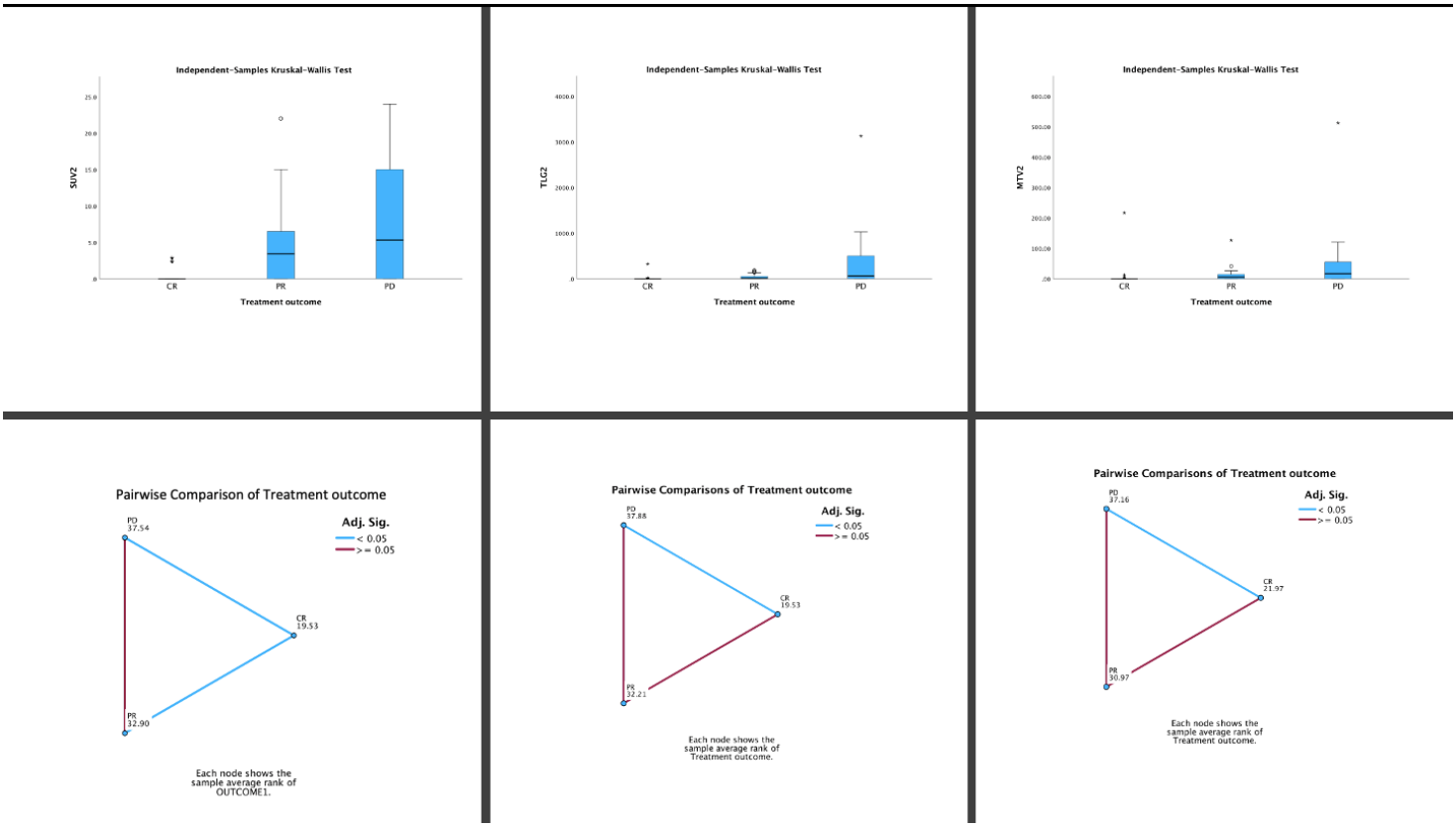


Fig. 3 Independent Kruskal-Wallis test and Pairwise Comparison subtest comparing the study three outcomes (CR & PR & PD) regarding the SUV2 – TLG2 – MTV2 (left to right).

Discussion

It is well known that PET-CT has been used as the gold standard method in lymphoma imaging owing to its combined anatomical and functional advantages.(Parihar et al., 2023)

In analyzing FDG PET, SUVmax is the most widely used index for various purposes relatively because of the suitability and great reproducibility of measurement; it reveals the metabolic activity of the most aggressive tumor cell (Im et al., 2018). Recently, new PET-CT parameters have shown to be effective in assessment of tumor metabolic activity, metabolic tumor volume (MTV) which is a measurement of tumor volume with a high metabolism, and total lesion glycolysis (TLG), which is the product of mean SUV and MTV. MTV and TLG are volume-based indexes that reflect tumor burden, and they are expected to be effective in response

evaluation (Prieto Prieto et al., 2020) (Zhou et al., 2020). In our study, active lymphomatous deposits were assessed in 61 patients, and quantitative indices at interim and the end of treatment (6–8 weeks after end of chemotherapy) were measured. We compared all PET/CT parameters between the three groups, namely PMR (partial metabolic response) and CMR (complete metabolic response), and PMD (progressive metabolic disease). We found that at end of treatment, the SUV max was statistically significant in differentiation between CMR and PMR, and between CMR and PMD, MTV was statistically significant in differentiation between CMR and PMD and TLG was statistically significant in differentiation between CMR and PMD. P values were 0.002, 0.01 and 0.005 respectively.

This agreed with the study by Christopher Melani et al. which showed a significant reduction in SUVmax in PET CT of non-progressors at the end of EPOCH-R (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab) regimen treatment compared to an increase in treatment failures.(Melani et al., 2018)

Another study by Hussein team showed that all metabolic measures (SUVmax, MTV and TLG) performed significantly better than DS at the end of the treatment scan. However, SUVmax was the strongest predictor of treatment outcome ($p<0.001$). (Hussien et al., 2015). In a large cohort of patients with early stage HL, Akhtari's group reported similar results with a high correlation between MTVs and freedom from progression (FFP). (Akhtari et al., 2018).

In a retrospective study done by Reed et al, who aimed to evaluate the prognostic value of metabolic and other parameters in paediatric and adolescent Hodgkin lymphoma. They recorded tMTV (total Metabolic Tumor Volume), TLG (Total Lesion Glycolysis), and SUVmax (maximum Standard Uptake Value) on baseline PET, as well the presence of bone marrow or visceral involvement. All patients received stage-specific standard of care therapy. Response assessment on end-of-treatment PET was evaluated according to the Deauville criteria. Among the quantitative PET-CT parameters, only baseline tMTV predicted treatment response ($p = 0.017$).(Reed et al., 2021)

In another study held by Wang et al, they found SUVmax, MTV, TLG on B-PET/CT, DS on I-PET/CT and DS on E-PET/CT may be significant prognostic indicators for PFS and OS in T cell lymphoma patients. Moreover, TLG tends to be superior to SUVmax and MTV on B-PET/CT for predicting survival. Therefore, response monitoring and prognostication assessments based on multiple PET/CT parameters should be considered in the management of those patients.(Wang et al., 2018)

Conclusions

This study concluded that PET/CT quantitative measures at end of treatment (SUV, MTV and TLG) achieved high correlation with treatment response in lymphoma patients with higher confidence than the traditionally used Deauville scoring system.

Abbreviations

18F-FDG::

18F-Fluorodeoxyglucose

PET/CT:

Positron emission tomography/computed tomography

HL:

Hodgkin lymphoma

NHL::

Non-Hodgkin lymphoma

CMR:

Complete metabolic response

PMR:

Partial metabolic response

SMD:

Stable metabolic disease

PMD:

Progressive metabolic disease

SUV:

Standardized uptake value

MTV:

Metabolic tumor volume

TLG:

Total lesion glycolysis

DS:

Deauville score

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