18F-fluoro-deoxy-glucose positron emission tomography (18F-FDG-PET) visualizes follicular lymphoma irrespective of grading

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Background: ¹8F-fluoro-deoxy-glucose positron emission tomography (¹8F-FDG-PET) has become a routine measure for staging and follow-up of patients with aggressive lymphoma. By contrast, its usefulness to visualize indolent lymphomas characterized by a lower cellular turnover has not clearly been defined. We have investigated accuracy and clinical usefulness of ¹8F-FDG-PET in patients with follicular lymphoma (FL).

Patients and methods: A total of 64 patients with FL WHO grade I – III (48, 5, and 11 patients) were imaged at our institution to assess the value of ¹8F-FDG-PET for imaging of FL of different gradings. A total of 115 scans (48 before therapy and 67 for response assessment after treatment) were performed, and findings were compared to conventional staging including CT-scan of thorax and abdomen, sonography of lymph nodes and bone marrow biopsy.

Results: Overall, ¹8F-FDG-PET had a sensitivity of 98%, a specificity of 94%, a positive predictive value of 95% and a negative predictive value of 98%. These results were significantly more accurate (P = 0.023) than the conventional radiology studies. There was no significant difference (P = 0.093) in the accuracy between patients with indolent (WHO grade I and II) versus aggressive FL (WHO grade III).

Conclusion: ¹8F-FDG-PET scan is a reliable method for staging and follow up of patients with nodal FL irrespective of tumor grading.

Key words: ¹8F-FDG-PET, follicular lymphoma, grading, staging

introduction

Follicular lymphoma (FL) is one of the most common lymphoma entities, constituting about 22% of adult lymphoma cases worldwide, and up to 35–40% in the United States [1]. It is characteristically composed of lymphoid cells originating in the follicle center, i.e. centrocytes and centroblasts, and displays a distinct molecular feature, the t(14;18) translocation involving rearrangement of the BCL2 gene in the large majority of cases. Upon presentation, most patients have disseminated disease affecting peripheral lymph nodes and/or bone marrow, while only about 1/3 have limited stage disease. The varying content of centroblasts and centrocytes has led to definition of three grades (grade 1–3) of FL corresponding to an increasing number of blasts per high power field as recognized in the recent WHO-classification of tumours of haematopoietic and lymphoid tissues [2]. While FL grade 1 and 2 is characterised by an indolent clinical course, FL grade 3 is a more aggressive disease. A further subdivision for FL grade 3 into two distinct subtypes has recently been proposed [3].

Probably the most challenging task in the diagnostic workup of patients with FL is the characterization of lesions deemed indeterminate with other imaging modalities. This problem arises not only before initiation of treatment in order to distinguish potentially curable (stage I/II) from advanced disease (stage III/IV), but also after completion of therapy, since up to 60% of patients with lymphomas will have a residual mass on computed tomography (CT) [4], but less than 20% will relapse [5].

¹8F-fluoro-deoxy-glucose positron emission tomography (¹8F-FDG-PET) has become a routine measure for staging and follow-up of patients with malignant lymphoma [6]. It is currently considered a standard imaging method in patients with Hodgkin lymphoma [7] and various types of aggressive lymphomas [8], but its role in imaging indolent types of lymphoma is less clearly defined [9]. It has been hypothesized that ¹8F-FDG uptake reflects the proliferative activity of lymphoma cells, and therefore is more pronounced in more
patients and methods

Patients with FL referred to our institution were retrospectively analyzed. All patients underwent conventional staging consisting of sonography of cervical, axillary and inguinal lymph nodes, CT-scan of thorax and abdomen, and a bone marrow biopsy. The accuracy of imaging results was evaluated by defining a standard of reference as previously described [13], analyzing all imaging, histological and surgical data for nodal lesions in conjunction with patient outcomes, treatment response and repeat imaging during follow up. The 18F-FDG-PET as well as the conventional imaging results for each patient were compared against this standard of reference and the findings were classified as true-positive, true-negative, false-positive or false-negative. If an imaging modality failed to show all lesions present in the standard of reference, it was classified as false-negative and if it showed more lesions, it was classified as false-positive. In case of inconclusive results additional biopsies were obtained from suspicious lesions. From these data sensitivity, specificity, as well as positive and negative predictive value were calculated. Results for bone marrow involvement as compared to histology were analyzed separately.

Whole body-18F-FDG-PET scans were performed using a dedicated full-ring PET scanner (Advance; General Electric Medical Systems) with an axial field of view of 15.2 cm. Patients were asked to fast for at least 4 h prior to 18F-FDG-application. 18F-FDG-PET scans were started not earlier than 40 min following the intravenous bolus injection of about 380 MBq of 18F-FDG. In most patients the following scan parameters were used: Emission scans of 5 min acquisition time per table position and subsequent transmission scans with 75,000,000 counts per bed position using the built-in 67Ge/68Ga rod sources were obtained. The images were reconstructed iteratively with ordered-subset expectation maximization (OSEM). The images were assessed visually on axial, coronal and sagittal reconstruction and the multi intensity projection (MIP) image by identifying regions with significantly elevated non-physiologic 18F-FDG-uptake. In addition we applied a semiquantitative analysis using the max SUV (standard uptake value) as activity in the region of interest (ROI) standardized to body weight. ROIs were drawn manually around areas of abnormal 18F-FDG uptake. The highest SUV per patient was used for statistical analyses. To evaluate disseminated bone marrow involvement the 18F-FDG-uptake in bone marrow (humerus, femur, pelvis, spine) was assessed visually. The following visual aspects were rated suspicious for bone marrow involvement: Diffuse 18F-FDG-uptake in hollow bones, the pelvis and the spine, diffuse 18F-FDG-uptake in hollow bones and inhomogeneous spinal uptake including focal spinal lesions. The results were compared with conventional imaging as stated above and histologic findings including bone marrow biopsy. In addition, we have analyzed the 18F-FDG-PET results in view of the clinical outcome in patients who had undergone pre- and posttherapeutic scans.

Statistical analyses were done with the SPSS 12.0 statistic program. Sensitivity, specificity, positive and negative predictive value were calculated according to the Bayes’s rule to describe the accuracy of the imaging methods. The chi-square test was performed for calculation of the relationship between the 18F-FDG-PET results and the histological grading as well as the relationship between scans and conventional radiology studies. The Mann-Whitney U test was used to survey the correlation of SUV values with grading. The results concerning bone marrow involvement were analyzed separately and were not included in the statistical calculations.

Due to the relatively small (statistically insignificant) number of patients with FL grade II, we grouped these patients together with the grade I FLs in view of the clinically similar indolent behaviour [2]. Additionally, all patients with either FL grade III, FL with a diffuse large B-cell lymphoma (DLBCL) component or transformed FL were grouped together as aggressive FL.

results

A total of 64 patients with a histologically verified diagnosis of FL were included in the study (Table 1). Forty-eight (75%) had FL WHO grade I, 5 (8%) had FL WHO grade II, 9 (14%) had FL WHO grade III and 2 (3%) had DLBCL/FL. In addition, one patient who was initially diagnosed with FL WHO grade I transformed to DLBCL in the course of the disease.

18F-FDG-PET was done before initiation of therapy in 48 patients and showed a positive predictive value (PPV) of 100% with a sensitivity of 98%. The radiology studies (RS) performed in these patients revealed a PPV of 98% and a sensitivity of 94% which was statistically not significantly different compared to the 18F-FDG-PET results.

Twenty-four patients underwent 18F-FDG-PET-scanning both before initiation as well as after completion of therapy. All of these patients had a positive scan before initiation of therapy and out of the 18 patients who achieved a clinical complete remission (CR) following treatment, 17 became 18F-FDG-PET negative whereas only 14 became negative in radiology studies.

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Total number of patients</th>
<th>64</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>37 (56%)/27 (44%)</td>
</tr>
<tr>
<td>Median age</td>
<td>52 (IQR: 44–64)</td>
</tr>
<tr>
<td>Grade</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>48 (75%)</td>
</tr>
<tr>
<td>II</td>
<td>5 (8%)</td>
</tr>
<tr>
<td>III</td>
<td>11 (17%)</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>8 (12%)</td>
</tr>
<tr>
<td>II</td>
<td>11 (17%)</td>
</tr>
<tr>
<td>III</td>
<td>10 (16%)</td>
</tr>
<tr>
<td>IV</td>
<td>35 (55%)</td>
</tr>
<tr>
<td>Totally performed F18-FDG-PET scans</td>
<td>115</td>
</tr>
<tr>
<td>F18-FDG-PET scans before therapy</td>
<td>48 (42%)</td>
</tr>
<tr>
<td>F18-FDG-PET scans after therapy</td>
<td>67 (58%)</td>
</tr>
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</table>

Abbreviations: IQR, interquartile range.
These three patients, who had persistent abnormal radiology findings (but normal 18F-FDG-PET results) following therapy, were rated as CR according to the absence of progression/relapse for a follow-up time of at least 11 months suggesting complete disappearance of the lymphoma. Thus, 5% of the 18F-FDG-PET scans and 14% of the RS were false positive after completion of therapy with no false negative results in both imaging techniques.

A total of 115 18F-FDG-PET scans, either before or after therapy or in the follow up period were performed. The analysis of these scans revealed an overall sensitivity of 98%, specificity of 94%, positive predictive value of 95% and negative predictive value of 98%. These results were significantly more accurate ($P = 0.023$) than the conventional radiology studies which revealed a sensitivity of 95%, a specificity of 80%, a positive predictive value of 86% and a negative predictive value of 93% (Table 2).

The 18F-FDG-PET scan correlated with the clinical outcome in 96%, with 3% false positive and 1% false negative results. Patients were followed for a median time span of 36 months (inter-quartile range: 11–54). False positive results were due to a reactive lymph node, an unspecific accumulation of 18F-FDG in the parotid gland and an increased tracer uptake in the stomach and small intestine in one patient each. One patient with relapsing lymphoma in the axillary and inguinal lymph nodes had a negative 18F-FDG-PET scan. In one patient, divergent results for abdominal and inguinal versus axillary and cervical lymph nodes were found in spite of identical histological findings (FL WHO grade I) in the affected areas. While abdominal and inguinal lymph nodes could readily be visualized, no focal tracer uptake was seen in axillary and cervical nodes.

Bone marrow infiltration, which was evident in 24 of the 28 patients with stage IV, could be imaged in 13 patients with 18F-FDG-PET scan by the above mentioned criteria: two showed diffuse homogeneous bone marrow uptake, seven showed slightly inhomogeneous and four patients showed markedly inhomogeneous spinal uptake. All four patients, rated as stage IV, with negative bone marrow biopsy results were negative concerning bone marrow uptake in 18F-FDG-PET. In the remaining nine patients with positive bone marrow biopsy the 18F-FDG-PET scan was rated indeterminate concerning bone marrow uptake.

**Figure 1.** (a) Multi intensity projection (MIP) of a 66-year-old female patient with FL WHO I (Stage IV, bone marrow involvement 35%) therapy naïve showing focal 18F-FDG uptake in cervical, mediastinal, abdominal and inguinal lymphnodes with a max SUV of 11.7. In addition it shows diffuse inhomogeneous uptake in humeri and femora rated positive for bone marrow involvement. (b) MIP obtained 3 weeks after six cycles of therapy with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP) showing return to physiological uptake in all lymph nodes. Humeri and femora show diffuse homogeneous (as opposed to the initial inhomogeneous pattern) 18F-FDG-uptake which was rated due to therapy with colony stimulating factors. Correspondingly, bone marrow biopsy showed CR. (c) MIP obtained 14 months after initial imaging depicting only physiological 18F-FDG uptake (including bone marrow) corresponding to ongoing CR as evidenced by CT, MR and bone marrow biopsy.
Table 2. Results

<table>
<thead>
<tr>
<th>Grade</th>
<th>Number of patients (before therapy)</th>
<th>Median SUV (IQR)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>I+II</td>
<td>40</td>
<td>5.7 (4–7.49)</td>
<td>0.093</td>
</tr>
<tr>
<td>III+FL/DLBCL</td>
<td>5</td>
<td>11.4 (5.2–20)</td>
<td></td>
</tr>
<tr>
<td>Bone marrow infiltration</td>
<td>No. of patients</td>
<td>Diffuse homogeneous</td>
<td>Slightly inhomogeneous</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>2 (8%)</td>
<td>7 (29%)</td>
</tr>
</tbody>
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Abbreviations: TP, true positive; TN, true negative; FP, false positive; FN, false negative; PPV, positive predictive value; NPV, negative predictive value; Sens, sensitivity; Spec, specificity; SUV, standard uptake value; No, number; IQR, inter quartile range; FL/DLBCL, follicular lymphoma with diffuse large b-cell lymphoma component.

Subgroup analysis with regards to the histologic grading and the accuracy of 18F-FDG-PET scan showed no significant difference (P = 0.093) between patients with indolent FL (i.e. WHO grades I and II) and aggressive FL. However, a tendency in favor of the aggressive lymphomas was noticed because the false negative results were in the indolent group only. The same was true for relation of SUV levels and grading as statistic analysis revealed no significant difference in SUV levels for indolent or aggressive FL, respectively (P = 0.085), yet a tendency to higher SUVs in the high grade group was observed (median SUV: 11.4 (IQR: 5.2–20) versus 5.7 (IQR: 4–7.4)).

discussion

Recent data suggest 18F-FDG-PET as a useful imaging method for various types of lymphoma, including preliminary data obtained in patients with FL [11, 13]. Furthermore, it was suggested that this method could probably differentiate between aggressive and indolent lymphoma due to differences in tracer uptake [12]. Apart from the well demonstrated ability of 18F-FDG-PET to visualize aggressive lymphomas [8], the question if it is also suitable for reliable visualization of indolent lymphomas remains open. Our data clearly indicate that 18F-FDG-PET is able to visualize FL irrespective of histologic grade. Overall, 18F-FDG-PET was able to visualize malignant lymphoid tissue in 47 of 48 patients with FL prior to therapy, with a positive predictive value of 100% and a sensitivity of 98%. The comparison with conventional radiological studies revealed a slightly, but not significantly higher PPV (100% versus 98%) and sensitivity (98% versus 94%) of 18F-FDG-PET. Only one patient had a false negative scan prior to therapy despite clinically apparent and histologically verified involvement of lymph nodes in the inguinal and axillary region. In an additional patient, inguinal and abdominal lymph nodes could readily be visualized, while cervical and axillary lymph nodes disclosed no elevated 18F-FDG-uptake. The latter lymph nodes, however, could also not be demonstrated on CT-scanning, but were seen on sonography and had been verified as FL grade I by histology. Due to the identical histology in all lymph nodes investigated in terms of grading and proliferative activity, we cannot offer an explanation for the discrepancies. In addition, the size of cervical and axillary lymph nodes was 1.5 cm, and is well above the established threshold for visualization with 18F-FDG. False negative results with 18F-FDG-PET are generally thought to occur either in tumors with relatively low metabolic activities or small tumors (<1 cm in diameter). The false negative results in our series were only seen in FL graded as indolent, yet there was no statistically significant difference (P = 0.093) between the indolent FLs (WHO grade I and II) and the more aggressive histologies (FL WHO grade III or FL/DLBCL). However, a tendency in favor of the high-grade group was noted because no false negative results occurred in this group. The same was true for the respective SUV values in indolent versus aggressive lymphoma. Opposed to a recent publication [12] we found no significant result concerning SUV and grading in our cohort of patients. Nevertheless, we did observe a tendency to higher SUV levels in more aggressive FL. Due to the relatively small subgroup of patients with aggressive FL, this result should be interpreted with caution.

In the 24 patients who were investigated before and after therapy, 18F-FDG-PET scans became negative in 95% of responding patients, while only 86% became negative in radiology studies. The retrospective analysis of these patients showed a false positive rate for 18F-FDG-PET and radiology studies in 5% and 14%, respectively. The false positive interpretations resulted from an elevated tracer uptake in a reactive lymph node, in the stomach and small intestine, and parotid in one patient each. The reactive nature of the lymph node was verified by ultrasound and clinical follow-up demonstrating spontaneous regression in one patient, and endoscopic and histologic evaluation of multiple biopsies taken from stomach and duodenum disclosed no evidence of lymphoma in the other case. The patient with bilateral parotid uptake was rated false positive in the course of follow up.

Taken together, a high accuracy of 18F-FDG-PET could be demonstrated in the overall evaluation of all 115 18F-FDG-PET scans. This imaging method achieved a PPV of 95%, a NPV of 98%, a sensitivity of 98% and a specificity of 94%. These values are significantly higher (P = 0.023) than the values achieved with conventional radiological studies, and comparable results have been reported in earlier series [13]. As already stated,
indeterminate residual lesions after therapy are a big disadvantage of conventional imaging techniques and were also the reason of the decreased accuracy in our study. In case of unclear lesions in conventional radiological studies, 18F-FDG-PET scan was extremely useful for investigating the activity of such lesions.

Furthermore, 18F-FDG-PET scan was able to detect bone marrow infiltration in 13 of 24 (54%) patients with positive bone marrow biopsy opposed to previous studies [11, 13]. These 13 patients showed an inhomogeneous diffuse elevation of 18F-FDG-uptake in the bone marrow rated positive for diffuse bone marrow involvement, which corresponded to the histological results of bone marrow biopsy. This is in contrast to other series in the recent literature [11, 13] which did not reliably visualize bone marrow infiltration. One potential confounding factor, however, is unspecific 18F-FDG uptake in the bone marrow of patients given hematopoietic growth factors following chemotherapy. Nevertheless, as our patients were therapy naïve, the tracer uptake evidenced in our series indeed appears to be related to lymphoma spread rather than effects of hematopoietic cytokines. In addition, 18F-FDG-PET could clearly identify the four patients with stage IV disease who had no bone marrow involvement. As the survey of bone marrow involvement is not a standardized approach in lymphoma imaging by 18F-FDG-PET we did not include the respective results in the statistical analysis as this may hamper the comparability to previous papers on 18F-FDG-PET on the one hand and to the radiology studies on the other hand.

In conclusion, our data prove 18F-FDG-PET as a reliable staging method for FL. It correlates significantly with standard radiology studies as well as clinical outcome and visualizes FL irrespective of tumor grading. Thus, we think the scepticism concerning the value of 18F-FDG-PET in indolent FL (WHO grade I and II) should finally be abandoned. In addition to providing important information about tumor staging prior to therapy, 18F-FDG-PET is capable to reliably distinguish residual lesions from lymphoma remnants after therapy. We therefore suggest that 18F-FDG-PET scanning should be incorporated into the standard staging procedures of FL.

references