Diagnostic accuracy of PET/CT in patients with extranodal marginal zone MALT lymphoma

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Abstract

Background: 18Fluoro-2-deoxyglucose (18FDG) positron emission tomography (PET) is widely used for initial staging and follow-up in patients with malignant lymphoma. While earlier studies suggested a limited role for PET in extranodal marginal zone mucosa-associated lymphoid tissue (MALT) lymphoma patients due to their non-FDG avidity, more recent reports have suggested that the issue is controversial. In the present study, we evaluated the diagnostic accuracy of PET integrated with CT (PETCT) in patients with MALT lymphoma and assessed its reliability in clinical staging and monitoring response. Methods: Thirty-three patients with biopsy proven MALT lymphoma in 37 sites, who underwent PET/CT at diagnosis, were enrolled. Medical records, PET/CT findings and data obtained by other diagnostic procedures were reviewed. Results: Common sites of MALT lymphoma were the stomach (18), lung (5), orbit (4), and parotid gland (3). PET/CT detected active disease in 18 of 33 patients (54.5%) at diagnosis. Sensitivity in gastric MALT (38.9%) was lower when compared with non-gastric MALT (75%). PET/CT detected active disease in 100% patients with advanced disease (stage III–IV) but only in 42.3% with early stage disease (I–II). The incidence of gastric FDG uptake was higher in patients showing gastric ulcer on gastroscopy than in subjects with minimal or no macroscopic findings. Of the 33 patients in the study cohort, 12 had a follow-up PET/CT which detected relapse in three patients. Conclusions: These data suggest that PET/CT is a useful tool for both, initial staging and follow-up after therapy in patients with MALT lymphoma. Its sensitivity depends on disease location and stage at initial diagnosis.

Key words marginal zone lymphoma; extranodal lymphoma; 18FDG-PET; CT/PET

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18-fluoro-2-deoxyglucose (FDG) positron emission tomography (PET) is a functional imaging technique that is now widely used for initial staging, follow-up and evaluation of response to therapy in various malignant diseases, including lymphoma. Previous studies have found PET-FDG imaging to be clinically valuable in patients with Hodgkin’s disease and non-Hodgkin’s lymphoma (NHL) in general, however, its role was different in histopathological subtypes.

The majority of studies performed in NHL patients have recognized PET-FDG as a useful tool for staging aggressive NHL, detecting at least one involved site in 100% of patients with diffuse large B cell and mantle cell lymphoma, while data regarding indolent lymphoma are more controversial (1–4).

Marginal zone lymphoma (MZL), a subgroup of indolent B-cell NHL, originating from cells of the ‘marginal zone’ of the secondary lymphoid follicle, is
the third most common type of NHL encountered. There are three distinct types of MZL: mucosa-associated MZL (MALT), which is the most frequent type seen (50–70% of all MZL), splenic lymphoma (with or without villous lymphocytes) and nodal MZL (5).

Currently, there is controversy in the reported literature regarding the accuracy of $^{18}$FDG avidity in MZL. In an earlier study by Elstrom et al., PET-FDG detected at least one site of involvement in only 67% of MZL patients (1). In a small cohort of MZL patients, increased FDG uptake was detected in most nodal MZL patients but not in those with extranodal disease, suggesting that the FDG-avidity depends on tumor location and/or the MZL subtype (6).

Recently, Beal et al., reported that 81% of 42 biopsy confirmed extranodal MZL patients who underwent PET-FDG scans for initial staging, had focal tracer uptake within verified tumor sites while an additional 5% had indeterminate uptake (7).

The use of PET/CT [combined PET and computed tomography (CT)], which allows PET and CT acquisition at the same clinical setting without changing the patient’s position, has evolved during the past years. Clinical experience with this novel technique indicates that the combination of the two modalities improves specificity as well as sensitivity in tumor imaging (8, 9). This is probably due to the fact that the fused functional-anatomic data appears to provide better localization of the lesions helping to distinguish physiological uptake from FDG uptake in tumors, thereby enabling the detection of unexpected lesions, which would otherwise be overlooked. However to the best of our knowledge, no study investigating the role of PET/CT in MALT lymphoma has been reported until now and its use in routine staging and monitoring therapy of this lymphoma type needs further investigation.

MALT lymphoma frequently arises in organs with physiological FDG uptake. In the gastrointestinal tract, for instance, focal intense physiologic FDG uptake may be detected in up to 30% of the evaluated patients and diffuse uptake or uptake of a less intensity is even more common (10). Because of these data, we hypothesized that the addition of morphological data provided by the CT part of the combined PET/CT may well improve the diagnostic accuracy of the $^{18}$F-FDG assessment mainly by sorting out the nature of equivocal FDG sites of uptake as well as identify sites of tumor involvement which are not FDG-avid.

In this retrospective study, we analyzed 33 patients with biopsy confirmed MALT lymphoma, who had a PET/CT performed at the time of initial diagnosis and assessed its reliability in clinical staging and monitoring of disease activity during clinical follow-up.

**Methods**

Thirty-three patients with biopsy proven MALT lymphoma, who underwent PET/CT at initial diagnosis, were enrolled including 13 males and 20 females, median age 63.5 yr (39–88 yr).

Twenty-eight of these patients had the PET/CT performed at the Tel Aviv Sourasky Medical Center (TASMC), while five others provided the PET/CT documentation for revision by the TASMC nuclear medicine specialists. PET/CT scans were interpreted at the TASMC by the same team of specialists (EES and UM) in a consensus reading.

Patients fasted for 4 h before receiving an intravenous injection of $370–666$ MBq (10–18 mCi) $^{18}$FDG. Oral contrast was added for better discrimination between physiologic bowel activity and uptake by abdominal tumor sites. Scanning from the base of the skull through the mid thigh was performed using the Discovery LS PET/CT system (GE Medical Systems, Milwaukee, WI, USA). Low-dose CT acquisition was performed first with $140$ kV, $80$ mA, and $0.8$ s per CT rotation, a pitch of 6 and a table speed of $22.5$ mm/s, without any specific breath-holding instructions. A PET emission scan was carried out immediately following acquisition of the CT, without changing the patient’s positioning. Several bed positions (5–8) were performed with an acquisition time of 5 min for each one. PET images were reconstructed using an OSEM algorithm. PET was considered positive either when focal increased uptake was detected in sites generally free of physiological uptake or if focal uptake of FDG was evident in tissues where some physiological uptake may sometimes be observed, but of a higher intensity to the surrounding background activity.

PET/CT interpretations were performed on the eNTEGRA or the Xeleris work stations (ELGEMS, Haifa, Israel) equipped with fusion software, which enables the display of PET images (with and without attenuation correction), CT images and fused data of both modalities. PET/CT was visually interpreted and standardized uptake value (SUV) analysis was not used in this retrospective study to differentiate between reactive and involved organs.

**Results**

Twenty of the 33 study patients had abnormalities on the CT part of the study, and of these 18 had a positive PET scan (Table 1). Additional two patients had morphological abnormalities on the CT part of the PET/CT without pathological uptake on the PET part of the scan.

Histopathological evidence of MALT lymphoma was detected in 37 sites in 33 patients. Common sites of involvement were the stomach (18), lung (5), orbit (4) and the
parotid gland (3). Other sites included breast, eyelid, lacrimal gland, prostate, esophagus and the small intestine.

The PET/CT detected active disease in 18 patients (54.5%) and in 22 of 37 (59.5%) sites of involvement (Figs 1 and 2). Pathological FDG uptake was detected in seven of 18 (38.9%) patients with gastric MALT lymphoma, compared to 12 of 16 patients (75%) with extra-gastric MALT lymphoma (one patient had both gastric and extra-gastric involvement), and in 15 of the 19 (78.9%) sites of involvement (Table 2).

Seven patients had advanced disease at the time of diagnosis (stage III–IV, according to the Ann Arbor classification) all of them had FDG-avid disease while only 11 of 26 (42.3%) patients with early disease (stage I–II) had increased FDG-uptake.

Seven of the 18 patients with gastric MALT, had a positive PET/CT scan and all of these had pathological macroscopic findings on gastroscopy (ulcer, gastritis), while only two of 11 patients with a negative scan had abnormal gastroscopic findings (Fig. 1).

Of the 33 patients in the cohort, four were lost to follow up and one died of a non-lymphoma related cause (ischemic heart disease).

Twelve patients had a follow up PET/CT [median follow up 21 months (6–48 months)]. Nine of these 12 patients had a positive scan initially at diagnosis and achieved a complete response after therapy, according to follow-up PET/CT scan, which also correlated with their clinical evaluation. Additional patient achieved a partial response according to PET/CT.

During follow up, five patients had biopsy proven relapse and one patient was shown to have disease progression. Three patients relapsed in the stomach (all had gastric MALT lymphoma at presentation, time to relapse 10–24 months). One patient, who presented with prostate involvement, relapsed in the prostate, bone marrow, and lymph nodes (time to relapse 36 months). Another patient who presented with pulmonary MALT lymphoma relapsed in the spleen and para-splenic lymph nodes (time to relapse 11 months). Follow up using PET/CT-detected subsequent relapse in three patients (including one who had a negative PET/CT at initial diagnosis) and disease progression in another patient.

### Discussion

Although the accuracy of FDG/PET for initial staging of lymphoma is in itself important, the even more clinically relevant role is its ability to stratify response to treatment and assess post-treatment surveillance of lymphoma patients, thereby, playing an increasingly important role in clinical decision-making (11, 12).

Nevertheless, while the sensitivity of FDG/PET is regarded as extremely high in aggressive (large cell) NHL, reaching close to 100%, it seems to be less sensitive in detecting indolent lymphoma. Intensity of FDG uptake has also been reported to be lower in indolent NHL when compared with aggressive NHL (13). Data

<table>
<thead>
<tr>
<th>Site of involvement</th>
<th>No.</th>
<th>Positive PET/CT No. (%)</th>
<th>Negative PET/CT No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric</td>
<td>18</td>
<td>7 (38.9)</td>
<td>11 (61)</td>
</tr>
<tr>
<td>Lung</td>
<td>5</td>
<td>5 (100)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Parotid</td>
<td>3</td>
<td>3 (100)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Orbit</td>
<td>4</td>
<td>2 (50)</td>
<td>2 (50)</td>
</tr>
<tr>
<td>Eyelid</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Lacrimal gland</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Breast</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Prostate</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Paravertebral mass</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Small bowel</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Esophagus</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>37</td>
<td>22 (59.5)</td>
<td>15 (40.5)</td>
</tr>
</tbody>
</table>

Figure 1 Shown, from left to right, are PET, CT and PET/CT fusion axial images of gastric MALT. Arrows in the CT (middle) image indicate the thickened gastric wall due to tumor infiltration.
regarding the utility of FDG/PET in patients with extranodal MZL are conflicting, as sensitivity seems to be diverse ranging between 0 and 81% in the sparse reports addressing this issue.

In the current study, we found PET/CT to detect extranodal MZL in 59.5% of a total of 37 sites of tumor involvement and detected biopsy confirmed relapse or disease progression in four of six patients. These data suggest that PET/CT is a useful tool for both initial staging and follow up in patients with extranodal MZL.

In our cohort of patients, FDG-avidity was influenced by the site of disease involvement: PET/CT was interpreted as positive in only 38.9% of patients with gastric MALT as compared to 75% of patients with extra-gastric disease and all patients with pulmonary involvement. The selectivity of FDG uptake according to the site of involvement coincides with a previous report where FDG/PET was positive in 100% of 11 patients with pulmonary MALT but in only 60% of patients with gastric MALT (7). A potential explanation is that MALT lymphoma originating at different organs may have a diverse pathogenesis. Another explanation may lay in the FDG tumor-to-background ratio: lung has almost no background uptake, thus the sensitivity is higher than in the stomach where the FDG uptake may be increased both physiologically and due to inflammation. Alternatively this may indicate that environmental factors influence local inflammatory reactions to the neoplastic process thereby affecting FDG uptake. Further investigation of organ specific histochemical and molecular biomarkers may shed more light on this issue. It seems that a positive PET/CT scan correlates with an advanced stage of disease at the time of diagnosis, which may be a reflection of a relatively more aggressive disease within an essentially indolent slow growing lymphoma.

Gastroscopic detection of an ulcer or gastritis appeared to be predictive for a positive PET/CT in patients with gastric MALT, while normal gastroscopy or findings other than an ulcer or gastritis (e.g. thickened

Table 2 Results of the CT and PET parts of the PET/CT scan given separately

<table>
<thead>
<tr>
<th>CT part</th>
<th>PET part</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>+</td>
<td>18</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>12</td>
</tr>
<tr>
<td>-</td>
<td>+</td>
<td>1</td>
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<tr>
<td>+</td>
<td>-</td>
<td>2</td>
</tr>
</tbody>
</table>

Figure 2 Shown, from left to right are PET, CT and PET/CT fusion axial images of a MALT lymphoma of the right orbit. Pre-treatment (upper panel) and post chemotherapy (R-CVP) and 3600 cGy radiation therapy (lower panel). Red marks indicate the orbital lesion.
gastric wall) were mostly associated with a negative PET/CT. It is indeed possible that FDG uptake in these cases reflects the presence of an inflammatory process in the stomach and not the existence of neoplastic MALTOMA per se. For this matter the positive PET is actually a false-positive finding.

In summary, the results of this study suggest that PET/CT may be a useful tool for staging and follow-up of extranodal marginal zone lymphoma. Sensitivity seems to be related to the sites of MALT involvement, stage of disease, and in the case of gastric MALT in particular, to the accompanying gastroscopic findings.

References