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Can positron emission tomography–computed tomography-based three target lesions' total lesion glycolysis predict therapeutic response in Hodgkin Lymphoma?

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Abstract

Background: Universally maximum standardized uptake value (SUVmax) and lactate dehydrogenase (LDH) are used as tools for response assessment in Hodgkin Lymphoma (HL) patients. Our objectives are to evaluate the predictive potential and response assessment of total lesion glycolysis (TLG) and metabolic tumor volume (MTV)—maximum three target lesions—as another alternatives and to investigate the correlation between TLG and MTV with LDH.

Results: Both initial SUVmax and TLG were significantly associated with early patient response (p value 0.03, 0.047, respectively). An optimal threshold for SUVmax and TLG less than or equal 19.52, and 158.6, respectively, correlated with better therapeutic response. Initial LDH was moderately correlated with initial values of TLG ($r_s = 0.4$, p value 0.01), MTV ($r_s = 0.44$, p value 0.01) and SUVmax ($r_s = 0.42$, p value 0.01).

Conclusion: TLG in correlation with LDH can be significant prognostic factors of therapeutic response in HL. They can be used for the identification of a subset of HL patients with a better outcome.

Keywords: Hodgkin Lymphoma (HL), Positron emission tomography (PET), Lactate dehydrogenase (LDH), Correlation

Background

Lymphomas are one of the most common solid tumors [1]. The role of imaging in management of lymphoma is essential [2]. Currently, positron emission tomography–computed tomography (PET/CT) has prominent applications as staging and during treatment to evaluate the individual chemosensitivity and subsequently to adapt further therapy by using Deauville scale [3].

Functional studies with quantitative parameters play a great role in oncologic management. The universal

metabolic quantitative parameter is the maximum standardized uptake value (SUVmax), which reflects the tumor glucose metabolism of the most aggressive cell component [4]. However, it is retrieved from only one voxel which makes it sensitive to image noise and impacted by various patient characteristics and imaging parameters. On the other hand, metabolic tumor volume (MTV) is a measurement of the viable tumor fraction and can better estimate tumor burden. The product of multiplying the mean SUV and the MTV yields the total lesion glycolysis (TLG) representing the metabolic burden of disease that depends on both tumor volume and glucose utilization rate. Thus, MTV or TLG may provide additional valuable information for prediction of tumor reaction to treatment [5]. Most studies are concerned with whole-body

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MTV (WBMTV) and whole-body TLG (WBTLG), with few available studies on target lesions' MTV and TLG.

In this study, we investigated the predictive value of both target lesions' MTV and TLG instead of WBMTV and WBTLG (which are time consuming and need advanced software) by using the new response evaluation criteria in lymphoma 2017 [6].

Moreover, despite the availability of multiple studies searching the correlation between TLG and MTV with Lactate Dehydrogenase (LDH) in various types of malignancies and lymphoma; yet, there were few available studies concerning Hodgkin Lymphoma (HL) [7]. We investigated the association of TLG and MTV with LDH in HL patients.

Materials and methods

After ethical committee approval, this prospective and prognostic study was applied in the period from July 2017 till December 2019 at Ain Shams University hospital. A total of 40 consecutive patients with biopsy proven HL underwent two PET/CT evaluations, one initial (prior to therapy) and other interim imaging (after 2–4 cycles with 3–4 months interval according to each patient's treatment protocol) using RECIL criteria as the golden standard of the current study. B-symptoms (weight loss more than 10%, fever and night sweats), laboratory data (LDH and erythrocyte sedimentation rate (ESR)) and histological specimen were registered from patients' medical records.

Inclusion criteria

Any patient presented with HL who did not receive any therapy, aged 19 years or older with no sex predilection was included.

Exclusion criteria

Those who were previously treated with chemotherapy, radiotherapy patients or who underwent any surgical intervention as line of treatment, with blood glucose level more than 200 mg/dl, with known allergy to intravenous contrast material or with renal impairment were excluded.

Patient preparation

Pre-procedural assessment of patient's weight and height. Blood glucose level of the both PET/CT scans in diabetic patients was adjusted by the physician to be in the range of 110–160 mg/dl at the time of examination. Additionally serum creatinine was done before the study and confirmed to be within normal range of 0.7–1.4 mg/dL.

¹⁸F-FDG PET/CT imaging

Initial and interim PET/CT were performed using combined PET/CT machine (Discovery IQ 5 ring GE). The imaging protocol included physical, dietary and laboratory instructions like fasting for a minimum of 6 h and controlling serum glucose level [6]. Each patient was injected 0.1 mCi/Kg of ¹⁸F-FluorodeoxyGlucose (¹⁸F-FDG) intravenously 50–60 min before image acquisition [8].

Mid-skull to the level of the mid-thighs contrast-enhanced PET/CT was performed. Low dose attenuation correction CT was used and about 90 ml of non-ionic iodinated contrast material was injected; then, CT study was done 90 s after contrast administration [9]. The entire patients PET scanning was performed by the three-dimensional acquisition mode. [10]. Reconstruction of PET image data sets using CT data for attenuation correction was done and co-registered images were displayed [11].

Image analysis

Both the initial and interim CT and PET/CT scans were analyzed by 2 experienced radiologists with at least 5-year experience in nuclear medicine field and decision was reached by consensus. The images were evaluated for whole-body detection, follow-up of FDG-avid lymph nodes and extra-nodal lesions as well as detection of any new FDG-avid lesions.

The assessment of tumor burden in lymphoma was performed using contrast-enhanced CT images by the sum of longest diameters of a maximum of three target lesions where the three largest ones being selected and preferably representing multiple sites or organs (Fig. 1) [6].

All PET/CT fused images were analyzed for visual assessment and quantitative FDG uptake measurements (Fig. 1). The SUVmax was determined as the highest SUV of the pixel in the region of interest (ROI). Either the liver background SUVmax or mediastinal blood pool SUVmax was calculated for each patient as an internal references with comparison of the tumor activity and avidity. Initial MTV, summing the volumes of target lesions, was computed using the SUVmax threshold of 41%. The TLG was calculated using the following equation: $TLG = MTV \times SUV_{mean}$. All parameters were corrected for Lean Body Mass (LBM) (Fig. 2) [12].

According to the RECIL classification, the interpretation of scans of lesions with FDG-avid profiles was by Deauville 5-point scale [6].

Regarding the splenic involvement, focal lesions was diagnosed by increased FDG uptake more than the splenic background [13]. Also hepatic involvement was

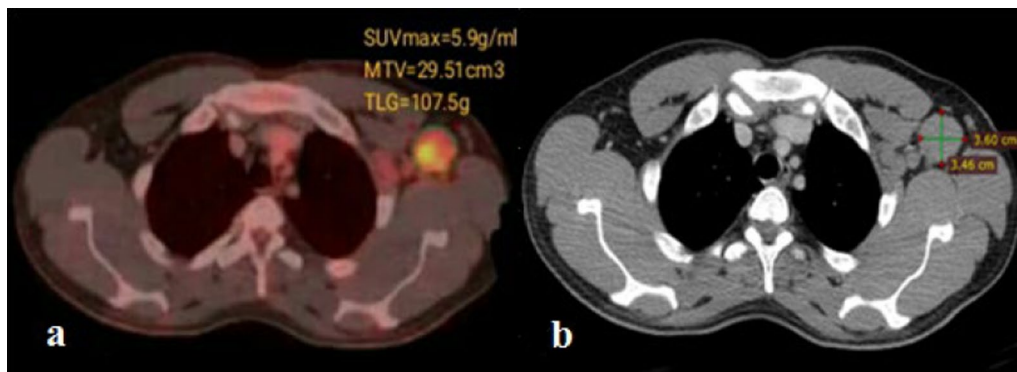


Fig. 1 A male patient, 31 years old, presented with HL **a** Axial CE CT image shows the dimensions of left axillary LN 3.6 × 3.46 cm. **b** Axial fused image of PET/CT shows the quantitative assessment of left axillary LN SUVmax=5.9 g/ml, MTV=29.51 cm³ and TLG=107.5 g

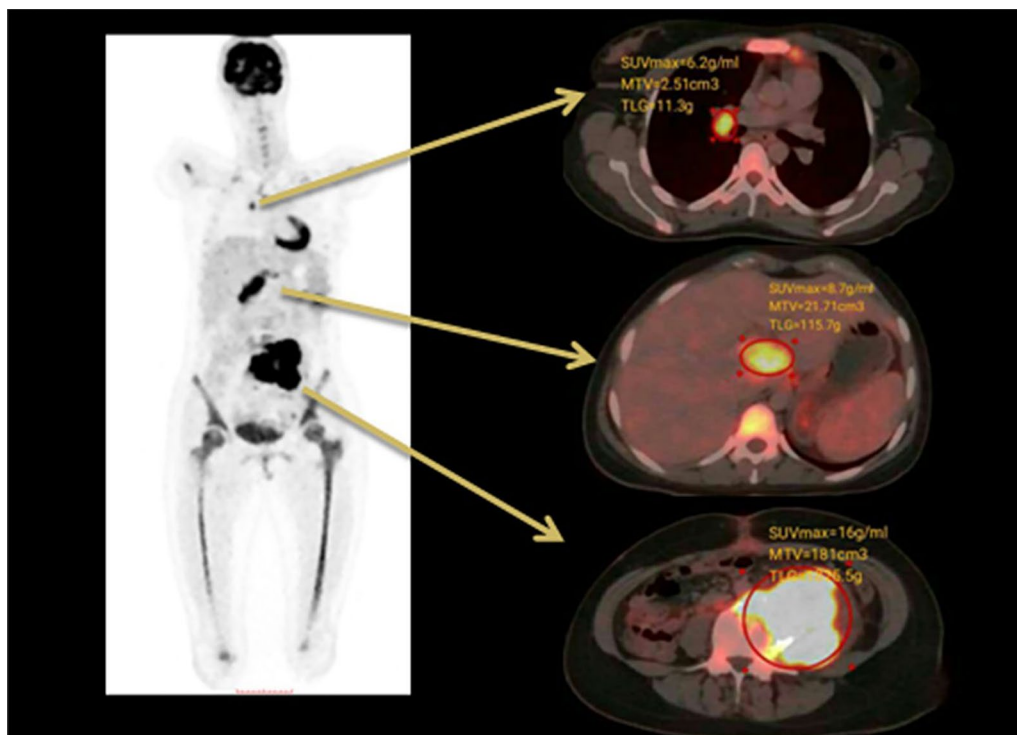


Fig. 2 Coronal MIP image and Axial fused images of PET/CT of a female patient, 19 years old, presented with HL showing the measurement of PET/CT parameters of three largest target lesions at different body sites (right hilar LN with SUVmax=6.2 g/ml, MTV=2.51 cm³ and TLG=11.3 g, porta hepatis LN with SUVmax=8.7 g/ml, MTV=21.71 cm³ and TLG=115.7 g and left paravertebral retroperitoneal soft tissue lesion with SUVmax=16 g/ml, MTV=181 cm³ and TLG=1825.5 g)

diagnosed by increased focal concentration of FDG against a background of relatively lower normal hepatocyte uptake [14]. Bone marrow involvement was either diffusely increased which is mostly nonspecific, or focally increased that denotes marrow lesions [15].

Initial and interim studies were compared to determine the radiological response after receiving chemotherapy.

According to the RECIL 2017 in response assessment, the patients were classified to two groups CR and nCR groups. The nCR was an umbrella term encompassing all response patterns other than CR, as described by the RECIL criteria while CR was a term applied on all patients who showed complete disappearance of either all target lesions and all lymph nodes with a long axis less

than 10 mm or 30% or more decrease in sum of longest diameters of target lesions with normalization of FDG PET (Deauville score 1–3) with neither bone marrow involvement nor new lesions. On the other hand, nCR is a term applied on all patients who showed either 30% or more decrease in sum of longest diameters of target lesions with positive FDG PET (Deauville score 4–5), or less than 30% reduction, or any increase in the summation of longest dimensions of the target lesions with any FDG PET findings associated with bone marrow involvement or new lesion [16].

As a part of the staging procedures in HL patients, serum LDH was routinely determined by the in-house laboratory. The tumor marker LDH was extracted from the clinical data base within 7 days before, up to 7 days after PET/CT. The upper limit of the reference range is 240 U/L.

In addition, we explored the possibility of association between the serum LDH and target lesions' TLG and MTV by direct correlation of their absolute values.

Statistical analysis

Statistical analysis was performed using MedCalc statistical software for Windows (MedCalc Software, Mariakerke, Belgium). Data for initial SUV, TLG and MTV were expressed as median and range while data for initial LDH, ESR and B-symptoms were expressed as both number and percentage. Mann–Whitney U test was used to evaluate the differences of initial TLG, MTV and SUV between CR and nCR groups. Receiver operator characteristic (ROC) curve analysis was performed to determine optimum thresholds and the diagnostic accuracy of the initial SUV and TLG in distinguishing the different groups. The diagnostic accuracy of both initial SUV and TLG was evaluated in terms of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under the ROC curve (AUC). Spearman's rank correlation was used to describe the correlations between the initial LDH and the initial PET/CT parameters (SUV, TLG and MTV). Chi-squared test was used for comparison of initial LDH, ESR and B-symptoms between the two groups. For all tests, all P values were two-tailed and a p value < 0.05 was considered significant.

Results

Clinical and demographic data of the studied patients

Initial demographic, clinical and pathologic characteristics of 40 patients are listed in Table 1. (21 males and 19 females). The median age was 30.5 years old ages (range, 19–85 years old). A maximum of three largest target lesions was assessed per patient with a total of 110 lesions in 40 patients. Twenty-six patients (65%) showed

Table 1 Clinical and demographic data of the studied patients

$n = 40$	
Age, median (range)	30.5 years (19–85 years)
Gender	
Male	21
Female	19
B symptoms	
Positive	24
Negative	16
LDH	
Normal	4
Elevated	36
ESR	
Normal	0
Elevated	40
Ann Arbor stage	
I	8
II	18
III	6
IV	8
Histology	
Nodular sclerosis	24
Mixed cellularity	16
Target lesions	
LNs	75
Other lesions	17
Splenic lesions	10
Bone lesions	8
RECIL response to CTH	
Complete response	26
Partial response*	8
Minor response**	4
Stable disease	0
Progressive disease	2

*Partial Response means 30% or more reduction of the summation of longest dimensions of the target lesions but not a complete response with Positive FDG-PET findings

**Minor Response means between 10 and 30% reduction of the summation of longest dimensions of the target lesions with FDG-PET findings

CR while fourteen (35%) showed a nCR on interim imaging (Figs. 3, 4, 5).

PET parameters Predictive ability

The initial PET metabolic parameters including SUVmax, MTV and TLG of both CR and nCR groups are listed in Table 2. Patients with CR were found to significantly had lower levels of SUVmax and TLG compared to patients with nCR (p value 0.03, 0.047, respectively).

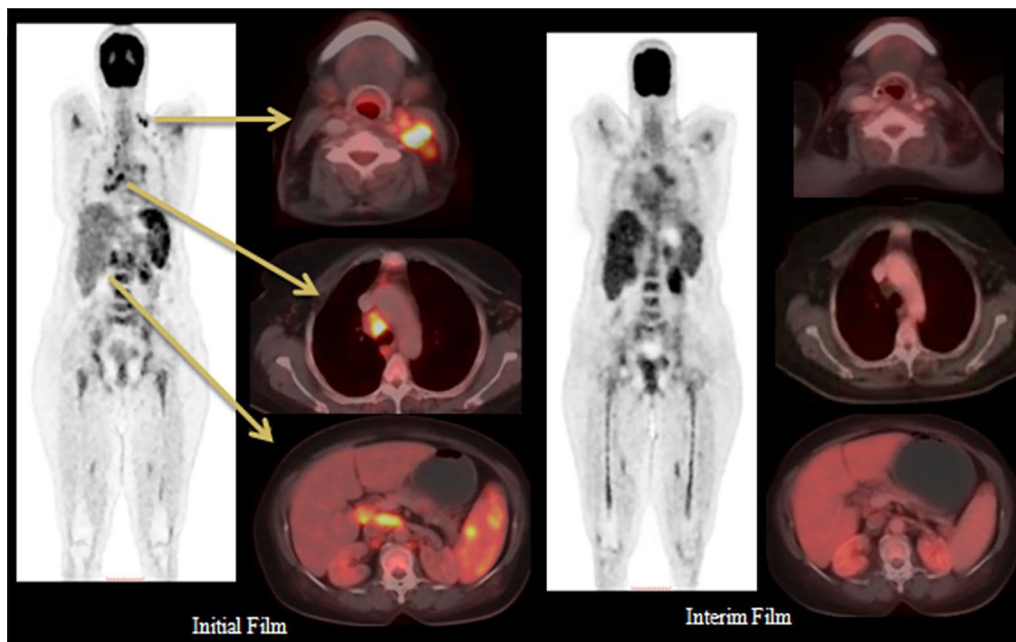


Fig. 3 Coronal MIP images and Axial fused images of PET/CT of a female patient, 47 years old, presented with stage III HL. On the left, the initial film shows three target lesions (left cervical level IV LN with SUVmax = 6.38 g/ml, MTV = 2.64 cm³ and TLG = 9.9 g, amalgamated retrocaval paratracheal LN with SUVmax = 6.96 g/ml, MTV = 9.97 cm³ and TLG = 38.9 g and preaortic and precaval LNs with SUVmax = 6.49 g/ml, MTV = 24.57 cm³ and TLG = 90.6 g). On the right, the interim film shows complete anatomical and metabolic clearance of the lesions on the left side (CR group)

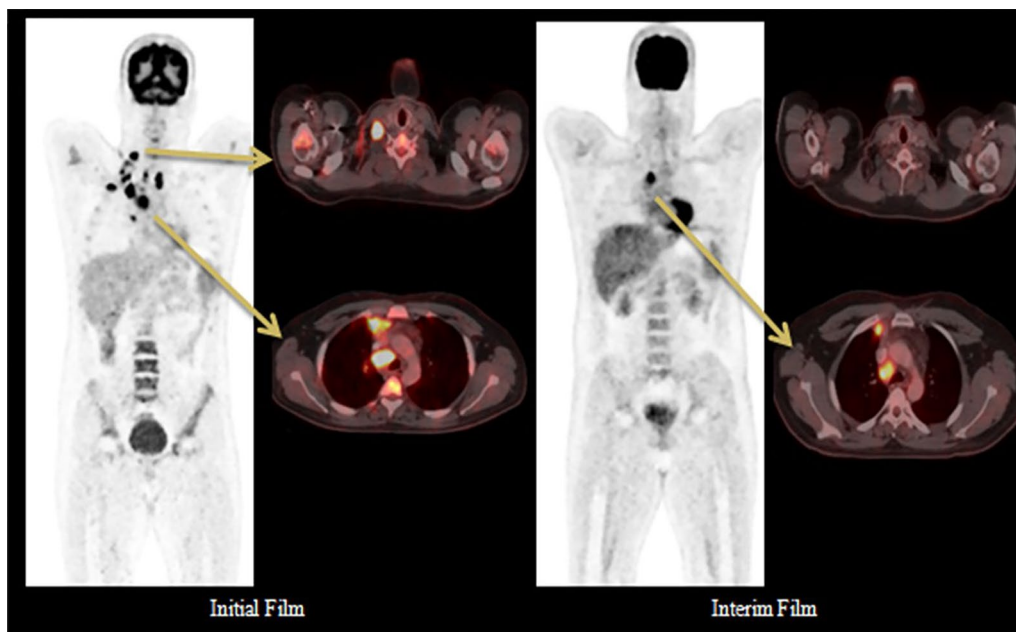


Fig. 4 Coronal MIP images and Axial fused images of PET/CT of a male patient, 24 years old, presented with stage II HL. On the left, the initial film shows two target lesions (right Supraclavicular LN with SUV max = 21.35 g/ml, MTV = 4.59 cm³ and TLG = 61 g and pretracheal retrocaval LNs with SUV max = 23.1 g/ml, MTV = 16.16 cm³ and TLG = 227 g). On the right, the interim film shows complete metabolic resolution with marked anatomical regression of right Supraclavicular LN while the other shows SUV max = 7.4 g/ml, MTV = 8.02 cm³ and TLG = 37 g denoting partial metabolic response (non-CR group)

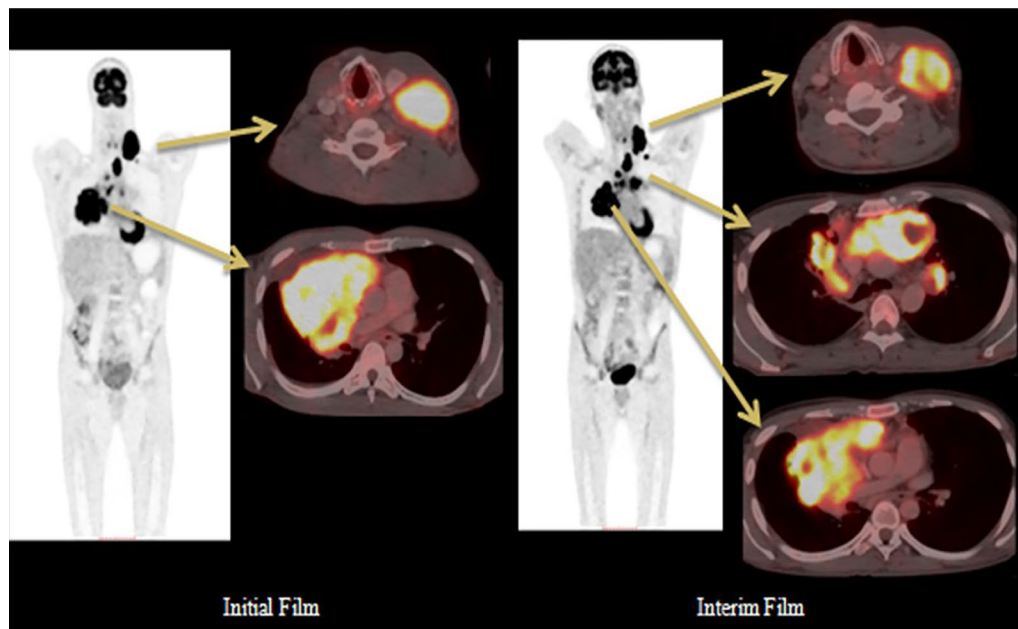


Fig. 5 Coronal MIP and Axial fused images of PET/CT of a male patient, 32 years old, presented with stage II HL. On the left, the initial film shows two target lesions (left cervical amalgamated LN with SUV max = 11.2 g/ml, MTV = 28.7cm³ and TLG = 279.7 g and amalgamated mediastinal nodal mass with SUV max = 12.2 g/ml, MTV = 3624cm³ and TLG = 2777.9 g). On the right, the interim film shows SUV max = 12 g/ml, MTV = 69.16cm³ and TLG = 552.2 g of cervical lesion, SUV max = 11.3 g/ml, MTV = 165cm³ and TLG = 1605.7 g of mediastinal lesion and denovo left hilar LN SUV max = 11 g/ml, MTV = 2.95cm³ and TLG = 28.9 g denoting progressive metabolic response (non-CR group)

Table 2 Comparison between quantitative PET/CT parameters of the CR and nCR groups

	CR	nCR	p value
Initial SUVmax			
Median	18.3	30.3	$p=0.03^*$
Range	4.7–74.4	13.6–108.3	
Initial TLG			
Median	138.0	288	$p=0.047^*$
Range	26.1–1613.4	57.9–3057.6	
Initial MTV			
Median	29.5	30.8	$p=0.26$
Range	2.7–203.3	8.8–390.5	

*Statistically significant

No significant association was found between the initial MTV of both groups (p value 0.26) (Table 2).

Their optimum threshold values to differentiate between CR and nCR groups were 19.52 for SUVmax and 158.6 for TLG with similar sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy and area under the curve (AUC) (Table 3).

Regarding their diagnostic performance in distinguishing CR group from nCR group, there was no statistically significant difference between initial SUV and initial TLG (p value 0.82) (Fig. 6).

LDH correlation to PET parameters

The initial LDH was moderately associated with initial values of TLG ($r_s=0.4$, p value 0.01), MTV ($r_s=0.44$, p value 0.01) and SUVmax ($r_s=0.42$, p value 0.01).

Table 3 The diagnostic accuracy of quantitative PET/CT parameters for differentiation of CR from the nCR group

Parameter	Optimum threshold value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	AUC	p value
Initial SUVmax	≤ 19.52	53.9	85.7	87.5	50	65	0.71	0.01*
Initial TLG	≤ 158.6	53.9	85.7	87.5	50	65	0.69	0.036*

* Statistically significant

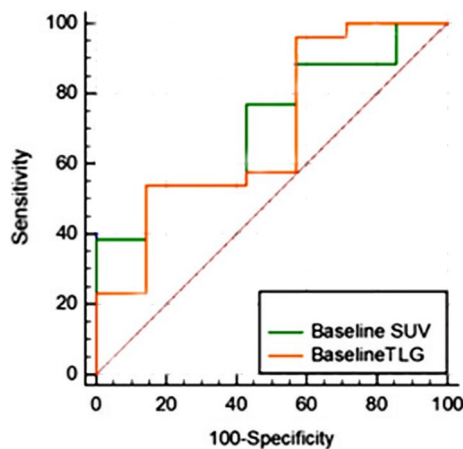


Fig. 6 Receiver operating characteristic curve analyses. The specificity and sensitivity of using baseline SUV and baseline TLG in differentiating CR and non-CR groups were compared. No significant differences existed between the AUCs of baseline SUV and baseline TLG

Clinical characteristics predictive ability

Other factors including initial LDH, ESR showed no significant association between their levels and treatment response ($\chi^2 = 2.33$, 3.6 and p value 0.13, 0.06, respectively) whereas B-symptoms were associated with treatment response where patients with no B symptoms at initial evaluation were significantly more prevalent in the CR group as opposed to the nCR group ($\chi^2 = 5.79$, p value 0.02).

Discussion

To improve HL treatments, the recent studies goal is to achieve the best chance of curing well with the least possible long-term risks of chemotherapy. Subsequently, modern approaches have attempted to investigate PET/CT parameters predictive ability to define subgroups of patients who will show early response after start of therapy [17]. The most commonly studied parameter is SUVmax, but unfortunately, it reflects the metabolic activity of the most aggressive tumor cell [5], while the functional imaging parameters (MTV and TLG) overcome SUVmax limitation as they evaluate the total volume and metabolic activity of tumor cells [18]. In our study, the predictive value of the initial quantitative indices of PET/CT (SUVmax, TLG, MTV) has been evaluated during the management of HL.

As many criteria were developed to assess the tumors therapeutic response, Tawfik et al. reported that PET response criteria in solid tumor (PERCIST) had improved the PET/CT predictive value [19]. So we adopt a new RECIL criteria with a simple approach of

estimating PET/CT parameters' values from maximum three largest target lesions rather than the whole-body approach. We have found that the initial SUVmax and TLG showed a good predictive value to distinguish between the patients with CR from those with nCR.

Similarly, the available literature has demonstrated the predictive value of TLG as an effective tool for response evaluation in FDG-avid lymphoma. Wang et al. reported that initial TLG tends to be superior to SUVmax and MTV in predicting survival [20]. Moustafa et al. suggested that TLG is an independent predictor of survival in malignant lymphoma especially in high risk patients and may be an influential predictor of lymphoma outcome [21].

Pike et al. and Zaucha et al. considered TLG as a very strong prognostic parameter which can improve the predictive value of PET/CT and was associated with interim PET response [22, 23]. El-Galaly et al. and Guo et al. suggested that high initial total TLG predicts significantly worse progression [24, 25].

Our threshold value of TLG is much lower than that of previous work by Pike et al. and Akhtari et al. who reported WBTLG cutoff value of 3318 in advanced HL and 1703 in early-stage HL, respectively. It is clear that this is variation is due to different methods of tumor burden assessment. However, our cutoff value requires more validation [22, 26].

Both initial SUVmax and TLG have similar sensitivity, specificity, accuracy, ROC as a diagnostic tool in distinguishing the CR from the nCR. We deduce that patients with low initial target lesions' TLG will have a better outcome than those with higher values. We suggest that TLG can be used as an alternative to SUVmax because SUVmax provides limited semiquantitative estimate of single voxel activity of a tumor mass and is affected by various factors like image noise, uptake period, body composition and plasma glucose level [5].

The study by Pike et al. was inconsistent with our results, where they demonstrated the predictive value of MTV as an effective tool for response evaluation. They measured the initial total MTV and MTV of the bulkiest lesion in advanced HL patients to evaluate whether both could predict prognosis and interim PET response. They reported that initial MTV is associated with interim PET response [22].

Moustafa et al. suggested that MTV is an independent predictor of malignant lymphoma survival and outcome [21].

Also El-Galaly et al., Guo et al. and Kanoun et al. studies were different with our results as they reported that tumor burden quantification by initial WBMTV may enhance prognostication and proved that lymphoma

patients with a low initial MTV had a better prognosis than those with a high MTV [24, 25, 27].

Zauchar et al. and Cottreau et al. considered MTV as a very strong prognostic parameter being superior to the available parameters [23, 28].

On the contrary, our results show that the initial MTV does not have significant difference between patients with CR and nCR. This difference may be attributed to the methodological differences regarding tumor burden assessment. We adopted quantitative assessment of only maximum three largest target lesions, while other investigators measured total MTV.

Unlike the three target lesion approach, the whole-body approach may more reliably reflect the patient's tumor status and treatment response in terms of MTV assessment. Son et al. and Pellegrino et al. stated that using the sum of PET/CT parameter of all patient's lesions was more expressive of the metabolically active tumor volume than measuring it at one site [29, 30].

Elevated LDH is associated with high tumor burden as cancer cells are dependent on anaerobic metabolism with subsequent production of lactate from glucose (Warburg effect) [31].

Subsequently, LDH can be used to monitor response to chemotherapy for certain types of cancers like lymphoma by assessing it at diagnosis, after treatment, and during follow-up [31]. Although there are few studies correlating LDH to SUVmax [7], to the best of our knowledge, there are no reports investigating the correlation of LDH with TLG or MTV in HL.

We have found a significant correlation between the initial LDH and initial SUVmax, MTV and TLG. A possible explanation for this correlation is attributed to the major role of nicotinamide adenine dinucleotide reduced/ nicotinamide adenine dinucleotide oxidized (NADH/NAD⁺) homeostasis in various metabolic reactions including glucose metabolism whereas NADH/NAD⁺ are up regulated in tumor cells in order to maintain its survival reduction of pyruvate to lactate (the Warburg effect) by LDH to produce NAD⁺ [32].

This increased glucose metabolism accounts for FDG accumulation into cancer cells and subsequently all quantitative parameters especially TLG which is theoretically superior to other measurements because it incorporates both parameters by taking into account the level of glucose accumulation within the total volume of all the regions of all ROIs [33].

Our finding regarding SUVmax correlation with LDH is consistent with Ucar et al. who found in 34 patients -13 patients had HL- that end of treatment (EOT) SUVmax are related to the EOT laboratory parameters such as LDH [34] and inconsistent with Li et al. who found

in 103 patients -19 had HL- that SUVmax at biopsy site was not significantly correlated with LDH [7].

This study was limited by few limitations. First, its short duration including only interim PET/CT studies with unavailability of EOT. Functional parameters of EOT would have given more comprehensive evaluation of the quantitative indices. However, the retrieved quantitative indices of initial scans could give insights into prognosis and the effectiveness of therapy. Second, the heterogeneous patient population in terms of the pathological subtypes and chemotherapy regimen. More prospective studies dedicated to specific pathological subtypes and treatment regimen will be more appropriate for proper functional indices assessment.

Conclusion

In conclusion, the initial three target lesions' TLG—based on RECIL criteria—in correlation with LDH can predict early interim therapeutic response in HL patients and may be used for identification of a subset of patients with a better outcome which subsequently may help later in decision making and management adjustment of these patients after more future studies to be with highest curative chance and the least possible long-term risks.

Abbreviations

SUVmax: Maximum standardized uptake value; LDH: Lactate dehydrogenase; HL: Hodgkin's lymphoma; TLG: Total lesion glycolysis; MTV: Metabolic tumor volume; PET: Positron emission tomography; NHL: Non-Hodgkin's lymphoma; 18F-FDG: 18F-FluorodeoxyGlucose; CT: Computed tomography; WBMTV: Whole-body metabolic tumor volume; WBTLG: Whole-body total lesion glycolysis; RECIL: Response evaluation criteria in lymphoma; ESR: Erythrocyte sedimentation rate; mg: Milligram; dl: Deciliter; mCi: Microcuries; Kg: Kilogram; LBM: Lean body mass; CR: Complete response; nCR: Non-complete response; ROI: Region of interest; AUC: Area under the curve; ROC: Receiver operating characteristic; PPV: Positive predictive value; NPV: Negative predictive value; R_s : Spearman rank correlation coefficient; LNs: Lymph nodes; CTH: Chemotherapy; PERCIST: PET response criteria in solid tumor; NADH: Nicotinamide adenine dinucleotide reduced; NAD⁺: Nicotinamide adenine dinucleotide oxidized; EOT: End of treatment.

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Authors' contributions

HY participated in data collection, image interpretations, statistical analysis and writing manuscript. SA participated in the design of study data collection, statistical analysis, editing, and supervision. AH participated in the design of study, editing, and supervision. AM participated in the design of study, editing, and supervision. MH participated in the data collection, image interpretation, editing, and supervision. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets generated and analyzed during the current study are not publicly available due to individual privacy but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by the ethical committee of "Research Ethics Committee at the Faculty of Medicine, Ain Shams University" with ethical committee approval number FMASU M.D. 235/2018. An informed written consent was taken from all subjects.

Consent for publication

The institutional review board of our institute approved this study, and the requirement to obtain informed consent was waived.

Competing interests

The authors declare that they have no competing interests.

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