Positron Emission Tomography in the Evaluation of Lymphoma

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Positron emission tomography (PET) using ^{18}F-fluoro-deoxyglucose (FDG) has emerged in recent years as an important tool for the evaluation of lymphoma patients during their course of disease. At diagnosis, FDG imaging is capable of detecting nodal and extra nodal sites of disease and provides accurate staging. FDG-PET is superior to computed tomography, during and at the end of first-line treatment or salvage therapeutic regimens, as a tool for monitoring therapeutic response. PET enables the differential diagnosis of residual viable tumor versus a remnant fibrotic or necrotic mass. PET also provides prognostic data of high clinical significance for both Hodgkin's disease and non-Hodgkin's lymphoma. Results of this metabolic imaging modality, interpreted in view of the pretherapy risk profile of the individual patient, are predictive of the immediate success of a certain therapeutic strategy, as well as of overall and disease-free survival. PET appears to play also an important role in the detection of lymphoma relapse. Data comparing ^{67}Gallium scintigraphy and FDG-PET indicate the latter as the functional imaging modality of choice for assessment of lymphoma patients. Preliminary studies show an additional value of fused PET/computed tomography imaging for further improved diagnosis, staging and definition of status of lymphoma.

LYMPHOMA is a general term that refers to a group of malignancies originating in the lymphoid tissue, including Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL). Lymphomas represent approximately 8% of adult malignancies[1] and 10% of childhood tumors.[2] The outcome of patients with lymphoma is, in general, better as compared with other cancers.[3] They are potentially curable malignancies. More than 70% of patients with newly diagnosed lymphoma respond to combination radio- and/or chemotherapy regimens.[3]

The appropriate selection of treatment after accurate staging and risk stratification, as well as improved therapeutic monitoring, has resulted in a high success rate in lymphoma management. Survival rates of lymphoma patients have increased during the last decades.[4,5] A subgroup of patients with HD at high risk for disease progression and those with recurrent disease may benefit from more aggressive treatment, such as high-dose chemotherapy and bone marrow transplantation.[4] On the other hand, in patients with low-risk HD, shorter treatment cycles, in an attempt to minimize side effects related to treatment, especially in children and young patients, are the goal in therapy planning.

NHL represents a group of patients with more complex clinical challenges. Based on histology and origin of NHL cells, their classification has a significant impact on patient management, prediction of outcome, and treatment planning.[6] More than 50% of patients with aggressive NHL reach complete response (CR) with first-line chemotherapy, followed by an annual relapse rate of about 7%.[6] The amount of tumor load at the time second-line aggressive treatment is instituted represents a major factor in determining the results of salvage therapy and is significant in governing future outcome.[7,8]

Precise classification and staging of lymphoma, timely evaluation of response to treatment, as well as early detection of recurrence, all play a crucial role in the proper management of patients with lymphoma. Using the appropriate diagnostic tests is of utmost significance for correct assessment of lymphoma. Positron emission tomography (PET) using ^{18}F-fluoro-deoxyglucose (FDG) is a metabolic imaging modality. Increased glycolytic activity in malignant cells is the basis for increased FDG uptake in lymphoma as well as in various other tumors. Despite the widespread availability of anatomic imaging tests, primarily computed tomography (CT), and of other well established functional nuclear medicine techniques, ^{67}Gallium (Ga-67) scintigraphy in particular, the use of PET has been advocated for assessment of both HD and NHL.

The technique for performing state-of-the-art PET studies in patients with lymphoma is similar to the protocol used in other malignancies. The administered dose of FDG (at least 370 MBq), the time of performing the study after injection of the tracer (60–90 min), and the type of imaging device and protocol used (dedicated PET, attenuation correction) are important technical factors. Careful attention to technical details enhances the quality and performance capabilities of the test in the routine clinical setting as well as for research purposes.

Interpretation of PET studies may be hampered by limitations inherent to the PET system or to the degree of disease metabolism. False-negative results can be related to small lesion size or to a low concentration of FDG in hypometabolic tumor types or individual lesions.[9-11]

Equivocal findings in areas of physiologic tracer distribution and abnormal FDG uptake in benign processes, unrelated to cancer, also have to be considered. Knowledge of these potential pitfalls is of particular

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importance in lymphoma, a multifocal disease that may involve any region of the body, and a malignancy where correct staging and localization of involved sites have a very important role in the future management of individual patients.

Accumulation of FDG is observed in normal tissues with increased glucose metabolism, such as the brain, liver, skeletal muscles, myocardium, and in the pathways of excretion of FDG, the intestinal tract, kidneys and urinary bladder. Although the pattern of physiological uptake is usually clearly defined, normal uptake can be interpreted as sites of active lymphoma or may hide adjacent sites of lymphomatous involvement.[12] High tracer uptake by macrophages and granulation tissue has been reported and can be the cause for FDG-avid processes such as sarcoidosis, Wegener granulomatosis, sinusitis, gastritis and thyroiditis. These conditions have at times been falsely related to lymphoma.[13]

Knowledge of previous treatment, as well as its timing in relationship to the performance of the study are important. PET performed less than 10 days after a chemotherapy cycle may lead to false-negative results whereas a study performed shortly after treatment may induce false positives as a result of inflammatory reactions in surgical scars after biopsy, chemotherapy induced alveolitis, or radiation induced lung or retroperitoneal fibrosis.[13] Up to 30% of children and young adults may show increased FDG activity in the thymus, appearing as an arrow-shaped or bilobar area of tracer uptake in the anterior mediastinum, further enhanced by treatment induced hyperplasia.[14,15] Diffuse increased uptake in the skeleton or in an enlarged spleen may also be the result of supportive drugs administered simultaneously with chemotherapy.[16,17]

These are still open issues that indicate the need for optimization of imaging techniques. The recent development of a new imaging modality makes it possible to perform sequential PET and CT studies on a single device in a same-day session. This provides simultaneous acquisition of anatomic and metabolic data related to the status of various types of malignancy, including lymphoma.[18] The clinical applications of PET-CT are currently being extensively explored. Preliminary, initial reports have shown this hybrid imaging to provide a precise anatomic localization of hypermetabolic lesions. Restaging of lymphoma using PET-CT has been found to be superior to PET and CT alone.[19] In a report on the clinical utility of PET-CT in the evaluation of advanced T-cell lymphoma of the skin, treatment was altered in most patients after PET-CT because of the detection of more extensive disease.[20] In the future PET-CT will provide more precise staging and restaging of lymphoma, which should have a significant impact on patient management.

FDG-PET IN THE DIAGNOSIS AND STAGING OF LYMPHOMA

Metabolic imaging using FDG-PET provides the functional characterization of tissues unrelated to morphologic criteria. The intracellular accumulation of FDG reflects the glycolytic metabolic rate in malignant cells, which is, as a rule, higher as compared with that of normal tissues.[21] In an initial study published 17 years ago, Paul was the first to describe increased FDG uptake in five patients with NHL.[22] Although high FDG-avidity has been reported in most types of lymphoma, there is some controversy regarding a lower degree of uptake by some histological subtypes of NHL. In a study by Newman and coworkers, all histological types of NHL were successfully imaged with FDG-PET, with no significant difference in standardized uptake values (SUV) among different sites and grades of disease.[23] The prospective comparison of PET and CT accuracy indicated that all sites of adenopathy demonstrated on CT were also detected on PET.[23]

FDG-PET was found to be of value in the diagnosis of HD and aggressive NHL.[24,25] Low-grade NHL, a more problematic group of lymphomas, has shown a relatively low sensitivity for detection of disease in some studies[26,27] whereas other authors have reported comparable performance indices to those of other histological types.[23,28,29] It is generally accepted that FDG-PET may have a role in diagnosis and staging of low-grade follicular NHL. For other subtypes of low-grade lymphoma (small lymphocytic and probably mantle cell lymphoma) the routine use of PET is still an issue that needs further evaluation.[24] The role of FDG-PET in diagnosis and evaluation of mucosa-associated lymphoid tissue (MALT) type lymphoma is questionable. PET did not detect disease in 10 patients with confirmed MALT lymphoma and was therefore not considered of value for staging and follow-up of this type of disease.[27] Similar discouraging results have been demonstrated in a small group of patients with follicular lymphoma of the duodenum.[30] In contrast, marginal zone B-cell lymphoma, an entity that was initially considered to originate from MALT lymphoma, but is, in recent reports, classified as a distinctive histologic type, was shown to take up FDG. Although extranodal sites of disease were not detected, FDG-PET appeared to allow for the diagnosis of lymph node involvement of marginal zone lymphoma.[31]

The role of FDG-PET in the evaluation of tumoral metabolic activity as a predictor of prognosis of patients with lymphoma has been assessed. These studies have investigated the relationship between the presence and degree of FDG uptake, indices of cell proliferation, and histologic grade of disease and report mixed results. Some studies have found a significant positive correlation between FDG uptake and histologic grade in newly diagnosed lymphoma. A higher degree of FDG uptake

was directly related to a higher histologic grade, associated also with increased proliferative activity.[32] Other studies have shown only a weak correlation between FDG uptake and indices of cell proliferation, and report that PET is not useful for further prediction of malignancy grade of NHL.[33,34]

A report in 21 lymphoma patients investigated the relationship between FDG uptake and prognosis and found that uptake values were higher in three patients with intermediate-grade NHL who had a poor prognosis and in one patient with high-grade lymphoma. The lowest value of FDG uptake was found in one patient with low-grade NHL.[35] In an additional study aimed to evaluate FDG-PET as a predictor of prognosis, aggressive and treatment-resistant tumors showed a trend toward higher uptake of FDG with an inverse relationship between the survival rate of patients and the degree of FDG uptake.[36]

One of the most important factors influencing overall and disease-free survival of lymphoma patients is, besides histology, the extent of disease. Accurate staging is essential for optimizing patient therapy and for determining the prognosis of patients with both HD and NHL.[4,5,37-40]

Clinical staging of lymphoma has traditionally included physical examination, laboratory data such as erythrocyte sedimentation rate and serum lactic dehydrogenase measurements, and bone marrow biopsy (BMB). Imaging of the thorax, abdomen and pelvis using CT have been widely used in staging of lymphoma. Anatomic imaging modalities, however, lack both sensitivity and specificity.[41,42] The definition of lymph node involvement on anatomic imaging modalities is based on size criteria.[41,43] An active tumor site in a small lymph node can be missed on CT while benign, inflammatory lymphadenopathy can be misinterpreted falsely as indicating lymphoma. This may further lead to erroneous under- or over-staging.

During the last decade PET using FDG has been introduced as an additional tool for noninvasive staging of lymphoma (Fig 1).[10] Several studies have assessed the value of FDG-PET in the baseline evaluation of HD and NHL. A study including 50 patients compared PET-FDG for staging of HD and NHL to CT.[29] The sensitivity and specificity of PET were 86% and 96%, respectively, for HD and 89% and 100% for NHL. The sensitivity and specificity of CT were 81% and 41% for HD and 86% and 67% for NHL. In this study FDG uptake was demonstrated in high- as well as low-grade NHL. PET-FDG was found to detect more lesions then CT or physical examination, however this additional information rarely resulted in a change in staging of disease.[44]

Moog and coworkers showed FDG-PET to be superior to CT in the initial staging of HD and NHL.[28] FDG-PET correctly identified all sites of nodal involvement seen on CT, detected additional lesions not demonstrated on CT and excluded the presence of lymphoma in one false-positive CT lesion. In this study, the information provided by PET led to a change in the initial stage in 8% of patients.

The complementary role of FDG-PET to conventional staging of 45 patients with newly diagnosed HD and NHL was investigated by Delbeke and coworkers[45] Discordant lesions were verified by biopsy or clinical follow up. In this study FDG-PET changed the initial staging in 16% of the study population, upstaging five and downstaging two patients. Furthermore, the change in staging led to a modification in the therapeutic approach in 13% of patients.[45] In addition to the positive impact of PET, these authors report that false-negative FDG imaging understaged three patients (7%), including two patients with low-grade NHL and one with HD. They concluded that FDG-PET is an efficient method for staging of lymphoma but should be used in conjunction with conventional staging as complementary modalities.

Fifty-two patients with lymphoma were prospectively investigated in a study aimed at assessing the role of FDG-PET for staging at diagnosis as compared with CT and BMB. With the exception of infradiaphragmatic sites of disease, a region where both modalities produced similar results, FDG-PET was found to be significantly superior to CT. The better performance of FDG-PET was demonstrated for both nodal and extranodal sites. Improved diagnosis by PET induced a modification in the therapeutic approach in 8% of this study population.[46]

Jerusalem and coworkers assessed FDG-PET in low-grade NHL and found it superior to conventional staging in follicular NHL but suboptimal and therefore inappropriate for staging small lymphocytic type lymphoma and for detecting bone marrow involvement.[47] An additional study reported the combination of PET, CT, and physical examination to be more sensitive than conventional staging alone for low-grade NHL with the exception of detecting bone marrow involvement.[48]

Extranodal lymphoma involving organs, such as the liver, spleen, bone and bone marrow, usually is accompanied by only subtle, difficult-to-detect anatomical changes.[49] Diagnosis of extranodal involvement may have a significant impact by altering the stage of disease. Bone marrow involvement is present in 10% and 25% of newly diagnosed HD and NHL, hepatic involvement in 3% and 15%, and splenic in 23% and 22%, respectively.[49] Stage 3 and extranodal stage 4 lymphoma have poorer prognosis. A number of studies have assessed the value of PET in the diagnosis of bone marrow, osseous and splenic involvement of lymphoma.[49-53]

In a study evaluating the role of FDG imaging for staging newly diagnosed HD, 41% of patients were upstaged based on PET results. In half of these cases, the upstage was due to FDG uptake in splenic or extranodal

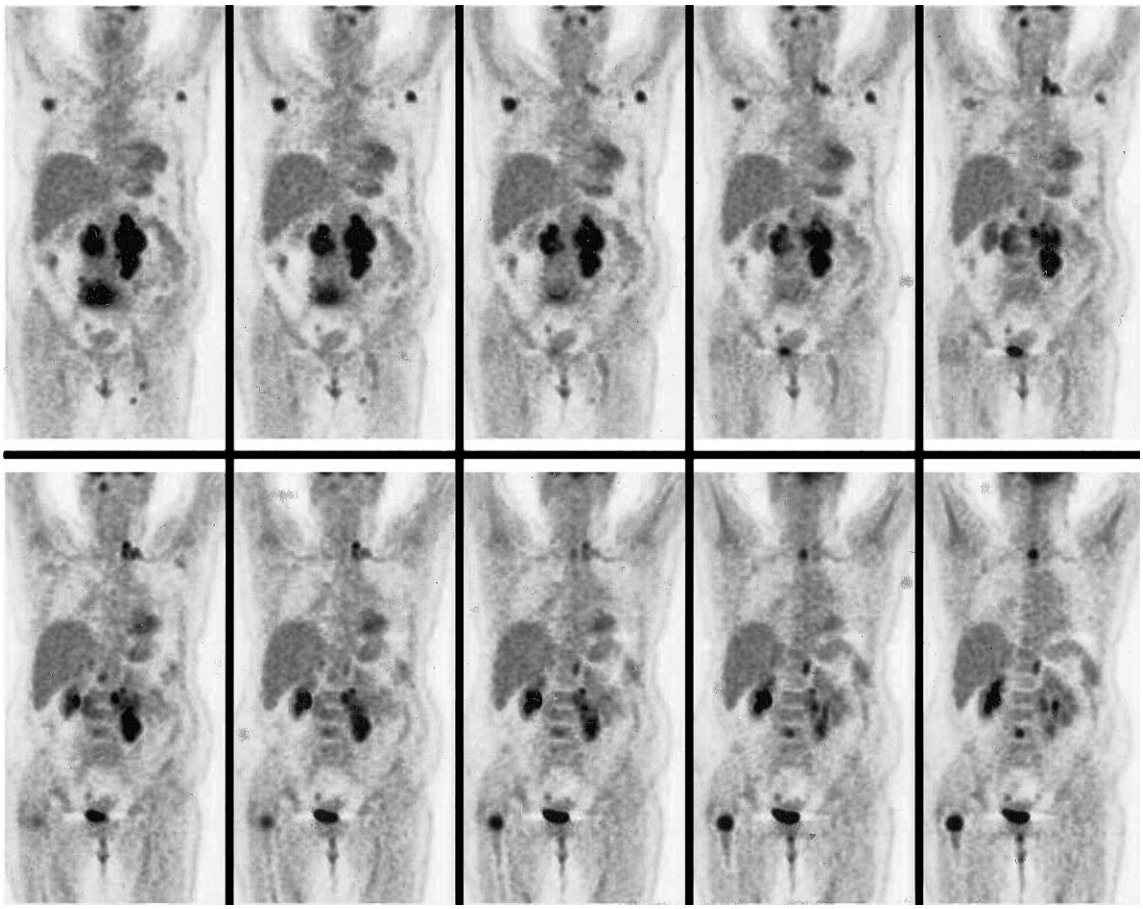

Fig 1. Positron emission tomography using ^{18}F-fluoro-deoxyglucose (FDG-PET) at diagnosis: staging of lymphoma after the detection of nodal and extranodal involvement. Baseline FDG-PET before treatment of a 56-year-old woman with follicular non-Hodgkin's lymphoma. There are foci of abnormal FDG uptake involving disease sites above and below the diaphragm: right oropharynx, left lower neck, both axillae, mesenteric, retroperitoneal, and left inguinal adenopathy. Additional extra-nodal foci of lymphoma are shown in skeletal sites involving thoracic and lumbar vertebrae and the right femur.

sites not visualized on CT.[38] Another study assessed the presence and degree of FDG uptake in the spleen at staging. FDG-PET correctly identified all patients with and without splenic involvement and was superior to CT for this purpose.[52] Moog and coworkers also compared the ability of FDG-PET to detect extranodal involvement to that of CT. Fourteen of 15 extranodal sites detected by PET were confirmed as lymphomatous involvement. In contrast, five of six extranodal lesions detected only by CT showed no further evidence of lymphoma.[49]

Some reports assessing PET for bone marrow involvement are encouraging. In one study, PET and marrow histology agreed in 78% of the patients.[53] A second study showed that beside detecting disease involvement histologically confirmed by biopsy, PET also detected bone marrow involvement in 10% of patients that had an initial negative BMB but were later confirmed as presenting with bone marrow disease.[50] Comparing the accuracy of PET for diagnosis of bone marrow involvement to that of unilateral BMB, widespread patterns of bone marrow involvement were found to be positive by both tests. PET was found to be superior to BMB in detecting focal skeletal or bone marrow infiltration and more accurate than CT for diagnosis of widespread infiltration.[46] Based on these reports, FDG-PET may have an important role in guiding other imaging modalities, such as MRI, and in directing biopsy for assessment of extranodal involvement. This should lead to further improvement in lymphoma staging.[10,50,54]

The cost-effectiveness of FDG-PET for accurate staging of lymphoma has been evaluated and compared with other imaging modalities in 18 patients. A hypothetical two arms strategy, one using conventional staging and the second using a whole-body FDG-PET based algorithm with additional selected imaging studies directed by PET, was evaluated. Both arms showed a similar diagnostic accuracy. The theoretically calculated difference in cost between the PET based and conventional

staging algorithm resulted, however, in total savings for this study population of about US $30,000 when using PET.[9]

FDG-PET appears to be a noninvasive, efficient, and cost-effective whole-body imaging modality with a high sensitivity, specificity, and accuracy for staging patients with most histological types of HD and NHL. It is generally accepted today that FDG-PET should be added as a clinically valuable tool to conventional staging modalities.[9,39,55,56]

FDG-PET FOR THE ASSESSMENT OF LYMPHOMA RESPONSE AFTER TREATMENT

Changes in volume of a tumor mass are neither sensitive nor specific enough for accurate definition of cancer response to therapy.[57,58] The presence or absence of increased FDG uptake, however, is an indicator of the tumoricidal effect of chemotherapy in lymphoma.[59] An initial study evaluated both Ga-67 and tritiated deoxyglucose in an experimental tumor model and demonstrated the unique ability of functional imaging tracers to assess tumor viability.[60] After this report, a large volume of data showing the preferential accumulation of FDG in viable tumor cells of various malignancies and lymphoma in particular has been published.

Accurate assessment of response at the end of therapy is of considerable prognostic importance with longer overall survival and disease-free survival for patients who achieve a CR[61]**.** Furthermore, with new therapeutic strategies available, even after initial treatment failure, accurate and timely response assessment is needed for further tailoring of the most appropriate therapeutic approach in the individual patient. The main dilemma in assessing response at the end of first-line treatment of lymphoma is the presence of residual masses in a large percent of patients.[58] The limitations of conventional morphologic imaging modalities in characterization of a residual mass are well documented.[57,58,62] FDG-PET, however, represents an accurate test for the assessment of patients' response after therapy, as well as for predicting long-term prognosis.[63-78] As shown previously for Ga-67 scintigraphy, the metabolic imaging concept of FDG-PET provides the foundation for post therapy assessment of residual masses in lymphoma patients.[79]

Initial studies have assessed response to treatment in heterogenous populations including both HD and NHL patients. Better specificity and positive predictive value (PPV) for FDG-PET (92% and 94%, respectively) as compared with that of CT (17% and 60%), have been reported in the post therapy assessment of 27 lymphoma patients.[63] In an early study of 44 patients with HD and aggressive NHL with residual abdominal masses, a positive PET after therapy detected all 13 patients who further relapsed while only 14 of 37 (38%) patients with positive CT after therapy had recurrent disease.[64] There was a statistically significant difference in 2-year relapse-free survival between patients with positive and negative FDG-PET at one month after completion of therapy. The majority of relapses (93%) occurred in sites showing persistent FDG uptake at the time of therapy completion.[64] A significant difference in the relapse rates in patients with positive and negative PET after treatment was found in other studies as well.[65-67] A PPV of 100% for PET, as compared with 42% for CT, was found in 54 patients with HD and aggressive NHL assessed after therapy. The negative predicitive values (NPV) of PET (83%) and CT (87%) were, however, not significantly different.[65]

PET and CT performed at the end of treatment play a complementary role in accurate assessment and prediction of response.[64-66] All patients with both positive PET and CT after therapy relapsed, whereas recurrence was diagnosed in 26% of patients with negative PET and positive CT, and in only 10% of patients with both negative PET and CT.[65] A combination of PET and CT at the end of first-line chemotherapy was suggested for patient stratification at risk for relapse. Both PET and CT negative studies after therapy indicated a low risk for further relapse, with a 2-years progression-free survival (PFS) rate of 87%. Positive residual CT with a negative PET predicted an intermediate risk with PFS rate of 60%, while positive PET indicated the highest risk, regardless of CT findings, with PFS of 0%.[65]

The high accuracy of posttreatment FDG-PET for characterization of residual masses and prediction of prognosis was also confirmed on separate studies in HD and NHL patients.[67-72] In a large series of 93 NHL patients, Spaepen and coworkers found that FDG-PET performed 1 to 3 months after completion of first-line chemotherapy, had a PPV of 100% and a NPV of 83%.[68] There was a significantly different relapse rate between patients with positive and negative PET, with a 2-year PFS of 4% versus 85% respectively. Additional studies further confirmed the prognostic superiority of PET over that of CT after therapy for NHL.[67,69,70] Similar results were also obtained in the analysis of posttreatment studies for HD.[70-75] In a study of 60 patients with HD, 55 patients (92%) had a negative PET after treatment with 50 of these 55 patients achieving a CR. All 5 patients with a positive PET relapsed. The 2-year PFS was 0% for patients with positive PET as compared with 91% for patients with negative PET.[73]

Discrepant results were reported regarding the predictive performance of FDG-PET after therapy, reporting suboptimal PPVs for predicting the further course of disease.[66,69,70,76-78] In 34 patients with HD and NHL, negative PET after treatment had a NPV of 100% and a PPV of 61%.[77] In the assessment of 58 lymphoma patients with residual masses, FDG-PET after therapy predicted recurrence with a NPV of 96% and a PPV of 62%.[69] In contrast, a recent study of 40 HD and NHL

patients, showed a low NPV with relapse being diagnosed in 23% of patients who had a negative PET after therapy.[66] These variable results may be the result of size-related issues of the study population, different imaging techniques and variable lengths of follow up periods. However, cumulative data analyzing different lymphoma types suggest that the predictive value of FDG-PET depends on the pretherapy prognostic profile of the patients and the resulting prevalence of treatment failure. The response rate in HD is usually higher than in NHL and therefore a negative PET study appears to be highly correlated with prolonged CR, especially in early stage disease. Negative PET in HD can be further used for confirmation of response, in particular in the presence of residual masses, which are frequently observed on CT. A positive PET is an infrequent finding at the end of treatment for HD and the chances of a false-positive result are relatively high as reflected by the lower PPV of PET relative to its NPV in patients with early stage HD.[71,72,74,75] In advanced-stage HD as well as in aggressive NHL, prevalence of relapse is higher and a positive PET after first-line therapy is highly predictive of treatment failure.[68,73] A negative PET in these patients does not exclude minimal residual disease and should not be used therefore as the sole indicator of disease eradication. Nevertheless, it should be noted that even a false-negative FDG-PET after treatment is still predictive of a longer PFS than a positive PET.[68]

Differential interpretation of PET after therapy in different types of lymphoma may improve the correct estimation of treatment response. This difference in threshold criteria used for PET interpretation in HD and NHL patients was demonstrated by Naumann and coworkers[69] In this study, only one of six HD patients with a positive PET relapsed, while none of 15 patients with equivocal, low degree FDG uptake had a recurrence. In contrast, while all NHL patients with definitely PET-positive studies relapsed, this also occurred in two of three patients with NHL and equivocal PET findings.[69]

In view of this potential limited independent prognostic power of PET, it has been suggested that a different algorithm should be applied for the clinical use of PET results after therapy in different types of lymphoma.[68,73] In NHL and high-stage HD a positive PET at the end of first-line therapy is highly suggestive of disease and requires intensive confirmatory investigations. A negative PET does not exclude the presence of minimal residual disease and future relapse, and requires close follow up. However, in early-stage HD, a negative PET can be used to define CR with favorable prognosis, even in the presence of residual masses on CT. A positive PET, especially if located in a site different from the residual mass, should be assessed with caution and benign or inflammatory etiologies should also be considered in the differential diagnosis of persistent disease.[69,73]

The precise fusion of morphologic and metabolic imaging data using hybrid PET-CT systems may be potentially useful for the management of a residual mass after therapy of lymphoma.[18,19] The precise localization of viable tissue within a residual mass on CT can direct further invasive diagnostic procedures. Uptake in other suspicious lesions may be better characterized by precise superimposition either on sites of disease or in areas of normal physiological and benign tracer biodistribution.

FDG-PET FOR THE DETECTION OF RECURRENCE

Early diagnosis of relapse will lead to early administration of salvage therapy with potential for a better outcome. The ability of FDG-PET to accurately detect mediastinal and hilar recurrence as well as for optimized restaging of recurrent HD and NHL, including detection of additional sites not seen on CT, has been described.[43,72,75,80] The accuracy of PET for diagnosis of recurrent HD was found to be superior to that of conventional imaging (83% versus 56%). PET accurately confirmed disease status in 15 of 18 sites, detected 10 sites of relapse and excluded disease in 5 lesions suspected on CT.[75] One study was aimed at assessing the value of FDG-PET performed during routine follow-up for early detection of recurrence.[81] A high NPV but low PPV was reported in this study of 36 HD patients. PET detected residual or recurrent disease in all 5 patients with disease, preceding other diagnostic modalities by 1 to 9 months. Negative PET accurately excluded relapse, even when clinically suspected. However, 6 of 11 positive PET studies were falsely positive. Repeat PET studies performed in these 6 patients without any further therapeutic interventions were negative. False-positive results were due to FDG uptake in a hyperplastic thymus, in the gastrointestinal tract and in an inflammatory lung lesion.[81]

Larger studies are necessary to evaluate the performance of PET for early detection of recurrence, and especially to assess the clinical impact of PET on patient management and outcome.[81] The advantages of PET-CT hybrid imaging in restaging of lymphoma was described in a study of 27 lymphoma patients assessed after therapy.[19] Although there was no significant difference in sensitivity, specificity or predictive values between FDG-PET and FDG-PET-CT, hybrid imaging modified the disease restaging in 3 of 14 patients with recurrent lymphoma.

FDG-PET FOR ASSESSING THERAPY RESPONSE DURING THERAPY

Long-term prognosis of lymphoma depends not only on pretherapy clinical factors but also on the chemosensitivity of the tumor in the individual patient. Rapidity of response during treatment appears to be an accurate

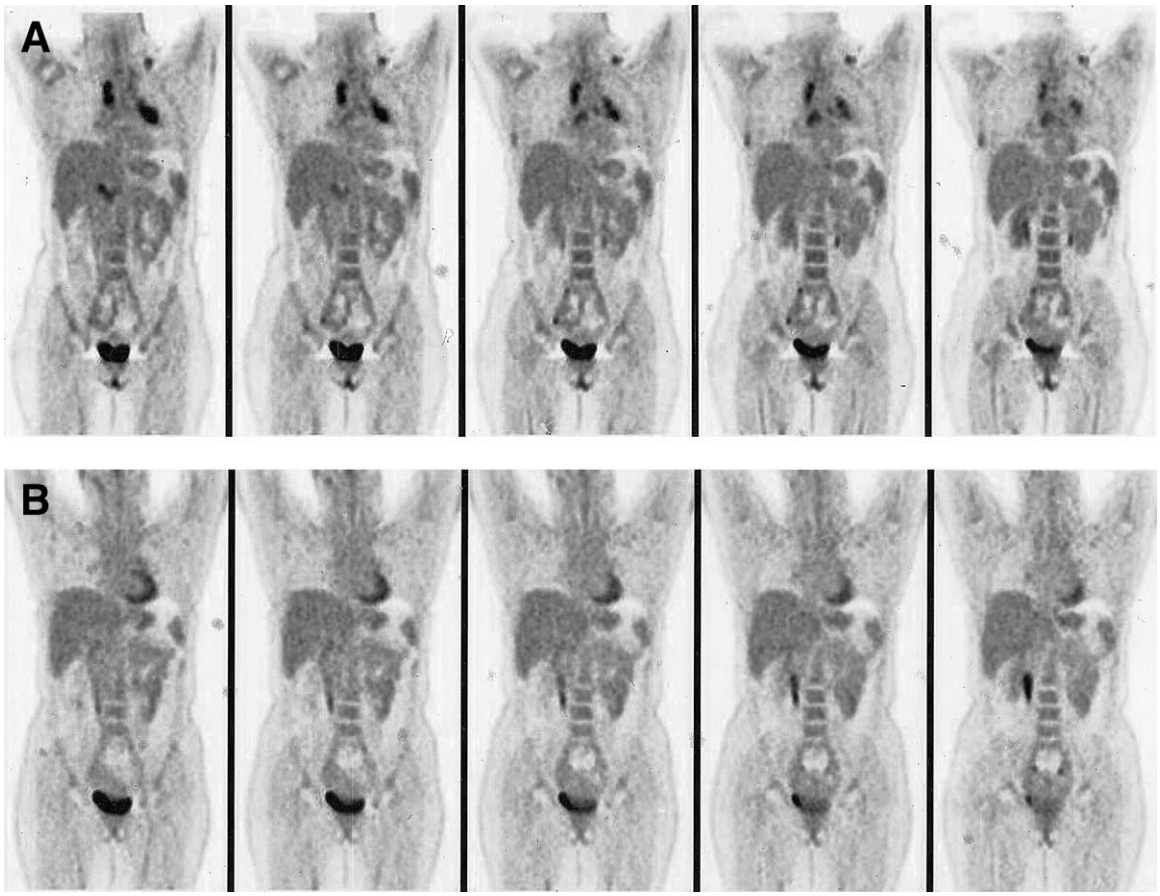

Fig 2. Negative positron emission tomography using ^{18}F-fluoro-deoxyglucose (FDG-PET) early during treatment: assessment of complete response and good prognosis. (A) Baseline PET study of a 34-years-old woman with Hodgkin's disease shows abnormal FDG uptake in sites of lymphadenopathy in the left supra-clavicular region, the right axilla, the mediastinum bilaterally, the left lung hilum, and the porta hepatis region. (B) Repeat FDG-PET, performed after one cycle of chemotherapy (BEACOPP protocol), is negative, showing no evidence of sites of active disease. The patient completed the planned chemotherapy protocol and is in complete remission at a follow-up of 15 months.

predictor of response, with early tumor regression indicating higher cure rates.[7] Accurate early assessment of response allows for timely institution of aggressive second line protocols in the presence of a smaller resistant tumor load, and, on the other hand, can potentially avoid treatment-related toxicity.

As shown previously for ^{67}Ga after one or two cycles of chemotherapy,[82] FDG-PET performed early during treatment allows for assessment of early response and for predicting long term prognosis.[39,83-85] (Figs 2 and 3) Initial data in small study groups showed a significant decrease in FDG uptake in chemosensitive lymphoma as early as after one cycle of chemotherapy.[39,83-85] A decrease of 60% in SUVs was observed at 7 days, and a total decrease of 76%, as compared with pretherapy values, was observed at 42 days after initiation of treatment. A cut-off SUV value of 2.5 differentiated responders from nonresponding patients.[39]

Although some authors suggested an improved estimate of response by repeat PET studies,[84] Romer and coworkers found that a single PET study performed after two cycles of chemotherapy was predictive of long-term prognosis.[39,84] Further larger scale studies confirmed these initial results.[86-88] Jerusalem and coworkers found visual assessment of FDG-PET predictive of therapy response in 28 patients with NHL who were evaluated after two to five cycles of chemotherapy.[86] Twenty-one of 23 patients with a negative PET achieved a CR, whereas four of five PET-positive patients did not respond to treatment. The 2-year PFS was 0% for PET-positive and 81% for PET-negative patients. As previously discussed, the better predictive value of positive versus negative PET during treatment, as well as at the end of chemotherapy, may be related to the high-risk patient population evaluated. In a different study of 23 NHL patients, FDG-PET after two to three cycles was used to predict

long-term outcome.[67] Relapse rate in patients with positive PET was 87% as compared with no relapses diagnosed in PET negative patients.

The earliest assessment of response during therapy was performed by Kostakoglu and coworkers using FDG-PET after 1 cycle of therapy in 30 patients with HD and NHL.[87] Imaging with a dual-head coincidence camera, they found a statistically significant difference in PFS between patients with positive and negative PET after the first cycle of chemotherapy. Visual definition of response early during therapy had a sensitivity, specificity and accuracy of 87%. PET after the first cycle had a lower false-negative rate (13%) than posttherapy PET (35%), possibly reflecting the presence of a small, but still detectable tumor load of resistent cells early, but not late in the therapy course.

In a large prospective study of a homogenous group of 70 patients with aggressive NHL, visual interpretation of FDG-PET performed after three to four cycles of first-line chemotherapy predicted PFS and overall survival independently from, and better than the international prognostic index.[88] Thirty-one of 37 PET negative patients achieved durable CR. Even when PET results were false negative, the PFS of these patients was longer than that of PET positive patients. All 33 PET-positive patients at mid-treatment failed to respond. Quantitative measurement of the percent decrease in SUV after one to two cycles of treatment as compared with baseline levels was shown to differentiate short-term responders from nonresponders in a group of 17 patients, most with advanced-stage lymphoma.[89] In the same study, visual analysis predicted 24 months outcome with a high PPV but lower NPV.

A number of studies have assessed the role of FDG-PET in predicting response to high dose chemotherapy with autologous bone marrow transplantation (HDT/ASCT).[90-93] The predictive value of FDG-PET performed before the therapeutic intervention for post transplantation prognosis was evaluated in 60 patients.[93] The study showed a significant difference in overall and progression-free survival after transplantation, between patients who had negative or positive PET before HDT/ASCT. Twenty-five of 30 patients with negative PET achieved a prolonged CR, whereas 26 of 30 patients with positive PET relapsed after ASCT. PET performed 2 to 5 weeks after initiation of salvage therapy was shown to predict outcome of HDT/ASCT better than CT.[92] A correlation between persistent response demonstrated on PET through the late phase of induction therapy and favorable outcome of transplant has been also demonstrated.[91] The need for optimized PET scheduling for the purpose of response assessment during different therapy protocols was demonstrated in a group of 14 patients assessed after ^{131}I-anti CD20 radioimmunotherapy (RIT).[94] A slower pattern of metabolic response of lymphoma to RIT was described in comparison with the previously reported response pattern to first-line chemotherapy. In patients receiving RIT, delayed FDG-PET, performed at 1 to 2 months after therapy had a better predictive value than early PET.[94]

A key factor for successful management of lymphoma is the ability to assess the presence and degree of an individual patient's response to therapy. Literature data indicate that FDG-PET provides an excellent tool for accurate assessment of response during and at the end of treatment and during follow up for diagnosis and restaging of recurrence. FDG-PET has been assessed for first-line induction therapy as well as for new and more aggressive treatment protocols. Despite this proven value of FDG-PET for monitoring therapy response, several open issues still need to be validated and standardized for optimized utilization of this test. The importance of the pretherapy baseline study for the assessment of response is still undefined. Today's limited literature data do not indicate that pretherapy PET has additional value for the accurate assessment of response after therapy.[65,67] The role of quantitative assessment of the degree of FDG uptake before and after treatment is unclear.[72] To date most conclusions are based on visual analysis of PET data while a quantitative evaluation has the potential to improve specificity and PPV of PET. Using an SUV value of 3 as a threshold for positive PET after treatment, the specificity of the test rose from 68 to 94% when compared with visual interpretation.[69] Quantitation, using SUV or other indices, may be of particular value in the early assessment of response during therapy, when slight changes in the degree of FDG uptake can occur.

The role of FDG-PET for assessing response to therapy of indolent NHL also needs to be addressed. Differences in natural history, prognosis and treatment options for this category of patients do not allow extrapolation of conclusions from the currently available literature data. Although FDG-PET appears to have a role for assessment of lymphoma response to treatment, large patient series need to be evaluated prospectively, using standardized protocols, to address additional open issues such as the epidemiologic characteristics of the study population, criteria for the qualitative and quantitative definition of imaging response on PET, and the timing, type, and length of follow up that should be implemented into routine clinical practice.

FDG-PET AND GA-67 SCINTIGRAPHY: COMPARATIVE STUDIES

More than two decades ago, Iosilevsky and coworkers showed that ^{67}Ga and ^{3}H-deoxyglucose are both indicators of a viable cancer tissue in an experimental tumor model.[60] They found a direct linear relationship between the amount of viable tumor tissue and the presence of uptake of both tracers. In treated fibrotic tumors, uptake of both ^{67}Ga and tritiated deoxyglucose was markedly

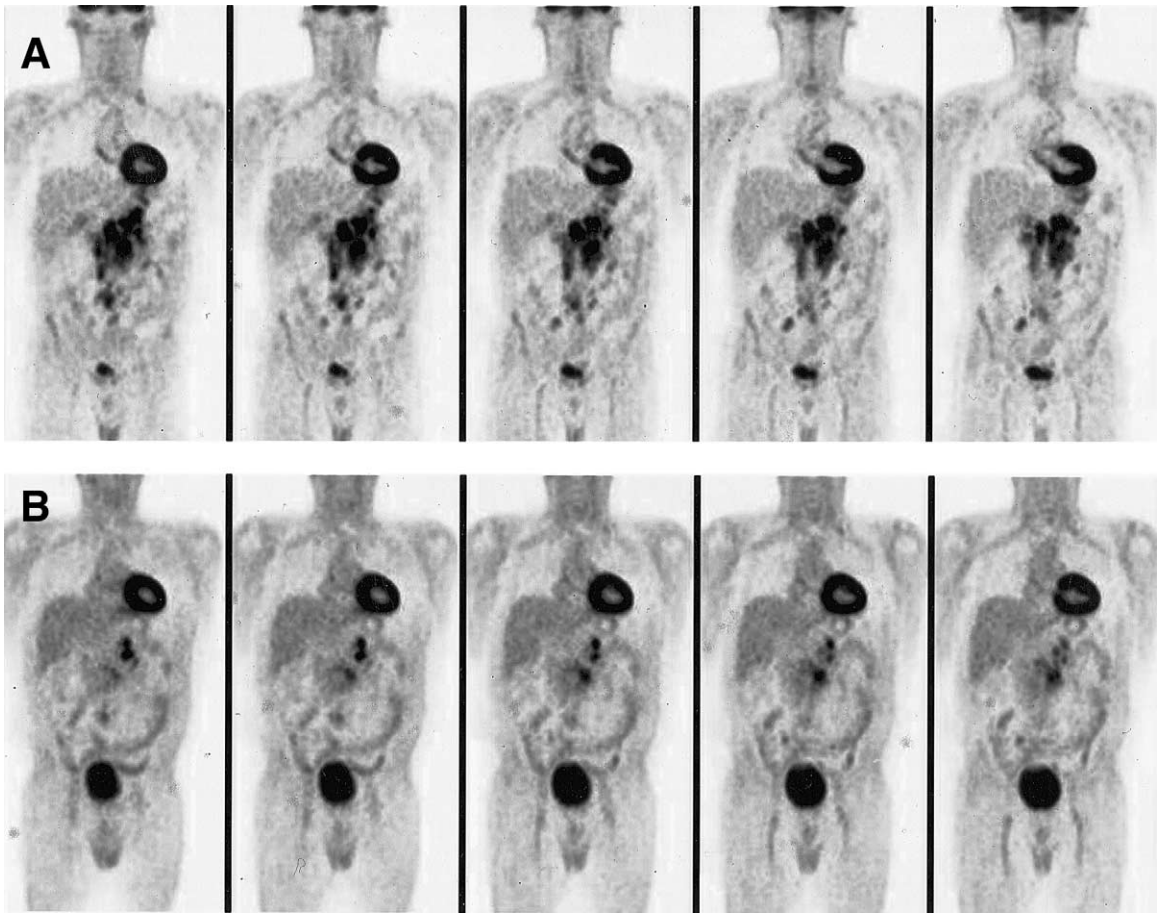

Fig 3. Positive positron emission tomography using ^{18}F-fluoro-deoxyglucose (FDG-PET) early during treatment; follow-up PET studies: assessment of partial response, prediction of poor outcome, and detection of recurrence. (A) Baseline FDG-PET of a 59-years-old patient with non-Hodgkin's lymphoma shows multiple areas of abnormal FDG uptake in sites of mesenteric and retroperitoneal adenopathy. (B) Repeat FDG-PET performed after two cycles of chemotherapy shows residual but less prominent abnormal FDG uptake in abdominal sites indicating partial response. (C) FDG-PET at the end of treatment is negative indicating that complete response was achieved. (D) Routine follow-up FDG-PET at 4 months of remission shows recurrent disease in abdominal sites.

decreased, while tumor size was not related to tumor viability. Large tumors consisting only of necrotic or fibrotic tissue showed lower ^{67}Ga and deoxyglucose uptake as compared with small but viable tumors that had been only partially treated previously.[60] Paul and coworkers, in a first report on FDG uptake in 5 lymphoma patients also performed a comparative analysis to ^{67}Ga uptake in the same patients. Four of the 5 patients had a positive PET study whereas only two of five demonstrated abnormal ^{67}Ga uptake.[22] In 21 patients with both HD and NHL of the head and neck who underwent both FDG imaging and ^{67}Ga scintigraphy, all tumor sites were detected by PET.[35] PET showed better performance than ^{67}Ga, but the fact that low doses of ^{67}Ga were injected and SPECT was performed in only a third of the study population should also be considered. FDG uptake also showed a better correlation with prognosis than Ga.[35]

Nuclear medicine techniques provide unique physiologic information about malignancies. Although both ^{67}Ga and FDG are tumor viability indicators, their mechanism of uptake by malignant tissue is based on different principles. ^{67}Ga is taken up by malignant cells, lymphoma in particular, probably based on an intracellular transferrin-related transport mechanism. Inside cells the tracer is incorporated in lysosome-like granules and shows a slower clearance from malignant as compared with normal tissues. FDG, as mentioned above, is incorporated in malignant cells with a high glycolytic metabolism, due to intracellular trapping of FDG-phosphate.[18]

For many years ^{67}Ga scintigraphy has been consid-

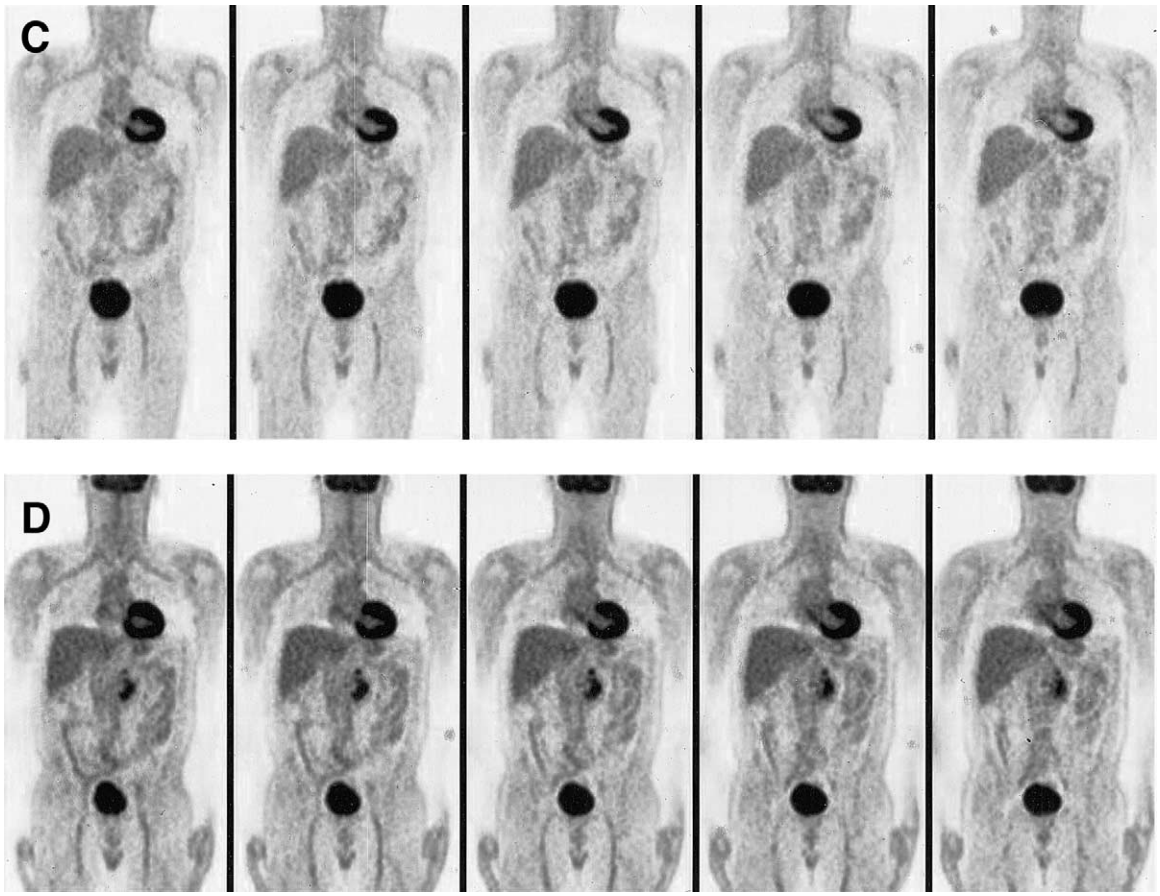

Fig 3 (cont'd).

ered the imaging modality of choice for functional assessment of lymphoma, and its value is well established. Despite technical progress in performing ^{67}Ga scintigraphy, poor count rates leading to low resolution images have made these studies difficult to interpret. Clear definition of sites of uptake and their exact topography are challenging for the inexperienced reader. With the advances in the availability of PET and FDG and subsequent widespread clinical applications, a number of studies have compared the performance capabilities of these two functional imaging modalities in the assessment of lymphoma.

A study comparing PET and ^{67}Ga evaluated 111 sites of disease in 25 patients with different types of lymphoma at diagnosis and relapse.[95] The sensitivity of PET was 96% versus 72% for ^{67}Ga. The false-negative ^{67}Ga studies were attributed to poor detection of low-grade NHL, bone and bone marrow involvement, as well as lesions smaller than 12 mm in diameter. PET was false negative in a single patient with low grade gastric NHL.[95] Sixteen patients with HD and NHL underwent both ^{67}Ga and PET for monitoring response to treatment or restaging of relapse.[96] Six of the 16 patients showed discongruent results between the two tests. Interestingly, in one study this discrepancy occurred early during treatment, after two cycles of chemotherapy. The high sensitivity of PET for detection of small tumor load that may be still present early during treatment has to be considered. The criterion of a negative ^{67}Ga study as the only good prognostic indicator may not, in the future, be applicable to PET results and needs therefore to be further explored.

The differences in the performance rate of PET, ^{67}Ga and CT for staging of HD and NHL were evaluated in 50 patients.[97] In this study the per-patient true positive yield for PET, ^{67}Ga and CT showed similar values (95%, 88% and 90% respectively). On a site-based analysis, PET showed superior values, 82%, as compared with both ^{67}Ga with 69% and CT, 68%. Fifty-one paired camera-based PET and ^{67}Ga studies were performed in 38 patients with HD and NHL at staging and restaging. The sensitivity of ^{67}Ga was 83% for patient analysis and 72% for lesion analysis in comparison with 100% for PET for both types of analysis.[98] Bar-Shalom and coworkers

have compared ^{67}Ga and camera-based PET in 84 patients with 219 suspected sites of disease.[99] ^{67}Ga defined the state of disease in 63% of patients and 33% of sites as compared with 83% and 87% for FDG imaging. In cases of discongruence between the two modalities, FDG imaging reports were confirmed as true positive in 71% and true negative in 92% of patients. A higher detection rate of camera-based PET was found for both nodal and extranodal lymphoma sites, in particular for accurate assessment of lymphomatous involvement of the skeleton.[99]

Diagnosis of splenic involvement, an additional common site of lymphoma, is difficult using nuclear medicine techniques because both ^{67}Ga and FDG are physiologically taken up in variable amounts by the normal spleen. In addition, lymphomatous splenic involvement is, as a rule, diffuse, thus increasing the diagnostic challenge. The value of PET and ^{67}Ga scintigraphy was compared in 32 patients with HD and clinically or surgically confirmed splenic involvement.[100] The sensitivity, specificity and accuracy of PET were 92%, 100%, and 97%, respectively, as compared with 50%, 95%, and 78% for ^{67}Ga.[99] As concluded by the authors, PET may be an accurate noninvasive modality for diagnosis of splenic involvement, leading to a potential decrease in the frequency of surgical staging.

A recent study has evaluated PET and ^{67}Ga after two cycles of chemotherapy in 26 patients with NHL. Overall, the authors concluded that PET allows for superior early monitoring of response to treatment as compared with ^{67}Ga.[101]

FDG imaging solves some of the clinical dilemmas previously reported for the use of ^{67}Ga scintigraphy. PET optimizes the correct characterization of viable or treated bone lymphoma as well as the diagnosis of visceral lymphoma involvement.[99] Benign perihilar ^{67}Ga uptake reported in a large number of patients, mostly during and after treatment has not been described for FDG-PET.[99] There are still a number of pitfalls common to both tests. Hyperplastic thymus demonstrates increased uptake of both FDG and ^{67}Ga. Various inflammatory processes also take up both tracers.[99] Technical characteristics, including better contrast and resolution, lower dosimetry, shorter scanning time with improved patient comfort, all favor FDG-PET imaging. It is indeed time to shift gears,[102] and this reality is taking place in most imaging centers that have access to PET and are active in evaluating lymphoma. Differences in the biological significance of FDG uptake and its dynamics in response to therapy, as compared with ^{67}Ga, should be considered in further clinical studies.

PET has made its way as the diagnostic modality for evaluation of HD and NHL into routine clinical practice, changing the management algorithm of lymphoma patients. In the future new PET tracers that will allow for a more accurate biological characterization of lymphoma and a specific treatment-oriented evaluation will enable the assessment of additional aspects related to the diagnosis and management of this potentially curable malignancy.

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REFERENCES

1. Boring C, Squires T, Tong T, et al: Cancer statistics. Ca Canc J Clin 44:7-26, 1994

2. Smith SD, Rubin CM, Horvath A, et al: Non-Hodgkin's lymphoma in children. Semin Oncol 17:113-119, 1990

3. Schoder H, Meta J, Yap C, et al: Effect of whole-body (18)F-FDG PET imaging on clinical staging and management of patients with malignant lymphoma. J Nucl Med 42:1139-1143, 2001

4. Hagemeister FB: Hodgkin's disease: the next decade. Leuk Lymph 21:53-61, 1996

5. Canellos GP: Current strategies for early Hodgkin's disease. Ann Oncol 7:S91-S93, 1996 (suppl 4)

6. Aisenberg AC: Coherent view of Non-Hodgkin's lymphoma. J Clin Oncol 13:2656-2675, 1995

7. Armitage JO, Wisenburger DD, Hutchins M, et al: Chemotherapy for diffuse large cell lymphoma—rapidly responding patients have more durable remissions. J Clin Oncol 4:160-164, 1986

8. Coiffier B, Bryon P, Berger F, et al: Intensive and sequential combination chemotherapy for aggressive malignant lymphomas (protocol LNH-80). J Clin Oncol 4:147-153, 1986

9. Hoh CK, Glaspy J, Rosen P, et al: Whole-body FDG-PET imaging for staging of Hodgkin's disease and lymphoma. J Nucl Med 38:343-348, 1997

10. O'Doherty MJ, Macdonald EA, Barrington SF, et al: Positron emission tomography in the management of lymphomas. Clin Oncol 14:415-426, 2002

11. Jerusalem G, Beguin Y, Fassotte MF, et al: Whole-body positron emission tomography using 18F-fluorodeoxyglucose compared to standard procedures for staging patients with Hodgkin's disease. Haematologica 86:266-273, 2001

12. Cook GJR, Fogelman I, Maisey MN: Normal physiological and benign pathological variants of 18-fluoro-2-deoxyglucose positron-emission tomography scanning: Potential for error in interpretation. Semin Nucl Med 26:308-314, 1996

13. Barrington SF, O'Doherty MJ: Limitations of PET for imaging lymphoma. Eur J Nucl Med Mol Imaging 30:S117-S127, 2003 (suppl 1)

14. Brink I, Reinhardt MJ, Hoegerle S, et al: Increased metabolic activity in the thymus gland studied with 18F-FDG PET: Age dependency and frequency after chemotherapy. J Nucl Med 42:591-595, 2001

15. Nakahara T, Fujii H, Ide M, et al: FDG uptake in the morphologically normal thymus: Comparison of FDG positron emission tomography and CT. Br J Radiol 74:821-824, 2001

16. Sugawara Y, Fisher SJ, Zasadny KR, et al: Preclinical and clinical studies of bone marrow uptake of fluorine-1-fluorodeoxyglucose with or without granulocyte colony-stimulating factor during chemotherapy. J Clin Oncol 16:173-180, 1998

17. Sugawara Y, Zasadny KR, Kison PV, et al: Splenic fluorodeoxyglucose uptake increased by granulocyte colony-stimulating factor therapy: PET imaging results. J Nucl Med 40:1456-1462, 1999

18. Bar-Shalom R, Yefremov N, Guralnik L, et al: Clinical performance of PET-CT in evaluation of cancer: Additional value for diagnostic imaging and patient management. J Nucl Med 44:1200-1209, 2003

19. Freudenberg LS, Antoch G, Schutt P, et al: FDG-PET-CT in re-staging of patients with lymphoma. Eur J Nucl Med Mol Imaging 31:325-329, 2004

20. Cohade C, Mourtzikos KA, Clark DP, et al: Utility of FDG PET-CT in patients with cutaneous T-cell lymphomas: initial evaluation. J Nucl Med 44:84P, 2003 (abstr)

21. Bar- Shalom R, Valdivia AY, Blaufox MD: PET imaging in oncology. Semin Nucl Med 30:150-185, 2000

22. Paul R: Comparison of Fluorine-18-2-fluorodeoxyglucose and Gallium-67 citrate imaging for detection of lymphoma. J Nucl Med 28:288-292, 1987

23. Newman JS, Francis IR, Kaminski MS, et al: Imaging of lymphoma with PET with 2-[F-18]fluoro-2-deoxy-D-glucose: Correlation with CT. Radiology 190:111-116, 1994

24. Jerusalem GH, Beguin YP: Positron emission tomography in non-Hodgkin's lymphoma (NHL): Relationship between tracer uptake and pathological findings, including preliminary experience in the staging of low-grade NHL. Clin Lymphoma 3:56-61, 2002

25. Friedberg JW, Chengazi V: PET scans in the staging of lymphoma: Current status. Oncologist 8:438-447, 2003

26. Leskinen-Kallio S, Ruotsalainen U, Nagren K, et al: Uptake of carbon-11-methionine and fluorodeoxyglucose in non-Hodgkin's lymphoma: A PET study. J Nucl Med 32:1211-1218, 1991

27. Hoffmann M, Kletter K, Diemling M, et al: Positron emission tomography with fluorine-18-2-fluoro-2-deoxy-D-glucose (F18-FDG) does not visualize extranodal B-cell lymphoma of the mucosa-associated lymphoid tissue (MALT)-type. Ann Oncol 10:1185-1189, 1999

28. Moog F, Bangerter M, Diederichs CG, et al: Lymphoma: Role of whole-body 2-deoxy-2-[F-18] fluoro-D-glucose (FDG) PET in nodal staging. Radiology 203:795-800, 1997

29. Stumpe KDM, Urbinelli M, Steinert HC, et al: Whole-body positron emission tomography using fluorodeoxyglucose for staging of lymphoma: Effectiveness and comparison with computed tomography. Eur J Nucl Med 25:721-728, 1998

30. Hoffmann M, Chott A, Puspok A, et al: 18F-fluorodeoxyglucose positron emission tomography (18F-FDG-PET) does not visualize follicular lymphoma of the duodenum. Ann Hematol 83:276-281, 2004

31. Hoffmann M, Kletter K, Becherer A, et al: 18F-fluorodeoxyglucose positron emission tomography (18F-FDG-PET) for staging and follow-up of marginal zone B-cell lymphoma. Oncology 64:336-340, 2003

32. Lapela M, Leskinen S, Minn HRI, et al: Increased glucose metabolism in untreated Non-Hodgkin's lymphoma: A study with positron emission tomography and Fluorine-18-Fluorodeoxyglucose. Blood 86:3522-3527, 1995

33. Rodriguez M, Rehn S, Ahlstrom H, et al: Predicting malignancy grade with PET in Non-Hodgkin's lymphoma. J Nucl Med 36:1790-1796, 1995

34. Okada J, Yoshikawa K, Itami M, et al: Positron emission tomography using Fluorine-18-fluorodeoxyglucose in malignant lymphoma: a comparison with proliferative activity. J Nucl Med 33:325-329, 1992

35. Okada J, Yoshikawa K, Imazeki K, et al: The use of FDG-PET in the detection and management of malignant lymphoma: Correlation of uptake with prognosis. J Nucl Med 32:686-691, 1991

36. Okada J, Oonish H, Yoshikawa K, et al: FDG-PET for predicting the prognosis of malignant lymphoma. Ann Nucl Med 8:187-191, 1994

37. Armitage JO: Drug therapy: Treatment of non Hodgkin's lymphoma. N Engl J Med 328:1023-1030, 1993

38. Partridge S, Timothy A, O'Doherty MJ, et al: 2-Fluorine-18-fluoro-2-deoxy-D glucose positron emission tomography in the pretreatment staging of Hodgkin's disease: influence on patient management in a single institution. Ann Oncol 11:1273-1279, 2000

39. Romer W, Schwaiger M: Positron emission tomography in diagnosis and therapy monitoring of patients with lymphoma. Clin Positron Imaging 1:101-110, 1998

40. Sandrasegaran K, Robinson PJ, Selby P: Staging of lymphoma in adults. Clin Oncol 94:149-161, 1994

41. Weihrauch MR, Re D, Bischoff S, et al: Whole-body positron emission tomography using 18F-fluorodeoxyglucose for initial staging of patients with Hodgkin's disease. Ann Hematol 81:20-25, 2002

42. Bangerter M, Moog F, Buchmann I, et al: Whole-body 2-[18F]-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) for accurate staging of Hodgkin's disease. Ann Oncol 9:1117-1122, 1998

43. Sasaki M, Kuwabara Y, Koga H, et al: Clinical impact of whole body FDG-PET on the staging and therapeutic decision-making for malignant lymphoma. Ann Nucl Med 16:337-345, 2002

44. Jerusalem G, Warland V, Majjar F, et al: Whole-body 18F-FDG-PET for the evaluation of patients with Hodgkin's disease and Non-Hodgkin's lymphoma. Nucl Med Commun 20:13-20, 1999

45. Delbeke D, Martin WH, Morgan DS, et al: 2-deoxy-2-[F-18]fluoro-D-glucose imaging with positron emission tomography for initial staging of Hodgkin's disease and lymphoma. Mol Imaging Biol 4:105-114, 2002

46. Buchmann I, Reinhardt M, Elsner K, et al: 2-(fluorine-18)fluoro-2-deoxy-D-glucose positron emission tomography in the detection and staging of malignant lymphoma. A bicenter trial. Cancer 91:889-899, 2001

47. Jerusalem G, Beguin Y, Najjar F, et al: Positron emission tomography (PET) with 18F-fluorodeoxyglucose (18F-FDG) for the staging of low-grade non-Hodgkin's lymphoma (NHL). Ann Oncol 2:825-830, 2001

48. Najjar F, Hustinx R, Jerusalem G, et al: Positron emission tomography (PET) for staging low-grade non-Hodgkin's

lymphomas (NHL). Cancer Biother Radiopharm 16:297-304, 2001

49. Moog F, Bangerter M, Diederichs CG, et al: Extranodal malignant lymphoma: Detection with FDG PET versus CT. Radiology 206:475-481, 1998

50. Moog F, Bangerter M, Kotzerke J, et al: 18-F-Fluorodeoxyglucose-positron emission tomography as a new approach to detect lymphomatous bone marrow. J Clin Oncol 16:603-609, 1998

51. Moog F, Kotzerke J, Reske SN: FDG PET can replace bone scintigraphy in primary staging of malignant lymphoma. J Nucl Med 40:1407-1413, 1999

52. Rini JN, Leonidas JC, Tomas MB, et al: 18F-FDG PET versus CT for evaluating the spleen during initial staging of lymphoma. J Nucl Med 44:1072-1074, 2003

53. Carr R, Barrington SF, Madan B, et al: Detection of lymphoma in bone marrow by whole-body positron emission tomography. Blood 91:3340-3346, 1998

54. Kostakoglu L, Goldsmith SJ: Positron emission tomography in lymphoma: Comparison with computed tomography and Gallium-67 single photon emission computed tomography. Clin Lymphoma 1:67-74, 2000

55. Klose T, Leidl R, Buchmann I, et al: Primary staging of lymphomas: cost-effectiveness of FDG-PET versus computed tomography. Eur J Nucl Med 27:1457-1464, 2000

56. Schiepers C, Filmont JE, Czernin J: PET for staging of Hodgkin's disease and non-Hodgkin's lymphoma. Eur J Nucl Med Mol Imaging 30:S82-S88, 2003 (suppl 1)

57. Radford JA, Cowan RA, Flanagan M, et al: The significance of residual mediastinal abnormality on the chest radiograph following treatment for Hodgkin's disease. J Clin Oncol 6:940-946, 1988

58. Surbone A, Longo DL, DeVita VT, et al: Residual abdominal masses in aggressive non-Hodgkin's lymphoma after combination chemotherapy: significance and management. J Clin Oncol 6:1832-1837, 1988

59. Reske SN: PET and restaging of malignant lymphoma including residual masses and relapse. Eur J Nucl Med Mol Imaging 30:S89-S96, 2003 (suppl 1)

60. Iosilevsky G, Front D, Bettman L, et al: Uptake of Gallium-67 citrate and [2-3H] deoxyglucose in the tumor model, following chemotherapy and radiotherapy. J Nucl Med 26:278-282, 1985

61. Coiffier B: How to interpret the radiological abnormalities that persist after treatment in non-Hodgkin's lymphoma patients? Ann Oncol 10:1141-1143, 1999

62. Jochelson M, Mauch P, Balikian J, et al: The significance of the residual mediastinal mass in treated Hodgkin's disease. J Clin Oncol 3:637-640, 1985

63. Cremerius U, Fabry U, Neuerburg J, et al: Positron emission tomography with 18F-FDG to detect residual disease after therapy for malignant lymphoma. Nucl Med Commun 19:1055-1063, 1998

64. Zinzani PL, Magagnoli M, Chierichetti F, et al: The role of positron emission tomography (PET) in the management of lymphoma patients. Ann Oncol 10:1181-1184, 1999

65. Jerusalem G, Beguin Y, Fassotte MF, et al: Whole-body positron emission tomography using 18F-fluorodeoxyglucose for post-treatment evaluation in Hodgkin's disease and non-Hodgkin's lymphoma has higher diagnostic and prognostic value than classical computed tomography scan imaging. Blood 94:429-433, 1999

66. Lavely WC, Delbeke D, Greer JP, et al: FDG PET in the follow-up management of patients with newly diagnosed Hodgkin and non-Hodgkin lymphoma after first-line chemotherapy. Int J Radiat Oncol Biol Phys 57:307-315, 2003

67. Mikhaeel NG, Timothy AR, O'Doherty MJ, et al: 18-FDG-PET as a prognostic indicator in the treatment of aggressive Non-Hodgkin's Lymphoma-comparison with CT. Leuk Lymphoma 39:543-553, 2000

68. Spaepen K, Stroobants S, Dupont P, et al: Prognostic value of positron emission tomography (PET) with fluorine-18 fluorodeoxyglucose ([18F]FDG) after first-line chemotherapy in non-Hodgkin's lymphoma: Is [18F]FDG-PET a valid alternative to conventional diagnostic methods? J Clin Oncol 19: 414-419, 2001

69. Naumann R, Vaic A, Beuthien-Baumann B, et al: Prognostic value of positron emission tomography in the evaluation of post-treatment residual mass in patients with Hodgkin's disease and non-Hodgkin's lymphoma. Br J Haematol 115:793-800, 2001

70. Montravers F, McNamara D, Landman-Parker J, et al: [(18)F]FDG in childhood lymphoma: clinical utility and impact on management. Eur J Nucl Med Mol Imaging 29:1155-1165, 2002

71. Weihrauch MR, Re D, Scheidhauer K, et al: Thoracic positron emission tomography using 18F-fluorodeoxyglucose for the evaluation of residual mediastinal Hodgkin disease. Blood 98:2930-2934, 2001

72. Dittmann H, Sokler M, Kollmannsberger C, et al: Comparison of 18FDG-PET with CT scans in the evaluation of patients with residual and recurrent Hodgkin's lymphoma. Oncol Rep 8:1393-1399, 2001

73. Spaepen K, Stroobants S, Dupont P, et al: Can positron emission tomography with [(18)F]-fluorodeoxyglucose after first-line treatment distinguish Hodgkin's disease patients who need additional therapy from others in whom additional therapy would mean avoidable toxicity? Br J Haematol 115:272-278, 2001

74. de Wit M, Bohuslavizki KH, Buchert R, et al: 18FDG-PET following treatment as valid predictor for disease-free survival in Hodgkin's lymphoma. Ann Oncol 12:29-37, 2001

75. Hueltenschmidt B, Sautter-Bihl ML, Lang O, et al: Whole body positron emission tomography in the treatment of Hodgkin disease. Cancer 91:302-310, 2001

76. Mikhaeel NG, Timothy AR, Hain SF, et al: 18-FDG-PET for the assessment of residual masses on CT following treatment of lymphomas. Ann Oncol 11:147-150, 2000 (suppl 1)

77. de Wit M, Bumann D, Beyer W, et al: Whole-body positron emission tomography (PET) for diagnosis of residual mass in patients with lymphoma. Ann Oncol 8:57-60, 1997 (suppl 1)

78. Cremerius U, Fabry U, Kroll U, et al: Clinical value of FDG PET for therapy monitoring of malignant lymphoma-results of a retrospective study in 72 patients. Nuklearmedizin 38:24-30, 1999

79. Bar Shalom R, Mor M, Yefremov N, et al: The value of Ga-67 scintigraphy and F-18 fluorodeoxyglucose positron emission tomography in staging and monitoring the response of lymphoma to treatment. Sem Nucl Med 31:177-190, 2001

80. Bangerter M, Kotzerke J, Griesshammer M, et al: Positron emission tomography with 18-fluorodeoxyglucose in the staging and follow-up of lymphoma in the chest. Acta Oncol 38:799-804, 1999

81. Jerusalem G, Beguin Y, Fassotte MF, et al: Early detection of relapse by whole-body positron emission tomography in the follow-up of patients with Hodgkin's disease. Ann Oncol 14:123-130, 2003

82. Front D, Bar-Shalom R, Mor M, et al: Aggressive non-Hodgkin lymphoma: Early prediction of outcome with Ga67 scintigraphy. Radiology 214:253-257, 2000

83. Hoekstra OS, Ossenkoppele GJ, Golding R, et al: Early treatment response in malignant lymphoma, as determined by planar fluorine-18-fluorodeoxyglucose scintigraphy. J Nucl Med 34:1706-1710, 1993

84. Dimitrakopoulou-Strauss A, Strauss LG, Goldschmidt H, et al: Evaluation of tumor metabolism and multi-drug resistance in patients with treated malignant lymphomas. Eur J Nucl Med 22:434-442, 1995

85. Wiedmann E, Baican B, Hertel A, et al: Positron emission tomography (PET) for staging and evaluation of response to treatment in patients with Hodgkin's disease. Leuk Lymphoma 34:545-551, 1999

86. Jerusalem G, Beguin Y, Fassotte MF, et al: Persistent tumor 18F-FDG uptake after a few cycles of polychemotherapy is predictive of treatment failure in non-Hodgkin's lymphoma. Haematologica 85:613-618, 2000

87. Kostakoglu L, Coleman M, Leonard JP, et al: PET predicts prognosis after 1 cycle of chemotherapy in aggressive lymphoma and Hodgkin's disease. J Nucl Med 43:1018-1027, 2002

88. Spaepen K, Stroobants S, Dupont P, et al: Early restaging positron emission tomography with (18)F-fluorodeoxyglucose predicts outcome in patients with aggressive non-Hodgkin's lymphoma. Ann Oncol 13:1356-1363, 2003

89. Torizuka T, Nakamura F, Kanno T, et al: Early therapy monitoring with FDG-PET in aggressive non-Hodgkin's lymphoma and Hodgkin's lymphoma. Eur J Nucl Med Mol Imaging 31:22-28, 2004

90. Becherer A, Mitterbauer M, Jaeger U, et al: Positron emission tomography with [18F]2-fluoro-D-2-deoxyglucose (FDG-PET) predicts relapse of malignant lymphoma after high-dose therapy with stem cell transplantation. Leukemia 16:260-267, 2002

91. Cremerius U, Fabry U, Wildberger JE, et al: Pretransplant positron emission tomography (PET) using fluorine-18-fluoro-deoxyglucose (FDG) predicts outcome in patients treated with high-dose chemotherapy and autologous stem cell transplantation for non-Hodgkin's lymphoma. Bone Marrow Transplant 30:103-111, 2002

92. Filmont JE, Czernin J, Yap C, et al: Value of F-18 fluorodeoxyglucose positron emission tomography for predicting the clinical outcome of patients with aggressive lymphoma prior to and after autologous stem-cell transplantation. Chest 124:608-613, 2003

93. Spaepen K, Stroobants S, Dupont P, et al: Prognostic value of pretransplantation positron emission tomography using fluorine 18-fluorodeoxyglucose in patients with aggressive lymphoma treated with high-dose chemotherapy and stem cell transplantation. Blood 102:53-59, 2003

94. Torizuka T, Zasadny KR, Kison PV, et al: Metabolic response of non-Hodgkin's lymphoma to 131I-anti-B1 radioimmunotherapy: Evaluation with FDG PET. J Nucl Med 41:999-1005, 2000

95. Shen YY, Kao A, Yen RF: Comparison of 18F-fluoro-2-deoxyglucose positron emission tomography and gallium-67 citrate scintigraphy for detecting malignant lymphoma. Oncol Rep 9:321-325, 2002

96. Van den Bossche B, Lambert B, De Winter F, et al: 18-FDG PET versus high-dose Ga-67 scintigraphy for restaging and treatment follow up of lymphoma patients. Nucl Med Commun 23:1079-1083, 2002

97. Wirth A, Seymour JF, Hicks RJ, et al: Fluorine-18 fluorodeoxyglucose positron emission tomography, Gallium-67 scintigraphy and conventional staging for Hodgkin's disease and Non-Hodgkin's lymphoma. Am J Med 112:262-268, 2002

98. Kostakoglu L, Leonard JP, Kuji I, et al: Comparison of fluorine-18 fluorodeoxyglucose positron emission tomography and Ga-67 scintigraphy in evaluation of lymphoma. Cancer 94:879-888, 2002

99. Bar-Shalom R, Yefremov N, Haim N, et al: Camera-based FDG PET and Ga-67 SPECT in evaluation of lymphoma: comparative study. Radiology 227:353-360, 2003

100. Rini JN, Manalili EY, Hoffman MA, et al: F-18 FDG versus Ga-67 for detecting splenic involvement in Hodgkin's disease. Clin Nucl Med 27:572-527, 2002

101. Zijlstra JM, Hoekstra O, Raijmaker PGH, et al: 18-FDG positron emission tomography versus Ga-67 scintigraphy as prognostic test during chemotherapy for non-Hodgkin's lymphoma. Brit J Haemat 123:454-462, 2003

102. Kostakoglu L, Goldsmith S: Fluorine-18 fluorodeoxyglucose positron emission tomography in the staging and follow up of lymphoma: Is it time to shift gears? Eur J Nucl Med 27:1564-1578, 2000