Utility of ^{18}F-FDG PET/CT as A Biomarker for Early Response Assessment of Target Therapy in Diffuse Large B-Cell Lymphoma

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Abstract

Background: **Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of aggressive non-Hodgkin lymphoma (NHL), and early evaluation of treatment response is crucial for optimizing outcomes.** ***Aim:*** **This study aimed to evaluate the prognostic utility of ^{18}Fluorine -Fluorodeoxyglucose Positron Emission Tomography-Computed Tomography (^{18}F-FDG PET/CT) in staging and early treatment response assessment of DLBCL using the Deauville scoring system and standardized uptake value (SUV).** ***Patients and Methods:*** **An analytical cross-sectional study was conducted on 80 histopathologically confirmed DLBCL patients at Ismailia Oncology Teaching Hospital, Egypt. Patients underwent baseline and interim PET/CT scans following 3–4 cycles of rituximab (Target therapy). FDG uptake was assessed semi-quantitatively via SUV_{max} and Deauville score. Correlations were evaluated between metabolic activity, staging, and treatment response.** ***Results:*** **Among 80 patients, 85% were metabolic responders, with 75% achieving complete remission. Significant reductions in SUV_{max} and Deauville scores were observed post-therapy among responders ($p<0.001$). Over half of responders showed no FDG uptake post-treatment. PET/CT showed high sensitivity (97.9%) and negative predictive value (91.7%) for response evaluation, supporting its prognostic accuracy.** ***Conclusion:*** **Interim ^{18}F-FDG PET/CT is a valuable prognostic tool in DLBCL, effectively identifying responders and guiding therapeutic decisions. However, standardization in interpretation is essential to ensure consistency and reliability across clinical settings.**

Keywords: DLBCL, PET/CT, Deauville score, SUV_{max}.

Introduction

Major changes have taken place in the staging and response assessment of malignant lymphoma in the last two decades. With the introduction of fluorodeoxyglucose-positron emission tomography (^{18}F-FDG PET/CT), the criteria for staging and monitoring response have changed dramatically. PET-CT is recommended for staging as well as response assessment following therapy, as it is the most accurate imaging modality. However, one of the characteristics of (molecular) metabolic imaging is to be able to assess metabolic changes early in treatment. The question arises whether ^{18}F-

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FDG PET/CT can be used as a biomarker to differentiate good and poor responders during treatment, in order to modify therapy and to improve outcome. Recent clinical trials have addressed these questions [1].

^{18}F-FDG PET/CT is also a quantitative imaging technique, allowing semi-quantitative imaging interpretation, using standardized uptake values (SUV). Reporting change of FDG uptake, usually expressed as a relative change, can also be used for interim response assessment. The reliability of the results depends on having comparable procedures for patient preparation and injection, and scanning and image reconstruction protocols, as well as comparable data analysis [2].

The Deauville 5-point scoring system is a standardized method used internationally to assess fluorodeoxyglucose (FDG) uptake in patients with Hodgkin and Non-Hodgkin lymphoma, based on FDG positron emission tomography (PET) imaging. It provides a semi-quantitative evaluation of residual metabolic activity in tumor sites, aiding in treatment response assessment and clinical decision-making. The scoring ranges from 1 to 5: Score 1 indicates no abnormal uptake; Score 2 represents uptake equal to or less than that of the mediastinum; Score 3 denotes uptake greater than the mediastinum but less than or equal to that of the liver; Score 4 signifies moderately increased uptake compared to the liver; and Score 5 reflects markedly increased uptake at any site. An additional category, Score X, is used for new areas of uptake that are unlikely to be related to lymphoma. This system enhances consistency in interpreting PET scans and plays a crucial role in guiding patient management.Scores of 1 and 2 are considered to be negative and 4 and 5 are considered to be positive. "Score 3 should be interpreted according to the clinical context but in many Hodgkin Lymphoma patients indicates a good prognosis with standard treatment [3, 4].

This study aimed to outline the role of ^{18}F-FDG PET/CT in staging of diffuse large B-cell lymphoma (DLBCL) as well as assessing DLBCL response to target therapy in the form of remission or relapse.

Patients and methods

This analytical cross sectional study was conducted on 80 histopathologically confirmed DLBCL patients at the PET CT unit – Radiology Department of Ismailia Oncology Teaching Hospital in Ismailia, Egypt with inclusion criteria; Patients more than 18 years old, confirmed diagnosis of DLBCL histopathologically and Patients with nodal or extra nodal DLBCL and exclusion criteria; Patients with other neoplasms other than DLBCL and DLBCL Patients who are previously treated with any type of oncotherapy.

In Deauville scoring, a cut off of 4 or higher was used in the current study to define PET positivity, indicating residual or active disease. Scores of 1 and 2 are considered PET negative and score of 3 requires clinical correlation but often indicated good prognosis.

Sample size

The total sample size was 72 participants. After adding 10% dropout, the total sample size was 80 participants.

Methods

Data were collected from the study population using the GE 2742PT01 PET scan unit via the PACS (Picture Archiving and Communication System). FDG uptake was quantified using SUV_{max} and assessed using the Deauville scoring system to evaluate the metabolic activity of FDG-avid lymph

nodes and lesions in patients with DLBCL before and after targeted therapy. Baseline PET/CT scans were also used to determine the initial staging of DLBCL, which was then compared to post-therapy staging to assess treatment response.

Prior to the PET/CT scan, patients were instructed to fast for 6 hours while being allowed to drink water, avoid strenuous exercise, and wear comfortable, metal-free clothing. The procedure was explained in advance, including the injection of a radiotracer into a vein in the arm or hand approximately one hour before imaging. During the scan, which lasts 30 to 60 minutes, the patient lies supine on a flatbed that moves into a cylindrical scanner. After the scan, patients are advised to drink plenty of water to help flush out the radiotracer, which typically clears within a few hours. They can return home the same day, as no side effects are expected.

The study was approved by the Research Ethics Committee of the Faculty of Medicine, Radiology Department, Suez Canal University, with approval number 5418, and all participants were fully informed using simple language about the procedures, confidentiality, radiation safety, their rights to withdraw at any time without consequences, the use of non-identifiable images, available communication with the researcher, access to study results, and the absence of any conflict of interest.

Data was fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp) Qualitative data were described using number and percentage. Significance of the results obtained was judged at the 5% level. The tests used were Chi-square test for categorical variables, to compare between different groups and Fisher's Exact: Correction for chi-square when more than 20% of the cells have expected countless than5.

The PET CT scans were reviewed by two experienced readers (a radiologist and a nuclear medicine specialist) who were blinded to clinical data

Results

Gender distribution indicates a slight male predominance, with 55% males (44 men) and 45% females (36 women). Regarding the age, more than two-thirds (66.25%) of participants aged between 20 to 60 years, while 33.75% of the population were above 60 years old. (Table 1)

The distribution of the studied population based on Ann Arbor staging, revealing that after target therapy, over three-fifths (62.5%) of cases had no LN or lesion, 12.5% got Stage I, 10% exhibited Stage II, and 7.5% had Stage III and IV, each. (Table 2)

Table (1): Distribution of the cases studied according to demographic data

	No.	%
Gender		
Male	44	55.0
Female	36	45.0
Age		
20-60	53	66.25
>60	27	33.75

Table (2): Distribution of the studied cases according to Ann Arbor staging (n = 80)				
	Initial staging		Staging after target therapy	
	No.	%	No.	%
Ann arbor staging				
No LN / lesion	1	1.3	50	62.5
Stage I	22	27.5	10	12.5
Stage II	17	21.3	8	10.0
Stage III	23	28.8	6	7.5
Stage IV	17	21.3	6	7.5

When investigating the activity impression among the participants, 85% were responders, three-quarters (75%) of the responders had complete metabolic remission, compared to only 10% of those possessed partial metabolic response. (Table 3)

Table (3): Distribution of the studied cases according to Activity Impression (n = 80)		
	No.	%
Activity Impression		
Responder	68	85.0
Complete metabolic remission	60	75.0
Partial metabolic response	8	10.0
Non Responder	12	15.0
No metabolic response/ stationary course	0	0.0
Progressive metabolic disease	12	15.0

Over half of responders had a previous markedly increased uptake compared to the liver and new lesions, while over two-fifths had a moderately increased uptake. Currently, 55.9% of responders have no uptake, while 22.1% have uptake equal to or less than mediastinum. Non-responders have a significantly higher SUV_{max} of the largest LN/lesion. (Table 4)

Over half (52.9%) of the surveyed responders had a previous markedly increased uptake compared to the liver or new lesions, while 45.6% of those got a previous moderately increased uptake. Currently, about 55.9% of the responders had no uptake, 22.1% got uptake equal to or less than the mediastinum, and 11.8% possessed moderately increased uptake compared to the liver. (Table 5)

50% of Stage I patients had uptake equal to or less than the mediastinum, while 37.5% had >mediastinum but < or= liver, and 50% had markedly increased uptake. (Table 6)

Table (4): Relation between Activity Impression and SUV_{max} of the largest LN/lesion (n = 80)					
SUV_{max} of the largest LN/lesion	Activity Impression				p
	Responder (n = 68)		Non Responder (n = 12)		
	No.	%	No.	%	
Previous					
No uptake	0	0.0	0	0.0	<0.001*
Uptake ≤ mediastinum	0	0.0	4	33.3	
Uptake > mediastinum but ≤ liver	1	1.5	0	0.0	
Moderately increased uptake compared to the liver	31	45.6	5	41.7	
Markedly increased uptake compared to the liver and /or new lesions	36	52.9	3	25.0	
Current					
No uptake	38	55.9	0	0.0	<0.001*
Uptake ≤ mediastinum	15	22.1	0	0.0	
Uptake > mediastinum but ≤ liver	7	10.3	0	0.0	
Moderately increased uptake compared to the liver	8	11.8	4	33.3	
Markedly increased uptake compared to the liver and /or new lesions	0	0.0	8	66.7	
*p: p value for comparing between different categories *: Statistically significant at p ≤ 0.05*					

Table (5): Relation between Activity Impression and Deauville score (n = 80)					
	Activity Impression				p
	Responder (n = 68)		Non Responder (n = 12)		
	No.	%	No.	%	
Deauville score previous					
Uptake<or=mediastinum	0	0.0	4	33.3	<0.001*
Uptake >mediastinum but<or= liver	1	1.5	0	0.0	
Moderately increased uptake compared to the liver	31	45.6	5	41.7	
Markedly increased uptake compared to the liver and/or new lesions	36	52.9	3	25.0	
Deauville score current					
No uptake	38	55.9	0	0.0	<0.001*
Uptake<or=mediastinum	15	22.1	0	0.0	
Uptake >mediastinum but<or= liver	6	8.8	0	0.0	
Moderately increased uptake compared to the liver	8	11.8	4	33.3	
Markedly increased uptake compared to the liver and/or new lesions	0	0.0	8	66.7	
Uptake<or=mediastinum & uptake >mediastinum but<or= liver	1	1.5	0	0.0	
*p: p value for comparing between different categories *: Statistically significant at p ≤ 0.05*					

Table (6): Relation between Ann arbor staging after target therapy and Deauville score current (n = 80)					
	Ann arbor staging after target therapy				
	No LN/lesion (n = 50)	stage I (n = 10)	stage II (n = 8)	stage III (n = 6)	stage IV (n = 6)
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
Current Deauville score					
No uptake	38 (76.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Uptake<or=mediastinum	9 (18.0%)	5 (50.0%)	0 (0.0%)	1(16.7%)	0 (0.0%)
Uptake >mediastinum but<or= liver	0 (0.0%)	2 (20.0%)	3(37.5%)	1(16.7%)	1 (16.7%)
Moderately increased uptake compared to the liver	2 (4.0%)	2 (20.0%)	4(50.0%)	2(33.3%)	2 (33.3%)
Markedly increased uptake compared to the liver and/or new lesions	1 (2.0%)	1 (10.0%)	1(12.5%)	2(33.3%)	3 (50.0%)

97.9% of cases were metabolically and morphologically responders to target therapy, with a significant difference between responders and non-responders. The study also found high sensitivity, specificity, PPV, NPV, and accuracy in the activity impression. (Table 7)

Table (7): Agreement (sensitivity, specificity and accuracy) for Activity Impression									
	Morphological impression				Sensitivity (95% C.I)	Specificity (95% C.I)	PPV (95% C.I)	NPV (95% C.I)	Accuracy (95% C.I)
	Non responder (n =32)		Responder (n = 48)						
	No.	%	No	%					
Activity Impression									
Non responder	11	34.4	1	2.1	97.92 (89.93–99.95)	34.38 (18.57–53.19)	69.12 (57.74–76.76)	91.67 (61.52–99.79)	72.50 (62.72–82.28)
Responder	21	65.6	47	97.9					
χ^2 (^{FE}p)	15.703*(<0.001*)								

χ^2: Chi square test FE: Fisher Exact test CI: Confidence Intervals p: p value for association between different categories
: Statistically significant at p ≤ 0.05 PPV: Positive predictive value NPV: Negative predictive value

Case presentation

Case One

Clinical history: a 24 years old male patient presented with right supraclavicular swelling, proved pathologically to be DLBCL.

Radiological findings

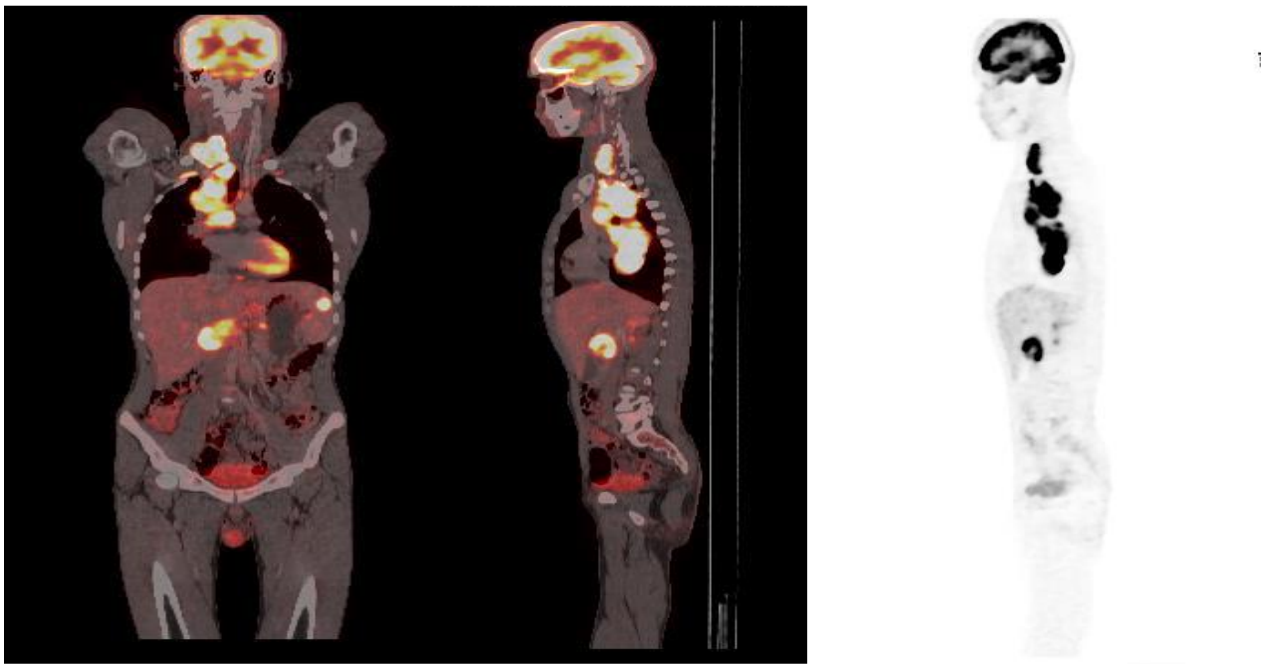

Figure (1): Coronal and sagittal 18F-FDG PET/CT images reveal extensive metabolically active lymphomatous involvement of both supra- and infra-diaphragmatic lymphoreticular chains, with variable-sized discrete and amalgamated lymph nodes. Supra-diaphragmatic involvement includes bilateral supraclavicular, sub-pectoral, sub-manubrial, anterior mediastinal, vascular, pre-tracheal, para-esophageal, carinal, and sub-carinal groups. Infra-diaphragmatic nodes include left gastric, porta hepatis, pre-pancreatic, para-aortic, and pre-caval regions. Splenic stromal infiltration is also noted. The largest lesion is a right-sided conglomerate mass extending from the supraclavicular region to the mediastinum, measuring 20 × 7.4 × 6.7 cm with a high SUVmax of 17.6 (Deauville Score 5; hepatic SUVmax 3, mediastinal SUVmax 1), indicating intense metabolic activity.

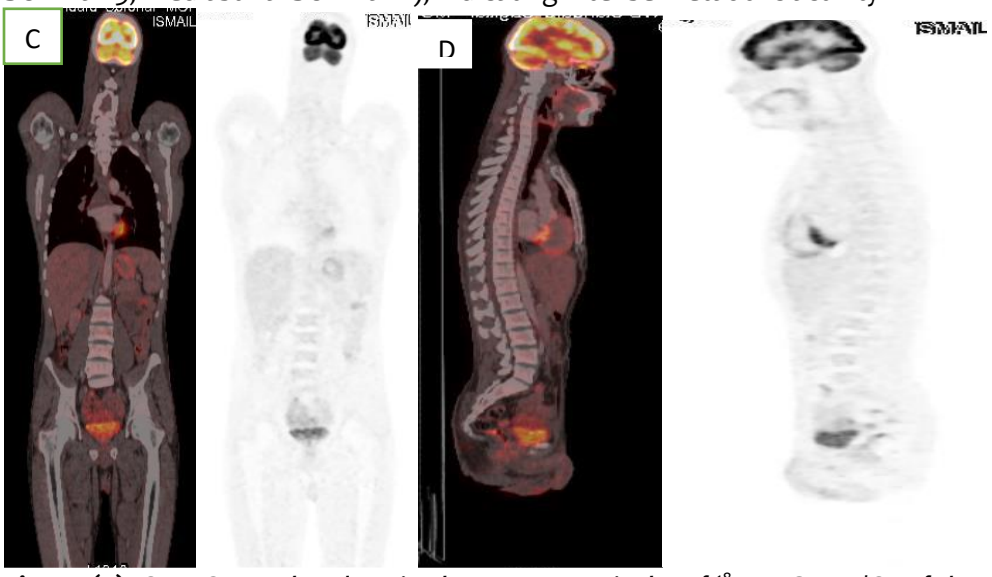

Figure (2): C, D. Coronal and sagittal cuts, respectively, of ^{18}F-FDG-PET/CT of the same patient after (3-4 cycles) of target therapy, revealed Complete metabolic remission of the previously observed uncountable widely spread metabolically active lymphomatous infiltrations

Case (2)

Clinical history: a 70 years old male patient with pathologically proven DLBCL, has not received therapy yet.

Radiological findings

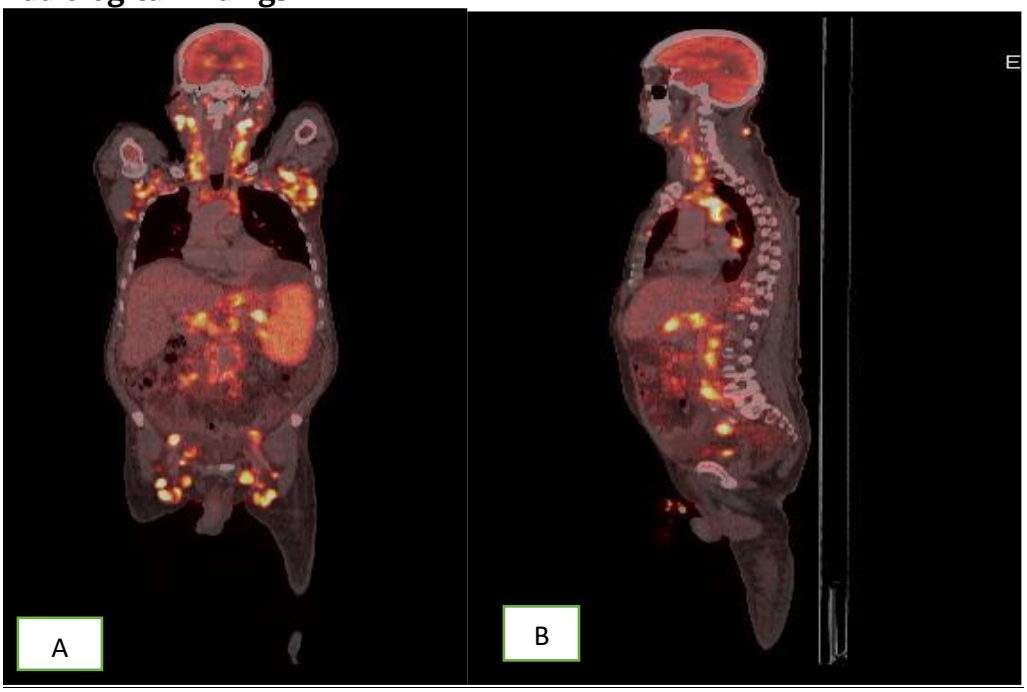

Figure (3): A, B are ^{18}F-FDG-PET/CT Coronal and sagittal cuts, respectively.The lymphoreticular chains are seen heavily studded with uncountable widely spread metabolically active lymphomatous infiltrations fading throughout the supra & infra-diaphragmatic chains by vary sizes discrete/ amalgamated lymph nodes with SUV $_{max}$ ranging **(6-12), where Hepatic reference of the patient SUV$_{max}$ 2 Mediastinal reference SUV$_{max}$ 1.2, DS 5.**

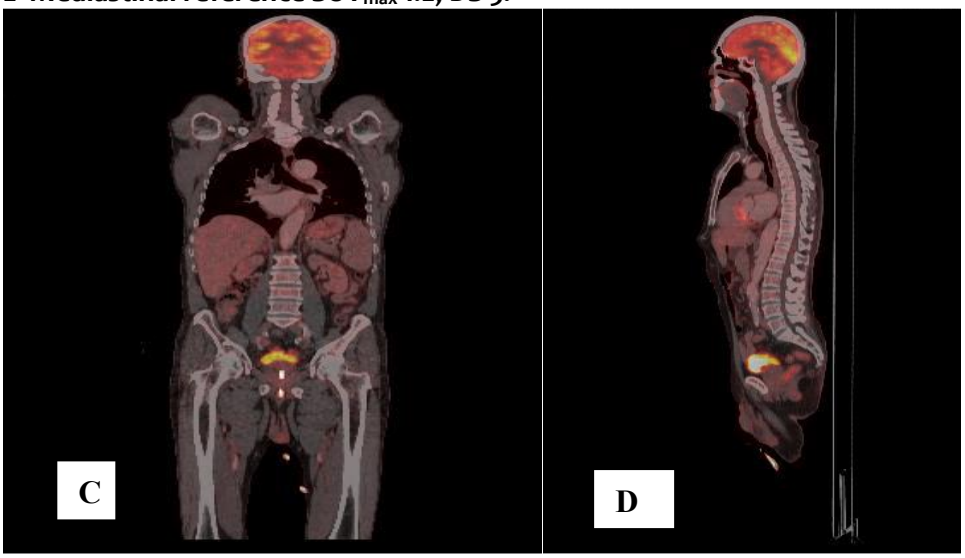

Figure (4): C, D. are Post-Therapy Negative PET/CT Scan for the same patient showing the following observations: Complete metabolic remission of supra/ infra-diaphragmatic lymphadenopathies. No newly developed metabolically active nodal or extra-nodal lesions. DS 1

Case (3)

Clinical history: a 90 years old male patient presented with right cervical swelling, proved pathologically to be DLBCL

Radiological findings

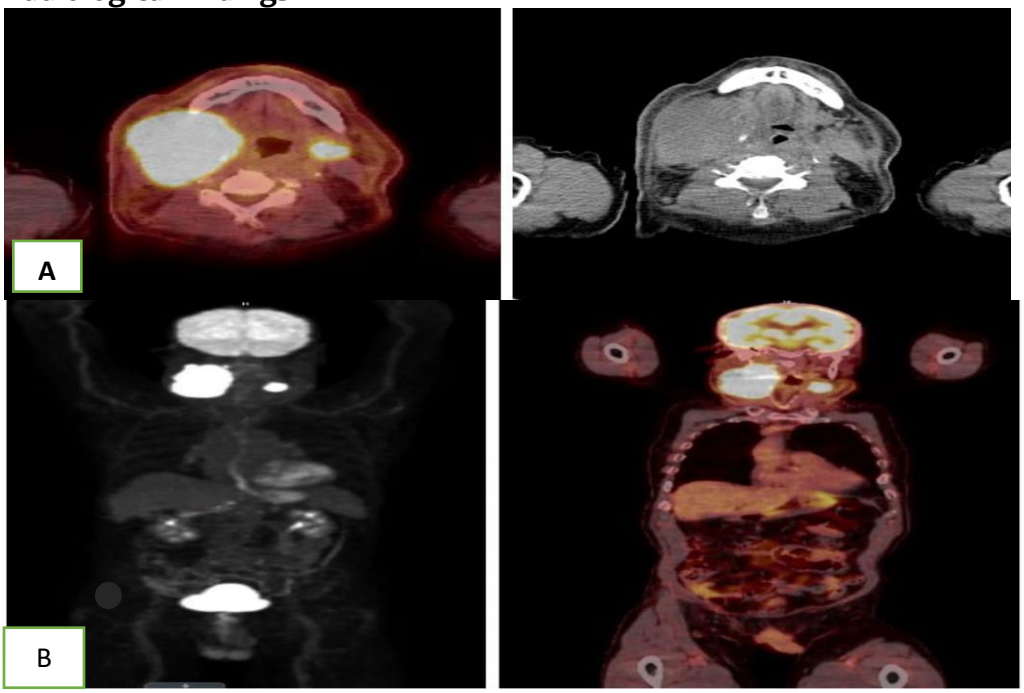

Figure (5): A, B are axial and coronal cuts of a baseline PET/CT scan, respectively. Both images show a large right cervical hypermetabolic lymphomatous mass measures 6.4 x 5.4 cm with $SUV_{max\ 32.8}$, in addition to FDG avid left cervical lymph node measures 2.1 x 1.9 cm, SUV_{max} 26.6, DS 5, where Hepatic reference= SUV_{max} 2.4 and Mediastinal reference =SUV_{max} 1.5

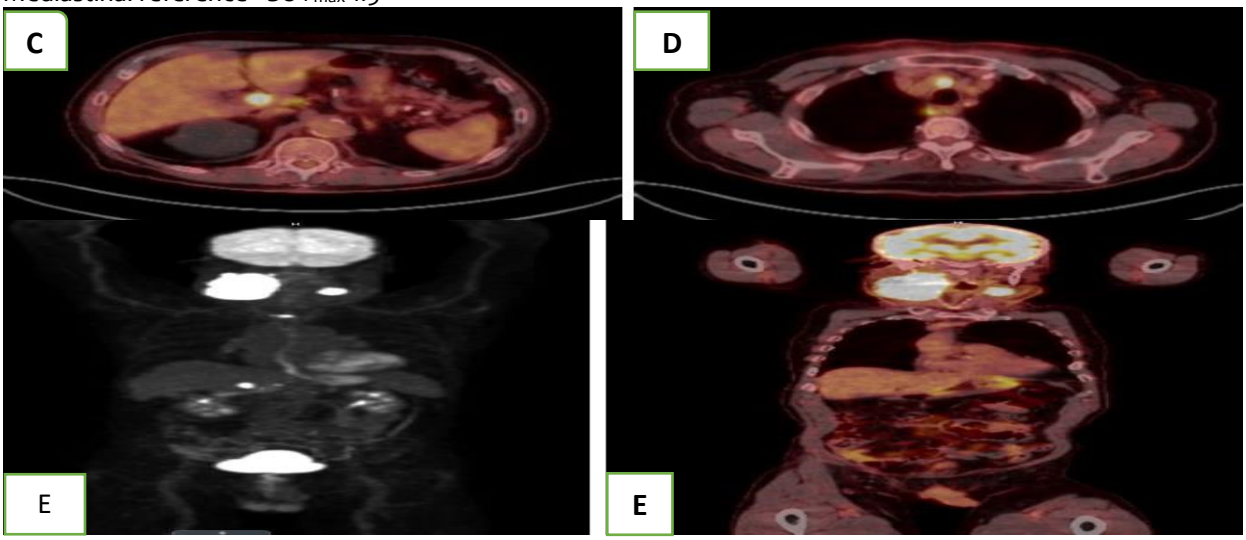

Figure (6): C, D & E are axial and coronal cuts of PET/CT scan **after target therapy**. Image C, D show **newly developed** porta hepatis lymph node measures 3 x 3 cm, SUV_{max} 19.9 and a pretracheal lymph node measures 3 x 2 cm, SUV_{max} 14.8, respectively. Image E is coronal cut showing still seen bilateral cervical FDG avid lymph nodes (SUV_{max} became 36.1 on the right side and 29 on the left side, in comparison to previous 32.8 and 26.6, respectively, with the newly developed porta hepatis and pretracheal lymph nodes **(progressive metabolic course),** DS **5**

Discussion

In the current cross-sectional analytical study, ^{18}F-FDG PET/CT was done as a baseline scan before target therapy for initial staging of pathologically proven DLBCL and another ^{18}F-FDG PET/CT scan was done after 3-4 cycles of Target Therapy rituximab to compare with pretherapeutic scan, to assess remission or relapse.

SUV_{max} is a widely used metabolic index to reflect tumor invasiveness [5]. In the current study, there is a statistically significant difference between the target therapy responders and non-responders regarding the previous ($p<0.001$) and current ($p<0.001$) SUV_{max} of the largest LN/lesion. Also, we found a statistically significant difference between both the previous and the current size and SUV_{max} of the largest LN/lesion. The standardized uptake value-based methods have also been used to assess response in DLBCL, most studies have applied the change in FDG uptake in the pixel with the highest uptake (SUV_{max}) before and during/after treatment (ΔSUV) [6,7].

Zaker et al. [8] found that for patients with heavy tumor load, its prognostic value is limited as SUV_{max} is susceptible to factors such as patient blood glucose, uptake time, acquisition and reconstruction methods, equipment, and population heterogeneity. Also, this is especially for low-uptake lesions, where uptake values often lead to false-positive results due to high background uptake.

In this study, there is a statistically significant difference between the target therapy responders and non-responders regarding Ann Arbor staging after target therapy ($p<0.001$).

Also, in agreement with our findings, Allioux et al. [9] found that on Kaplan–Meier univariable analysis, Ann-Arbor Stage, was predictor of 2-year event-free survival whereas age was not among patients who were

newly diagnosed with DLBCL and referred for baseline PET and EoT PET after 6 or 8 courses of chemotherapy.

The current study results have revealed that, there is a statistically significant difference between the target therapy responders and non-responders regarding the previous ($p<0.001$) and current ($p<0.001$) interim Deuville score. The Deauville criteria, laid by a consensus committee of nuclear medicine physicians, hematologists, and oncologists recommends a 5-point scale rather than taking a binary decision (namely PET positive or negative). This is based upon visual analysis, with background uptake as reference. International validation studies are on to assess the utility of these criteria [10].

Our findings are in line with Michaud et al. [11] who found that interim $DSUV_{max}$ was significant predictors of PFS and OS. They also found that, combining interim PET parameters Deauville score and $DSUV_{max}$ demonstrated that patients with Deauville scores of 4–5 and positive $DSUV_{max}$ (10% of the cohort) had extremely poor prognosis. These results combining visual and quantitative assessments are similar to Casasnovas et al. [12] who previously reported in an independent cohort after 4 cycles of induction treatment. Thus, it appears that adding $DSUV_{max}$ to visual analysis may be a robust and reproducible tool for identifying high-risk patients with DLBCL. Combining the 2 interim PET parameters identifies patients who have a poor outcome with standard chemoimmunotherapy and may help define a cohort of patients for evaluation

of alternative therapeutic approaches, such as CAR T-cell therapy.

In the current study, there is a statistically significant difference between the target therapy responders and non-responders regarding the previous (p=0.008) and current (p<0.001) tumor size.

Similarly, the relationship between chemotherapy outcomes and pretreatment tumor volume in patients with DLBCL was investigated by Tout et al. [13]. They found that as tumor volume increased, it increased the difficulty in chemotherapeutic drug penetration, which may have contributed to the poor prognosis observed in their study.

In our study, agreement was assessed for the activity impression against the morphological impression, we found that the activity impression sensitivity was 97.92%, specificity was 34.38%, PPV was 69.12%, NPV was 91.67%, and the accuracy was 72.50%.

In line with our findings, Zhao et al. [14], Fruchart et al. [15], and Kostakoglu et al. [16] studies, have a reported PPV of 71%–100% for interim ^{18}F-FDG PET in aggressive non-Hodgkin lymphoma (NHL), and Terasawa et al. [17] a meta-analysis, found a sensitivity of 0.78 and specificity of 0.87 for interim ^{18}F-FDG PET in DLBCL. However, these studies have important limitations. For instance, the meta-analysis included 311 DLBCL patients from 6 studies who had stage I–IV disease and were treated with a variety of regimens, with and without rituximab, radiation, and even consolidative stem cell transplantation. Median follow-up ranged from 15 to 36 mo, and ^{18}F-FDG PET was performed after 2, 3, or 4 cycles of therapy. In fact, the authors of the meta-analysis could not draw a conclusion about the value of interim ^{18}F-FDG PET in DLBCL because of the heterogeneity of the available studies.

Mikhaeel et al. [18] study of 121 patients with NHL, which assessed the utility of ^{18}F-FDG PET after 2-3 cycles of chemotherapy found that ^{18}F-FDG PET had a high predictive value for progression-free survival and overall survival.

Conclusion

The prognostic value of interim ^{18}F-FDG PET/CT in DLBCL, demonstrating its role in early identification of treatment response and guiding timely therapeutic adjustments. While PET/CT aids in predicting outcomes and optimizing management, its reliability is limited by variability in interpretation and technical factors, underscoring the need for standardized imaging protocols to ensure consistent and accurate prognostic evaluation.

Limitations of The Current Study: While interim PET/CT scans offer valuable prognostic information, variability in scan interpretation and the influence of factors such as patient glucose levels and imaging techniques can affect the reliability of results.

Recommendations: Further Research and Trials should continue to evaluate the impact of treatment adaptations based on interim PET results on overall survival rates, helping to refine treatment protocols for DLBCL.

Abbreviations:

18F-FDG PET/CT	18Fluorine-Fluorodeoxyglucose-positron emission tomography
DLBCL	Diffuse large B-cell lymphoma
PACS	Picture Achieving and communication system
DS	Deauville score
NHLs	Non-Hodgkin lymphomas
SUV	Standardized uptake value
LN	Lymph node
$\chi 2$	Chi square test
FE	Fisher Exact test
p	p value for association between different categories
PPV	Positive predictive value
NPV	Negative predictive value
CI	Confidence Interval
CAR T-cell	Chimeric antigen receptor T cell

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