Original Article, PET/CT.

Role of FDG/CT Scan Quantitative Analysis in Assessment of both Hodgkin and Non-Hodgkin lymphoma.

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ABSTRACT:

Background: ^{18}F-FDG PET/CT is used for management evaluation of lymphoma with different parameters for PET and CT. However, there is no definite parameter to be used as golden standard. ***Aim of the Work:*** Evaluation of role of ^{18}F-FDG PET/CT in assessment of lymphoma management with comparison of different parameters. ***Patients and Methods:*** One-hundred patients with different lymphoma histopathology attended to clinical oncology and nuclear medicine department - Kasr Al-Ainy hospital (NEMROCK), had been retrospectively studied looking for different parameters like PET and CT parameters for evaluation of the lesions together with assessment of treatment response. ***Results:*** This study included 36 patients with Hodgkin disease (HD) and 64 with Non-Hodgkin lymphoma (NHL). Comparison between initial mean values of SUVmax with ±S.D in Hodgkin and non-Hodgkin lymphoma shows no significant difference ($p>0.05$). Responders were found to be 86% and 14% were non-responders with very high degree of matching between qualitative and quantitative PET parameters and poor matching between them and CT assessment for response. Regression analysis revealed that the most determinant factors for assessment of therapeutic response were Lugano and Deauville (30% impact for each) together SUVmax and delta SUVmax (33% for both together).

Conclusion: ^{18}F-FDG PET/CT is an important tool for assessing response and survival in lymphoma.

Key words: Lymphoma, SUVmax, Lugano, Deauville.

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INTRODUCTION:

Lymphoma, which includes Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL), is a group of more than 50 histologically and physiologically different lymphoid cancers. The prognosis and optimal treatment strategy for each subtype largely rely on the disease's current stage. Especially for NHL, the 5-year survival rate has risen as a result of exceptional advances in diagnosis and therapy seen in Europe [1, 2].

The incorporation of FDG PET/CT into the standard criteria of evaluation has helped improve clinical care in lymphoma patients by providing a staging and response assessment tool for FDG-avid lymphoma [3,4].

PET/CT has a significant predictive value in assessing remission in HL and aggressive NHL; it also appears to be a good predictor of outcome in indolent lymphomas, particularly in follicular lymphomas (FL) [5.6].

CT scans are commonly used for detecting residual masses following ending therapy; however PET/CT provides a more accurate distinction between active diseased cells and fibrotic scar tissue [4].

Both PET tracer uptake and the extent of Remaining lesions quantifiable on CT scans are used in accordance with the standards established by the Imaging Subcommittee of the International Harmonization Project (IHP) to assess therapy [2, 3].

Use of these criteria in clinical practice and scientific experiments is strongly encouraged. Deauville Criteria (DC) is an alternate scale that uses the mediastinum blood pool and hepatic activity as the reference standard. Patients with HL and aggressive NHL have been studied to determine the prognostic usefulness of PET using the DC after one to three cycles of chemotherapy (interim PET) and the possible benefits for clinical management. It was recently suggested that a five-point scale (5PS) be used for reporting PET results during and after treatment [1].

AIM OF THE WORK:

The goal of the current study is to compare the numerous metrics now available for use in assessing the efficacy of 18F-FDG PET/CT in therapy of lymphoma, and to determine prognostic value of several qualitative (visual) and quantitative approaches, including maximal standardized uptake value (SUVmax).

PATIENT AND METHODS:

The study included 100 patients (58 females and 42 males) with pathologically proven lymphoma (36 HL and 64 NHL) ranging in age from 18 to 60 years, who were documented in Clinical Oncology and Nuclear Medicine Department, Kasr Al-Ainy hospital (NEMROCK). They were sent to our department for an initial FDG-PET/CT scan either before starting treatment or after it had been discontinued in the period between January 2016 and December 2018. We excluded patients younger than 18 years old and patients with non- FDG-avid lymphoma. Proper disease history was obtained with pathological reports recording of all patients.

This retrospective analysis of data of 100 patients with lymphoma, we confirmed that tracer uptake in normal tissues was kept to a minimum while target tissue uptake is preserved as much as possible during preparation. Routinely, a paper of instructions was given to our patients before the study. These instructions include fasting before the scan for 4 to 6 hours to decrease physiologic glucose levels. Contrast allergy was checked for, and patients who had a serum creatinine level beyond the normal range were not given intravenous contrast. The blood glucose level was checked (below 160 mg/dl at time of FDG injection). The ^{18}F-FDG was administered intravenously via cannula and the dose was determined according to body weight (dose of 0.125 mCi/Kg). In a quiet, low-light and warm room, the patients were awaited before and after tracer injection. Patients were instructed to drink 500 mL of water and to evacuate urinary bladder just before starting PET/CT examination.

PET/CT imaging:

The PET scan of the entire body took place in overlapping bed positions, with the same axial coverage as the CT scan, and each bed position was acquired for 2 minutes. Using an ordered-subset expectation maximization iterative reconstruction technique, attenuation-corrected PET images were reconstructed.

CT acquisition: PET/CT scanner from Philips Healthcare in Cleveland, Ohio, which has a modular, LYSO-based PET part and a 64-channel CT part, was used.

Using 35 mAs and 120 kVp, a preliminary scout view was acquired. Finally, a spiral CT was performed with exposure parameters of sixty mAs (quality reference), 120 kVp, and a reconstructed slice thickness of five mm for low-dose CT.

Patients performed whole body ^{18}F-FDG PET/CT in the following conditions:

- **Initially (PET1):** before treatment (base-line) or after two cycles and it was positive in all case.
- **Post-therapy (PET2);** after end of therapy to reassess response to treatment.

PET/CT was done at least three weeks after chemotherapy. Imaging was performed from the skull base to the mid-thigh with the arms extended above the head 60±10 minutes after FDG injection.

Interpretation:

The PET/CT studies were interpreted by nuclear medicine physicians. PET, CT, and fused PET/CT images were digitally archived and exported to dedicated workstations, using the imaging standard 'Digital Imaging and Communications in Medicine' (DICOM). The program converts the intensity values automatically to SUV. The images obtained in the post-therapy PET_2 are analyzed and compared with the PET_1 scan for assessment of metabolic response via the following qualitative and semi-quantitative measures.

STATISTICAL ANALYSIS:

All patients' data had been subjected to statistical analysis using SPSS version 20 software. All numeric (parametric) data had been subjected to descriptive (mean ±S.D) and univariate analysis using t-test for two independent and dependent parameters, and analysis of ANOVA for more than two parameters. Non-parametric data had been subjected to test of proportion and qui square. Degree of matching between response assessment by PET and CT had been done using Kappa test for agreement. Total actuarial survival had been generated by ***Kaplan Meyier*** test. Finally, multivariate analysis and step wise regression had been applied to all variables to determine the most deterministic (predictor) for total actuarial survival. Probability <0.05 was applied as a level of significance.

Univariante analysis:

- To determine if the patient is responding to treatment or not, we compared post-therapy images to initial one by using delta SUVmax (Initial SUVmax - End SUVmax / Initial SUVmax), delta CT (initial CT- End CT/ initial CT) and qualitative assessment. Cut-off level 66% change in δSUV max had been applied as a level of significant response (CR and PR).
- Each parameter (SUVmax and CT) was used individually for post-therapy assessment in both HD and NHL to know if there is any significant difference in their therapeutic response and also pathological sub-types of both HD and NHL were assessed according to SUVmax and CT parameters.

Multivariate analysis:

- We compared between PET/CT (quantitative and qualitative) and CT parameters to assess degree of matching between these parameters' findings in both pathological types of lymphoma.
- We assessed actuarial survival rate in all responders by using SUVmax, Lugano and CT parameters.
- Degree of matching between PET/CT (quantitative and qualitative) parameters and CT in assessment of actuarial survival rate was assessed.
- Degree of matching between PET/CT (quantitative and qualitative) and CT parameters in post-therapeutic response was analyzed.
- Degree of matching between quantitative and qualitative parameters in post-therapeutic response was also analyzed.
- Regression analysis of survival of Lugano, Deauville and delta SUVmax, was done and it is found that they are the most important in prediction of survival.

RESULTS:

Demographic Data: Our study consisted of 100 patients (58% females and 42% males) with ages ranging from 20 to 60-year-old (mean age 39.34) are already diagnosed with lymphoma. The pathological type's prevalence of lymphoma among our cases is demonstrated as following: 36% Hodgkin disease and 64% Non-Hodgkin's disease.

Hodgkin disease subtypes: 22% classic type, 10% Mixed cellularity and 4% Nodular sclerosis. Non-Hodgkin's disease: 44% B-cell lymphoma, 6% Malt type, 4% Atypical and 10% Malignant ***Table (1)***. In our study 6% of cases received 2-4 cycles of chemotherapy, 48% of cases received 4-6 cycles of chemotherapy and 46% of cases received more than 6 cycles ***Table (1)***.

Table (1): Patients' demographics and disease details for 100 lymphoma cases.

Variable			Number of patients	Percentage
Sex	Female		58	58%
	Male		42	42%
Histopathology	Hodgkin disease (n=36)	Classic type	22	61.1%
		Mixed cellularity	10	27.8%
		Nodular sclerosis	4	11.1%
	Non-Hodgkin's disease (n=64)	B-cell lymphoma	44	58.8%
		Malt type	6	9.4%
		Atypical	4	6.2
		Malignant	10	15.6%
Number of cycles of chemotherapy	2-4		6	6%
	>4-6		48	48%
	>6		46	46%

Our cases are assessed by Deauville score in the initial study then they were reassessed after end of therapy by Deauville and Lugano score ***Table (2)***.

Table (2): Deauville score and Lugano score.

Variable		Number of patients	Percentage
Deauville score	1	42	42%
	2	28	28%
	3	10	10%
	4	12	12%
	5	8	8%
Lugano score	CR	70	70%
	PR	14	14%
	SD	12	12%
	PD	4	4%

Univariante Analysis:

Comparison between initial mean values of SUVmax ±S.D in Hodgkin disease and non-Hodgkin lymphoma are 8.74±0.6 and 12.6±11.3 respectively with no significant difference between both types (p>0.05). Mean values with ±S.D of SUVmax measured after end of therapy in Hodgkin and non-Hodgkin lymphoma are 2.69±3.72 and 3.1±5.3 respectively with no significant difference either (p>0.05). Mean value of δSUV max ±S.D after end of therapy in Hodgkin and Non Hodgkin lymphoma are 67.3±40.9 and 76.5±34.7 respectively with no apparent distinction between the two variants (p>0.05) ***Table (3)***.

Table (3): Comparison of mean values of SUVmax in Hodgkin disease and non-Hodgkin lymphoma.

Variable	HD		NHL		p-value
	Mean	±S.D	Mean	±S.D	
Initial SUV max	8.74	±0.6	12.6	±11.30	>0.05
End SUV max	2.69	±3.72	3.1	±5.3	>0.05
δSUV max	67.3	±40.9	76.5	±34.7	>0.05

Initial mean values of SUVmax ±S.D of classic Hodgkin disease, mixed cellularity and nodular sclerosis subtypes are 8.92±5.6, 8.56±3.6 and 8.23±2.6 respectively with no significant difference (p>0.05). End mean values of SUVmax ±S.D of classic Hodgkin disease, mixed cellularity and nodular sclerosis subtypes are 2.01±1.7, 1.12±1.1 and 10.1±6.2 respectively with significant difference in mixed cellularity and nodular sclerosis subtypes. Mean value of δSUV max ±S.D of classic Hodgkin disease, mixed cellularity and nodular sclerosis subtypes are 72.9±30.4, 86.6±12.8 and -12.1±47.4 respectively with significant difference in mixed cellularity and nodular sclerosis subtypes ***Table (4)***.

Table (4): Comparison of mean values of SUVmax in Hodgkin disease subtypes.

Variable	Classic			Mixed cellularity			Nodular sclerosis		
	Mean	±S.D	p-value	Mean	±S.D	p-value	Mean	±S.D	p-value
Initial	8.92	±5,6	>0.05	8.56	±3.6	>0.05	8.23	±2.6	>0.05
End	2.01	±1.7	>0.05	1.12	±1.1	<0.0001	10.1	±6.2	<0.0001
δSUV max	72.9	±30.4	>0.05	86.6	±12.8	<0.0001	-12.1	±47.4	<0.0001

In non-Hodgkin disease initial mean values of SUVmax ± S.D of large B-cell, Malt and atypical lymphoma are 12.6±9.0, 3.3±0.6 and 32.8±12.7 respectively with significant difference in Malt and atypical subtypes. End mean values of SUVmax with ± S.D of large B-cell, Malt and atypical lymphoma are 3.3±5.5, 0.57±0.8 and 7.6±8.1 with no significant difference. Mean values of delta SUVmax ± S.D of large B-cell, Malt and atypical lymphoma are 0.72±0.39, 0.81±0.29 and 0.83±0.18 respectively with significant difference in Malt subtype ***Table (5)***.

Table (5): Comparison of mean values of SUVmax in non-Hodgkin disease subtypes.

Variable	Large B-cell			Malt			Atypical		
	Mean	±S.D	p-value	Mean	±S.D	p-value	Mean	±S.D	p-value
Initial	12.6	±9.0	>0.05	3.3	±0.6	<0.0001	32.8	±12.7	<0.001
End	3.3	±5.5	>0.05	0.57	±0.8	>0.01	7.6	±8.1	>0.05
δSUV max	0.72	±0.39	>0.05	0.81	±0.29	<0.05	0.83	±0.18	>0.05

Hodgkin and non-Hodgkin disease were compared by measuring size of lesions by CT. Mean value ±S.D of initial size of Hodgkin lymphoma is 7.66±3.64 while mean value of end size is 1.7±1.6 with change in lesion size 5.9±13.9 (% of change 53.6±36.4%). Mean value of initial size with ± S.D of non-Hodgkin lymphoma is 5.29±1.3 while mean value of end of therapy size is 1.6±2.8 with change in lesion size 3.7±6.1 (% of change 55.8±51.7) with no significant difference between both types ***Table (6)***.

Table (6): Comparison of mean values of lesion size (as assessed by CT) in Hodgkin and non-Hodgkin disease.

Variable	HD		NHL		p-value
	Mean	±S.D	Mean	±S.D	
Initial Size	7.66	±3.64	5.29	±1.3	>0.05
End size	1.7	±1.6	1.6	±2.8	>0.05
Change in the lesion size	5.9	±13.9	3.7	±6.1	>0.05
% change	53.6	±36.4	55.8	±51.7	>0.05

Multivariate analysis: Assessment of total actuarial survival in responders and non-responders: as assessed by CT (RECIST) and PET parameters (both delta SUVmax and Lugano) ***Table (7)***.

Table (7): Frequency of responders and non-responders as assessed by PET parameters (Quantitative [SUV] and Qualitative [Lugano]) and CT (RECIST).

Response			Number	Percentage
CT (RECIST)	Responders (n=86)	CR	48	55.8%
		PR	48	55.8%
	Non-responders (n=14)	SD	10	71.4%
		PD	4	28.6%
Quantitative PET (Δ SUVmax)	Responders (n=90)	CR	64	71.1%
		PR	26	28.9%
	Non-responders (n=10)	SD	6	60%
		PD	4	40%
Qualitative PET (Lugano score)	Responders (n=84)	CR	70	83.3%
		PR	14	16.7%
	Non-responders (n=16)	SD	12	75%
		PD	4	25%

Stepwise regression analysis of all variables revealed that the most predictive factors of therapeutic assessment are Lugano score and Deauville score followed by SUVmax and delta SUVmax ***(Table 8)***.

Table (8): Stepwise regression analysis of PET parameters (Lugano score, Deauville score, SUVmax and Δ SUVmax)

Variable	R	R2	p-value
Lugano score	-0.554	30.7%	<0.0001
Deauville score	-0.550	30.3%	<0.0001
SUVmax	-0.452	20.4%	<0.001
Δ SUVmax	0.36	13%	<0.01

DISCUSSION:

It has been established that 2-deoxy-2-[^{18}F] fluoro-D-glucose positron emission tomography/computed tomography (FDG-PET/CT) is the diagnostic preferred method for initial staging and assessing response to therapy in both diffuse large B-cell lymphoma (DLBCL) and Hodgkin lymphoma (HL). FDG PET/CT has been demonstrated to be clinically useful in the management of lymphomas in a number of trials. Among these are crucial pieces of information that have been collected and compiled with regards to the generalization of reproducibility and interpretability of FDG PET/CT **(7)**. However, calibration and quality assurance are necessary for quantitative imaging (QA). Continued research and development of PET/CT and other quantitative approaches is in progress. The development of simple qualitative criteria with high inter-rater reliability, low repeatability burden, and high diagnostic performance that can also provide predictive information will, on the other hand, be of great benefit **(8)**. Patients' treatment and quality of life can be greatly enhanced with the early detection of tumor recurrence, evaluation of therapeutic efficacy and subsequent follow-up **(9)**.The current study was designed with an aim to analyze the potential prognostic function of several qualitative and quantitative methodologies in the form of maximal standardized uptake value using ^{18}F-FDG PET/CT in the assessment of lymphoma management (SUVmax).

One hundred lymphoma patients (thirty-six with HL and sixty-four with NHL) were analyzed retrospectively using clinical and histopathological evaluations, ^{18}F-FDG PET/CT assessments that included measurements of lesion size using both modalities, and the RECIST (CT measurement), PERCESIT (quantitative PET), and Deauville (qualitative PET) classification systems. After treatment for all patients, PET/CT was performed as a follow-up. Lymphomas represent a diverse range of illnesses that can develop from any of the immune system's cell types or their progenitors. Lymphoma comes in a variety of subtypes, each with its own unique molecular features and biological behavior. This entity is classified into aggressive and indolent subtypes based on observable clinical features. Histologic subtype and disease extent are the most influential determinants in therapy decisions and prognosis. **Isasi et al**. **(10)** reported in a meta-analysis of 854 patients, 90% avidity in HD, while **Weiler-Sagie et al. (11)** reported that 94% of HD patients were FDG avid. These data confirmed the current study which reported 94.4% of HD cases were FDG avid with high initial SUVmax in all subtypes of HD disease with statistically insignificant difference. On the other hand, NHL was divided into indolent and aggressive disease according to clinical data. It had been reported that, aggressive disease was found to be avid in 97% of cases versus 83% for indolent cases. Similar to the current study where, B cell lymphoma, malignant and atypical types were found to be statistically avid to FDG (100%) vs 60% in MALT. Staging the disease gives more illustrating image for accurate post-therapy evaluation of cases. Most previous studies assess stages of lymphoma in all cases; our study has a lack in this step because it is a retrospective study. Therapeutic response evaluations should reliably identify a subset of patients with a good prognosis, including those who will be cured, as well as those with partial responses or advancing disease that could benefit from early intervention with additional medications **(9)**. Comparing Lugano and SUV max after therapy, 88% matching had been noted in the current study with the note that out of 70 CR by Lugano 6 had been reported to PR by SUVmax after therapy. This difference could be attributed by the fact that SUVmax was affected by several factors, e.g. The inability to compare SUVs acquired at different centers is due to variations in image acquisition parameters (scanner, scatter and attenuation correction, reconstruction technique) **(12,13)**.

Since the impact is present in both regions and will at least partly cancel each other out, normalizing the tumor SUV to a reference region such as the liver in the same scan significantly decreases this issue, however it has not been confirmed. On the other hand, Deauville criteria (DC) had been validated as a reliable means of interpreting scans in FDG-avid histological types and predict outcome, confirming earlier results using less stringent criteria [14,15].

Accordingly, with respect to response assessment, the Lugano Classification recommended the Deauville 5PS for interpretation of FDG/PET for treatment assessment, and included as a metabolic complete remission those patients with a persistent mass that was no longer FDG-avid [16].

Patients who are PET-negative in regions with remaining tissue and at extremely low risk of relapse can be safely detected with PET, according to a number of studies. After first-line therapy, the negative predictive value of PET has been shown to be continuously strong, reaching values of >95% even in patients with advanced disease and remaining tissue [7, 16, 17]. A negative PET scan was found to be the strongest indicator for successful treatment [18].

The current study confirmed these data. However, the best way to characterize reaction in order to predict overall survival (OS) is still up for debate.

It has been investigated whether the response to ^{18}F-FDG PET/CT can be used to prognosticate the outcome of lymphomas. Patients who were PET-positive after 2 courses of treatment (PET-2-positive) had a 2 year event-free survival (EFS) rate of 41%, while patients who were PET-negative after 2 courses of treatment (PET-2-negative) had a 2 year EFS rate of 76%, according to a study conducted by ***Mamot et al***. using central review and the Deauville five- point scale (5PS) criteria ($p<0.001$) [19]. The current study confirmed these findings where responders (i.e. PET negative) showed 84% survival at 24 months and 50% at 36 months, versus 30% at 24 months and 2% at 36 months in non-responders.

Itti et al. [20] added in a retrospective study 81% survival at 36 months for responders as assessed by Deauville 5PS criteria and inferior results by using Δ SUVmax 59% survival which is similar to the current study 36% using δSUV max. ***Nols et al.*** confirmed that the Δ SUVmax reduction of >66% was not superior to the Deauville 5PS criteria for the prediction of survival ($p<0.0001$ vs $p=0.02$) [21].

With a median follow-up of 2.4 years, a subset of patients (n=33) with a positive age-adjusted International Prognostic Index (IPI) score and a negative interim PET result (either by Deauville 5PS or SUVmax criteria) had a very favorable prognosis (PFS, 88%; OS, 94%). This confirmed the stepwise regression of the current study which revealed the superiority of PET data especially the Lugano classification which has 61% impact on the prediction of survival followed by SUVmax which had 33.4% impact.

Also, the current study corroborated the findings of ***Cheson and Kostakoglu*** [(22)], who said that, despite some promising results, the 'SUVmax-based analysis has yet to be prospectively tested to confirm or contradict the findings of the aforementioned studies [(22)].

In conclusion, ^{18}F-FDG PET/CT is an important tool for assessing response and survival in lymphoma. Lugano Classification and Deauville criteria are valid parameters to assess response of therapy in FDG avid lymphomas.

Declaration of competing interest: Authors declares that there is no conflict of Interest.

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