Original Article

PET/CT in initial staging and therapy response assessment of lymphoma

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ABSTRACT

Objective: To detect accuracy of PET/CT in the initial staging, response during the course and end of treatment in lymphoma patients compared to contrast CT.

Materials and methods: We studied 50 patients divided into 3 groups with pathologically proven lymphoma with a mean age = 27. All patients performed CT and PET/CT for initial staging, during the course of chemotherapy and at the end of treatment.

Results: PET/CT and CECT were agreeable in 75% of cases. 61% during treatment and 41% agreement at the end of treatment.

Conclusion: PET/CT proved higher sensitivity and specificity over CECT. The major strength of PET/CT over CECT was its higher ability for detection of extra-nodal sites of lymphoma and excluding active disease in residual nodal mass lesions on follow-up.

1. Introduction

Lymphoma comprises a histological heterogeneous group of cancers derived from the cells of the immune system [1,2]. The hallmark of the disease is the enlargement and proliferation of lymph nodes or secondary lymphoid tissues [3,4].

18F-FDG PET/CT has been widely used for staging, detection of recurrence, and monitoring of treatment response in patients with Hodgkin’s disease and NHL. In the past, the imaging evaluation and follow-up of lymphoma patients were 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 [3–6]. The residual lymph node mass was a commonly encountered diagnostic challenge because it is difficult at CT to differentiate post-treatment fibrosis from residual viable malignant changes [6,7].

18F-FDG PET/CT studies show a high sensitivity for tumor detection and add important functional information to the inherent anatomic data provided with CT [6]. PET/CT scanning allows the investigator to visualize and measure the intensity of residual metabolic activity within a lesion as well as estimating its size. Hodgkin’s lymphoma is FDG avid [7,8].

By assessing metabolic activity within a node, 18F-FDG PET/CT is not directly reliant on nodal size to determine the presence or absence of malignancy. Nodes that are not enlarged can be shown to contain tumor on 18F-FDG PET/CT images, and nodes that are enlarged can be shown to be reactive in nature. For this reason, PET has been shown to be more sensitive and specific than CT for identification of sites of disease. Studies have shown that
18F-FDG PET/CT may be superior to computed tomography (CT), gallium-67 scintigraphy, and bone scintigraphy in the staging and treatment evaluation of lymphoma because of good spatial resolution and the functionality of 18F-FDG PET/CT scans [8–10]. However limited literature on the use of 18F-FDG PET/CT evaluating the response to first line of treatment and follow-up after the end of treatment was found. Our aim was to show the accuracy and contribution of 18F-FDG PET/CT in the initial staging, response during treatment and at the end of treatment in lymphoma patients in comparison with contrast enhanced CT (CECT) study.

2. Materials and methods

2.1. Study population

This prospective study was conducted on 50 patients with pathologically proven lymphoma from April 2013 to August 2015. Their ages ranged from 2 up to 70 years (mean age = 27), including 27 males and 23 females. Exclusion criteria were diabetes mellitus and pregnancy. Histopathological diagnosis of lymphoma was established in all cases after biopsy whether surgical or image guided. None of the cases received any previous oncological treatment. The following clinical data were obtained from all patients: sex, age, clinical stage, extra-nodal involvement, presence of B symptoms, bulky disease, histological subtype according to the WHO classification, albumin, and erythrocyte sedimentation rate (ESR), hemoglobin, leukocyte count and lymphocyte count. All patients included in the study performed CT and 18F-FDG PET/CT for initial staging, after the first course of chemotherapy (after 4–6 weeks) and after the end of treatment (after 2–4 months) with median follow-up period of 14 months. Staging was defined according to the Ann Arbor staging system [8]. Treatment of early-stage disease was given according to the Nordic Lymphoma Group protocols. The first line of treatment was Adriamycin, bleomycin, vinblastine, dacarbazine (ABVD) in standard doses every 2 weeks (one cycle = 4 weeks) with dose modification, granulocyte stimulation, or delays depending on blood counts with or without local radiotherapy. The study was approved by the ethics committee in our University and informed written consents were taken.

![Table 1](image-url)
2.2. Patient preparation

This prospective study was carried out in the Radiology departments of Nasser Institute hospitals using GE Discovery 690 PET/CT scanner as well as Siemens Biograph PET/CT scanner. Prior to the examination, all patients were asked to fast for 6 h, empty their bladders, remove metallic items, avoid any kind of strenuous activity, and administer 1 l of negative oral contrast agent (5% mannitol) 1 h before the examination. An I.V. cannula was inserted in the patient’s arm for administration of 3–7 MBq/kg of 18F-FDG 45–90 min before examination. Then the patients were instructed to rest in a quiet room, devoid of distractions, and they were also asked to keep their movements, including talking, at an absolute minimum.

2.3. Imaging protocol

FDG PET/CT scans were performed with integrated PET/CT scanners (Biograph 16, Siemens). Blood glucose levels

![Fig. 2. Relation between HD subtypes and SUV uptake.](image)

![Fig. 3. Relation between NHD subtypes and SUV uptake.](image)

<table>
<thead>
<tr>
<th>Stage</th>
<th>CT stage</th>
<th>18F-FDG PET/CT</th>
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<tbody>
<tr>
<td>I</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>II</td>
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<td>3</td>
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<tr>
<td>No change</td>
<td>4/12 (33%)</td>
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</tr>
<tr>
<td>Upstaging</td>
<td>8/12 (66%)</td>
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* Statistically significant (p < 0.01).
were recorded prior to FDG injection in all patients. Patients were instructed to fast for at least 6 h prior to the administration of FDG to decrease physiological blood glucose levels and to reduce serum insulin levels to near baseline. Patients were not premedicated with muscle relaxants or sedated. 18F-FDG (0.21 mCi/kg of body weight [7.78 MBq/kg]) was injected intravenously at a flow rate of 4 mL/s. PET and low-dose CT images (20–120 mA/s) in the whole body were obtained in an arms-up position with scanning times of approximately 20–30 min. In all patients, emission images were acquired for 3 min per bed position in a three-dimensional mode. PET/CT, PET, and CT images were displayed and reconstructed in the transaxial, coronal, and sagittal planes.

2.4. Image analysis

All 18F-FDG PET/CT examinations were analyzed by a consensus of two experienced observers of nuclear medicine physicians and radiologists in a blind fashion. In all contrast material was not administered. Once patients were positioned in the scanner, 125 ml of iohexol (Omni-paque 240 or 300; GE Healthcare, Princeton, NJ) was injected intravenously at a flow rate of 4 mL/s. PET and CT images were obtained in the arms-up position with scanning times of approximately 20–30 min. In all patients, emission images were acquired for 3 min per bed position in a three-dimensional mode. PET/CT, PET, and CT images were displayed and reconstructed in the transaxial, coronal, and sagittal planes.

Fig. 4. Initial staging by CT versus 18F-FDG PET/CT among 12/50 patients (initial staging group).

Fig. 5. CT versus 18F-FDG PET/CT among 12/50 patients (initial staging group).

Fig. 6. Treatment assessment results of 18F-FDG PET/CT in relation to CT.

Fig. 7. CT versus 18F-FDG PET/CT among 18/50 patients at the end of the therapy (end of treatment follow-up group).
cases estimation of 18-FDG uptake was done using SUVmax values for each group of enlarged nodes or mass lesion and comparison of values was done in the follow-up studies respecting the ROI position as much as possible. Response evaluation criteria in solid tumours (RECIST) assessment was used as a secondary method for interpreting findings as positive or negative. According to the IHP definitions (Fig. 1), residual masses of 2 cm or more in greatest transverse diameter (GTD) with 18F-FDG activity visually exceeding that of mediastinal blood pool structures are considered PET positive, whereas residual masses 1.1–1.9 cm are considered PET positive only if their activity exceeds surrounding background activity. A smaller residual mass or a normal-sized lymph node (e.g., <1 × 1 cm) should be considered positive for disease if its activity is higher than that of the surrounding background. 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. In the liver and spleen, focal or diffuse FDG uptake with activity greater than that in surrounding liver or spleen parenchyma is considered 18F-FDG PET/CT positive keeping in mind the absence of other confounding factors, such as physiological hyperplasia after cytokine administration. The presence of single or multiple foci of clearly elevated FDG uptake within the bone marrow also is considered positive for 18F-FDG PET/CT. For follow-up and evaluation of treatment response, firstly pretreatment baseline PET/CT was evaluated, followed by analysis of the follow-up PET images, and complete response (CR) was defined as disappearance of all detectable disease or lymph nodes >1.5 cm must decrease to ≤1.5 cm. Partial response (PR) was defined as more than 50% in SPD. Stationary (SD) was defined as less than 50% decrease in SPD. Progressive disease (PD)/relapse was defined as new lesion or SPD increase >50% from nadir of any lymph node.

2.5. Standard of references

The final diagnosis made was established in all cases by means of histopathological examination of surgical or image guided biopsy.

2.6. Statistical analysis

Data were statistically described in terms of range, mean ± standard deviation (±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. For comparing categorical data, Chi square (\(\chi^2\)) test was performed. Sensitivity, specificity, positive and negative predictive values, accuracy, and \(P\) value were calculated to test validity of 18F-FDG PET/CT. Exact test was used instead when the expected frequency is less than 5. \(P\) values less than 0.05 were considered statistically significant. All statistical calculations were done using computer programs Microsoft Excel 2007 (Microsoft Corporation, NY, USA) and SPSS (Statistical Package for the Social Science).

3. Results

The study included 50 patients with pathologically proved lymphoma with 27.5 mean age. We had 33 cases who had Non Hodgkin’s disease (66%) and 17 cases who had Hodgkin’s disease (34%). Most subtypes of HD show high SUVmax, while in NHD B cell lymphoma shows high SUVmax in nearly total cases recording in contrast to indolent follicular and marginal zone lymphoma (Table 1, Figs. 2 and 3).

3.1. In the initial staging

In our study out of the 12 cases came for initial staging, 18F-FDG PET/CT and CECT were concordant in staging of 9 cases (75%) while 18F-FDG PET/CT disagreed with CECT in the initial staging of 3 cases (25%) where it upstaged 3 cases (25%) from stage II to IV. In all the upstaged cases, the additional value of 18F-FDG PET/CT in all cases was not in detection of the active subcentimetric lymph nodes as in the previously described study but in the detection of the extra-nodal sites of disease that were not determined by CECT. 18F-FDG PET/CT proved higher sensitivity and specificity over CECT in our study. The major strengths of 18F-FDG PET/CT over CECT were in its higher ability for detection of extra-nodal sites of lymphoma. There were statistically significant results in the initial staging PET-CT (\(P\) value = 0.004) (Table 2, Figs. 4, 5 and 8).

3.2. Evaluating response to therapy

In our study, in first follow-up during the course of chemotherapy, out of the 18 cases, 18F-FDG PET/CT and CECT were concurrent in results in 13 out of the 18 cases (68.2%) and discordant in the other 5 cases (31.8%) detailed as follows: CECT detected complete regression in 2 cases (11.11%), partial regression in 2 cases (11.11%), stationary course in 4 cases (22.22%), progression in 9 cases (50%), while 18F-FDG PET/CT detected complete regression in 2 cases (11.11%), partial regression in 3 cases (16.66%), stationary course in 0 case (0%), and progression in 14 cases (77.77%).

Fig. 9. A 25 years old female: pretreatment PET-CT images: A, B, C, and D showed metabolically active 18-FDG avid right supraclavicular lymph node, RT subphrenic lymph node and pulmonary infiltrates (arrows). PET CT images at end of therapy: E, F, G, showed total resolution of the previously seen 18-FDG avid lesions denoting complete remission.
As in initial staging, the additional value of 18F-FDG PET/CT in all cases was not in detection of the active sub-centimetric lymph nodes as in the previously described study but in the detection of the extra-nodal sites of disease that were not determined by CECT. The difference was less statistically significant in the follow-up during treatment in 18F-FDG PET/CT study (P value = 0.138) (Table 3, Figs. 6, 9 and 10).

3.3. Follow up

Out of 20 cases CECT detected complete regression in 9 cases (45%), partial regression in 6 cases (30%), stationary course in 5 cases (25%) while 18F-FDG PET/CT detected complete regression in 5 cases (25%) and disease relapse in 15 cases (75%). There were statistically significant results in the follow-up of 6 months after the end of chemotherapy 18F-FDG PET/CT study (P value = 0.006). 18F-FDG PET/CT proved higher sensitivity and specificity over CECT in our study which was in keeping with the results of the other similar studies. The major strengths of 18F-FDG PET/CT over CECT were in its higher ability to exclude active disease in addition to its ability for early detection of relapse sites which also can help in directing biopsy procedure in indeterminate cases where histopathology is mandatory (Table 4, Figs. 7 and 11).

4. Discussion

CT is the most readily available and most commonly used tool for staging lymphoma. Fundamental limitations of CT are that recognition of lymph node involvement is based solely on size and that detection of bone marrow and extra-nodal tissue involvement may be limited. In

<table>
<thead>
<tr>
<th>Stage</th>
<th>CT</th>
<th>18F-FDG PET/CT</th>
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<tbody>
<tr>
<td>Complete regression</td>
<td>9/18 (45%)</td>
<td>5/18 (25%)</td>
</tr>
<tr>
<td>Partial regression</td>
<td>6/18 (30%)</td>
<td>0/18 (0%)</td>
</tr>
<tr>
<td>Stationary</td>
<td>5/18 (25%)</td>
<td>0/18 (0%)</td>
</tr>
<tr>
<td>Disease relapse</td>
<td>0/18 (0%)</td>
<td>13/18 (70%)</td>
</tr>
<tr>
<td>Missed findings staging</td>
<td>0/18 (0%)</td>
<td>0.183</td>
</tr>
<tr>
<td>No change</td>
<td>5/18 (25%)</td>
<td></td>
</tr>
<tr>
<td>Additional findings</td>
<td>13/18 (70%)</td>
<td></td>
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</table>

Table 4

CT versus 18F-FDG PET/CT among 18/50 patients at the end of the therapy (end of treatment follow-up group).

Fig. 10. A seven year old boy: pretreatment Axial CT and axial PET-CT images: A and B showed large nodal metabolically active 18-FDG avid amalgamated mass encasing the great abdominal vessels (thin large arrows). Interterm Axial CT and axial PET CT images: C axial CT showed minimal changes in the size of the previously noted amalgamated nodal mass (CT overstating), on the other hand PET-CT showed SUV ~ 25 recorded at the aortic bifurcation site (max. SUV ~ 12.6) denoting partial remission.
addition to depicting nodal sites of lymphoma with greater accuracy than CT, PET/CT can detect the activity of the lesion and has greater sensitivity for sites of extra-nodal involvement and correspondingly has been found to improve baseline staging compared with conventional staging with CT alone [10]. Hodgkin’s lymphoma is 18F-FDG PET/CT avid, and PET/CT is more accurate in initial staging than CECT.

In this study out of the 12 cases came for initial staging, 18F-FDG PET/CT and CECT were concordant in staging of 9 cases (75%) while 18F-FDG PET/CT disagreed with CECT in the initial staging of 3 cases (25%) where it upstaged 3 cases (25%) from stage II to IV. The concordant in staging in our study between 18F-FDG PET/CT and CT was nearly similar to that detected by Riad and Omar. They found a 73.2% concordance [11] and less than that of Pelosi et al. who found a 12% upstaging by 18F-FDG PET/CT compared to CT [12], and the additional value of 18F-FDG PET/CT causing upstaging in our cases was not in detecting active subcentimetric lymph nodes as in the study conducted by Ranani et al. [13] but in detecting the extra-nodal thoracic sites of disease that were not determined by CECT. Downstaging of cases was documented in previous studies [12,13], as they detected enlarged lymph nodes by CT yet, not metabically active on PET/CT. No similar cases that needed downstaging were found in our study because our patients had early stage lymphoma disease.

An important and valid application of 18F-FDG PET/CT is to detect viable tumor in residual lesions after the treatment of patients with HL and NHL. A residual mass at the end of therapy is not a rare finding and is considered a clinical challenge in HL and intermediate/high grade NHL restaging. 18F-FDG PET/CT has proved to be much more accurate in distinguishing fibrosis from viable tumor, since fibrosis does not show high metabolic activity in contrast to viable residual tumor [14]. This fact made FDG PET/CT extremely useful for therapy response assessment.

Our study confirmed the value of 18F-FDG PET/CT in initial staging and planning that involved field radiotherapy. We showed that 18F-FDG PET/CT detected a 60% complete regression ratio compared to only 14% by CT scan. In the future this may be relied upon to minimize chemotherapy cycles in favorable group of patients, hence reducing the side effects of treatment [2].

In the follow-up study during chemotherapy cycles, 18F-FDG PET/CT and CECT were concurrent in results in 11 cases (61%) and discordant in 7 cases (39%). In the follow-up study after the end of chemotherapy cycles, 18F-FDG PET/CT and CECT were concurrent in results in 9 cases (44%) and discordant in 11 cases (56%) in contradic-
tion to Ranani et al. who showed much higher agreement percentage between both modalities (90%) and less disagreement [13]. Several studies compared CECT to 18F-FDG PET/CT in detection of extra-nodal lymphoma; all were around 88% sensitivity and 100% specificity for 18F-FDG PET/CT compared to 50% sensitivity and 90% specificity with CECT [3,13]. We reported 100% sensitivity and specificity for PET-CT compared to 62.5% sensitivity and 97.6% specificity for CECT in detection of extra-nodal disease sites. 18F-FDG PET/CT proved higher sensitivity and specificity over CECT in our study. The major strength of 18F-FDG PET/CT over CECT was its higher ability for detection of extra-nodal sites of lymphoma at initial staging and its much higher ability to exclude active disease in residual nodal mass lesions on follow-up studies. The use of early response to therapy of lymphoma patients by 18F-FDG PET/CT may tailor the dose of chemotherapy avoiding unnecessary toxic treatment.

Limitation of the current study includes, high coast, relatively small number of patients and relative short median follow-up period.

5. Conclusion

18F-FDG PET/CT scan has become an important part of the management of lymphoma, and been recommended for staging, detection of recurrence, evaluation of response to treatment, and prediction of response in patients with lymphoma due to the high sensitivity and specificity rates. Even though an interim PET scan possesses the predictive value, its role in directing treatment remains investigational. Any alteration during the treatment should be confirmed by the biopsy.

Conflict of interest

The authors declare that there are no conflict of interests.

References

[2] Fludeoxyglucose F 18 PET scan-guided therapy or standard therapy in treating patients with previously untreated stage I or stage II Hodgkin's lymphoma (the H10 EORTC/GEA/IIL randomized intergroup trial on early FDG-PET scan guided treatment adaptation versus standard combined modality treatment in patients with supradiaphragmatic stage I/II Hodgkin’s lymphoma), July 2010.