FDG-PET/CT in re-staging of patients with Non Hodgkin lymphoma and monitory response to therapy# in Egypt

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Aims and objectives

Malignant lymphoma is the most common primary hematopoietic malignancy (1).

The classification of lymphoma is based on the World Health Organization (WHO) classification system, which helps determine not only malignancy grade, but also prognosis (2).

To receive the most appropriate therapy, patients with lymphoma should be accurately classified into one of several prognostic groups (3).

For decades, CT scans were considered sufficiently reliable for staging and restaging of lymphoma. CT provides relatively high sensitivity and specificity in pretreatment staging, but has low specificity in response assessment following therapy. CT scan determine the size and location of masses, but is unable to distinguish viable tumor from necrotic or scar tissue (4).

Positron emission tomography (PET), with or without integrated computed tomography (CT), using 18-fluorodeoxyglucose (FDG) is based on the principle of increased glucose metabolism in malignant tumors (5).

Integrated FDG PET/CT is now considered the most accurate tool for diagnosis, assessment of treatment response, and prognosis in patients with Hodgkin lymphoma and aggressive NHL (2).

Integrated PET/CT has been widely used for staging and for evaluation of treatment response in many cancers, including malignant lymphoma. FDG PET/CT can also help predict response during the course of treatment, and it provides essential clinical information (6).

An advantage of PET/CT for lymphoma is that it can differentiate between actively malignant tissue and necrotic tissue, whereas CT alone is unable to tell the difference. CT identify abnormal masses, nodal enlargement, and alteration of normal anatomy, whereas PET/CT demonstrates the metabolic activity of the cancer cells (7).

FDG PET has been widely used for staging of disease, detection of recurrence, and monitoring of treatment response in patients with malignant lymphoma, in the past, the imaging evaluation and follow-up of lymphoma patients was based solely on findings at contrast-enhanced CT. However, contrast-enhanced CT has limited sensitivity in detecting lymphomatous involvement of normal-sized lymph nodes, bone marrow, spleen, and extra-nodal tissues. Several studies have shown the value of FDG PET/CT for staging, restaging, and therapy monitoring (8).
Also, diagnostic whole-body CT has a high radiation dose, up to 30 mSv, whereas a PET scan accompanied by a low-dose CT scan typically has a radiation dose of 7 mSv from the CT component and 8 mSv from the 18F-FDG, for a total of 15 mSv \(^{(1)}\).

Recent evidence suggests that lymphoma patients undergoing dual-modality PET/CT may not need to additionally undergo whole-body CT. The study, by Raanani et al., showed that PET/CT, as opposed to CT alone, changed patient care management decisions in 25\% of NHL patients and 33\% of HD patients \(^{(9)}\).

For these reasons, FDG PET/CT has assumed an important role in guiding management in patients with lymphoma, although some limitations have been recognized \(^{(5)}\).

**So the aim of this study:** was to evaluate the clinical significance of combined fluorine-18 fluorodeoxyglucose positron emission tomography and computed tomography (FDG-PET/CT) in restaging of patients with non Hodgkin lymphoma in Egypt and monitoring response to therapy.
Methods and materials

Patients:

This is a prospective study, which was conducted on 45 Egyptian patients with NHL, of which 29 were males and 16 were females.

Patients were recruited from Radiodiagnosis, Nuclear medicine departments in Sharq El Madina Hospital and Oncology department in Tanta University during the period of May 2013 to August 2014.

In accordance with the ethical guidelines of the hospital institutional review board after signed written informed consent was obtained.

**Inclusion criteria:**

- All patients had histopathological diagnosis of non hodgkin lymphoma diagnosed by biopsy whatever surgically or image guided.

- Patients were staged according to the Ann Arbor staging criteria\(^{(10)}\).

- All the patients had complete physical examination and laboratory testing including (LDH, ESR, CBC, LFTs and RFTs) for good estimation and evaluation before the start of treatment as well as before imaging the patients for more diagnosis.

**Exclusion criteria:**

- Pregnant woman.

- Patients with chronic renal impairment (high serum creatinine).

**Imaging**

Exams were done and data were obtained using Siemens Bio-graph true point PET/CT scanner. These dedicated systems integrate a PET scanner with a multi-section helical CT scanners permit the acquisition of co-registered CT and PET images in one session.

**Imaging protocol:**

**Patient Preparation:**

- All patients were asked to fast for six hours prior to scan. All metallic items were removed from the patients.

- Patients were asked to empty the urinary bladder before the procedure.
· An I.V. cannula was inserted in the patient’s arm for administration of 18F-FDG.

· The patients were instructed to avoid any kind of strenuous activity prior to the examination and following injection of the radioisotope to avoid physiologic muscle uptake of FDG and the patient was asked to void prior to scan.

· Serum glucose was routinely measured prior to 18F-FDG injection, and fasting levels were 70-170 ng/dl.

· In breast feeding women, it was recommended that breast feeding discontinue for approximately 24 hours after the 18F-FDG injection because of 18F-FDG accumulation in breast milk.

· The strategies for decreasing brown fat were; providing a controlled-temperature (warm) environment for patients before 18F-FDG injection and high-fat, low-carbohydrate, protein-permitted diet before the examination.

**Dosage Administration:**

One liter of negative oral contrast agent (5% mannitol) approximately one hour before the exam. A dose of 3-7 MBq/Kg (10 mci) of 18F-FDG IV injection 45-90 minutes before examination was administered. This period is referred to as the uptake phase and is the necessary amount of time for the FDG to be adequately bio-distributed and transported into the patient’s cells. Patients were asked to rest in a quiet room, devoid of distractions, and they were also asked to keep their movements, including talking, at an absolute minimum. This minimizes physiologic uptake of FDG into skeletal muscle, which can confound interpretation of the scan. Patients should be comfortable and relaxed.

**Patient position:**

The patients were positioned in a comfortable head fixation with arms up.

**CT Technique:**

Helical CT was performed following injection of 125 mL of a low-osmolarity iodinated contrast medium at a rate of 4 m/sec using a power injector. For a typical whole body PET -CT study (neck, chest, abdomen, and pelvis), scanning began at the level of the skull base and extended caudally to the level of the upper thigh. The total length of CT coverage was an integral number of bed positions scanned during acquisition of PET data. The study was performed with the patient breathing quietly. Scanning parameters are collimation width of 5.0 mm, pitch of 1.5, and gantry rotation time of 0.8 second and field of view of 50cm. The helical data are retrospectively reconstructed at one mm intervals.

**PET Technique:**
PET was performed following the CT study without moving the patient. Approximately six to seven bed positions are planned in the three-di-mensional acquisition mode for scanning the entire patient with 3-5 minute acquisition at each bed position.

**PET/CT Fusion**

Hundreds of trans-axial PET and CT images were first reconstructed. These are then reformatted into coronal and sagital images to facilitate image interpretation. For each of these sets of PET and CT images, corresponding fusion images, combining the two types of data, also were generated. The whole acquisition time for an integrated PET/CT scan was approximately 25-30 mins. PET image data sets were reconstructed using CT data for attenuation correction and co-registered images were displayed using special software.

**Timing of exam:**

CECT and PET/CT scan were performed at 10 days after the 4th cycle of chemotherapy.

CECT and PET/CT were underwent within less than one week apart of each other.

**PET/CT Interpretation:**

All PET/CT examinations were analyzed by a consensus of two experienced observers of nuclear medicine physicians and radiologists. The PET images and the volume of CT scans were evaluated for the presence and extent of 18F-FDG-positive lymphoma in different lymph nodes groups and the presence of extra-nodal disease involvement in the initial studies as well as for residual/recurrent abnormalities during/after therapy.

Abnormal 18F-FDG uptake was defined as radiotracer accumulation outside the normal anatomic structures and of greater intensity than background activity, excluding normal areas of physiological uptake.

In all cases estimation of 18- FDG uptake was done using SUVmax values for each group of enlarged nodes or mass lesion.

If there was a clearly multifocal increase in FDG uptake in the bone marrow, the patient was considered as PET positive excluding cases where there is diffuse pattern of uptake of reactive bone marrow hyperplasia after chemotherapy.

**Treatment:**

Patients in this study received chemotherapy as the treatment protocol varies from (ABVD, CHOP, RCHOP, MINE) or other according to the oncology decision.

Patients were carefully prepared before each cycle as regarding blood picture, liver function and kidney function.
Proper evaluation was done after 3 cycles of treatment to categorize the patient response which defined as:

- Complete Cure (CC) if there was disappearance of known disease.

- Partial Response (PR) was considered to be $\geq 50\%$ decrease in tumor area calculating by multiplying the longest diameter by the greatest perpendicular diameter which mean regressive disease.

- Progressive Disease (PD) was defined as a greater than 25% increase in the size of the target lesion or the appearance of a new lesion.

- Stable or stationary Disease (SD) was defined as a bidimensionally measurable decrease of less than 50% or increase of less than 25% in the sum of products of the largest perpendicularly diameters of the measurable lesion.

**Data analysis:**

Data were statistically described in terms of range, mean $\pm$ standard deviation ($\pm$ SD), median, frequencies (number of cases) and percentages when appropriate. Comparison of quantitative variables between the study groups was done using Kruskal Wallis analysis of variance (ANOVA) test.

All statistical calculations were done using computer programs Microsoft Excel 2010 (Microsoft Corporation, NY, USA) and SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.
Results

Patient characteristics: The study included 45 patients with NHL, with their age ranging from 19 to 78 years at the time of diagnosis (median 48.2 years). Most of their tumors were of diffuse large B-cell type. The majority of cases were stage II or greater, and male sex, (Table 1).

The 45 patients included in this study underwent CECT & PET/CT scanning to monitor treatment response after 4 cycles of chemotherapy with 12 month follow up as standard of reference.

19 cases revealed complete remission by CECT while 2 of them revealed solitary lymph node FDG uptake by PET-CT and upstaged them to stage I and one case upstaged to stage II.

PET-CT upstaged 2 cases from stage II to stage IV by detecting metastatic FDG avid osseous deposits confirmed by MRI especially in bone marrow involvement, another 3 cases upstaged from stage II to stage IIE, III & IIIS by detecting extranodal extension & splenic involvement (confirmed by US).

In contrast, one case downstaged from stage IV to stage II, the FDG-PET pathological finding at the bone marrow level proved to be false positive at biopsy (bone uptake due to mastocytosis).

One case was downstaged by PET scan from stage IIE to stage II due to false positive residual mass results by CT (fibrosis).

Otherwise PET-CT agreed with CECT which were mainly stage III and IV.

Differences between FDGPET/CT and CECT were statistically significant (P<0.001) (table 2)

Change of treatment after PET-CT:-

The oncological treatment was modified according to PET-CT results. In two patients upstaged to stage IV with bone involvemnet, involved-field radiation of the bone lesions was added to chemotherapy. In the other three patients (two with iliac nodes and spleen involvement and one with liver involvement), the chemotherapy protocol was reinforced in two cases and stem cell implantation was added in the third case due to disease relapse.

The course of the disease was divided into three groups according to PET-CT results which was done after CECT. (Table 3)
PET-CT improve The sensitivity, specificity, Positive predictive value, negative predictive value and overall accuracy of restaging of NHL and detection response to therapy. (Table 4)

**Case No. 1**

Fig. 1: Axial CECT. (fig 2): Axial fused PET-CT. (fig 3): PET MIP(maximum intensity projection)

A 33 years female with NHL stage IIA for follow up after end of chemotherapy treatment.

The patient reveal complete remission by CECT (stage 0)

[18F]fluorodeoxyglucose positron emission tomography/computed tomography scan correctly identified the presence of pathological tracer uptake (max. SUV 5.2) in a solitary lymph node in the cardio-phrenic recess of the left side and so upstage the disease to stage I.

**Case No. 2**

(fig 4): Axial CECT (fig 5,6 )Coronal and axial fused PET-CT

A 19 years male with NHL for restaging and treatment assessment.

CECT reveal amalgamated lymphomatous adenopathies involving the left inguinal and left femoral lymph node stations (arrows) (stage II).

Restaging by PET-CT revealed the CECT detected lymph nodes with additional pathological tracer uptake at right supraclavicular lymph node (max SUV 4.7) and so upstage the disease to stage III

**Case No. 3**

(fig 7): Axial CECT (fig 8.9.10.11.12) axial fused PET-CT , (fig 13) PET MIP

54 years male with NHL stage IV for restaging and treatment assessment.

CECT revealed multiple enlarged groups of abdominal LNs.

PET-CT in accordance with CECT (max SUV 10) in the abdominal LNs (stage IV).

Also, pathological FDG tracer uptake in Metastatic osseous deposits are seen in right femoral mid shaft (max SUV 19), outer aspect of right iliac crest max SUV 11),medial and lateral ends of left clavicle (max SUV 9) and left humeral head (max SUV 12).
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No.</th>
<th>Percentage</th>
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<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>29</td>
<td>64.4%</td>
</tr>
<tr>
<td>Female</td>
<td>16</td>
<td>35.5%</td>
</tr>
<tr>
<td><strong>Age</strong></td>
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<tr>
<td>Median</td>
<td>48.2</td>
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<tr>
<td>range</td>
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</tr>
<tr>
<td><strong>Types of NHL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diffuse large B-cell</td>
<td>18</td>
<td>40%</td>
</tr>
<tr>
<td>Follicular lymphoma</td>
<td>11</td>
<td>24.4%</td>
</tr>
<tr>
<td>Marginal zone B-cell</td>
<td>8</td>
<td>17.7%</td>
</tr>
<tr>
<td>Precursor T-lymphoblastic</td>
<td>7</td>
<td>15.5%</td>
</tr>
<tr>
<td>Anaplastic large cell</td>
<td>1</td>
<td>2.2%</td>
</tr>
<tr>
<td><strong>Initial staging</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>12</td>
<td>26.6%</td>
</tr>
<tr>
<td>II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>9</td>
<td>20%</td>
</tr>
<tr>
<td>IIIE</td>
<td>7</td>
<td>15.5%</td>
</tr>
<tr>
<td>III</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>10</td>
<td>22.2%</td>
</tr>
<tr>
<td>IIIIE</td>
<td>2</td>
<td>4.4%</td>
</tr>
<tr>
<td>IV</td>
<td>5</td>
<td>11.1%</td>
</tr>
</tbody>
</table>

**Table 1**: Characters of 45 patients with NHL included in the study:

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<table>
<thead>
<tr>
<th>Stage</th>
<th>CECT</th>
<th>PET-CT</th>
</tr>
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<tbody>
<tr>
<td>(0)</td>
<td>19</td>
<td>16</td>
</tr>
<tr>
<td>(I)</td>
<td>I</td>
<td>2 cases</td>
</tr>
<tr>
<td>(II)</td>
<td>II</td>
<td>7 cases</td>
</tr>
<tr>
<td></td>
<td>IIIE</td>
<td>3 cases</td>
</tr>
<tr>
<td>(III)</td>
<td>III</td>
<td>4 cases</td>
</tr>
<tr>
<td></td>
<td>IIIIE</td>
<td>2 cases</td>
</tr>
<tr>
<td></td>
<td>IIIIS</td>
<td>2 cases</td>
</tr>
<tr>
<td></td>
<td>(IV)</td>
<td>6 case</td>
</tr>
</tbody>
</table>

**Table 2:** Comparison between CECT and PET-CT in restaging of 45 patients with NHL after 4 cycles of chemotherapy:

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Table 3: Comparison between CT and PET-CT in assessment of treatment response.

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<table>
<thead>
<tr>
<th></th>
<th>PET-CT</th>
<th>CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>97.7%</td>
<td>82.2%</td>
</tr>
<tr>
<td>Specificity</td>
<td>66.6%</td>
<td>66.6%</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>97.7%</td>
<td>97.7%</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>66.6%</td>
<td>20%</td>
</tr>
<tr>
<td>Overall accuracy</td>
<td>100%</td>
<td>86.6%</td>
</tr>
</tbody>
</table>

Table 4: Analysis of PET/CT results in the studied cases.

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**Fig. 1**: CECT

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**Fig. 2:** Axial fused PET-CT.

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Fig. 3: PET MIP

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Fig. 4: Axial CECT

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Fig. 5: Coronal fused PET-CT

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Fig. 6: axial fused PET-CT

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**Fig. 7:** Axial CECT

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Fig. 8: axial fused PET-CT

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**Fig. 9:** axial fused PET-CT

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Fig. 10: axial fused PET-CT

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Fig. 11: axial fused PET-CT

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**Fig. 12:** axial fused PET-CT

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Fig. 13: PET-CT PET MIP

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Conclusion

Due to the rapid development of modern imaging methods and also of medical oncology, there has been a significant progress in diagnosis and treatment of malignant lymphomas in the last few years (11).

18F-FDG-PET is expected to play a significant role in the management of malignant lymphoma patients even after effective treatment is initiated (12).

FDG-PET has a high diagnostic accuracy for the evaluation of staging and restaging in lymphoma patients (13). In the study of Isasi et al. (13) who did a meta-analysis of 20 studies evaluating the diagnostic performance of whole body FDG-PET in the staging of patients with HL and NHL, concluding a relative advantage of this technique over standard imaging (CE-CT and BMB (bone marrow evaluation) and/or MRI). The pooled true positive value of FDG-PET was found to be 90%, with an upstaging rate ranging from 8% to 17% and a downstaging rate ranging from 2% to 23%. Our Results agree with these studies, as the true positive results of PET/CT is 95% with an upstaging percentage is 17.7%, and downstage percentage is 2.2%.

Freudenberg et al. (14) who evaluated the diagnostic accuracy of FDG-PET in combination with CT, and found an improvement in sensitivity and specificity over each imaging modality alone. They reported a higher sensitivity and specificity for FDG-PET when compared with CT in the restaging of lymphoma patients. The accuracy of FDG-PET was reported to be 95% and the accuracy for CT was 84%. Their study is coincide with our results as the accuracy of CT in our study is 86% while slightly different as we report high accuracy of PET/CT which reach 100%.

The concordance in staging between 18F-FDG-PET and CT was reported to be 80-90% (15, 17). This is agree with our results and the concordance was reported mainly in stage III and IV.

The study of Isohashi K. et al (12) demonstrated that the frequency of concordant positive findings between 18F-FDG-PET and CT/MRI was especially low in relation to the treatment response, and most of the discrepant findings were correctly diagnosed by 18F-FDG-PET. It has been reported that alterations in glucose metabolism become evident earlier than morphologic alterations (18-21). The results of our study reveal also that PET/CT reveal no tumor activity in a case of residual soft tissue mass revealed by CECT and downstage it as its SUV equal to 1.9.

The limitation of this study is the systemic nature of the disease and difficulty of determining the presence of lesions in lymphoma and validating the obtained imaging results. Also very small lesions can be missed by PET scan. Correct interpretation of
abdominal FDG uptake can be difficult, because FDG uptake can be physiologically increased in small and large bowel combined with mobility of the bowel during examination.

**The points of strength** in our study as we focused on non Hodgkin lymphoma type and restrict the study on Egypt as Non-Hodgkin lymphoma was among the 5 most common cancers in Lower Egypt.

**Conclusion:**

FDG-PET/CT improved the sensitivity and accuracy in restaging of non Hodgkin lymphoma after initial treatment and prediction of response to therapy. Therefore, FDG-PET/CT imaging is a promising technique for better management of the patient after treatment.
References


