The role of PET imaging in lymphoma

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Summary

Positron emission tomography using fluorine-18 (FDG-PET) is increasingly used in the staging and follow-up of malignant lymphomas, although its precise role has not yet been determined. This review considers the results reported at the different stages in the disease history and separately considers the major histological subtypes. Attention is given to the situations in which PET scanning is most likely to influence management. Finally, this review discusses ongoing developments in PET scanning with improved resolution and different radiolabelled tracers.

Keywords: 2-fluoro-2-deoxy-D-glucose-petitomography, positron emission tomography, lymphoma, non-Hodgkin’s lymphoma, hodgkin lymphoma/disease.

Positron emission tomography using fluorine-18 (FDG-PET) is a functional imaging technique that is now widely used in the management of malignant disease including lymphoma. It is based on the principle that most malignant tumours have increased rates of glucose uptake and metabolism compared with normal tissues. The tumour cells take up the radiolabelled glucose analogue, 2-fluoro-2-deoxy-D-glucose (FDG). This is phosphorylated by hexokinase and then trapped within the cell as FDG-6-PO4, which cannot enter the subsequent glycolytic pathway, and dephosphorylation occurs at a relatively slow rate (Hong et al., 2003). There is little doubt that FDG-PET has a high sensitivity for malignant tissue (Paul, 1987; Kostakoglu & Goldsmith, 2000, 2003) and is informative in malignant lymphomas although its precise role in disease management has not been well defined. This is because FDG-PET has been introduced into the clinical environment without randomized trials or the rigorous testing that ideally requires the investigator and patient to be ‘blinded’ to the results of the new imaging modality. In addition it can be difficult to be sure of the significance of any differences detectable between a new imaging modality and standard staging procedures unless further biopsies are taken, a situation that is often not justified.

In lymphomas, FDG-PET imaging can be used in initial staging, response evaluation and follow-up and the issues surrounding these scenarios are different. Furthermore, the different histological types of lymphoma must be considered separately as not only may the efficacy of FDG-PET vary according to the histological type, but the therapeutic implications of any new information obtained may also be different. As with any staging technique, false positive and false negative results can occur. False positive results can be obtained at sites of inflammation and infiltration of necrotic tumour by macrophages is a potential problem (Kubota et al., 1992). Other tissues, such as the brain and non-relaxed muscle (including heart and gut), have high glucose uptake but this is widely recognized and is rarely problematic. Following chemotherapy increased uptake may also be seen in the bone marrow, spleen and thymus (O’Doherty et al., 2002).

Staging

Hodgkin lymphoma

A number of studies have assessed the use of FDG-PET scanning in the staging of Hodgkin lymphoma (HL) at diagnosis or at the time of relapse. Comparisons have been made with clinical findings, computed tomography (CT) scans and in some cases gallium-67 scintigraphy (Ga-67). Huetenschmidt et al. (2001) assessed the clinical value of FDG-PET in 25 patients for primary staging compared with conventional imaging modalities with verification by histology and/or by follow-up evaluation. On a patient-to-patient analysis, FDG-PET scans were positive, showing pathologic foci indicative of HL, in 24 of 25 (96%) cases. A brief report by Elstrom et al. (2003) of 47 patients with HL, either at presentation or relapse, demonstrated that 46 (98%) had at least one tumour site that was FDG avid. The only case not detected was in early relapse demonstrated by biopsy of a sub-centimetre sub-pleural pulmonary nodule. However, the number of sites thought to be positive by conventional staging that were FDG-PET negative is not clear. A study by Moog et al. (1997) demonstrated, by biopsy or clinical follow-up, that discordant areas between FDG-PET and CT scanning had disease present in areas of increased FDG uptake and no evidence of disease in enlarged nodes on CT that were FDG
negative. Two other studies of newly diagnosed patients have not shown such high positivity rates with FDG-PET. A study by Bangerter et al (1998) was particularly valuable as, when results of FDG-PET differed to those obtained by conventional methods, re-evaluation was performed using magnetic resonance imaging (MRI) or re-biopsy whenever possible. In the 44 patients studied, FDG-PET imaging was positive in only 38 (86%) patients at sites of documented active disease. FDG-PET failed to visualize sites of HL in four patients and in two patients FDG-PET positive axillary lymph nodes were detected without any nodal enlargement being detected by CT and ultrasound. The FDG-PET scan results were thus considered to be false positives but without biopsy this must be treated with caution. Weihrauch et al (2002) studied 22 patients who underwent FDG-PET and conventional staging. Seventy-seven lesions were observed on FDG-PET or CT or both. In 48 (62%) lesions both FDG-PET and CT were positive, in 20 (26%) FDG-PET was positive and CT negative and in six patients FDG-PET failed to detect nine (12%) CT positive sites. Overall there is little doubt that FDG-PET detects disease in sites that are not positive on CT scanning by size criteria, but not all disease is detected and it is difficult to ascertain, from the literature, the rate of false positivity with FDG-PET imaging.

A number of studies have compared FDG-PET with Ga-67, which is a frequently used functional imaging modality in HL. FDG-PET has been shown to be more sensitive than Ga-67, detecting nearly all disease visualized by Ga-67 scanning and detecting additional disease in many instances. Kostakoglu et al (2002a) reported on contemporaneous FDG-PET and Ga-67 scintigraphy studies performed on 13 patients at initial diagnosis or clinical recurrence of HL. Correlation was made on a site-by-site basis, comparing sites of disease on FDG-PET and Ga-67 images. Discordant findings were correlated with CT findings or clinical evaluation. FDG-PET imaged 100% of disease sites whereas Ga-67 imaged 65%. From this study of imaging before therapy, it was found that FDG-PET had significantly higher site and patient sensitivity than Ga-67 scintigraphy (100% vs. 71.5% and 100% vs. 80.3% respectively). A study by Friedberg and Chengazi (2003) of 36 newly diagnosed patients with HL who underwent FDG-PET scanning demonstrated that FDG-PET was superior to gallium scanning in detecting occult splenic disease. Five of 36 patients had isolated splenic disease not detected with Ga-67 scanning. In three of these patients infra-diaphragmatic disease was only detected on FDG-PET scanning and this may be due to the fact that gallium uptake occurs in the bowel, obscuring small lesions.

The series by Elstrom et al (2003) also assessed the accuracy in detection of bone marrow involvement by comparison with iliac crest bone marrow biopsies. In this study FDG-PET was not reliable for detection of bone marrow involvement in HL as FDG uptake was demonstrated in bone marrow that was not confirmed histologically. It is possible though, that these false positive cases arise because patchy bone marrow involvement has not been detected by blind bone marrow biopsy. A further study by Carr et al (1998) compared FDG-PET scans of 12 patients with unilateral bone marrow biopsy. Two cases were concordantly positive, six were concordantly negative and in four cases the FDG-PET scan was positive and biopsy was negative. Subsequent biopsy in one case confirmed BM involvement, two cases were confirmed to be falsely negative and one case remained equivocal. In the series by Bangerter et al (1998), 36 of 44 patients had concordant negative findings for bone marrow involvement comparing FDG-PET and conventional staging. Of eight patients with bone marrow involvement seven were positive by FDG-PET. The one patient with a false negative FDG-PET result was confirmed to have an unusually diffuse lymphomatous infiltration on histological examination. From these studies it is possible that FDG-PET scanning may improve the sensitivity of disease detection in HL over blind bone marrow biopsy.

Bangerter et al (1998) study also assessed the consequences of the FDG-PET results on final staging. Additionally detected disease resulted in upstaging in five cases and in one case a suspicious nodal lesion on a CT scan was FDG-PET (and subsequent biopsy) negative, resulting in a downstaging. Similarly, in a study by Partridge et al (2000) 44 patients with HL, at diagnosis or relapse, underwent staging by FDG-PET and CT prior to commencing treatment. The number and sites of disease were assessed for each patient. Twenty-one patients (47.7%) changed stage as a result of the FDG-PET scan. Eighteen patients (40.9%) were upstaged with additional sites detected by FDG-PET. Nine of these were due to FDG uptake in splenic or extranodal sites not detected by CT. Three patients were downstaged by the FDG-PET result. In a study by Weihrauch et al (2002) FDG-PET altered stage in four of 22 (18%) patients. By contrast to these studies that showed an overall upstaging, a study by Jerusalem et al (2001a) reported a downstaging in four and upstaging in three of 33 patients. Discrepant lesions although were not usually biopsied and follow-up was used to assess the accuracy of the original observations. Similarly in the study by Hueltenschmidt et al (2001), FDG-PET led to a downstaging in seven of 25 patients (28%) and a upstaging in only three of 25 (12%) of cases, compared with the stage assessed with other imaging methods.

A key issue is whether a change in staging changes the therapy given. This was the case in all six of the discrepant cases in the series of Bangerter et al (1998), in 50% of patients reported by Partridge et al (2000), but only applied to two cases in the study by Hueltenschmidt et al (2001) and in one case in each of the other series (Jerusalem et al, 2001a; Weihrauch et al, 2002). The implications of a change in stage will depend not just on the precise change but also the therapeutic options in use at a given centre at a particular time. In general, patients with good risk localized disease (typically stage Ia and IIA) are treated with a limited course of chemotherapy and involved field radiation, whereas more advanced disease is treated with a full course of combination chemotherapy. A change from Ia to IIA disease may influence the extent of the radiation fields and a change from IIA to IIIA
would usually result in more prolonged chemotherapy and vice versa. Naumann et al (2004) reported a study on the impact of FDG-PET imaging on the therapy decision in patients with HL. They prospectively assessed 88 HL patients with FDG-PET that suggested a change in clinical stage in 18 patients (20%). This would have resulted in a change in management in 16 patients (18%) – intensification in nine patients (10%) and minimization of treatment in seven patients (8%). Of importance were those nine of 44 patients (20%) with stage IA–IIB disease in who upstaging would have resulted in a significant change in treatment strategy.

A change in therapy does not necessarily translate into improved survival, as a notable feature of HL is the success of salvage treatment after the failure of initial less intensive therapy. A parallel example is the use of staging laparotomy in clinical stage IA and IIA disease, which upstages about 20–30% of cases (Leibenhaut et al., 1989; Mauch et al., 1990; Ng et al., 1999) but ultimately has no impact on survival. It should be noted however that improved staging, especially if it results in upstaging, can lead to improved results for both localized and advanced disease but there will be a higher proportion of patients deemed to have advanced disease so the overall results may not change. This can confound comparisons of results with previous trials. It thus appears that in HL FDG-PET improves the accuracy of staging but in the absence of evidence that this leads to survival benefits, the high cost of FDG-PET will remain an issue.

Non-Hodgkin’s lymphoma

The majority of studies carried out using FDG-PET have been conducted in the non-Hodgkin’s lymphoma (NHL) setting. These have suggested that the validity of FDG-PET is dependent on the histological subtype. FDG-PET is now recognized as a useful tool for staging histologically aggressive NHL. In histologically indolent NHL, however, there is less conclusive evidence as fewer studies have been conducted and results are often conflicting.

NHL – histologically aggressive disease

Elstrom et al (2003) performed a retrospective evaluation of FDG-PET imaging in 70 histologically aggressive NHL patients, either at presentation or relapse. Results were correlated with the pathologic diagnosis according to the World Health Organization classification system (Jaffe et al., 2001). Disease was detected in at least one site in 100% of patients with diffuse large B cell lymphoma (DLBCL) and mantle cell lymphoma. Only 40% of peripheral T cell lymphomas were detected, suggesting that FDG-PET is more useful for B- rather than T cell lymphomas. Disease sites were also detected in patients with anaplastic large cell lymphoma and Burkitt’s lymphoma but the number of patients was too small to assess the utility of FDG-PET in these situations.

As with HL, studies have been performed comparing FDG-PET with other imaging modalities. Kostakoglu et al (2002a) reported on FDG-PET and Ga-67 scintigraphy studies performed on 38 patients. On comparison it was found that 100% and 65% of disease sites respectively were imaged. Wirth et al (2002) reported on 50 patients who underwent FDG-PET, Ga-67 and CT scanning at diagnosis or at indication of progressive disease. Case positivity rates were 95%, 88% and 90%, respectively. These studies demonstrate that FDG-PET has higher sensitivity and detects significantly more disease sites compared with Ga-67 scintigraphy in the initial evaluation of this group of patients.

The role of FDG-PET in the assessment of bone marrow involvement in NHL is not yet established. The study by Elstrom et al (2003) compared iliac crest bone marrow biopsies with FDG-PET and concluded FDG-PET was not reliable for the detection of bone marrow involvement in any NHL subtype. Again, as with HL, in some cases false negative results were obtained whereas for patients with DLBCL, FDG uptake was demonstrated in bone marrow that was not confirmed histologically. In these cases, it is not clear whether the FDG-PET scans were falsely positive or if there was patchy bone marrow involvement not detected by bone marrow biopsy. Wirth et al (2002) described four patients with a positive bone marrow biopsy, of which none had marrow involvement suspected on FDG-PET or Ga-67 scanning. Of patients with a negative bone marrow biopsy, FDG-PET suggested marrow involvement in one patient and Ga-67 scanning suggested marrow involvement in two patients but there was no independent confirmation. These results are in contrast to a study by Carr et al (1998) that compared FDG-PET scans of 38 patients with NHL with unilateral bone marrow biopsy. The FDG-PET scan and marrow histology agreed in 31 patients (75%) – concordantly positive in 11 and concordantly negative in 20 patients. In four patients the PET scan showed increased FDG uptake but the staging biopsy was negative. In four of these patients with DLBCL the PET scan showed a normal marrow background with focal FDG avidity distant from the site biopsied whereas in five patients FDG uptake was diffuse (peripheral T cell lymphoma, anaplastic large cell lymphoma). In three patients the marrow biopsy specimen was positive but the FDG-PET scan normal. Two of these three patients had DLBCL whose malignant cells were not FDG avid at lymph node or marrow disease sites and the other case was of mantle cell lymphoma. Therefore, there were only three patients in whom there was a difference between the FDG-PET scan and biopsy result that could not be fully explained. Buchmann et al (2001) also showed that FDG-PET was superior to CT and equivalent to bone marrow biopsy in detecting bone marrow infiltration.

As with HL, an important issue is whether the increased detection of disease sites using FDG-PET alters staging and consequently, the therapy given. In a study by Shen et al (2002), FDG-PET upstaged six patients in whom Ga-67 scintigraphy only partially detected disease sites. Kostakoglu
et al (2002a) revealed higher stage disease in 13 patients by FDG-PET compared with Ga-67 imaging. In the study by Wirth et al (2002) FDG-PET and Ga-67 imaging upstaged seven cases (14%). In this study, patient management was altered by FDG-PET in nine cases (18%) and Ga-67 scanning in seven cases (14%). In the study by Buchmann et al (2001) in four of 52 patients (8%) FDG-PET led to an upstaging and a change of therapy. It should be noted, however, that many centres use the same therapy for all stages of histologically aggressive NHL (with the possible exception of stage I A disease with no adverse risk factors), and in such circumstances the rationale for FDG-PET staging is to improve the evaluation of response-assessment scans.

NHL – histologically indolent disease

Elstrom et al (2003) performed a retrospective evaluation of FDG-PET imaging in 55 histologically indolent NHL patients, either at presentation or relapse. Disease was detected in at least one site in 98% of patients with follicular lymphoma but it is not clear whether any other sites with definite disease were FDG-PET negative. A study by Najjar et al (2001) involved 36 patients with histologically proven low grade NHL. FDG-PET was performed at the time of initial diagnosis (n = 21) or for disease recurrence (n = 15) prior to any treatment. The sensitivity and specificity of FDG-PET was 87% and 100%, respectively. In the study by Wirth et al (2002) a positivity rate of 90% was achieved for indolent lymphomas with both FDG-PET and Ga-67, the only false negative case being that of small lymphocytic lymphoma in abdominal nodes. These studies are in contrast to the majority of other studies, suggesting that the accuracy of FDG-PET is reduced in the histologically indolent subtype. Jerusalem et al (2001b) prospectively investigated 42 patients at initial diagnosis (n = 26) or first relapse (n = 16) who underwent conventional staging procedures that were compared with FDG-PET. Investigators were blinded to the results of conventional imaging when analysing the FDG-PET scans. Response to treatment and follow up data were used to assess the accuracy of the original evaluation. Although FDG-PET detected more abnormal lymph node areas than conventional staging in follicular lymphoma, its use was inappropriate for the staging of small lymphocytic lymphoma as less than 58% of abnormal lymph node areas were detected. In the study by Elstrom et al (2003) FDG-PET detected disease in only 67% of marginal zone lymphoma (MZL). Hoffman et al (2003) performed FDG-PET studies in 20 patients with MZL, extranodal (n = 14) and nodal (n = 6). Five of six patients with nodal MZL showed significant FDG uptake within the affected lymph nodes but none of the patients with extranodal MZL showed focal tracer uptake within verified tumour sites. There is further evidence that sensitivity of detection of the disease sites by FDG-PET is determined by location. Jerusalem et al (2001b) found that FDG-PET demonstrated more lesions than conventional staging for peripheral (34% more lymph nodes detected) and thoracic lymph node (39% more detected) areas but not for abdominal or pelvic lymph nodes (26% fewer areas detected). FDG-PET identified more cases of splenic or hepatic infiltration but CT showed more cases of pleural or lung infiltration. In this study FDG-PET was as effective as conventional procedures for detecting extranodal localizations although a few were only detected by FDG-PET and a few by only conventional modalities.

Various studies have assessed the accuracy of determination of bone marrow involvement. In the study by Najjar et al (2001) on assessment of bone marrow infiltration, FDG-PET and biopsy were concordant in 24 patients, with 11 true positive and 13 true negative results. However FDG-PET was falsely negative in 11 patients and no biopsy was performed in one patient. Jerusalem et al (2001b) showed that, for all histological subtypes, the sensitivity to detect bone marrow infiltration was unacceptably low for FDG-PET (11 of 28 detected = 39%). From this study FDG-PET alone would have led to an incorrect downstaging in 14 patients on account of bone marrow infiltration not being detected. These studies suggest therefore FDG-PET results are unreliable and that it is necessary to additionally perform a bone marrow biopsy. Overall, in light of the frequent unreliability of FDG-PET scanning and the general lack of impact of stage alone on the therapy given, the rationale for including FDG-PET scanning in the routine diagnostic work up of the histologically indolent lymphomas is not strong.

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<thead>
<tr>
<th>Role of PET in lymphoma staging: summary points</th>
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<tbody>
<tr>
<td>1 HL – FDG-PET/CT imaging should ideally be performed in all patients but particularly in stage I or II disease, where a change in staging will alter disease management.</td>
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<td>2 Histologically aggressive NHL – FDG-PET/CT imaging is valuable to provide a baseline for later response evaluation. It is also valuable in stage I disease where fewer cycles of chemotherapy may be considered.</td>
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<tr>
<td>3 Histologically indolent NHL – not generally indicated.</td>
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Response assessment

The majority of studies evaluating the role of FDG-PET have been conducted to assess response to therapy (see Fig 1). Residual abnormalities occur in 30–60% of patients after therapy and are usually considered to represent persistent lymphoma as CT imaging cannot differentiate between benign fibrous tissue, an inflammatory process or persistent malignant disease (Radford et al, 1988; Goiffier et al, 1991; Glenn & Kumar, 1991). However, only a maximum of 10–20% of residual masses at the completion of treatment are reported to be positive for lymphoma on biopsy (Jochelson et al, 1985; Israel et al, 1988; Surbone et al, 1988; Segall, 2004 Blackwell Publishing Ltd, British Journal of Haematology, 126, 772–784 775
2001; Hoskin, 2002; Lowe & Wiseman, 2002) and a further study has shown that only 18% will eventually relapse (Canellos, 1988).

**Hodgkin lymphoma**

Hueltenschmidt et al (2001) assessed the clinical value of FDG-PET compared with conventional imaging modalities for treatment monitoring and assessment in 81 patients with HL. Verification was made histologically and/or by follow-up evaluation. FDG-PET studies were undertaken for treatment monitoring after the completion of treatment in 63 patients and FDG-PET showed an accuracy of 91% compared with 62% for other imaging methods. The negative predictive value of FDG-PET was 96% as determined by continued remission at a mean of 20.4 months. In 18 patients FDG-PET was performed in cases of suspected recurrence of HL and FDG-PET findings were true positive in 10 of 12 cases and true negative in five of six cases, resulting in an accuracy rate of 83%. This compared favourably with the accuracy rate of 56% for other imaging methods.

In a further study by Guay et al (2003) 48 patients with HL were studied who underwent FDG-PET imaging on completion of chemotherapy. FDG-PET and CT results were compared with clinical follow-up. Relapse was defined as a positive biopsy or the introduction of second line treatment. Fourteen patients relapsed during a mean follow-up of 197 d. The sensitivity and specificity of FDG-PET to predict relapse was 79% and 97%, respectively. The diagnostic accuracy of FDG-PET was significantly higher than CT (92% vs. 56%) and patients with positive FDG-PET had a shorter median disease-free interval than those with positive CT (79 d vs. 1143 d). Three cases of false negative FDG-PET studies occurred in patients whom underwent their FDG-PET study within 49 d of chemotherapy.

Two further studies have evaluated the predictive role of FDG-PET in HL patients with a residual mass at the end of treatment, which is a frequent and clinically challenging situation. De Wit et al (2001) studied 37 HL patients with a residual mass and performed 50 FDG-PET scans before and after additional radiotherapy. In the prediction of disease-free survival FDG-PET showed a sensitivity and specificity of 91% and 69% respectively. Weihrauch et al (2001) studied 28 HL patients with a residual mass of at least 2 cm within 4 months of initial or salvage therapy whom underwent prospective FDG-PET scanning, allowing remission status to be documented. Their results showed a one-year progression-free survival (PFS) of 95% for the FDG-PET negative group compared with 40% for the FDG-PET positive group. These and other similar findings are important in making management decisions (De Wit et al, 1997; Jerusalem et al, 1999; Cremerius et al, 2001; Weihrauch et al, 2003). They suggest that any HL patient with a residual mediastinal mass who has a negative FDG-PET scan is unlikely to relapse within 12 months, if ever, and therefore offers reassurance. A patient with a positive FDG-PET scan however requires more intense follow-up. In both studies a
Persistently abnormal FDG uptake was seen in 26 patients and imaging offered no additional value in predicting relapse. Relapsed at a median follow-up of 2 years. Conventional seven patients had normal FDG-PET scans, of which 11 (16%) 3 months after completion of first line chemotherapy. Sixty-ically aggressive, 14 histologically indolent) between 1 and body FDG-PET scans on 93 patients with NHL (79 histolog-

prevent disease progression. PFS correlated with FDG-PET findings after the first cycle of therapy better than with FDG-PET results at completion of therapy. This predictable earlier response to chemotherapy has also been demonstrated in the HL series from Harvard (Friedberg et al, 2004) where FDG-PET scanning after three cycles of chemotherapy had a higher positive predictive value for disease recurrence than FDG-PET scanning at completion of therapy.

In view of these findings, there is a current National Cancer Research Institute randomized phase III trial in clinical stage IA/IIA HL aiming to determine the role of FDG-PET imaging. Patients with early stage, low risk HL receive three cycles of ABVD (adriamycin, bleomycin, vinblastine, dacarbazine) chemotherapy followed by FDG-PET imaging if in complete or partial remission. Individuals who are FDG-PET positive receive a further fourth cycle of ABVD followed by involved field radiotherapy. Those who are FDG-PET negative are randomized to receive either involved field radiotherapy or no further treatment. All patients are followed up with surveillance CT scans at 6, 12 and 24 months. The prime objective is to determine whether patients who have a negative FDG-PET scan after three cycles of ABVD require consolidation radiotherapy to areas of previous involvement in order to delay or prevent disease progression.

Non-Hodgkin’s lymphoma

A Belgian study by Spaepen et al (2001a) performed whole body FDG-PET scans on 93 patients with NHL (79 histologically aggressive, 14 histologically indolent) between 1 and 3 months after completion of first line chemotherapy. Sixty-seven patients had normal FDG-PET scans, of which 11 (16%) relapsed at a median follow-up of 2 years. Conventional imaging offered no additional value in predicting relapse. Persistently abnormal FDG uptake was seen in 26 patients and all had disease progression. Twelve patients had immediate additional therapy, as conventional diagnostic methods were also positive. In 14 patients only FDG-PET predicted persistent disease and no salvage treatment was administered until relapse was proven by biopsy or progressive disease on alternative imaging. All 14 relapses occurred in the FDG avid site on PET. Interestingly, a shorter PFS was associated with a positive PET scan (median 73 d vs. 42 d with a negative PET scan) in the relapsed patients. The 2 year actuarial PFS rate for negative FDG-PET patients was 85% compared with 4% for positive FDG-PET patients. A further study (Mikhaeel et al, 2000) reported 45 patients with large cell lymphoma. All nine patients with persistently positive FDG-PET scans at the end of therapy had disease progression. Only six of 36 patients with negative FDG-PET scans at the end of therapy experienced progression. These two studies highlight the significance of a FDG-PET positive scan post-therapy and suggest it is indicative of relapse as no false positive scans were obtained. It is of interest that in these and other studies in NHL patients a positive FDG-PET scan post-treatment is indicative of persistent disease whereas a negative scan does not confirm the absence of disease (Zinzani et al, 1999). This is in contrast to many studies performed in HL patients where it has often been concluded that a negative scan is more predictive as false positive rates are high (Maisey et al, 2000).

The optimal timing of imaging during therapy has yet to be established (Jerusalem et al, 2000; Spaepen et al, 2002). As with HL there is evidence that imaging after one cycle of chemotherapy is more predictive than later imaging. Front et al (2000) assessed early prediction of outcome using Ga-67 scintigraphy in NHL patients. Findings after one cycle were predictive of outcome in aggressive NHL and there was a significant difference in failure-free survival between patients with positive and negative Ga-67 scintigraphy. A study by Ben-Haim et al (1996) supports these results for histologically indolent lymphoma. In studies using FDG-PET imaging, Kostakoglu et al (2002b) performed FDG-PET scans pre- and post-one cycle of chemotherapy in 17 patients with NHL. 100% of NHL patients with positive FDG-PET results after one cycle of chemotherapy experienced disease relapse with a median PFS of 6 months. Eighty-three per cent of patients with negative FDG-PET findings remained in complete remission (CR) with a minimum follow-up of 18 months. PFS after one cycle and at completion of treatment was statistically significantly different comparing patients with negative and positive FDG-PET results. PFS correlated with FDG-PET results after the first cycle of therapy better than with those at completion of therapy. Romer et al (1998) assessed the change in FDG uptake in malignant tissue that occurs in response to chemotherapy. They performed FDG-PET imaging 1 week before and day 7 and 42 after therapeutic intervention in 11 patients with newly diagnosed histologically aggressive NHL. In this study, chemotherapy caused a rapid decrease in tumour FDG uptake by 60% as early as 7 d after treatment and FDG
uptake continued to decline during therapy but uptake at 42 d post-therapy was a better predictor of long-term outcome.

FDG-PET therefore has a high prognostic value for evaluation of therapy as early as after one cycle in HL and aggressive NHL. Persistently abnormal FDG uptake seen after the first cycle of chemotherapy means the chance of relapse is significantly high, presumably reflecting inherent chemotherapy resistance. Negative FDG-PET results after the first cycle are highly suggestive of long-term remission, whereas negative results after the completion of chemotherapy are less accurate. Although tumour progression or disease relapse may still develop in a few patients with negative FDG-PET results early during treatment, FDG-PET after the first cycle of chemotherapy remains far more predictive of outcome than late FDG-PET imaging.

**Role of PET in response assessment: summary points**

1. HL – a negative FDG-PET scan is highly indicative of long-term disease-free survival. Its particular use is in those patients with a residual mass on CT scanning.
2. Histologically aggressive NHL – a positive FDG-PET scan is strongly predictive of disease persistence or recurrence. There is a significant incidence of false negative FDG-PET scans.
3. For both HL and histologically aggressive NHL, early assessment of response appears to be more predictive of long-term outcome than on completion of therapy. Randomized trials in this situation should be considered.
4. Histologically indolent NHL – the high rate of false negative FDG-PET scans mean that FDG-PET imaging is unreliable.

**Role of PET scanning in the pretransplantation setting**

The use of FDG-PET has been discussed above in the various aspects of lymphoma management. There are certain situations where FDG-PET may be particularly prognostic and pretransplantation assessment may be such a scenario. There are limited studies evaluating tumour response prior to high dose therapy (HDT) followed by stem cell transplantation (SCT) but an excellent study by Spaepen et al (2003) studied 60 patients (19 HL, 41 NHL) after salvage chemotherapy prior to high dose chemotherapy with SCT. All patients had failed induction or had relapsing chemosensitive disease. 30 patients had negative FDG-PET scans (10 HL, 20 NHL) and 30 patients had positive FDG-PET scans (9 HL, 21 NHL) prior to HDT. Of 30 patients with negative scans 25 remained in CR at median 4 year follow-up. Two treatment-related deaths occurred but with no evidence of disease relapse and three relapsed (1 HL, 2 NHL). Of 30 patients with positive scans 26 progressed – 16 died secondary to disease (2 HL, 14 NHL), six are still receiving treatment and four have obtained a further CR. For these four patients who remain in CR it is possible that the FDG-PET scan was falsely positive as two patients had infection at the time of imaging and two had recently received radiotherapy to residual mediastinal masses.

Two other studies have provided comparable results. Becherer et al (2002) performed FDG-PET imaging to predict relapse after HDT and autograft by performing scans after chemotherapy and 8 weeks prior to HDT in 16 patients (6 HL, 10 NHL). On performing FDG-PET imaging five patients had negative scans and all five patients remain in CR. Eleven patients had positive FDG-PET scans ranked as weakly, moderately or strongly positive and in total eight relapsed (only one from weakly positive group). It is difficult to make direct comparisons with the Spaepen et al (2003) study as this was a smaller study and included patients with chemotherapy refractory disease. A study by Cremerius et al (2002) performed FDG-PET scanning before and after up front HDT/SCT in 22 patients with high risk NHL. Six of seven (86%) patients who did not achieve a partial metabolic response relapsed whereas 10 of 15 (67%) patients in complete or partial remission did not progress. PFS at 1 year for FDG-PET positive and negative scans was 29% and 72% respectively. Survival at 1 year was 72% and 87% respectively which differed from that reported by Becherer et al (2002). Again it is difficult to compare results as this study was conducted in a different patient population.

Further studies need to be conducted to assess whether these results are reproducible but suggest that a positive FDG-PET scan prior to HDT/SCT is predictive of a much worse prognosis. This raises the suggestion whether further salvage chemotherapy, aiming to achieve a better remission prior to HDT/SCT, is applicable and whether transplantation should occur at all. Of interest, Spaepen et al (2003) reported that, for patients with a positive FDG-PET scan, although the progression rate post-HDT/SCT was similar for HL and NHL patients, those with HL responded better to subsequent salvage chemotherapy as is typical of the disease.

**Relapse**

Many of the publications on the diagnostic value of FDG-PET have combined patients at the time of initial diagnosis or at relapse and there is no evidence that the sensitivity or specificity differs in these two scenarios. This section focuses therefore on the potential value of FDG-PET to detect early relapse before it is apparent by other modalities. The value of FDG-PET would be apparent if it could detect a higher proportion of preclinical relapses, allowing salvage chemotherapy to commence earlier and ultimately influencing survival.

**Hodgkin lymphoma**

A study by Jerusalem et al (2003) investigated 36 patients with histologically verified HL whom had FDG-PET imaging
performed prospectively 1 month after the end of treatment and then every 4–6 months for 2–3 years after the completion of therapy. A confirmatory scan was performed 4–6 weeks later in any patient with abnormal FDG uptake. CT imaging at the end of treatment showed 17 patients were in CR-11 of these had a negative FDG-PET scan and did not relapse whereas six patients had a positive FDG-PET, of which 50% relapsed. The remaining 19 patients had residual masses on CT. Fourteen of these had a negative FDG-PET scan and have not relapsed. Five patients had a positive FDG-PET scan, of which two relapsed. In total, 11 patients had a positive FDG-PET scan, of which only five patients were confirmed to have relapsed and therefore 6 (55%) FDG-PET scans were falsely positive but in each case the confirmatory FDG-PET was negative. All five relapses were correctly identified by FDG-PET and never initially diagnosed by clinical examination, laboratory results or CT imaging. Confirmation of relapsed disease was obtained by biopsy in four patients median 4 (1–9) months after FDG-PET and by unequivocal clinical symptoms and CT in one patient 3 months after FDG-PET. No patient relapsed when the FDG-PET scan was negative.

This suggests a role for FDG-PET in detecting preclinical relapse, enabling patients to receive salvage chemotherapy with minimal disease rather than at overt relapse. The results indicate that FDG-PET may have a role in identifying HL relapse in asymptomatic patients or in patients with equivocal radiology. For conventional radiological procedures clinical symptoms are generally present before relapse is identified (Radford et al, 1997; Torrey et al, 1997). In the study by Jerusalem et al (2003) FDG-PET was positive up to 9 months prior to histological confirmation of relapse. Although the positive predictive value is high, histological or other evidence of disease recurrence should be sought prior to commencement of salvage chemotherapy because of the high rate of false positives. It remains to be ascertained how detecting preclinical relapse ultimately impacts on treatment and outcome.

**Non-Hodgkin’s lymphoma**

Only 6% of relapses of DLBCL are detected before the development of symptoms using conventional imaging procedures (Weeks et al, 1991). Very few studies have solely studied the role of FDG-PET in predicting relapse in NHL.

In the study by Kostakoglu et al (2002b) negative FDG-PET findings after the first and last cycles of chemotherapy resulted in relapse rates of 17% (1/6 patients) and 40% (4/10 patients), respectively. The relapse rates after the last cycle of chemotherapy appeared to be higher than those reported for an earlier study (Spaepen et al, 2001b). The Spaepen study included only patients evaluated at initial staging that underwent first-line therapy and included patients with low-grade lymphoma. The series by Kostakoglu et al (2002b) included both patients at initial staging and patients at relapse before salvage therapy who were at a higher risk of disease recurrence. The minimal follow-up period was 18 months compared with 12 months in the previous study. As with HL the impact on treatment and outcome needs to be ascertained.

**Future advances in PET scanning**

**Hardware development**

Isolated PET scanners lack anatomical detail and in certain situations this can reduce sensitivity. PET scanners are therefore being replaced progressively by combined PET/CT scanners in which the images produced are fused allowing for improved data interpretation (Antoch et al, 2003). The CT scanner used in a combined PET/CT machine is identical to the stand-alone CT scanner. The initial systems with two or four slice spiral CT scanners have been upgraded to eight and 16 slice devices and, although it is possible to further increase the number of slices, this will rarely be required. A study by Freudenberg et al (2004) compared FDG-PET/CT staging results with those of FDG-PET and CT alone in 27 patients with lymphoma. Each patient had clinical follow-up for at least 12 months. Patient-based evaluation showed a sensitivity of 78% for CT alone, 86% for FDG-PET alone, 93% for CT and FDG-PET read side by side, and 93% for combined FDG-PET/CT imaging. Region-based evaluation showed sensitivity for regional lymph node involvement of 61%, 78%, 91% and 96% respectively. A report by Charron et al (2000) has also demonstrated PET/CT as a more useful diagnostic tool than PET alone in cancer patients.

In recent years the speed of PET scanning has increased and the time for a whole body study (mid-brain to mid-thigh) has been reduced from 45 to 25 min and even shorter times are achievable. The additional CT scanning adds little to the overall time. The spatial resolution of PET scanning is 4–5 mm and although minor improvements are being reported, a major improvement is unlikely in the foreseeable future. Considerable improvements may arise, however, by compensation for movement artefacts by respiratory and cardiac gating.

**Alternatives to FDG in PET imaging**

Although FDG is the most frequently used PET radiolabelled tracer, it does have limitations in its ability to evaluate the extent of tumour tissue. Non-specific uptake can result in false positive results and the occurrence of high background FDG uptake in some areas, such as the brain, prevent small amounts of tumour tissue being detected.

Radiolabelled amino acids are an alternative method of metabolic imaging. These work on the same principle that, as FDG depends on increased glucose metabolism, protein metabolism also occurs at a faster rate in tumour cells. Protein metabolism incorporates amino acid uptake and protein synthesis and the increased transport rate of amino acids is most significant in malignant cells. Uptake of radiolabelled amino acids, unlike FDG, is proportional to the amount of viable cells and therefore the size of the tumour mass can be
artificial amino acids, for example methionine, would have downstaged the disease in one patient. Some artificial amino acids, for example l-3-[123I]iodo-α-methyltyrosine and l-3-[18F]fluoro-α-methyltyrosine, have been studied more recently (Jager et al, 1999).

Clinical studies on lymphoma detection by radiolabelled amino acids are limited. Methionine is the most commonly used and it is known that it accumulates strongly in most lymphomas. Its metabolism is altered in malignant cells and accumulation occurs secondary to its increased transport across the plasma membrane of neoplastic cells. Autoradiography has confirmed that methionine uptake occurs predominantly in viable tumour cells with low uptake in macrophages and non-neoplastic cells. This is in contrast to FDG, which is increased in the acute and chronic phase of inflammation predominantly due to neutrophil and macrophage activity, respectively. A study by Leskimen-Kallio et al (2003) of 14 patients with NHL showed that methionine was more sensitive than FDG in detecting high and low grade lymphomas. Another study (Sutinen et al, 2000) assessed 19 patients with untreated, histologically proven malignant lymphoma who underwent PET imaging with FDG and methionine within 1 week before treatment. In this study results were comparable in detecting lymphoma but visual interpretation of the images was hampered by physiological accumulation of methionine more than FDG in some sites, especially extranodal sites, such as bone marrow and liver. In this study, FDG and methionine PET would have upstaged the disease in three patients and methionine would have downstaged the disease in one patient in comparison with CT imaging. Further studies have been less conclusive for the use of methionine. Rodriguez et al (1995) investigated 23 lymphoma patients and concluded that FDG uptake was associated with malignancy grade but there was no relationship between methionine uptake and grade of malignancy. Also, Leskimen-Kallio et al (2003) found that FDG was superior to methionine in being able to distinguish high-grade tumours from other grades. There is some suggestion that methionine may be preferable to FDG in some situations where FDG is inaccurate, for example in hyperglycaemic patients.

In a study by Hustinx et al (2003) 10 patients with histologically proven lymphomas underwent FDG-PET and F-TYR-PET imaging. F-TYR-PET was found to be inferior as FDG-PET correctly identified all lesions, whereas F-TYR-PET visualized less lesions and did not detect any additional lesions. Four of 10 patients were inappropriately downstaged by F-TYR-PET. A further study by Kole et al (1999) comparing the two modalities was performed in 55 patients with a suspected soft tissue tumour. Their results suggested that FDG gives a better indication of tumour stage whereas tyrosine is more accurate in predicting mitotic rate and proliferation especially after treatment.

A feature of FDG-PET is its limited ability to assess tumour proliferation rate and transformation of lymphoma. In the Hoffman et al (1999) study a patient with evidence of lymphoma transformation had no demonstrable FDG avidity. 3'-deoxy-3'-[18F] fluorothymidine (FLT) has been suggested as a new marker of monitoring tumour proliferation and response to therapy. The uptake of FLT is regulated by thymidine kinase 1 and is upregulated in malignant tissues (Shields et al, 1998). In a preclinical study (Barthel et al, 2003), changes in tumour volume and biodistribution of FLT and FDG were measured in mice untreated and at 24 and 48 h after chemotherapy. FLT-PET was demonstrated to measure tumour response to therapy and decrease in uptake was more pronounced with FLT than FDG, allowing assessment of the proliferation fraction. A second study (Wagner et al, 2003) evaluated 11 cell lines from patients with indolent and aggressive lymphoma. FLT was comparable with FDG in detecting malignant lesions by PET scan and there was close correlation between FLT values and the Ki67 labelling index of the tissue biopsies, suggesting that FLT-PET imaging could assess the proliferation rate in lymphoma. Clinical studies are now required to determine the role of FLT-PET imaging in lymphoma management, particularly in indolent lymphomas where there is suspected transformation.

Conclusion

FDG-PET scanning undoubtedly enhances staging at diagnosis as it detects occult disease missed by conventional imaging. This provides a more accurate basis on which treatment regimens are devised, although the impact on clinical outcome has not yet been determined.

FDG-PET scanning is also valuable in the assessment of response and is the most useful non-invasive modality in differentiating between residual tumour and fibrosis. False positive and negative results do occasionally occur and for this reason an initial FDG-PET scan at diagnosis is desirable. In general, a negative scan in HL is indicative of a good prognosis whereas a positive scan should be interpreted in concert with other staging investigations. In histologically aggressive NHL, by contrast, there appear to be few false positive results but negative FDG-PET scans must be viewed with some caution. There is also data that very early FDG-PET scans after initiating therapy may predict for drug resistance and allow the early switch to, hopefully, more effective therapies. FDG-PET scanning may also facilitate the early detection of relapse and although this might improve the ultimate outcome, this is unproven. FDG-PET scanning may be particularly useful after salvage therapy, and allow improved selection of which patients should proceed to transplant procedures with attendant cost-savings.
The development of PET scanning in lymphoma management has not been scientifically rigorous but it is likely that its use, and that of PET/CT in particular, will increase and become a component of the standard diagnostic procedures and both early and late response assessments.

Data was collected by performing a Medline search using the key words 'FDG-PET', 'PET', 'Positron Emission Tomography', 'Lymphoma', 'Hodgkin', NHL, HL or HD.

References


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