Fluorine-18-fluorodeoxyglucose – Positron Emission Tomography Metabolic Imaging in Patients with Lymphoma

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Fluorine-18-fluorodeoxyglucose (FDG) positron emission tomography (PET) provides unique information about the metabolic behavior of the malignant tumors, independent of morphological criteria. This technique is more sensitive in imaging lymphoma prior to therapy than conventional computed tomography (CT) imaging and Ga-67 scintigraphy. FDG-PET performed in patients with lymphoma offers important additional information on the presence of viable disease in residual masses of the tumor. It is also of great value in assessing therapy response in patients with Hodgkin’s disease and non-Hodgkin’s lymphoma, because of its ability to differentiate between fibrosis and active tumor. More studies are needed to assess the value of this method in long-term follow-up. In our institution this method is mostly used for clarification of residual post-therapy abnormalities that fall under the category of unconfirmed/uncertain complete remission. Our preliminary data on 14 patients indicate that this non-invasive, metabolic imaging is superior to CT and other conventional diagnostic methods in the post-therapy staging of lymphoma.

Key words: fluorodeoxyglucose F 18; Hodgkin disease; lymphoma, non-Hodgkin; tomography, emission computed

Lymphomas are typically highly sensitive to treatment with chemotherapy or radiotherapy (1). The continuous improvement in both treatment modalities has resulted in high overall survival rates in patients with Hodgkin’s disease and non-Hodgkin’s lymphoma. However, the price of therapy success is reflected in late effects in long-term survivors (2,3). There is a need to individually tailor the intensity of treatment for each patient. Functional imaging with fluorine-18-fluorodeoxyglucose (FDG) positron emission tomography (PET), alongside conventional imaging, is an additional method for more accurate assessment of disease stage and therapy response (4,5). With this method clinicians can avoid over-treatment of the patients with better prognosis and under-treatment of the patients with poorer prognosis.

Lymphoma Staging

Computed tomography (CT) is still the principal imaging modality for the staging and monitoring of lymphoma, but it does not identify lymphoma in normal-size lymph nodes or differentiate nodes enlarged due to other causes. FDG-PET provides unique information on the metabolic behavior of the disease independently of morphological criteria. Compared with CT, PET showed greater sensitivity and revealed more lesions, which resulted in significant upstaging or, in some cases, downstaging of patients with lymphoma (4,5,7-9). Schoder et al (4) reported that 44% of pa-
Patients in their study were upstaged or downstaged after FDG-PET scanning, whereas treatment modality was changed in 62% of them. In the study of Yap et al (10) clinical stages of 50% patients altered after FDG-PET imaging, resulting in major management changes in all of them. The whole-body FDG-PET scan can be used in the initial staging of patients (Fig. 1).

FDG-PET is also more sensitive than conventional Ga-67 imaging in detecting lymphoma before therapy (11-13). Ga-67 imaging suffers from low spatial resolution, lack of specificity, and low sensitivity in infradiaphragmatic disease because of hepatic uptake and excretion of Ga-67 into the bowel. Ga-67 is very useful for imaging supradiaphragmatic disease, particularly in institutions without PET scanners (14).

Residual Mass

Residual masses occur after completed therapy in up to 64% patients with mediastinal disease and in up to 41% in patients with intra-abdominal masses (15,16). However, the discrimination between active tumor tissue and fibrotic residues remains a clinical challenge. Only a maximum of 10-18% of residual masses were reported positive for lymphoma at the end of treatment (15,16). CT cannot differentiate residual disease from fibrosis and has a false-positive rate of up to 25% (17,18). FDG-PET performed in lymphoma patients with residual masses appears to offer important additional information on the presence of viable disease in these residual lesions (19,20). Weihrauch et al (20) reported that patients with Hodgkin’s disease with a residual mediastinal mass are unlikely to relapse within a year if FDG-PET finding is negative, whereas a positive finding indicates a significantly higher risk of relapse (20). In the study of Naumann et al (21), the patients with PET-positive residual mass had a recurrence rate of 62.5%, whereas the patients with negative findings showed a recurrence rate of 4%. Positive FDG-PET finding correlated with a significantly poorer progression-free survival (21). Residual mass is sometimes FDG-negative, but some other metabolically active lesions can be found, as it was the case in one of our patients with non-Hodgkin’s disease (Fig. 2).

Monitoring Therapy and Prognosis

The value of FDG-PET imaging has been confirmed in assessing therapy response in patients with Hodgkin’s disease and non-Hodgkin’s lymphoma due to its ability to differentiate between fibrosis and active tumor by detecting glycolysis rate. Repeated FDG-PET scan in our patient with non-Hodgkin’s lymphoma showed the regression of the neck lesions, but new lesions found in the left lung suggested relapse of the disease (Fig. 3).

FDG-PET is also very useful when performed during chemotherapy. Mikhaeel et al (22) showed that a negative PET scan after two or three cycles of chemotherapy has a highly negative predictive value and that at this point it may be sufficient to curtail therapy without compromising outcome. Spaepen et al (23,24) showed that persistent FDG uptake was highly predictive for residual or recurrent disease in patients with non-Hodgkin’s lymphoma and Hodgkin’s disease a year after first-line chemotherapy. In relapsing patients, progression-free survival was significantly shorter after a positive FDG-PET scan than after a negative one (23-25). A recently performed study in lymphoma patients who were treated with stem cell transplantation showed that none of the 5 patients with a negative FDG-PET finding relapsed before high-dose therapy with stem cell transplantation, whereas 7 out of 8 patients with positive FDG-PET scan relapsed (26). Therefore, it is logical to postpone bone marrow transplantation in the FDG-PET negative patients.
positive patients and cure residual disease before transplantation (Fig. 4).

Limitations of FDG-PET

FDG-PET imaging has some shortcomings, which should be considered before its use.

Physiological Uptake

FDG is normally accumulated in the cortex of the brain, which is a limitation for detection of cerebral metastases. In such cases magnetic resonance imaging remains the standard diagnostic modality. In the myocardium, the accumulation of the FDG varies and is greater postprandially or after a glucose load.

Unlike glucose, FDG is not reabsorbed in the renal tubules after glomerular filtration, which may be the cause of artifacts in the region of kidneys and bladder. In the muscular system, FDG uptake is low when muscles are in the resting state, but after exercise accumulation of FDG in some muscular group may mimic metastases (Fig. 5). Therefore, it is important to keep the patient in the resting state after FDG injection (27).

Type and Site of Lymphoma

A direct correlation between FDG uptake and patient’s prognosis was reported by Okada et al (28),
who found that the uptake was highest in clinically most aggressive lymphomas. On the other hand, the degree of uptake can be low in low-grade lymphomas. However, according to Najjar et al (5), the combination of PET, CT, and physical examination seems to be more sensitive than the conventional approach alone. FDG-PET is usually false-negative in extranodal mucosa-associated lymphoma tissue (MALT)-type B-cell lymphoma. Hoffman et al (29) did not find any positive PET scans in 10 patients with MALT lymphoma. FDG-PET is usually false-negative in extranodal B-cell MALT lymphoma.

Inflammatory Lesions
Activated macrophages and granulation tissue avidly take up FDG, which makes the specificity of this investigation for neoplastic tissues similar to that of Ga-67 (32). Therefore, active inflammatory lesions, granulomas, and abscesses can be falsely interpreted as malignant processes.

FDG-PET in Croatia
At the moment, FDG-PET imaging is regularly performed in only one institution in Croatia (Department of Nuclear Medicine and Radiation Protection, Zagreb University Hospital Center). Because of the limited budget, FDG-PET with triple-head Philips co-incidence technology is performed in only 4-6 patients per month, usually for clarification of residual post-therapy abnormalities that fall under the category of unconfirmed/uncertain complete remissions. We showed that FGD-PET revealed more lesions in patients with lymphoma than CT and other conventional methods (Table 1). The most important consequence was that the treatment modality was changed in almost all FDG-PET-positive patients. The possible shortcoming of our and most other studies is the lack of histological confirmation because lymphoma is not surgically curable disease. Therefore, the accurate follow-up is needed.

Conclusion
FDG-PET provides unique information about the metabolic behavior of the lymphoma, independent of tumor morphology. Today it should be used in the evaluation of disease extent and staging before therapy, in the evaluation of response to therapy (early and after completion of therapy), in the prediction of outcome, and specially, in resolving residual mass dilemma. More studies are needed to assess the value of this method in long-term follow-up. According to published data, FDG-PET is not indicated in the evaluation of bone marrow involvement after therapy nor in extranodal B-cell MALT lymphoma.

Table 1. Therapy modifications indicated by fluorine-18-fluorodeoxyglucose (FDG) positron emission tomography (PET) findings in 14 patients with lymphoma

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Histology</th>
<th>Disease stage CIM</th>
<th>Reason for FDG-PET modification</th>
<th>FDG accumulation/uptake</th>
<th>FDG-PET vs CIM</th>
<th>Treatment modification</th>
</tr>
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<tr>
<td>1</td>
<td>50</td>
<td>M</td>
<td>NHL</td>
<td>IVA</td>
<td>– therapy monitoring</td>
<td>– FDG = CIM</td>
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<td>no</td>
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<tr>
<td>2</td>
<td>45</td>
<td>M</td>
<td>NHL</td>
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<td>+ mediastinal residual mass</td>
<td>– FDG &lt; CIM</td>
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<td>yes</td>
</tr>
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<td>3</td>
<td>39</td>
<td>M</td>
<td>HD</td>
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<td>+ FDG &gt; CIM</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>4</td>
<td>19</td>
<td>M</td>
<td>HD</td>
<td>IIIA</td>
<td>+ mediastinal residual mass</td>
<td>– FDG &lt; CIM</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>5</td>
<td>49</td>
<td>M</td>
<td>HD</td>
<td>IIIA</td>
<td>+ mediastinal residual mass</td>
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<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>6</td>
<td>35</td>
<td>F</td>
<td>HD</td>
<td>II A</td>
<td>+ mediastinal residual mass</td>
<td>– FDG &lt; CIM</td>
<td>yes</td>
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<tr>
<td>7a</td>
<td>43</td>
<td>F</td>
<td>HD</td>
<td>IVB</td>
<td>+ follow-up</td>
<td>+ FDG &gt; CIM</td>
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<td>yes</td>
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<tr>
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<td>F</td>
<td>HD</td>
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<tr>
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<td>HD</td>
<td>II A</td>
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<td>IVB</td>
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<td>+ FDG &gt; CIM</td>
<td>yes</td>
<td>yes</td>
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<td>10b</td>
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<td>M</td>
<td>NHL</td>
<td>IVB</td>
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<td>11</td>
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<td>+ follow-up</td>
<td>+ FDG &gt; CIM</td>
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<td>yes</td>
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<tr>
<td>14</td>
<td>39</td>
<td>F</td>
<td>HD</td>
<td>IIIB</td>
<td>+ follow-up</td>
<td>+ FDG = CIM</td>
<td>no</td>
<td>no</td>
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