Original Article

THE ROLE OF FDG - PET IMAGING IN LYMPHOMA

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ABSTRACT

Positron Emission Tomography (PET) imaging using (F-18) fluorodeoxy glucose (FDG), has been introduced for the first time in Egypt in October 2004, and since that time, this technique has created a new trend in the diagnosis and management of the lymphomas, providing unique metabolic information.

FDG uptake in lymphoma is a function of increased anaerobic metabolism as well as longer residence time of FDG in malignant cells relative to most normal tissues.

Over several decades computed tomography (CT) has been the principal imaging modality for the staging and restaging of Lymphoma, although it can have shortcomings originating from its sized-based criteria, particularly, in the post-therapy status.

Purpose: To evaluate the impact of FDG-PET on management of patients with lymphoma and compare its findings with the conventional investigational methods, mainly the contrast enhanced CT and to evaluate the common causes of discrepant findings between the two modalities.

Patients and Methods: A group of 460 consecutive patients with diagnosis of lymphoma (Males: 228, Females: 172, Age range:6-73 years, median age:29 years), were included. They comprised 118 newly diagnosed cases, 182 cases for therapy monitoring and 160 cases with suspicious relapsed disease. The group consisted of a mixture of NHL (n=311 patients) and HL (n=149).

All patients underwent FDG PET and contrast enhanced CT within a maximum of 4 weeks time window.

A final diagnosis was established at 1850 sites for comparison between PET and CT.

Concordant PET and CT findings were regarded as positive or negative for disease. Discordant findings were defined as positive for disease, if it was confirmed by the histological examination, by the clinical progressive course or by the follow up CT.s.

Results: Accuracy, Positive Predictive Value and Negative Predictive Values of FDG-PET and contrast enhanced CT were 95.8%, 96.4% and 91.1% vs. 85%, 85% and 55% respectively. Agreement of both methods was excellent (k = 0.89). A difference with $p<0.05$ was considered significant regarding the exclusion of disease with FDG PET, compared with contrast enhanced CT.

Conclusion: FDG PET is more accurate than the conventional investigational methods; including contrast enhanced CT in evaluation of Lymphoma and can yield findings that lead to change in treatment strategy.

Key words*: Positron Emission Tomography and Lymphoma.*

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INTRODUCTION

The evolution of combined chemotherapy regimen and radiation therapy strategies has resulted in high overall survival rates in patients with Hodgkin's Lymphoma (HL) and certain subtypes of Non-Hodgkin's Lymphoma (NHL) particularly diffuse large cell lymphoma (1). Staging has an important role in the management of most malignancies and can serve to assess prognosis and to define therapy for patients with lymphoma. In particular, accurate staging and determination of response (re-staging) can determine whether radiation therapy may be indicated for an individual lymphoma patient (2).

Unnecessary use of radiation could result in excess toxicity (such as second malignancies and myocardial impairment), while appropriate use could potentially decrease the risk of disease recurrence and allow administration of fewer chemotherapy cycles, reducing toxicity. Also, patient's quality of life, both during and following treatment, may also be improved with individually tailored therapy defined by staging (3).

Position Emission Tomography (PET) imaging using (F18) fluorodeoxy glucose (FDG) has the potential to provide physiological information that can be useful in staging as well as monitoring response to therapy.

FDG uptake in tumors is proportional to the glycolytic metabolic rate of viable tumor cells related to increased metabolic demand for glucose (4).

Alteration in FDG uptake as measured by various methods including visual and quantitative analyses, provides useful information on response to anti-tumor therapy, especially using the standardized uptake value (SUV), which is a semi-quantitative method that measures FDG uptake in the tumor per volume, normalized to the injected activity per body mass.

Quantitative PET imaging may have its greatest impact in fact in the evaluation of therapy response (5).

PATIENTS AND METHODS

A group of 460 consecutive patients with a confirmed diagnosis of lymphoma were referred to us for imaging between 01/2005 and 06/2006. All PET studies were performed at the International Medical Center (IMC). The study subjects included 288 men and 172 women with a median age of 29 years (range, 6 – 73 years).

Three hundred eleven patients (311 pt.) were proven histo-pathologically to be (NHL) and **one hundred forty nine** patients (149 pt.) to have (HL).

A total of one hundred eighteen (118) studies were performed for initial staging in patients who had been subjected to histopathology evaluation, **one hundred eighty two** (182) studies were performed for therapy monitoring and o**ne hundred sixty** (160) studies were performed for re-staging and follow up after disease remission or suspicious relapse.

Of the 182 studies performed of therapy monitoring, seventy four (74/182) were performed for therapy response prediction after the first cycle of chemotherapy, thirty six (36/182) were performed for mid-course response assessment after 3 cycles and seventy two (72/182) were performed after therapy completion and disease remission confirmation. FDG-PET was performed at least three – four weeks after the last cycle of chemotherapy and at least 3 months after the completion of radiation therapy to minimize false-positive results.

Imaging:

Patients fasted at least 4 hours prior to intravenous injection of FDG, 2 MBq /Kg, for an average dose of 150 MBq (4

mCi). Imaging was performed with a C-PET plus system (Philips). This system has an axial field of view of 24 cm. with transverse resolution of 8 mm and axial resolution of 6 mm full width at half maximum. Data obtained from the six crystals were used to reconstruct the image on flight via RAMLA software.

Emission and transmission acquisitions were commenced simultaneously, one hour after injection. Six to seven bed positions were usually done, each bed position lasted about 8-9 minutes (6).

PET interpretation:

All PET images were interpreted at the time of the study by two nuclear medicine doctors who had access to the clinical data. Images were viewed in axial, coronal and sagittal planes using an interactive display system. PET images were read in conjunction with CT images whenever possible. All images were re-read after receiving feed back data from either the referring doctors or the patients themselves and consensus was reached by final agreement of the two nuclear medicine specialists.

Standardized uptake value (SUV) and target-to-background ratio (T/B ratio) were determined.

In order to be able to compare the PET images of different patients, the PET data calibrated to activity concentration are normalized for image analysis with respect to injected activity and patient weight.

The resulting transverse parametric slices represent a standardized measure of the regional tracer concentration at the point of uptake. This is referred to the "standardized uptake value" (SUV).

The other alternative is the target-to-background ratio, in which we calculate the ratio of the mean counts in a region of interest almost surrounding the lesion to a similar area in the contra-lateral sound side of the body.

Based on review of literature, we considered a value of SUV > 2.5 and (T/B) ratio > 1.5 to be abnormal (7).

Statistical Analysis: Accuracy; Sensitivity and Specificity were calculated on the basis of true positive, true negative, false positive and false negative findings as described at the same anatomic locations. Agreement of both PET and CT was determined with Cohen k and McNemar tests on a per-lesion basis.

The agreement of PET and CT findings was assessed separately for lesion-based analysis and for patient-based analysis. The agreement was determined as follows: 0-0.20; very poor, 0.21-0.40; poor, 0.41-0.60; fair, 0.61-0.80; good, and 0.81-1.0; excellent. To evaluate the difference in probability assignment between PET and CT, we applied the McNemar test with a confidence level of 95% (a difference with $p < 0.05$ was considered significant). This test was performed on a per-patient basis so dependency or clustering did not occur (8).

RESULTS

(a) Initial Staging:

In patient-based analysis, patients in the staging group had evidence of HD or NHL at one or more lymph node stations, and this evidence was correctly demonstrated with both PET and CT. Furthermore, in the group of patients undergoing an initial staging evaluation, 12/118 patients (10.2%), PET depicted additional nodal involvement, which was not detected at contrast enhanced CT.

Contrast enhanced CT did not depict any nodal involvement that was not seen in PET studies. So, these 12 patients were upstaged on the basis of PET results and FDG-PET affected their clinical management (Fig. 1).

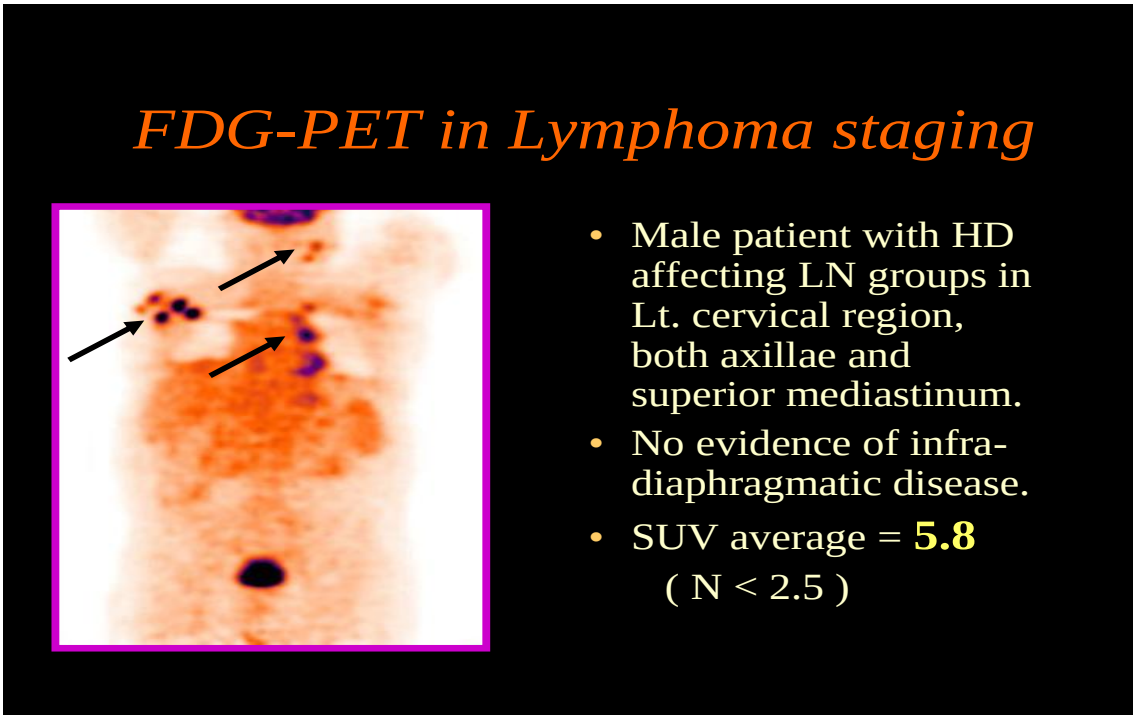

Fig. (1)

(b) Assessment of Therapy Response:

In early assessment of therapy response PET demonstrated, 40/74 patients (54%) had marked response with less glucose avid disease after one cycle of therapy, whereas 34/74 patients (46%) had residual glucose-avid disease. Of these 34 patients, 30 (89.8%) never achieved remission.for at least 12 months of follow up.

In 36 patients, the utility of FDG-PET was assessed after 3 cycles of chemotherapy, 29 patients (> 80%) achieved marked response, while only 7 patients (< 20%) had residual glucose-avid lesions. Of these 7 patients, 6 (85.7%) never achieved remission for at least 12 months of follow up.

In 72 patients, the utility of FDG-PET was assessed 3-4 weeks after completion of therapy, 54 patients (75%) achieved complete remission and the study was negative. Only four patients out of them (7.3%) showed disease relapse during the first year of follow up. In the remaining 18 patients (25%), with residual disease and positive FDG-PET study, 16 (89.8%) never achieved remission for at least one year of follow up (Fig. 2).

(c) Follow Up and Re-Staging:

In the 160 patients undergoing follow up and re-staging evaluation, 103/160 patients' results of PET and CT were matched, including 63 negative and 40 positive studies, whereas in 57/160 patients, PET depicted additional nodal involvement in 32 patients, which was not detected on contrast enhanced CT. In the rest 25 patients, contrast enhanced CT

depicted additional nodal involvement not shown by PET including retro-caval, peri-vascular sites in the thorax, especially in young patients with brown atrophy and muscular uptake. Only five patients of them (5/25) were proved positive by biopsy. So, PET results were correctly upstaging disease in 32 patients (20%) and downstaging it correctly in 20 patients (12.5%) in comparison to CT in follow up and restaging (Fig. 3).

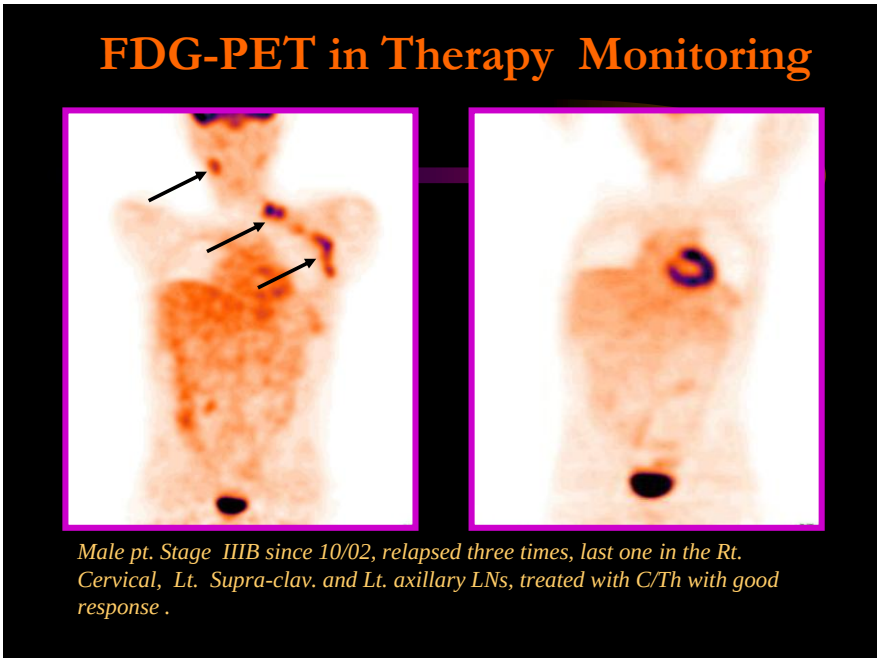

Fig. (2)

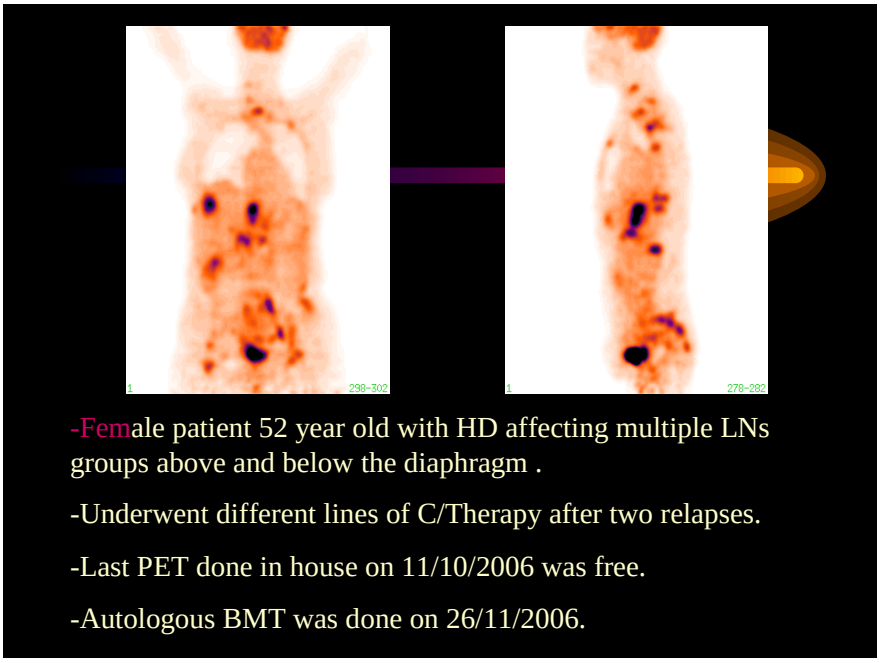

Fig. (3)

***Lesion-based Analysis comparing PET and CT*:**

A final diagnosis was established at **1650 sites** that were positive for tumor by FDG-PET.

Clinical evidence of tumor progression was accepted as positive evidence at (275 sites, 17%); most of them were cervical and axillary's lymph nodes. 45 lesions showed size reduction/absence in next clinical visits.

Abnormal imaging findings (880 sites, 53%) were validated by demonstration of disease progression (525 sites) or stationary disease (355 sites) at a second CT imaging, while only 15 sites completely disappeared in next follow up CTs.

The positive diagnosis was established histologically at 495 sites (30%), surgically at 122 and by needle biopsy at 373 sites (23%).

A further 180 sites that were negative by PET, 164 sites out of them were confirmed, clinical evidence of absence of disease for one year or more after the PET study was accepted as negative evidence at 60 sites despite CT abnormality; and in 104 sites, which were normal in a second CT.

On lesion-based analysis, 1590 sites were true positive by PET, 164 sites were true negative, sixty sites were false positive and sixteen sites were false negative.

Our study showed accuracy of PET of 95.8 %, compared with 91.4% for CT (95% confidence intervals for the difference between the modalities in their accuracy). The positive and negative predictive values for FDG PET were around 94%. (table 1)

Table (1): Diagnostic Performance of PET scan by patients.

	Staging		**Re-staging & FU**		**Therapy Monitoring**		**Total**	
Findings	**PET**	**CT**	**PET**	**CT**	**PET**	**CT**	**PET**	**CT**
True Positive	118	106	72	45	52	40	242	191
True Negative	0	0	83	63	110	80	193	162
False Positive	0	0	0	20	9	20	9	40
False Negative	0	12	5	32	11	23	16	67

	PET		***CT***	
Sensitivity	*242/258*	*(93.8%)*	*191/258*	*(74%)*
Specificity	*193/202*	*(95.5%)*	*162/202*	*(80.2%)*
Accuracy	*435/460*	*(94.6%)*	*353/460*	*(76.7%)*
Positive Predictive Value	*242/251*	*(96.4%)*	*191/231*	*(82.7%)*
Negative Predictive Value	*193/209*	*(92.3%)*	*162/229*	*(70.7%)*

The McNemar test for the comparison of the probability assignment of suspicious lesions between PET and contrast enhanced CT indicated excellent agreement between both methods (0.88).

The agreement with k values is as follows: 0.0 – 0.2; very poor, 0.21-0.4; poor, 0.41-0.6; fair, 0.61-0.8; good and 0.81-1.0; excellent.

Table (2): Diagnostic Performance of PET scan by lesions.

	Staging		**Re-staging & FU**		**Therapy Monitoring**		**Total**	
Findings	**PET**	**CT**	**PET**	**CT**	**PET**	**CT**	**PET**	**CT**
True Positive	778	736	472	445	340	330	1590	1511
True Negative	0	0	63	55	101	107	164	162
False Positive	30	40	21	29	9	20	60	89
False Negative	0	12	5	32	11	24	16	68
Sensitivity	*1590/1606*		*(99.0%)*		*1511/1579*		*(95.7%)*	
Specificity	*164/224*		*(73.2%)*		*162/251*		*(64.5%)*	
Accuracy	*1754/1830*		*(95.8%)*		*1673/1830*		*(91.4%)*	
Positive Predictive Value	*1590/1650*		*(96.4%)*		*1511/1600*		*(94.4%)*	
Negative Predictive Value	*164/180*		*(91.1%)*		*162/230*		*(70.4%)*	

DISCUSSION

In malignant lymphoma, precise staging is a vital pre-requisite for proper selection of therapy which could improve the prognosis in individual patients. Contrast enhanced CT is the first line imaging modality for staging in HD and NHL, which allows the detection of morphologic abnormalities such as lymph node enlargement or changes in contrast enhancement that suggests organ involvement (9).

CT and MRI are anatomic imaging modalities that do not identify lymphoma in normal size lymph nodes nor do they differentiate nodes that are enlarged due to benign causes. Thus, the significance of lymph node size is an ongoing debate that directly affects the accuracy of these modalities. (10).

In the current study, the *k* statistic factor revealed excellent agreement between PET and contrast enhanced CT for the delineation of lymph node involvement, independent of the purpose of the examination for staging or re-staging. Basically, pathologic FDG uptake in lymph nodes of any size was considered as lymph node involvement. Also, false positive contrast enhanced CT findings in 40 patients were reported due to residual lymph node involvement at staging and re-staging examinations. In particular, the residual soft tissue densities on contrast enhanced CT images that were regarded as persistent disease reflect the delayed morphologic response to the successful therapy, and follow up CT scans in those patients revealed normal results after a time. In these cases, PET findings confirm the absence of active tumor biology with delineation of soft tissue masses and without evidence of glucose utilization, corresponding to scarred tissue (11).

A diagnostic imaging modality with high accuracy in the differentiation

of residual viable disease from benign post-therapy changes could potentially affect patient management and outcome, particularly if it can help to select patients who require additional therapy or a change in treatment regimen (12). This becomes important when we realize that in post-therapy setting, up to 25% of patients with negative CT scans will ultimately relapse, particularly in intra-abdominal lymphoma (13).

Our findings regarding the accuracy of PET are similar to those obtained by other investigators: Hoh, et al (1997) reported 94% sensitivity for PET in (HL), Bangerter, et al (1997) reported 96% sensitivity and 94% specificity in the staging and follow up of lymphoma in chest and Buchmann, et al (2001) reported 99% sensitivity and 100% specificity in detection and staging of lymphoma.

Also, Friedberg, et al (2004) reported that FDG-PET had a higher specificity (92% vs. 17%, $P< 0.01$), accuracy (96% vs. 63%, *$P < 0.05$), and positive predictive value (*94% vs. 60%, $P< 0.05$) than did CT (14).

These results are concordant with the results of the current study which, in addition, has a much higher number of patients. It was found that of the 60 patients with positive PET findings and negative CT findings; independent to the clinical question, whether staging, re-staging & follow up or for therapy monitoring; 51 patients experienced local relapse or progression of disease within 12 months; only nine of the 40 patients with negative FDG PET findings and positive CT findings had experienced disease relapse within 12 months.

In a recently published retrospective analysis of 75 patients with lymphoma with standard therapy regimen whose disease was restaged with PET and CT, a correlation was found between positive findings on restaging PET and clinical relapse. Dedicated CT was also performed. After the end of therapy, 59 patients (79%) had negative PET findings, whereas only 16 patients had positive PET findings. Follow up of these patients revealed that 14 of the 16 PET-positive patients had disease relapse or progression (at a median of 9 months after completion of therapy), whereas none of the 59 PET-negative patients had local disease relapse ($P = 0.00001$) (15).

PET is significantly more accurate than CT for lymphoma staging, restaging and therapy monitoring (16).

Similarly, when the PET and CT results were combined, it was found that out of the 5 patients with positive PET findings and negative CT findings after therapy, 4 experienced local relapse or progression of disease 3-12 months after re-staging; while none of the 30 patients with negative FDG-PET findings and positive CT findings had experienced disease relapse 6-15 months later (17).

The sensitivity of FDG PET in detecting tumors depends on two facts: tumor size and uptake of FDG and minimal detectable size of PET scanner is 5 mm**...** In our study, we failed to detect 16 lesions, twelve of them were less than 7 mm. in diameter and four were indolent lymphoma i.e. lesions with weak glucose utilization capacity.

Physiologic tracer accumulation in normal structures as well as tracer utilization by inflammatory tissue, are other possible sources of errors in PET**.** In our study 60 sites were falsely interpreted due to presence of inflammation in 50 sites and asymmetrical muscular uptake vs. adipose brown atrophy in 10 lesions.

CONCLUSION

FDG-PET has a potential role in accurately staging disease, in predicting response to therapy, re-staging and follow up of malignant lymphoma.

This role has the potential to affect both the initial choice of chemotherapy and the decision to alter management based on the initial response to therapy. PET performed early in a chemotherapeutic regimen has demonstrated a role in identifying patients who will experience relapse and may require change of treatment strategy, but attention to the timing of the scan in relation to chemotherapy and radiotherapy is crucial.

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