

Review Article, PET/CT.

Update of Assessment of Early Response Using PET/CT in Malignant Lymphoma.

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ABSTRACT:

¹⁸F-FDG PET/CT is an eminent widely used diagnostic imaging modality utilized for staging and evaluating therapy response in malignant lymphomas. The pre-eminence of ¹⁸F-FDG PET/CT over CT to recognize viable lymphomatous tissue after two cycles of chemotherapy cycles has lately directed to reconsideration of criteria of early therapy response.

Numerous recent researches have also confirmed that early response assessment within early two to three chemotherapy cycles is mandatory to evaluate chemo sensitivity and may have the potential to guide additional risk-adapted treatment modalities in malignant lymphoma patients. Early response evaluation depends mostly upon quantitative Deauville criteria which may subjective dichotomous interpretation if evaluated by more than one interpreter.

Therefore, assessment of therapy response might necessitate a more objective quantification methodology of ¹⁸F-FDG uptake alterations. Standardized uptake value (SUV) is currently the most regularly used semi-quantitative parameter allowing non-invasive evaluation of ¹⁸F-FDG metabolic rate.

Novel Volume based parameters as MTV and TLG have recently gained researchers attention as they are considered more representative of total tumour burden than single voxel based parameter; SUV. They may have the potential for early prediction of therapy response, prognosis of clinical outcome, and tumour delineation for radiotherapy planning. However, lack of standard method for tumour segmentation hinders the routine use of more inclusive volume based parameters.

Key Words: F-18 FDG PET/CT, Volume Based Parameters & Malignant Lymphoma.

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INTRODUCTION:

^{18}F -FDG PET/CT has been well recognized as a tremendous functional imaging modality for tumors as a result of its higher scanner spatial resolution and its PET images tomographic nature. ^{18}F -FDG PET/CT imaging role in lymphoma particularly, supplemented appreciated diagnostic data ⁽¹⁾. FDG is transported by facilitated diffusion into cells and inverted into FDG-6-phosphate using hexokinase; the initial enzyme in the process of glycolysis. Precise evaluation with ^{18}F -FDG PET/CT of the level and metabolic activity of disease necessitates appropriate patient preparation ⁽²⁾.

^{18}F -FDG PET/CT utility has grown to be the recognized standard of care for evaluating entirely FDG-avid lymphomas, and recommended by the 2014 *Lugano criteria* ⁽³⁾, which substituted the well-known Ann Arbor staging system ⁽⁴⁾. Many researches have verified the role of ^{18}F -FDG PET/CT in the initial staging of lymphoma. Also, ^{18}F -FDG PET/CT been found valuable in evaluation of therapy response due to its enhanced utility in distinguishing benign fibrosis with low or absent ^{18}F -FDG uptake from residual

active lymphoma with high ^{18}F -FDG uptake ⁽⁵⁾.

Centered upon visually comparing FDG uptake in lesions to FDG uptake with FDG uptake in the reference regions of interest; mediastinal blood pool uptake and hepatic uptake. It generally categorizes residual lymphomatous lesions from one up to five ⁽⁶⁾. Numerous studies have revealed greater accurateness and inter-observer settlement of lymphoma response evaluation based on ^{18}F -FDG PET/CT whenever utilizing the Deauville scoring system and attribution to a quick incorporation of the anticipated scheme into reporting method used in daily routine. Significantly, categorized evaluation caused interpretation to be further easier, because this methodology permits amendment of the cut-off amongst positive and negative outcomes liable upon the clinical background ⁽⁶⁾.

^{18}F -FDG PET/CT Image

Interpretation:

There are several approaches to evaluate images and compare serial scans including qualitative and Semi-quantitative approaches.

A. Qualitative (Visual) assessment:

Visual assessment is usually used for diagnosis of a tumor and staging, and is founded on variations in contrast from tumor and adjacent normal tissue.

This is a basic technique demanding only a solitary static image at a certain time post FDG administration and can be correspondingly applied to evaluate the extent of tumor therapeutic response. In the visual procedure, it is essential to modify the image concentrations of the tumor and contiguous normal soft tissue to the similar gray or color scales ⁽⁷⁾.

In 2009, the first international workshop on interim ¹⁸F-FDG PET/CT in lymphoma produced the so-called “Deauville criteria” recommendation. It resulted in a simple and reproducible rules for visual interpretation of interim ¹⁸F-FDG PET/CT in cases diagnosed with malignant lymphomas, these criteria were delineated in three major declarations: Visual assessment is favored, but SUV determination can be utilized in selected cases, Interim ¹⁸F-FDG PET/CT interpretation must always be done by comparing ¹⁸F-FDG uptake foci to those previously reported in the initial ¹⁸F-FDG PET/CT study, and ¹⁸F-FDG uptake intensity must be graded according to a five-point scale that must include reference

organs as the mediastinum and the liver, that are utilized to describe variable grades of ¹⁸F-FDG uptake ⁽⁸⁾.

The Deauville scoring system has remained functional for treatment stratification in numerous clinical studies and advanced such that it became a well-known approach for evaluating response to therapy. Conversely, there are continuing considerations on the techniques of FDG uptake interpretation. However, *Barrington et al.* lately directed a minor investigation for patients diagnosed with Hodgkin lymphoma and testified that a Deauville score of five was accompanied by inferior results in their study, in which score five was demarcated quantitatively as three times or more than the hepatic FDG uptake ⁽⁹⁾.

In both GHSG trials HD16 and HD18, Deauville scoring of three demonstrated not to be significant for prognosis of either relapsed or progressive disease, on the other hand, Deauville scoring of four proved to be significant ⁽⁶⁾. Despite the fact that mainstream of patients scored with a Deauville score of four are treated, those personnel demonstrated considerably diminished PFS and OS. Comparable results were described for DLBCL patients.

That is why Deauville scoring of four or five should be interpreted as a positive

qPET Scoring System:

Another semi-quantitative assessment, which is considered an extension of the Deauville scoring system, to assess therapy response in interim ¹⁸F-FDG PET/CT scans is the qPET.

Table 1: Q-PET cut values.

Q-PET Value	Deauville Score
0	1
<0.95	2
0.95 to <1.3	3
1.3 to <2.0	4
≥2.0	5

Quoted from Osmany et al.,⁽¹¹⁾.

B. Quantitative assessment:

Quantitative approaches, likewise named the kinetic methods embrace two approaches: Compartmental analysis and *Potlak* analysis. Compartmental analysis is founded on evaluating arterial activity utilizing serial sampling and soft tissue activity utilizing serial imaging. The metabolic glucose rate obtained through

outcome at whatever time complete remission is the chief intention⁽¹⁰⁾.

It provides a semi-automatic quantification of interim ¹⁸F-FDG PET/CT response in lymphoma prolonging Deauville scoring to a continuous scale by using SUV peak of the residual divided by SUV mean of the liver. Deauville scores match up to certain Q-PET cut values⁽⁸⁾. (*Table 1*).

this technique is conveyed as moles/min/ml.

Potlak analysis delivers analogous data nevertheless necessitates less data. Both approaches are too complicated and requiring for resources, and consequently are less satisfactory for routine clinical utilization⁽⁷⁾.

C. Semi-quantitative assessment

In semi-quantitative approaches, static images are used to associate between the relative tumors to normal tissue ratio (T/N). The ratios are self-determining of the injected dose, weight of the patient, or serum glucose blood level. The T/N ratio evaluation is rather comparable to visual assessment. The selection of a suitable normal reference region of interest, especially in the abdominal and pelvic regions, is essential in this evaluation.

1. Standard uptake value (SUV)

The supreme flexible semi-quantitative method is the standard uptake value (SUV) technique that is extensively utilized by nuclear medicine and molecular imaging. Characteristically, neoplastic tissue have an SUV exceeding 2.5–3.0, while normal tissues; non neoplastic tissue, have SUVs varying from 0.5 to 2.5. SUV approximation is utilized principally in evaluating ambiguous lesions or during follow-up of FDG-avid lesions ⁽¹²⁾.

The SUV of a certain region of interest is measured from the counts-per-pixel normalized to body weight (BW) using the following formula ⁽¹³⁾:

Tracer activity in tissue ($\mu\text{Ci}/\text{gm}$)

Administered radiotracer dose
(mCi)/patient weight (kg)

The SUV of a certain region of interest can be portrayed as the minimum, maximum or mean in that region of interest. SUV max is the count obtained from the highest pixel occurring in the selected region of interest, while SUV mean is the count obtained from the average of counts occurring in all pixels in the selected region of interest ⁽¹³⁾. Δ SUV max is the percent change amongst SUV max on the interim ¹⁸F-FDG PET scan versus the initial ¹⁸F-FDG PET scan ⁽¹⁴⁾. It is measured using the following formula;

$$\Delta \text{ SUV max} = (\text{SUV max1} - \text{SUV max2}) / \text{SUV max1} \times 100.$$

SUV max demonstrated to expand the predictive significance of initial ¹⁸F-FDG PET/CT whenever it is applied in concordance with visual assessment; nevertheless, in some researches SUV mean may possibly be more appreciated because a single voxel value may not be illustrative of the overall ¹⁸F-FDG tumoral uptake in a non-homogeneous neoplasm ⁽¹⁵⁾.

Deviations in the SUV have been demonstrated as in the glucose-corrected SUV and SUV normalized by surface area or lean body mass.

It is vital to standardize the duration interval between administration of the radiotracer and the PET scanning since SUV inconsistency with this duration has been well recognized ⁽¹⁶⁾.

It is essential to document that several factors can have an impact on the SUV values. The time interval between tracer administration and scanning is possibly the chief solitary basis of fault in calculating the SUV. Interval required to reach maximum uptake in a specific region of interest differs according to the type and condition of tissue of concern as diverse types of malignancy as well as in the same tissues pre and post therapy.

FDG tissue uptake lessens with elevated serum blood glucose level leading to affection of the SUV calculations. Extra adipose tissue misleadingly increases the SUV for that reason many nuclear medicine personnel accurate utilizing body lean mass as a substitute to body weight. Similarly, several personnel established improved values of SUVs utilizing body surface area instead of body weight. The utilization of maximum pixel count density against mean value for all pixels in a region of interest too changes the SUV values, though the mean value nowadays is

less frequently utilized ⁽⁷⁾.

2. Volume Based Metabolic Parameters:

a. Metabolic Tumor Volume

Metabolic tumor volume (MTV) is defined as the metabolically active volume of the tumor segmented utilizing ¹⁸F-FDG PET/CT. It has been revealed to be beneficial in predicting outcome of patient and in evaluating therapy response. MTV is calculated by producing a 3D iso-count contour to delineate tumor boundaries (ROI) post applying a predefined threshold of the SUV max value in the selected region of interest utilizing semi-automatic contouring software (*Table 2*).

Unfortunately, this might not be applicable in cases of low tumor-to-background ratios or in cases in which the vicinity of organs demonstrate high ¹⁸F-FDG uptake as brain, myocardium, kidneys, or urinary bladder. In such cases the region of interest automatically generated must be checked visually and drawn manually in order to ensure that it is large enough to embrace all the volume of the tumor and satisfactory enough to eliminate physiological areas of ¹⁸F-FDG uptake ^(17,18).

Table 2: Common methodologies for MTV calculation with their chief characteristics:

Threshold	Advantages	Disadvantages
Fixed absolute (e.g., SUV 2.5 or 4.0)	High reproducibility	Overestimation if tumor lies adjacent to areas of high physiologic uptake
	Observer-independence	Underestimation in tumors that have many voxels with an uptake less than the threshold
Reference regions (e.g., liver or mediastinum)	Adjusted to patient and scan	More time-consuming
		Low availability on commercial software
Fixed relative (e.g., 41% of tumor SUV max)	Observer-independence	Overestimation in case of low lesion-to-background ratio
		Underestimation of tumors with heterogeneous uptake and high SUVmax
Adaptive (e.g., signal-to-background ratio)	Adjusted to patient and scan	More time-consuming
		Low availability on commercial software

Quoted from Voltin et al., [18]

Visual segmentation Technique:

This is the most frequently utilized technique for target demarcation ⁽¹⁹⁾. Nuclear medicine physicians define the nature and borders of tumor after modifying the window level, regularly with reference to normal organs FDG uptake as uptake within liver tissue. Though this technique may be dependable in eliminating physiological and inflammatory FDG uptake, it is principally operator reliant and is predisposed to inter and intra-observer discrepancies.

The usage of a standardized delineating procedure with window and color settings that are previously defined in advance can aid in reducing the discrepancies in the target delineation ⁽²⁰⁾.

Mean MTV (Δ MTV) is measured as the percent of change amongst MTV on the interim ¹⁸F-FDG PET/CT scan versus the initial ¹⁸F-FDG PET/CT scan using the following formula; $(MTV1 - MTV2) / (MTV1) \times 100$.

b. Total Lesion Glycolysis:

The thought of total lesion glycolysis (TLG) was first presented by *Larson and Ginsberg* in their printed work in 1999, which they so-called Larson Ginsberg Index (LGI) ⁽²¹⁾. It was demarcated as “Mean SUV of the lesion multiplied by the metabolic tumor volume (MTV)”. The chief intentions of quantifying the uptake inside the entire tumor volume, alternative to quantifying a solitary pixel value as in the setting of SUV max, is to surmount heterogeneity of the tumor and improved evaluation of the gross tumor.

Total Lesion Glycolysis (TLG) is calculated as the summation of the mean SUV multiplied by MTV of all lesions.

Mean TLG (Δ TLG) is measured according to Larson-Ginsberg Index (LGI), and recognized as Δ TLG (LGI): $[(SUV_{mean1} \times Vol1) - (SUV_{mean2} \times Vol2)] / [(SUV_{mean1} \times Vol1)] \times 100$.

The fore mentioned volume based parameters are hypothetically more appropriate parameters than single pixel values. They were assumed to deliver appreciated information concerning tumor aggressiveness and accordingly, they might be regarded as possible prognostic

indices for tumors. The most important hindrance to the widespread application of TLG is the technique utilized to quantify the MTV ^(22, 23).

MTV and TLG that are delivered by the means of ¹⁸F-FDG PET/CT scanning possibly will additionally tailor therapy modalities of lymphoma.

Hence, prospective studies are desired to authenticate the prognostic and predictive worth of quantitative ¹⁸F-FDG PET/CT measures, assumed their unlimited possibility as guides aimed at shaping the forthcoming management of personnel diagnosed with lymphoma ⁽²⁴⁾.

¹⁸F-FDG PET/CT delivers biomarkers for instance the metabolic tumor volume (MTV) or total lesion glycolysis (TLG), which integrates data regarding burden of the tumor and activity of the disease. *Cottreau et al.*, stated that the MTV improves baseline risk classification for patients initially diagnosed with early-stage Hodgkin lymphoma in comparison to presently utilized staging methodologies ⁽²⁵⁾. Patients initially diagnosed with early-stage unfavorable disease could also be sub-classified into low risk or high risk groupings grounded on the MTV and TLG, as displayed elsewhere ⁽²⁶⁾.

Mettler et al., Identified in a retrospective analysis comprising 310 individuals that pretreatment MTV is likewise a prognostic utility for early response post two cycles of chemotherapy in cases identified as advanced-stage Hodgkin lymphoma ⁽²⁷⁾.

Additionally, metabolic measures were testified to have a predictive significance in cases initially diagnosed with non-Hodgkin lymphoma.

Mikhaeel et al., Illustrated that MTV at the phase of staging is an essential predictive tool for DLBCL and that conjoining MTV with outcomes of early ¹⁸F-FDG PET/CT response evaluation increases the prognostic influence ⁽²⁸⁾.

Vercellino et al., Has described that MTV is a reliable predictor in aging personnel DLBCL treated with R-CHOP and reported that elevated MTV pre therapy is considerably accompanied by inferior outcomes in PFS and OS in that age cluster ⁽²⁹⁾.

Cottreau and colleagues as well studied the radiomic features role in illustrating lesion distribution and described that coalescing them with baseline MTV additionally improves risk classification in patients diagnosed with DLBCL ⁽³⁰⁾.

A total of 57 adult patients with non-Hodgkin Lymphoma. Initial ¹⁸F-FDG PET/CT scan was done before and end of chemotherapy. The initial TMTV and TLG were found statistically significant (p 0.005) & (p 0.010) respectively. On multivariate analysis; Δ SUV max was found to be statistically significant (p <0.001). Regarding 2Y relapse free survival rate; initial ¹⁸F-FDG PET/CT TLG quantitative parameter was found statistically significant where 2Y-RFS rates for high- and low-TLG groups were 100% and 66.7% respectively (p 0.011) ⁽³¹⁾.

CONCLUSIONS:

The Deauville scoring system has remained functional for assessment of early treatment response as proved in numerous clinical studies and became a well-known approach for evaluating response to therapy. Quantitative ¹⁸F-FDG PET/CT has the possibility to significantly advance prediction in patients diagnosed with malignant lymphoma. An incorporation of metabolic measures including MTV and TLG is now intended by numerous working assemblies and will offer additional confirmation of prognostic in malignant lymphoma.

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