ORIGINAL ARTICLE

FDG-PET scan in assessing lymphomas and the application of Deauville Criteria

Umm-e-Kalsoom Awan,[1] Neelam Siddiqui,[2] Mohammad SaadUllah,[3] Humayun Bashir,[4] Zia Salman Farooqui,[5] Narjis Muzaffar,[6] Mohammad Tariq Mahmmood[7]

Abstract

Objective: To evaluate the role of Fluorine-18-fluorodexoyglucose Positron Emission Tomography (FDG-PET) scan in staging and its implications on the treatment of lymphoma, and to study the concordance between visual assessment and Deauville criteria for the interpretation of interim scans.

Methods: The prospective single-arm experimental study was conducted at the Shaukat Khanum Memorial Cancer Hospital, Lahore, from May 2011 to October 2011. It comprised 53 newly diagnosed lymphoma patients who agreed to participate in the study. All patients underwent scans with contrast-enhanced computerised tomography at baseline. Treatment plan was formulated based on the final stage. Interim scans were acquired after 2 cycles of chemotherapy and were reported using visual criteria and compared with the 5-point Deauville criteria. Score of 1-3 was taken as disease-negative, while 4-5 was taken as disease-positive. SPSS 19 was used for statistical analysis.

Results: Of the 53 patients, 35 (66%) had Hodgkin's Lymphoma, while 18 (34%) had Non-Hodgkin's Lymphoma. Scans resulted in disease upstaging in 4 (7.5%) patients, and detecting increased disease burden in 12 (23%). On interim scans, complete remission was achieved in 38 (71%) patients (Deauville score 1-3); 12 (23%) showed partial response (Deauville score 4-5); and 3 (6%) had progression. Kappa test was statistically significant (kappa 0.856; p <0.001).

Conclusion: The positron emission tomography helped to upstage lymphoma and reflected increased disease burden. The Deauville criteria correlated very well with visual assessment criteria and can be applied in the patient population.

Keywords: FDG-PET scan, Lymphoma, Deauville criteria. (JPMA 63: 725; 2013)

Introduction

Fluorine-18-fluoroDexoyGlucose Positron Emission Tomography (FDG-PET) scanning has emerged as a powerful tool for staging and response evaluation of malignant lymphoma. The advent of hybrid scanners which acquire FDG-PET and computed tomography (CT) during the same visit has made correlation between functional and morphological imaging much easier and accurate.[1-3] A positive FDG-PET scan is determined visually by comparing the intensity of the suspected area of malignancy to the intensity of activity in the background and mediastinal blood pool.[3]

In patients with typically FDG-avid lymphomas, integrated PET/CT scanning improves the accuracy of determining treatment response and has been incorporated into the International Workshop Criteria of treatment response.[4] However, its effect on the prognostic value of the International Prognostic Index (IPI) is unknown.[5,6] In this prospective study we assessed the impact of FDG-PET scan on lymphoma staging and its implications on treatment. We compared the visual assessment criteria with the 5-point Deauville criteria for reporting interim scans in order to see if we can apply this in our population.

Patients and Methods

The prospective single-arm experimental study was conducted at the Shaukat Khanum Memorial Cancer Hospital (SKMCH), Lahore, from May 2011 to October 2011. The Male and female patients, more than 18 years of age with a good performance status were eligible if they had histologically proven lymphoma of any Ann Arbor[7] stage. Patients were excluded if they were previously treated, had uncontrolled cardiac disease or had any other malignancy simultaneously. Females who were pregnant at presentation were also not included. A total of 53 patients with untreated lymphoma consented for the study. Pre-treatment staging work up was completed and they were then treated with one of the chemotherapy protocols ABVD (Adriamycin, Bleomycin, Vinblastine and Dacarbazine), CHOP (Cyclophosphamide, Doxorubicin, Vincristine and Prednisolone), R-CHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine and Prednisolone), according to the histology and risk stratification. After 2 cycles of chemotherapy, they underwent interim FDG-PET/CT scans. All patients completed their initially planned therapy courses

[1,2,6]Department of Medical Oncology, [3,4]Department of Nuclear Medicine, [5]Department of Diagnostic Radiology, [7]Department of Pathology, Shaukat Khanum Memorial Cancer Hospital & Research Center, Lahore, Pakistan.

Correspondence: Umm-e-Kalsoom Awan. Email: ummekalsoom@yahoo.com

irrespective of the interim scan results. The exceptions were those who had disease progression.

This study is presenting interim analysis of the study as of April, 2012. The patients will be followed further till at least 24 months from the end of the therapy to see survival differences in PET-positive and PET-negative patients at the mid-therapy scans, and will correlate the results with their respective IPI and International Prognostic Score (IPS).

PET/CT was performed using Gemini TF (Philips) PET scanner and a 16-slice CT scanner. The patients had to be fasting for at least 4 hours before PET acquisitions, with a blood glucose level less than 7mmol/l. They were then injected with 5MBq/kg of 18F-FDG (maximum 400MBq) intravenously. One hour later, an 18F-FDG-PET/CT scan was acquired from skull vault up to the mid-thigh level. A diagnostic CT scan using intravenous contrast (100-150mA) was performed first. CT images were used for attenuation correction of the 18F-FDG-PET emission data as well as for exact anatomical localisation. PET images were re-constructed using a three-dimensional row action maximum likelihood algorithm.

All baseline and interim PET/CT scans were evaluated by a pair of readers, a nuclear medicine expert and a radiologist, who interpreted the images in consultation. Baseline and interim FDG-PET/CT scans were reported on visual assessment with recording of standardised uptake values (SUVs). Uptake higher than the background was considered positive. Interim scans were initially reported on visual assessment scale and later correlated with the Deauville criteria (Table-1).

Complete response (CR) was defined as disappearance or reduction of FDG uptake to levels equal to liver uptake at documented sites of disease as seen on baseline scans (Deauville score 1-3). Partial response (PR) was taken as persistent FDG activity greater than that of liver (Deauville score of 4-5). Stable disease (SD) was persistence of FDG activity at all initial sites, while progressive disease (PD) was taken as uptake at a new site with score 4-5. Contrast-enhanced CT scans were reported as CR, PR, SD and PD, according to the Recist Criteria.[8]

At the institution, baseline workup of biopsy-proven lymphoma patients includes FDG-PET/CT, bone marrow biopsy, multi-gated acquisition (MUGA) scan for patients above 40 years or a history of cardiac disease along with a battery of biochemical tests. Data collection was started after getting approval from the Scientific Review Committee and later by the Institutional Review Board. All the patients were informed and written consent was obtained. All data was collected prospectively.

Table-1: Five-point Deauville Criteria.

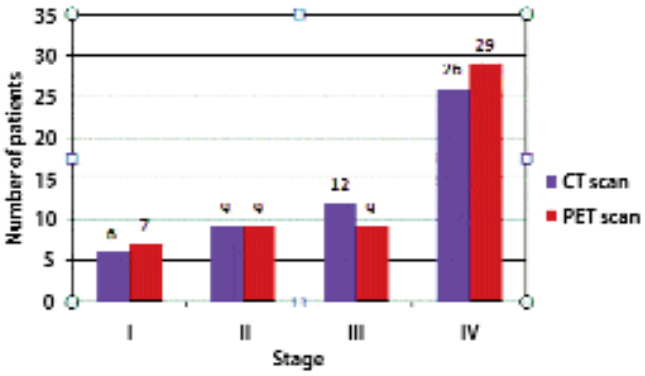
Score 1	No uptake
Score 2	Uptake $\leq$ mediastinum
Score 3	Uptake $\geq$ mediastinum$<$ liver
Score 4	Uptake moderately increased above liver at any site
Score 5	Markedly increased uptake at any site including new sites of disease

Statistical analysis was done with SPSS 19. Quantitative data was described as mean ± standard deviation and range, while qualitative data as frequencies and percentages. The measure of concordance between staging through CT and FDG-PET scans was done by Cohen's kappa, according to Fleiss's guidelines.[9]

Results

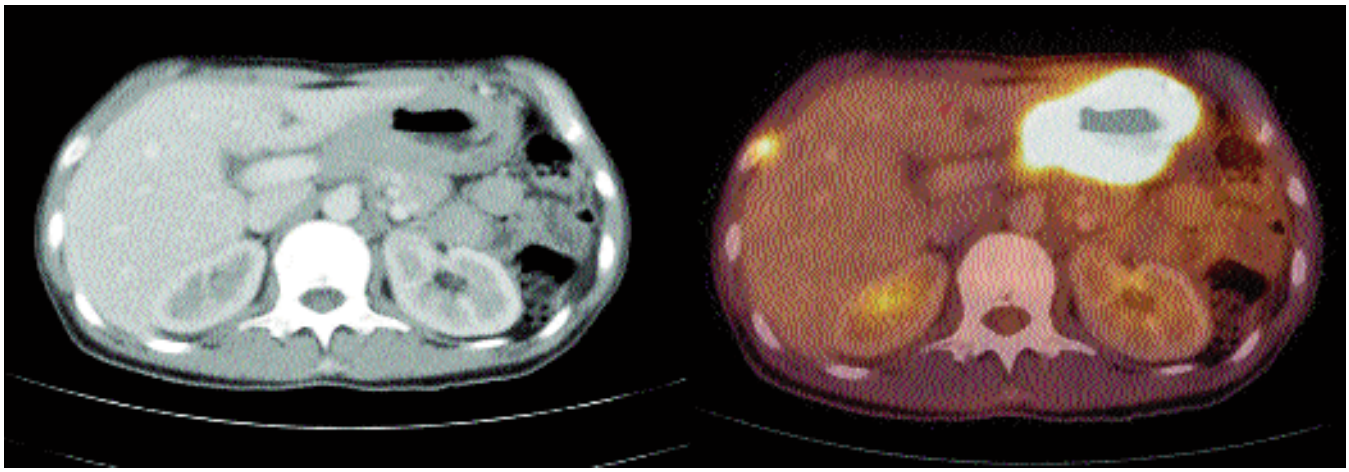
Of the 53 subjects, 40 (75.5%) were males and 13 (24.5%) were females with a median age of 26 years (range: 18-51). There were 35 (66%) patients of Hodgkin's Lymphoma (HL), while 18 had Non-Hodgkin's Lymphoma (NHL) (Table-2).

FDG-PET scan upstaged lymphoma from stage-III to stage-IV in 4 (7.5%) patients. All of them had multifocal skeletal involvement which was not evident on correlative CT scan. However, FDG-PET scan reflected increased disease burden in 12 (23%) patients, including the 4 who were upstaged. One (1.88%) patient had sub-centimetre lung nodules on CT scan, convincing for disease involvement, but these were not hyper-metabolic on FDG-PET scan. This case was reviewed in lymphoma board and was ascribed stage-IV disease based on CT features and limited resolution of FDG-PET for sub-centimetre lesions. These nodules remained stable on interim and end-of-therapy (EoT) scans and, in retrospect, appear unrelated to lymphoma. Comparison of stage as detected by CT and FDG-PET scans was recorded (Figure-1). Kappa



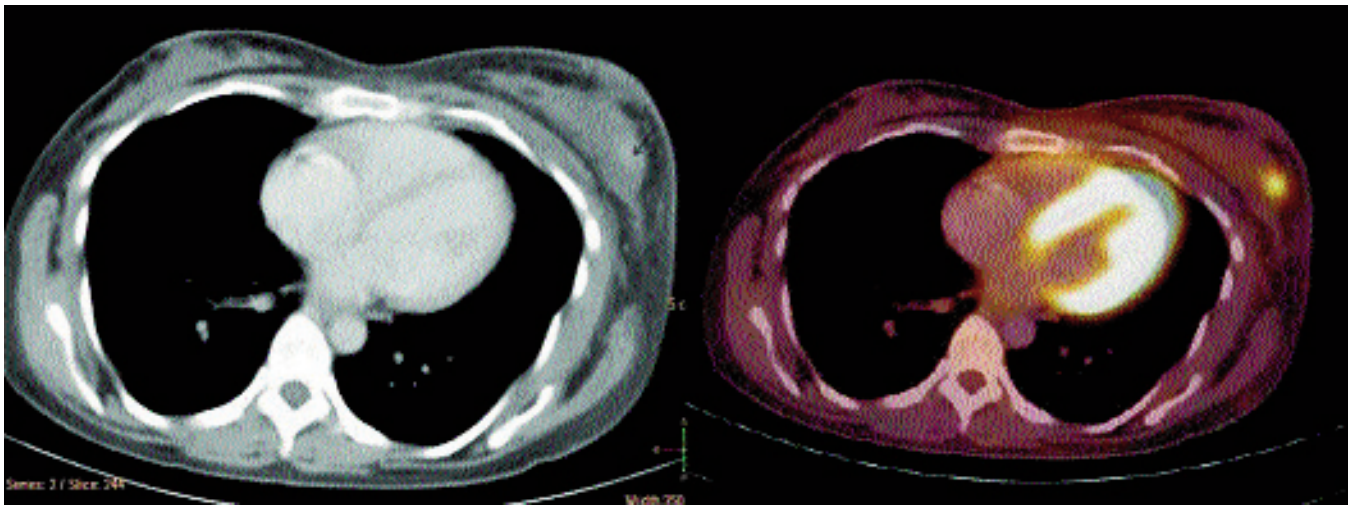
CT: Computed tomography. PET: Positron emission tomography.

Figure-1: Comparison of disease stage between CT scan and FDG-PET scan.



CT: Computed tomography. PET: Positron emission tomography.

Figure-2: Circumferential thickening of stomach wall on CT scan, showing metabolic activity on FDG-PET scan.



CT: Computed tomography. PET: Positron emission tomography.

Figure-3: Left breast nodule seen on CT(black arrow) and showing FDG uptake on PET scan.

test was used to assess the degree of agreement between the outcomes of interest,[9] FDG-PET versus CT scan. The measure of concordance between staging through CT and FDG-PET scans was high (kappa 0.856; p <0.001).

Twenty-nine (54.71%) patients had stage-IV disease on FDG-PET scan; 18 (34%) had abnormal FDG uptake in bone/bone marrow, while 6 (11%) patients had osseous lesions on CT scan. On bone marrow biopsy, 8 (15%) patients were found to have bone marrow involvement; one with NHL, while the rest had HL. Five of these patients (62.5%) had skeletal lesions as well. No discrepancies in FDG-PET and CT were found regarding the detection of non-osseous extra-nodal disease. Corresponding metabolic and morphological extra-nodal disease was found in 7 (13%) patients. Sites included muscle, brain, pleura, stomach (Figure-2), small intestine, rectum and pancreas. Breast involvement in HL was recorded in one female (Figure-3).

On interim analysis, FDG-PET scan showed complete metabolic response in 38 (71%) patients, while complete morphological response was seen in only 3 (6%) patients on the CT scan (Table-3). Besides, 48 (91%) and 2 (4%) patients attained PR and PD on CT scan, respectively. None of the patients had SD on interim analysis. Patients

Table-2: Patient characteristics.

Parameter	Number (n)	Percentage (%)
Age (years)		
Mean	30.7±9.80	
Median	26	
Range	18- 51	
Gender		
Male	40	75.5
Female	13	24.5
Histology		
HL	35	66
Classic HL	34	97
Lymphocyte predominant	1	3
NHL	18	3
ALCL	2	4
DLBCL	16	30
Bone marrow involvement		
Yes	8	15
No	45	85
B symptoms		
Yes	27	51
No	26	49
Bulky Disease		
Yes	24	27
No	66	73
IPS		
I	6	17
2	4	11
3	6	17
4	7	20
>5	3	8.5
N/A	9	25.5
IPI		
0	4	22
1	3	17
2	2	11
3	3	16
4	1	6
5	0	0

Hodgkin's Lymphoma, Non-Hodgkin's Lymphoma, Diffuse Large B Cell Lymphoma, Anaplastic Large Cell Lymphoma, International Prognostic Score. International Prognostic Index.

with CR or PR continued with their planned therapy, whereas those with PD were offered salvage regimens after histological confirmation.

Interim FDG-PET scan results (Table-4) showed that 47 (88.67%) patients had nodal involvement at the cervical area, 29 (54.7%) had mediastinal involvement and 25 (47%) had disease at axillary and pectoral regions. Interim FDG-PET scan evaluation using the Deauville criteria showed that majority of the patients had no disease/uptake at the initial site of involvement after two cycles of chemotherapy (Table-4).

EOT scans were done 3 months after completing the treatment. To date, 35 patients underwent EOT scans, which are in complete harmony with their mid-treatment scans.

Table-3: Interim response on PET and CT scan.

Response	PET scan No. of patients (%)	CT scan No. of patients (%)
CR	38(71)	3(6)
PR	12(23)	48(91)
PD	3(6)	2(4)

CR: Complete response. PR: Partial response. PD: Progressive disease.
CT: Computed tomography. PET: Positron emission tomography.

Table-4: Region-wise interim FDG-PET findings using Deauville's criteria.

Regions	No of Patients	Score 1	%	2	%	3	%	4	%	5	%
Weldeyer's Ring	8	6	75.0	0	0.0	0	0.0	0	0.0	2	25.0
Cervical area	47	24	51.1	18	38.3	2	4.3	1	2.1	2	4.3
Infraclavicular area	12	11	91.7	1	8.3	0	0.0	0	0.0	0	0.0
Axillary & Pectoral region	25	16	64.0	8	32.0	1	4.0	0	0.0	0	0.0
Mediastinum	29	15	51.7	7	24.1	3	10.3	2	6.9	2	6.9
Hilum	20	12	60.0	5	25.0	2	10.0	0	0.0	1	5.0
Para aortic nodes	30	16	53.3	10	33.3	1	3.3	1	4.4	2	6.7
Mesenteric nodes	8	6	75.0	1	12.5	0	0.0	0	0.0	1	12.5
Iliac area	20	16	80.0	2	10.0	1	5.0	0	0.0	1	5.0
Inguinal & Femoral	12	9	75.0	0	0.0	0	0.0	2	16.7	1	8.3
Popliteal	15	14	9.3.	0	0.0	0	0.0	1	6.7	0	0.0
Lung	7	4	57.1	2	28.6	0	0.0	0	0.0	1	14.3
Liver	13	10	76.9	0	0.0	0	0.0	1	7.7	2	15.4
Spleen	21	13	61.9	6	28.6	0	0.0	1	4.8	1	4.8
Skeleton	19	15	78.9	3	15.8	0	0.0	0	0.0	1	5.3
Extra nodal area	7	5	71.4	0	0.0	0	0.0	1	14.3	1	14.3

Discussion

Accurate staging of lymphoma is of utmost importance as it has definitive therapeutic and prognostic implications. The use of baseline FDG-PET in lymphoma has been reported to change the stage and, hence, its treatment in approximately 10-20% of the patients.[10,11] Hutchings et al showed that the treatment changed as a result of PET scanning in 9% of 99 prospectively recruited patients, and in 17% of patients who underwent integrated PET/CT, resulting in an upstaging and intensification of therapy.[12]

In our study, we aimed to see changes in disease stage and its implications on treatment as a result of baseline FDG-PET scan. Upstaging was seen in only 4 patients. The causes of fewer upstaging in our practice are explained by the fact that PET and the CT components are not being done and reported separately. Moreover, the scans are reported by a pair of radiologists and physicians in nuclear medicine simultaneously. This might lead to

reporting being overshadowed by the twin modality. In addition, our reporters had access to patients' clinical data which could have been helpful in reporting. Moreover, majority of our patient population presented with advanced disease. Therefore, in cases where FDG avidity was seen in viscera like gut or breast, an advanced stage had already been identified by conventional imaging method or a bone marrow biopsy report. In such cases, FDG-PET was helpful in identifying additional tumour burden and, hence, a reliable tool in response assessment. FDG-PET scan did not lead to any change in the number of chemotherapy cycles because there was no upstaging from early to advance stage disease and the treatment recommendations for stage-III and IV are similar. However, the impact on management may show up on longer follow-up.

In this study, FDG-PET scan showed involvement of skeleton in 18 patients, while CT scan showed it in 6. The interim FDG-PET scans showed uptake within physiological limits in all the 18 patients. This further proves that osseous lesions even in the absence of bone marrow involvement can be taken as stage-IV disease. Hence, FDG-PET scan and bone marrow biopsy report complement each other, but FDG-PET probably cannot replace it. In clinical practice 'response to treatment' is increasingly being considered as the new gold standard.

Several studies have shown that patients with a negative FDG-PET after a few cycles of chemotherapy rarely relapse.[13] The prognostic value of early FDG-PET has been reported to be superior to the prognostic value of conventional IPS.[14] Early interim FDG-PET scans are being done after 2, 3 and even after one cycle of chemotherapy/immunotherapy. We did interim scans after 2 cycles and would like to see its impact on survival in the long run.

There are several criteria for reporting the interim scans, including the International Harmonisation Project (IHP), semi-quantitative and quantitative technique using SUV. International Workshop Criteria is being used for reporting NHL and the Cotswold Criteria for HL.[15,16] However, the main issue with these criteria was the assessment of residual masses at the EOT scan. The problem of residual masses was taken up by the IHP.[17] Particularly noteworthy is the elimination of the CRu category (i.e., the cases in which the tumour remains on the image, but does not change its size over 3 months without treatment). Particularly noteworthy is the elimination of the complete response uncertain (CRu) category (i.e., the cases in which the tumour remains on the image but does not change its size over 3 months without treatment. Most of the cases classified as CRu will now be designated as CR if there is morphologic mass on the scan but it is metabolically inactive or a PR if the residual mass is PET positive.[4-16,17]

The first International Meeting on Interim FDG-PET Interpretation in Lymphoma that took place in Deauville (France) proposed to grade the intensity of FDG uptake according to a 5-point scale.[18,19] The Deauville criteria categorised FDG-PET as negative scan (Score of 1-3) and positive scan (score 4 and 5). There is considerable debate regarding uncertainty about the nature of the uptake with intensity between that of the mediastinum and the liver (score-3). Majority take it as negative, but the few sensitive readers tend to report score-3 as positive uptake.[19,20] The current study read score-3 as negative for disease involvement. Around 80% of the previously involved sites on interim scans showed no or negligible activity (score 1-3) and, hence, CR. Three out of 53 patients had PD (score 4-5) and they were switched to salvage therapy. Patients with score-3 at interim scans can be confidently taken as PET-negative.

Further prospective studies using the Deauville criteria are required to delineate the significance of score-3 and 4. We intend to follow the patients over a minimum of 2 years from EoT to document their progression-free survival and to see the positive and negative predictive value of the interim FDG-PET. We would also like to see the effect of IPI and IPS on disease relapse.

Conclusion

The Deauville criteria for reporting interim scans has proved useful in evaluating response to treatment. Follow-up of these patients is required to see the positive and negative predictive value of interim scans.

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