

Initial Staging of Lymphoma With Positron Emission Tomography and Computed Tomography

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Lymphomas represent a diverse range of diseases with manifold presentations, outlook, and therapeutic approaches. Key to the modern management of lymphoma is accurate delineation of the extent of disease. The inability of computed tomography (CT) to identify the involvement of nonenlarged nodes and its relatively poor sensitivity in the detection of extra-nodal sites of involvement limit the performance of noninvasive staging techniques. Functional imaging techniques such as Ga-67 scintigraphy have been used for many years to improve the evaluation of patients with lymphoma. While providing complementary information to CT in many clinical settings, functional imaging has never had sufficient accuracy or localizing ability to seriously challenge conventional primary staging paradigms. ¹⁸F-Fluorodeoxyglucose positron emission tomography (FDG PET), however, has been demonstrated to have both higher sensitivity and specificity than CT in many comparative series. Now that this technology also can be performed at the same time as structural imaging in the form of hybrid PET/CT devices, clinicians are rethinking the methods used to select, plan, and monitor therapy of lymphoma patients. In our institution, FDG PET/CT has become the preferred initial staging tool for patients with lymphoma.

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The lymphomas are a group of related diseases for which the prognosis and management options often are determined by the anatomical extent of disease. This is termed the disease “stage” and is universally expressed using the Ann Arbor criteria, which are discussed elsewhere in this issue of the *Seminars in Nuclear Medicine*. Because lymphoma can involve almost any tissue in the body, staging evaluation often involves the use of a range of diagnostic modalities, including structural and functional imaging, and invasive procedures, such as bone marrow biopsy and, in rare cases, laparoscopy or laparotomy, including splenectomy. Imaging-based staging traditionally has been based on the detection of nodal or extra-nodal masses. Lymph node involvement usually is de-

termined by the presence of nodal enlargement, although an increased number of small nodes may be considered suspicious in some clinical circumstances.¹ Contrast-enhanced computed tomography (CT) scanning has been the most widely used and informative lymphoma imaging modality, but chest x-ray, magnetic resonance imaging (MRI), ultrasound, and lymphography frequently are used to provide additional information in individual cases. In some institutions, functional imaging techniques such as bone, Ga-67, Tl-201, and peptide receptor radionuclide scanning also have complemented these investigations. Some of these functional imaging techniques also are the subject of articles in this issue of the *Seminars in Nuclear Medicine*. However, all of these imaging modalities have significant limitations as stand-alone staging tests, which account for their frequent use in combination. On the basis of encouraging preliminary results,² positron emission tomography (PET) with ¹⁸F-fluorodeoxyglucose (FDG) has been evaluated extensively in various clinical situations, including staging, therapeutic monitoring, and surveillance in patients with lymphoma.

In our facility, the use of FDG PET has grown markedly during the past few years, particularly since the availability of PET/CT in late 2001 (Fig. 1). In 2004, 845 of 3616 (23%) PET studies performed in our facility were for lymphoma. This scan indication is now our most frequent one. Increas-

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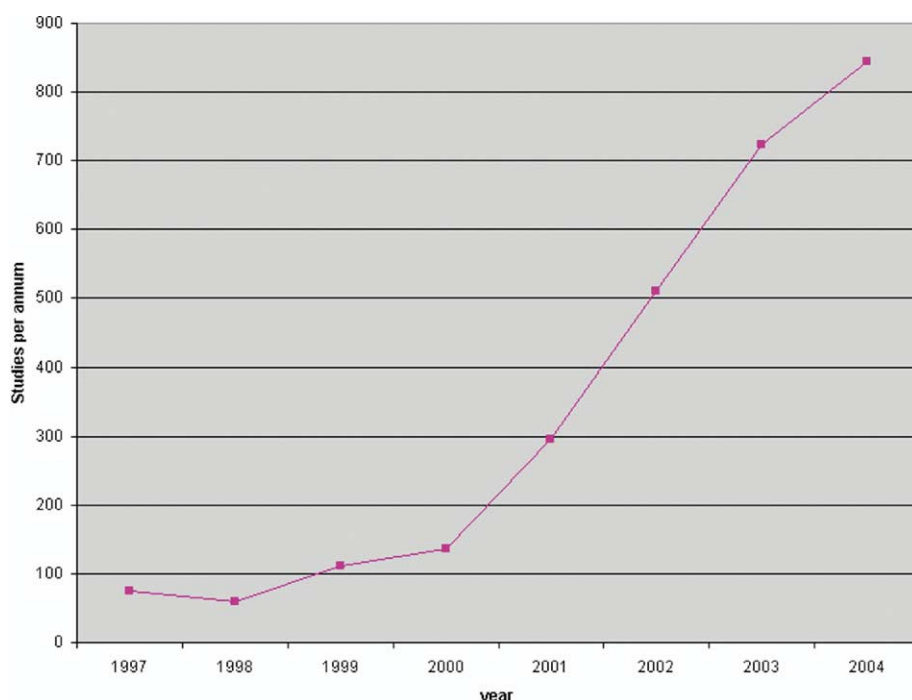


Figure 1 Since the establishment of our PET facility in late 1996, there has been a progressive increase in the number of studies performed for the evaluation of lymphoma. A marked acceleration in the utilization of PET coincided with installation of a PET/CT scanner in late 2001. (Color version of figure is available online.)

ingly, PET/CT is replacing stand-alone diagnostic CT as the preferred method of staging, therapeutic monitoring, and surveillance of lymphoma patients and has replaced Ga-67 scanning in our facility, except for the rare circumstances in which FDG PET imaging is either not practically possible or provides suboptimal imaging (eg, poorly controlled diabetes). This change in the initial staging paradigm is consistent with a recently published article demonstrating that diagnostic CT adds little to PET/CT in the evaluation of lymphoma.³

To understand the appropriate clinical use of FDG PET in the primary staging of lymphoma, it is important to first consider the clinical features of the principal subtypes of lymphoma, the different stage-based management options, and the decision points and management dilemmas that may confront treating clinicians when dealing with a patient with newly diagnosed disease. The preceding review by Dr. Lu in this issue of the *Seminars in Nuclear Medicine* provides a useful background in this regard. To provide an overview of how these factors influence the use and interpretation of PET findings, we will briefly discuss the rationale for the use of FDG PET in various clinical scenarios related to the initial staging of lymphoma.

Rationale for the Use of PET Scanning in Primary Staging

The key issue with respect to understanding the potential utility of FDG PET in "lymphoma" is that this term covers a wide range of diseases with differing natural histories, patterns of organ spread, and response to therapy. Although the World Health Organization/Revised European-American Classification of Lymphoid Neoplasms (ie, WHO/REAL) classification has 3 major categories of lymphoid malignancies, ie, Hodgkin's lymphoma (HL) and the non-Hodgkin's

lymphomas (NHL) of B-cell or T-cell/natural killer (NK) cell origin,⁴ within each group there is very significant variability in management and prognosis.^{5,6} Nevertheless, in both HL and NHL, prognosis and treatment depend critically on histological type and disease stage. Biological characteristics, including histologic grade, also may influence outcome and can potentially be assayed by PET.

For patients with early-stage classical HL (nonbulky stage I or II), extended-field radiation therapy historically has been the most common treatment approach and can achieve excellent cure rates. Because of concerns about the long-term toxicity of wide-field high-dose irradiation and alkylating-agent based chemotherapy regimens, such as MOPP,⁷ a move has been made toward the use of combined modality protocols, employing fewer cycles of modern nonalkylating-agent based polychemotherapy regimens, such as ABVD, followed by lower dose (20-30 Gy) irradiation of smaller involved fields. This combined modality strategy has been compared with radiotherapy alone, demonstrating improved failure-free survival (usually >90% at 5 years), but a clear difference in overall survival is not yet apparent.⁸ For patients with bulky (>10 cm) stage I-II disease, treatment usually consists of a full course of chemotherapy (6-8 cycles), as is used normally in patients with advanced disease, followed by radiotherapy directed at the sites of initial bulk, most commonly anterior mediastinal mass. Patient with stages III and IV are treated with full-course chemotherapy, but radiotherapy may be delivered to sites that were bulky at presentation or that failed to respond completely to chemotherapy.

Thus, in the primary staging setting, detection of more extensive disease by PET than by conventional imaging would be of major relevance for patients with apparently limited stage HL in whom upstaging could alter management from being radiation-based to chemotherapy alone or com-

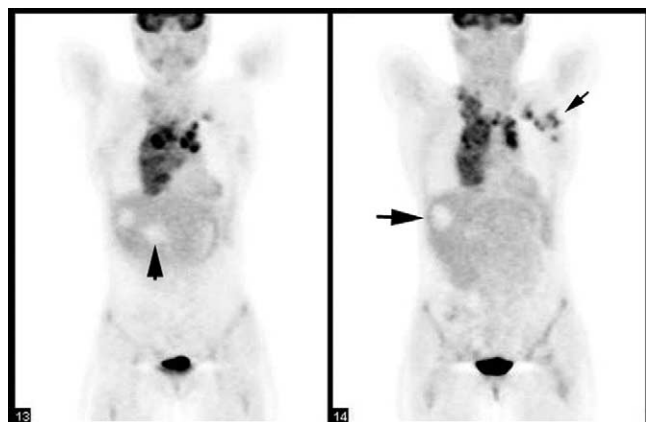


Figure 2 This patient with bulky mediastinal HL was planned for chemotherapy followed by radiotherapy. Focal liver lesions were considered equivocal for disease on CT with hepatic cysts being a differential diagnosis. PET confirmed low metabolic activity in the hepatic lesions (vertical and horizontal arrows). The extent of metabolically active disease in the mediastinum lower right neck and left axilla was used to guide radiotherapy. The left axillary nodes (oblique arrow) were not clinically or radiologically involved.

bined modality therapy. It also may help to better define radiation treatment volumes in both early and more advanced disease stages by better defining gross tumor volume (Fig. 2). Demonstration of disease in normal-sized lymph nodes could be of particular importance for planning radiation therapy, given that the quality of radiation therapy delivery has a major impact on overall survival.⁹ Improved prognostic stratification also may be an important justification for FDG PET staging in evaluation of newly diagnosed cases, although the prognostic implications of previously occult disease detected by PET require further evaluation. Although unproven, it is intuitively likely that PET-detected stage III or IV patients (Fig. 3) will have a prognosis paralleling that of similar patients with equivalent volume stage III or IV disease detected by conventional modalities. Nodular lymphocyte-predominant HL has a more indolent biology compared with classical HL, and results of treatment of early-stage disease with radiation therapy alone are excellent.¹⁰ If chemotherapy is not used to treat potential systemic microscopic disease in HL, then the accurate tailoring of radiation therapy fields to cover all gross disease becomes even more critical.

A similar rationale exists for the use of PET in many subtypes of NHL. The more-than 35 clinicopathologic entities described within the spectrum of NHL can be divided into the more clinically useful groups of “indolent” or “aggressive” lymphomas. The most common “indolent” lymphomas are the follicle-center cell (“follicular”) lymphomas, and the most common “aggressive” lymphomas are the diffuse large B-cell lymphomas. For both “indolent” and “aggressive” NHL, stage has a critical role in the selection of treatment. Noncontiguous lymph node involvement and extra-nodal involvement, both uncommon in HL, are more common in patients with NHL and, therefore, sensitive whole-body evaluation is likely to be of major importance in accurately staging these dis-

eases. In particular, bone marrow and hepatic involvement are more common in patients with NHL than HL and may be difficult to detect on conventional imaging. This is important because prognosis is strongly influenced by the number of extra-nodal sites involved.⁶ One of the difficulties in staging NHL is detection of focal, as opposed to diffuse, bone marrow involvement because the former can potentially be missed on bone marrow biopsy, particularly if suboptimal samples are obtained for evaluation or if suboptimal evaluation methods used.¹¹ Radionuclide bone scanning is relatively insensitive, and MRI is more sensitive but may require multiple sequences to achieve adequate sensitivity.¹² As discussed below, PET may have particular advantages for evaluating extra-nodal involvement (Fig. 4), including focal bone marrow disease (Fig. 5), splenic (Fig. 6), and small bowel disease (Fig. 7).

With respect to therapy selection, early stage (I and II) “indolent” NHL can be effectively treated with radiation therapy, including all known sites of disease, with approximately 40% to 50% of conventionally staged patients likely to be cured,¹³ although there is some evidence to support the use

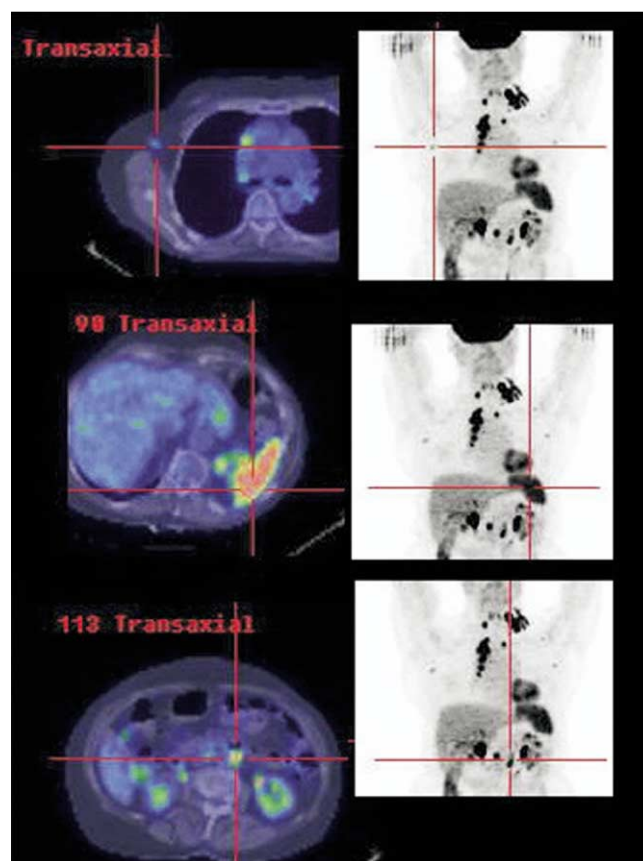


Figure 3 On conventional staging this patient with low-grade (follicular) NHL had stage 2A disease. CT demonstrated left lower cervical and mediastinal lymphadenopathy. There was no splenomegaly, and bone marrow biopsy was negative. FDG PET/CT demonstrated abnormal uptake in nonenlarged axillary and para-aortic nodes and intense splenic uptake, upstaging the patient from stage 1 to stage 3 disease and changing our treatment to chemotherapy. (Color version of figure is available online.)

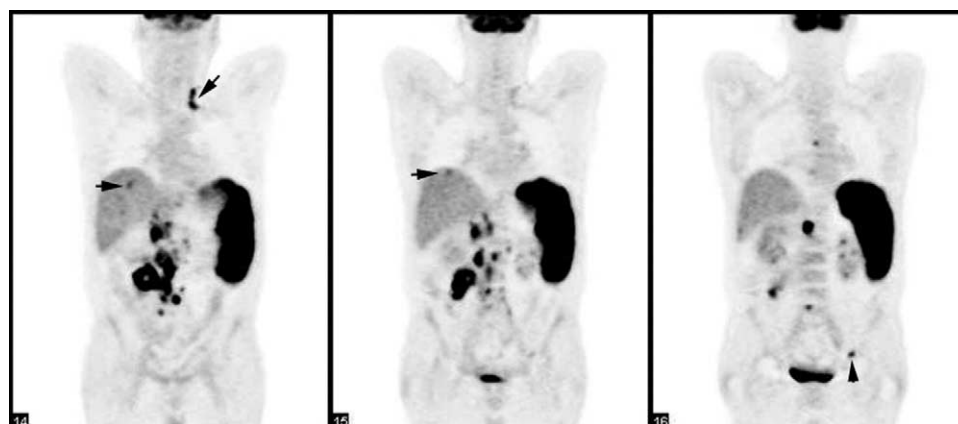


Figure 4 This patient presented with weight loss and epigastric pain and was found to have an epigastric mass with abdominal para-aortic lymphadenopathy and splenomegaly on CT. Biopsy of the mesenteric mass was inconclusive, and bone marrow biopsy was negative. FDG PET confirmed known sites of abnormality and additional focal liver (horizontal arrows), bone (vertical arrow and other sites not displayed in these coronal planes), and left supraclavicular nodal disease (oblique arrow). The patient was subsequently confirmed to have stage IV NHL with focal bone lesions on MRI.

of chemotherapy as an adjuvant treatment to involved field radiotherapy.¹⁴ Accordingly, accurate delineation of disease sites also may have implications for radiotherapy planning and by better inclusion of gross tumor volume may improve progression-free survival and overall cure rates, although this might be difficult to demonstrate given the relatively favorable median survival of such patients even with current techniques. Chemotherapy is not used routinely as sole therapy

for early-stage disease, except in rare cases where radiotherapy is contraindicated or in investigational protocols.

It needs to be recognized that the vast majority of patients with advanced “indolent” NHL are not cured with current therapies, although the addition of immunotherapy with monoclonal antibodies directed toward CD-20 (such as rituximab) to standard chemotherapy regimens appears to be capable of improving progression free survival¹⁵ and perhaps

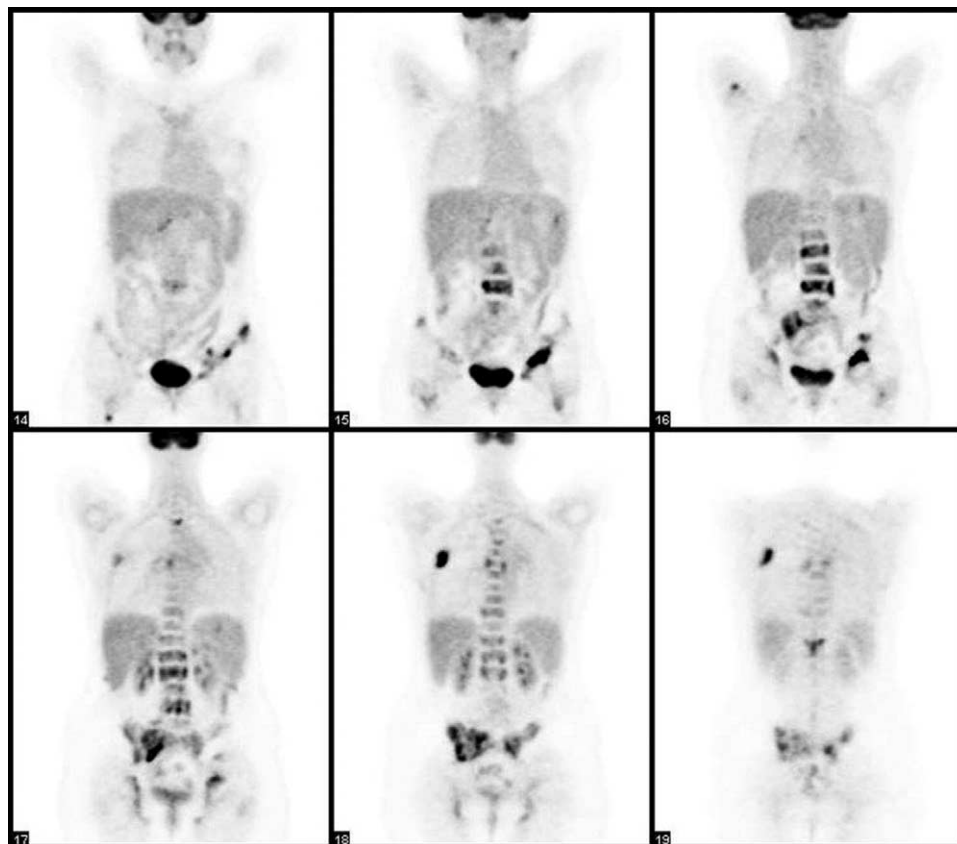
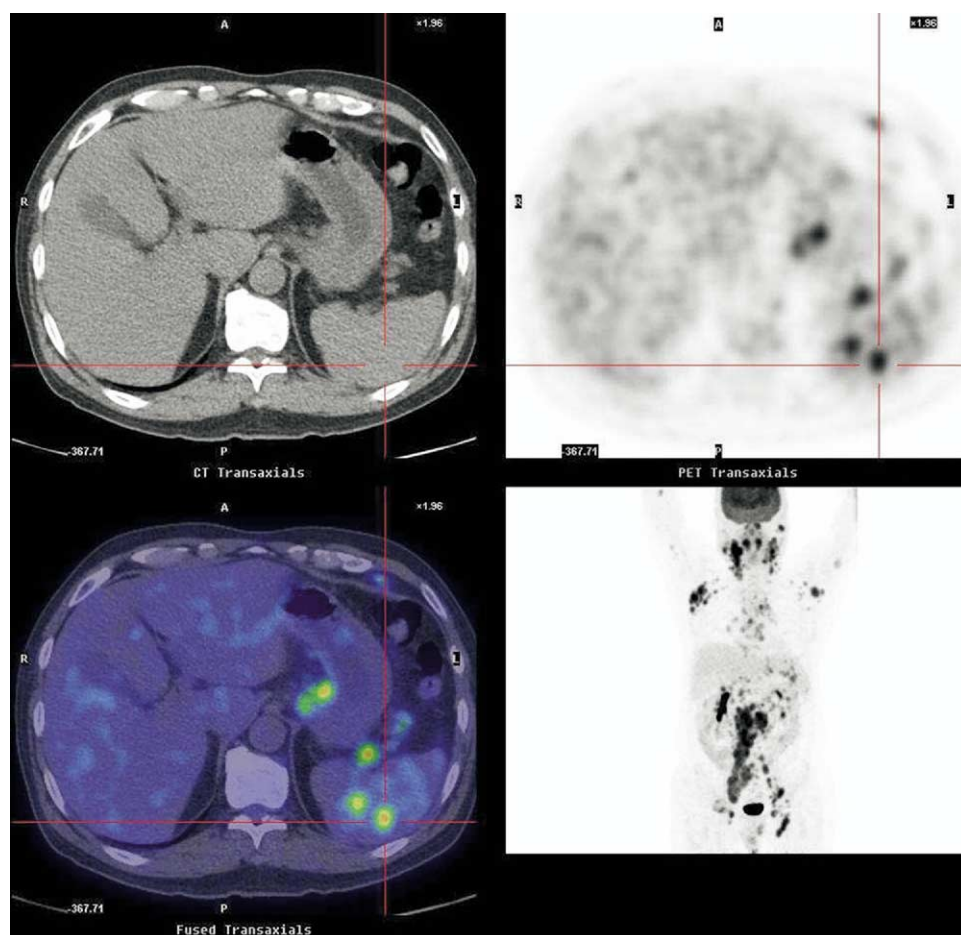


Figure 5 Because of normal physiological activity in the bone marrow, it can be difficult to confidently diagnose diffuse marrow infiltration, particularly if the intensity of uptake is not particularly marked and there is no evidence of bone marrow expansion. In this setting, bone marrow biopsy is likely to be more sensitive than FDG PET. However, in cases with multifocal bone involvement FDG PET, as demonstrated in this case, sampling error may yield a false-negative bone marrow biopsy result. In such cases, PET and particularly PET/CT can be used to guide biopsy.

Figure 6 In addition to its ability to detect diffuse splenic infiltration by virtue of diffusely and, often, intensely increased FDG uptake in the spleen relative to the liver, PET also can detect focal splenic deposits, even in the absence of structural abnormality. As well as uptake in non-enlarged lesser curve and splenic hilar nodes, several focal splenic nodules are clearly apparent, particularly on fused PET/CT images. (Color version of figure is available online.)



overall survival for patients with advanced disease.¹⁶ Treatment options, therefore, are quite varied and range in aggressiveness from observation through to total body irradiation and bone marrow transplantation. None of the various treatment strategies has yet been shown to be clearly superior. It remains to be established whether disease burden and other metabolic characteristics that may be able to be characterized on PET may help to determine which patients might benefit from more aggressive treatment strategies. However, in these

patients a staging FDG PET may be important as a baseline for subsequent assessment of therapeutic response. At this time, the clinical utility of adding FDG PET to the staging of patients with clinically advanced “low-grade” NHL remains unclear but it is possible that the whole-body staging capability of PET and PET/CT may simplify the staging process and offer a convenient alternative to multiple other investigations that might otherwise be performed.

For patients with stage I or stage II “aggressive” NHL, pri-

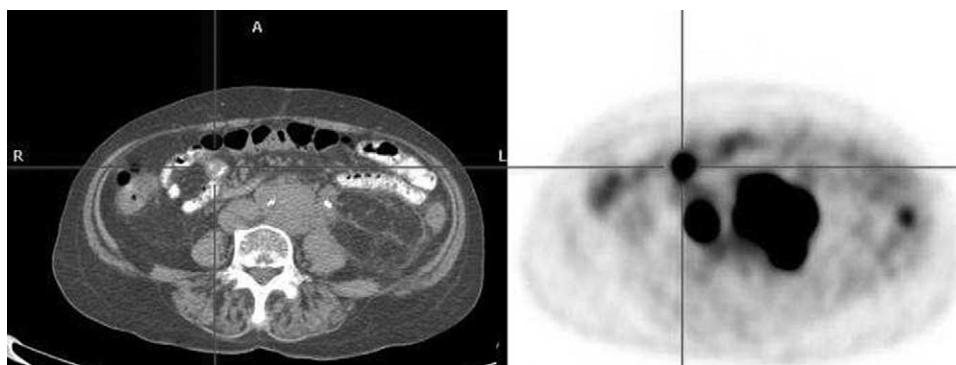


Figure 7 This patient presented with abdominal pain, and bulky para-aortic lymphadenopathy was identified on CT. FDG PET demonstrated high uptake in multiple abdominal nodes as well as several discrete foci with slight elongation, suggesting small bowel involvement. Coregistered PET images and CT with oral contrast obtained contemporaneously on hybrid PET/CT demonstrate intense uptake corresponding to mural thickening of small bowel.

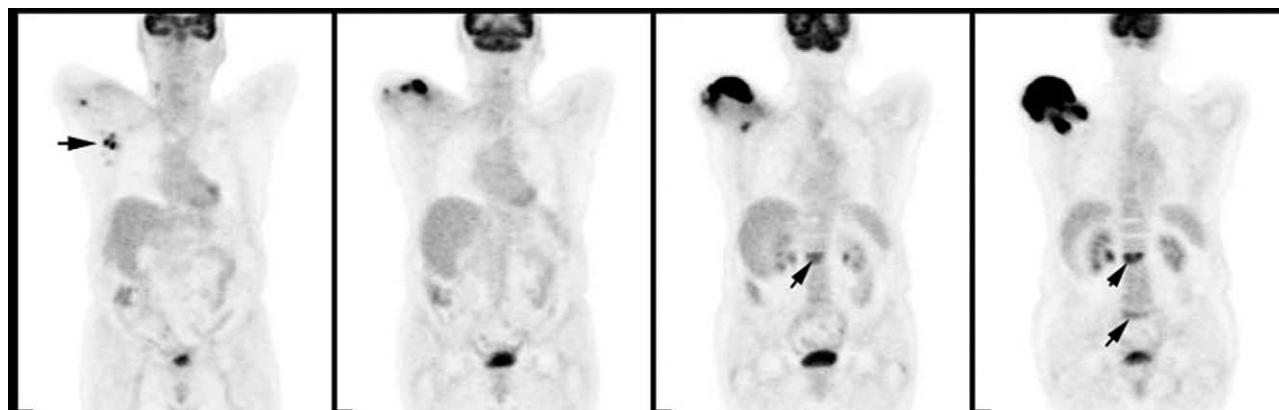


Figure 8 Aggressive (diffuse large B-cell) lymphoma of the right shoulder girdle diagnosed using MRI and biopsy. Conventional staging indicated stage IE disease. As well as demonstrating previously unrecognized axillary nodal involvement (oblique arrow), PET also revealed focal bone marrow lesions in the lumbar spine and sacrum (oblique arrows). It is our experience that aggressive lymphomas often spread in a manner analogous to solid tumors, with regional nodal and systemic metastases from primary extra-nodal sites.

marily diffuse large B-cell lymphoma, combined modality therapy with limited CHOP chemotherapy and involved field radiotherapy has been demonstrated to be a treatment approach associated with high efficacy and relatively low toxicity, especially in patients with favorable prognostic factors. The current treatment of choice for patients with advanced stages of “aggressive” NHL is combination chemotherapy. The addition of immunotherapy with rituximab also appears to improve outcomes in patients with aggressive B-cell disease,¹⁷ either alone or supplemented by local-field irradiation. Autologous bone marrow or peripheral stem cell or allogeneic bone marrow transplantation for consolidation therapy of patients at high risk of relapse has not been shown to be of benefit, and this strategy is reserved for patients who subsequently relapse. Because local radiotherapy is used relatively infrequently in advanced disease, FDG PET is less likely to influence treatment delivery in extensive “aggressive” NHL but may provide prognostic information and have utility for subsequent therapeutic monitoring studies (Fig. 8).

Key issues regarding the utility of FDG PET in lymphoma staging are its relative accuracy for definition of disease extent versus conventional diagnostic approaches and its ability to determine the biological aggressive of the disease process (grading). These issues are reviewed below.

Comparison of the Accuracy of FDG PET and Conventional Staging Techniques for Staging Lymphoma

One of the major difficulties with validating imaging results obtained in patients with lymphoma is the multitude of possible sites of tumoral involvement. In many cases of advanced disease it would be neither practical nor ethical to sample all sites of abnormality detected by the range of imaging studies that a patient might have. Similarly, it can be difficult, if not impossible, to exclude disease at sites without abnormality

because the biopsy of morphologically normal sites is again neither feasible nor ethical. Even follow-up is not necessarily proof of absence of disease at a given site because patients usually will have systemic treatment that would be expected to alter the natural history of their disease. Additionally, because of the indolent nature of many lymphomas, lack of progression after a limited period of follow-up may not necessarily indicate the absence of disease. Consequently, the diagnostic accuracy of FDG PET in staging lymphoma has been difficult to validate. Nevertheless, there has been at least one study that has attempted to rigorously obtain pathological confirmation of the true status of positive sites on PET or CT.¹⁸ This prospective study involving 45 patients with newly diagnosed and 4 with relapsed HL used surgical pathology findings in 11 patients and biopsy of all sites of disease identified on CT as well as sites of PET abnormality without concordant CT abnormality in another 38 patients to validate imaging findings. In the patients who underwent surgical staging, PET had sensitivity, specificity, positive, and negative predictive values of 100%. This compared very favorably to CT, which had a sensitivity of 20%, specificity of 83%, a positive predictive value of 50%, and a negative predictive value of 56%. In the 38 patients validated by biopsy, PET correctly upstaged 21, equally staged 16, and downstaged 1 patient compared with CT. Overall, PET changed stage in 59% of the study population.

In the absence of histopathological confirmation of all sites of abnormality, most other reported studies have determined the accuracy of FDG PET by comparison with results of CT and any other investigations performed before or subsequent to PET and by clinical follow-up. Although these studies often have included a diverse range of histological types of lymphomas and patients at various stages of treatment, they have consistently demonstrated that PET is either superior to the other type of imaging to which it is compared or performs as well as a range of other tests used in combination. For example, in a prospective study involving 60 consecutive patients, Moog and coworkers¹⁹ evaluated the accuracy of

PET compared with CT by analysis of results for 740 lymph node regions. Of 25 additional suspected disease sites found by PET, only 2 were proven false positive whereas 3 of 6 additional sites on CT not seen on PET were false-positive and 3 remained unresolved. In a partially overlapping population, Bangerter and coworkers²⁰ compared the accuracy of FDG PET for staging HL to conventional staging involving CT, ultrasound, bone scanning, bone marrow biopsy, liver biopsy, and laparotomy in 44 newly diagnosed patients. They found that PET identified all 128 abnormal lymph node sites identified by conventional techniques plus an additional 11 sites not previously recognized by these modalities. PET resulted in 5 cases (11%) being upstaged. Another case was true negative at a site of CT suspicion resulting in downstaging. Overall, PET changed management in 6 (14%) cases. Even in the cases in which PET was deemed to be incorrect in this series, some doubt remained as to the final diagnosis, or the diagnosis was probably beyond the capability of any imaging modality. Another study by Moog and coworkers²¹ compared PET and CT in 81 consecutive and previously untreated patients with NHL ($n = 43$) and HL ($n = 38$). Of 24 additional sites of disease found by PET, 14 of 15 (93%) verifiable sites were true positive. In contrast, of 7 additional findings on CT, only 1/6 (17%) was true positive. These data suggest that it is probably inappropriate to use CT as the "gold standard" for evaluating the performance of FDG PET.

Nevertheless, most studies have used CT as the reference standard and have reported good comparative results. For example, Bangerter and coworkers²² calculated the diagnostic accuracy for thoracic PET scans for primary staging in 89 patients with a range of lymphoma types. Using CT as the reference standard, the sensitivity of FDG was 98%, specificity 94%, positive predictive value 92%, and negative predictive value 98%, which yielded an overall accuracy of 94% for the detection of thoracic nodal involvement. The results obtained with FDG PET in staging lymphoma have primarily involved study acquired dedicated PET systems but have not necessarily used optimal methodology. For example, attenuation correction was used relatively infrequently in earlier studies. In other studies coincidence imaging using modified gamma cameras also has been used. Although such studies have demonstrated superior sensitivity of FDG coincidence imaging compared with Ga-67 scintigraphy,²³ a direct comparison of dedicated FDG PET and coincidence imaging with a gamma camera in 30 patients with NHL by Tatsumi and coworkers²⁴ demonstrated inferior sensitivity (77% versus 87%) of the gamma camera-based technology. This was particularly evident for lesions smaller than 1.5 cm, which accounted for 18 of 20 of sites analyzed by dedicated PET but missed on coincidence imaging. Because much of the incremental value of FDG PET compared with CT arises from the ability to detect disease in nonenlarged nodes, coincidence imaging may not provide the same clinical impact as dedicated PET despite providing comparable overall staging results with both dedicated PET and CT in most cases. Similarly, it most likely that the major impact of dedicated PET will be its ability to detect involvement of nonenlarged nodes, as well as of morphologically normal organs.

Results for specific types of lymphoma have been somewhat difficult to ascertain from mixed series of lymphoma patients. Stumpe and coworkers²⁵ evaluated pretreatment staging and restaging after treatment by PET and CT in 50 patients with HL or NHL, but only 17 of these were staging scans. For 9 comparable scans used in the pretreatment staging evaluation of patients with HL, both PET and CT had a sensitivity of 88%, specificity of 100%, and accuracy of 89%. An additional PET study for which no CT comparison was available did not alter the diagnostic performance of PET. Despite comparability of diagnostic performance, this study did not address the potential for PET to influence management, for example, by altering radiation treatment volume in patients of comparable stage. For patients with NHL, PET sensitivity was 83%, specificity was 100%, and accuracy was 86%, whereas CT demonstrated a sensitivity of 75%, specificity of 33%, and accuracy of 57%, including all 7 scans. Combining the results PET scans on all 16 patients undergoing initial staging with comparable CT examinations, PET had a sensitivity of 86%, specificity of 100%, and accuracy of 88%, whereas CT had a sensitivity of 83%, specificity of 50%, and accuracy of 75%. This study did not address the clinical impact of the improved specificity of PET compared with CT in the patients with NHL.

More recently, a larger study from Germany²⁶ evaluated 81 patients with HL undergoing 106 FDG PET studies. Of these, 25 were for initial staging. On the basis of patients scanned, 24 (96%) were true positive and, on a lesion-to-lesion analysis, PET had an accuracy for determination of disease stage of 96% compared with 56% for conventional imaging methods that included CT plus, in some cases, MRI and ultrasonography. PET resulted in a change in stage in 40% of cases. A further prospective study performed by 2 German centers compared FDG PET with CT and bone marrow biopsy²⁷ in 52 patients undergoing primary staging of lymphoma. In this study PET changed stage in 4 (8%) leading to a change in treatment. Using receiver-operating characteristic curve analysis for comparison of diagnostic accuracy in 1297 nodal, extra-nodal and bone marrow sites, PET was significantly ($P < 0.05$) more accurate than CT for all sites and was comparable with bone marrow biopsy for detecting marrow involvement. When disease sites were separated in relationship to the diaphragm, PET remained significantly superior to CT for supradiaphragmatic but not for infradiaphragmatic sites where it was equivalent. It should be noted however that 40 of the 52 scans were performed without attenuation correction. Because the benefits of attenuation correction are greatest in the abdomen, this may account for the lack of incremental accuracy observed below the diaphragm. Improvements in instrumentation, particularly the advent of combined PET/CT scanners²⁸ that allow more rapid and statistically robust CT-based attenuation, may thus further enhance the diagnostic performance of PET.

Although, as discussed below, FDG uptake tends to be related to tumor grade, the accuracy of PET in "indolent" lymphoma still appears to be acceptable, at least in those with follicular histology. In a study involving 42 patients with "low-grade" NHL, Jerusalem and coworkers²⁹ found that PET

identified 40% more abnormal lymph node sites than conventional staging in the 24 patients with follicular histology but less than 58% of the abnormal lymph node sites on CT in the 11 patients with small lymphocytic lymphoma (the tissue manifestation of chronic lymphocytic leukemia). However, preliminary results with mucosa-associated lymphoid tissue (MALT) type NHL appear to be poor based on lack of visualization of known sites of disease in 10 patients.³⁰ However, this may relate to the background tracer uptake in the organs usually involved by MALT NHL, such as the stomach and salivary glands, rather than the biology of the lymphoma per se, as areas of nodal involvement are usually accurately detected by PET in our experience.

Because Ga-67 is a well-validated technique for staging, therapy monitoring and, particularly, restaging³¹ of lymphoma and is more widely available than PET, it is pertinent to consider the relative merits of each. As early as 1987, the importance of this comparison was recognized with publication of a report using planar imaging of both Ga-67 and FDG using a collimated gamma camera in 5 patients with NHL.³² This study yielded 4 positive scans with FDG versus only 2 with Ga-67, suggesting the potential superiority of FDG as a radiotracer in this disease. A larger study was reported by Kostakoglu and coworkers²³ in which 50 patients were studied by both FDG PET using coincidence gamma camera technology and high-dose Ga-67. This study demonstrated superior PET sensitivity for both site (100% versus 72%) and patient (100% versus 80%) involvement. Because coincidence PET systems may miss small lesions detectable on dedicated PET,²⁴ these results may underestimate the true incremental diagnostic benefits of dedicated FDG PET compared with Ga-67. In a study using a dedicated PET scanner, Wirth and coworkers³³ reported on 50 patients who had concurrent high-dose gallium with comprehensive delayed imaging and routine single-photon emission computed tomography (SPECT) scanning and FDG PET scans. The case sensitivity of PET was 95%, which compared favorably with a sensitivity of 88% for gallium scans, although the difference was not statistically significant. However, the site sensitivity was superior for PET compared with Ga-67 at 82% versus 69% ($P = 0.01$). Both PET and Ga-67 altered stage in 14% of patients compared with CT and altered management in 18% and 14% of patients respectively ($P = 0.6$). This study used a high-dose, delayed imaging Ga-67 protocol with comprehensive SPECT evaluation of the neck, thorax, abdomen, and pelvis. This protocol is an onerous one for both the patient and technologist staff, and we believe that the convenience of PET is an important factor supporting its more routine use. The high contrast apparent on FDG PET also increases diagnostic and referring clinician confidence in the results obtained. As stated previously, our experience in comparing dedicated PET to Ga-67 SPECT scanning has led to a major shift in our use of these technologies with FDG PET essentially replacing SPECT for the evaluation of lymphoma in our institution.

A potential advantage of FDG PET over Ga-67 and CT for the staging of lymphoma is its ability to simultaneously evaluate both nodal and extra-nodal sites of disease. In particular, several studies suggest that FDG PET is superior to conven-

tional techniques in the evaluation of bone marrow involvement and is potentially complementary to bone marrow biopsy, which can suffer from sampling errors. Carr and coworkers³⁴ evaluated the accuracy of PET for detection of bone marrow involvement in 50 patients. Verification of true disease status was available in 43 patients by biopsy. If the 7 unverified patients are excluded, the sensitivity of PET was 82%, the specificity and positive predictive value were 100%, the negative predictive value was 90%, and the overall accuracy was 93%. The University of Ulm Group has also evaluated the role of FDG PET for evaluating bone marrow involvement in lymphoma. Comparing FDG PET results to bone marrow biopsy in 39 patients with untreated NHL and 39 with untreated HL, Moog and coworkers³⁵ found that although PET missed biopsy-confirmed marrow involvement in 5% of patients, it detected bone marrow involvement in 13% of patients with negative conventional biopsy. Of the 10 patients in whom PET scanning was discordantly positive, 8 were confirmed and 2 remained unresolved. If the 2 unconfirmed patients are excluded from the analysis, PET had an overall accuracy of 95% whereas bone marrow biopsy had an accuracy of 89%. In contrast to these results, Jerusalem and coworkers²⁹ found that FDG PET was insufficiently sensitive in "indolent" NHL to allow exclusion of bone marrow biopsy with detection of only 11/28 (39%) of biopsy-confirmed cases. This may reflect the lower FDG-avidity of "indolent" tumors or a tendency for more diffuse rather than focal marrow infiltration, making differentiation of normal physiological marrow activity and involvement more difficult.

Evaluation of Tumor Grade and Prognostic Stratification

Preliminary studies comparing FDG uptake with tumor grade have demonstrated that "aggressive" lymphomas tend to have higher FDG avidity than "indolent" histologies. These studies generally have used semiquantitative measures of FDG uptake, such as the standardized uptake value (SUV), or a similar parameter termed the differential uptake ratio (DUR). Some studies have compared SUV results with quantitative measures of glucose metabolic rate using compartmental modeling. Okada and coworkers³⁶ showed a relationship between quantitative and semiquantitative measures of glucose utilization and proliferative activity in 23 patients with untreated lymphoma. Lapela and coworkers³⁷ compared both SUV and glucose metabolic rates in 22 patients with NHL and found significant associations between both parameters and histologic grade based on the previous International Working Formulation classification of NHL, in which diseases are categorized into 3 separate "grades" of clinical and histological aggressiveness ("high," "intermediate," and "low"). Although not the primary aim of the article, Goldberg and coworkers³⁸ found that the DUR was significantly different for "high-," "intermediate-," and "low-grade" NHL ($P < 0.05$). In a study involving 23 patients, Rodriguez and coworkers³⁹ reported that FDG discriminated between "high-" and "low-grade" tumor whereas 3 transformed NHL

cases (development of “high-grade” disease in the setting of prior “low-grade” disease) had intermediate FDG avidity.

Okada and coworkers⁴⁰ also evaluated the independent prognostic value of the FDG avidity on PET in the primary staging of 31 patients with NHL and 3 with HL involving the head and neck region, who they followed for 15 to 50 months after treatment. On the basis of clinical outcome, patients were divided into 3 groups: group 1 achieved complete remission and did not relapse, group 2 achieved complete remission but relapsed, whereas group 3 did not achieve a remission. They found that group 3 patients had statistically significantly higher semiquantitative uptake of FDG than groups 1 and 2.

The Impact of PET on Clinical Management of Patients With Lymphoma

The evaluation of the clinical impact of PET on the management of lymphoma patients has not been the primary focus of most of the aforementioned studies. The purpose of most of them was to validate the diagnostic accuracy of FDG PET compared with conventional staging techniques. Accordingly, the patients were not necessarily selected based on clinical uncertainty regarding optimal management, nor were they always managed on the basis of PET information. Nevertheless, several studies have reported changes in management that arose because of incremental information provided by PET. Changes of stage do not necessarily mean a change of treatment, nor does it follow that lack of stage migration after PET will not be associated with change in management. For example, if chemotherapy was already the chosen treatment for a patient with stage III NHL, upstaging to stage IV may not influence treatment, even though there may be prognostic implications. Similarly, a patient with stage II disease planning to have radiotherapy could have their radiation portal changed on the basis of PET without having a change in stage. Reflecting this, our own series³³ found that PET upstaged only 14% of patients but altered management in 18%. Earlier work also has demonstrated discordance between stage migration and management impact, although not necessarily in the same direction. In a study looking at the clinical impact and cost-effectiveness of FDG across a range of oncological indications, Valk and coworkers⁴¹ indicated that PET changed stage in 5/25 (20%) of patients with untreated HL and thereby but resulted in management changes in only 3/25 (12%) of patients. Young and coworkers¹⁸ evaluated PET in the staging of 49 patients. PET altered the clinical stage of 29 of 49 patients (59%): 27 patients had their clinical stage increased by PET information and 2 had clinical stage decreased by PET information. The authors indicated that all patients except one were treated according to PET stage; however, the management changes were not detailed.

A recent study assessed clinicians' impression of the influence of PET on the management of their patients performed in routine clinical practice.⁴² This study suggested substantially a higher impact, with more than 60% of cases having

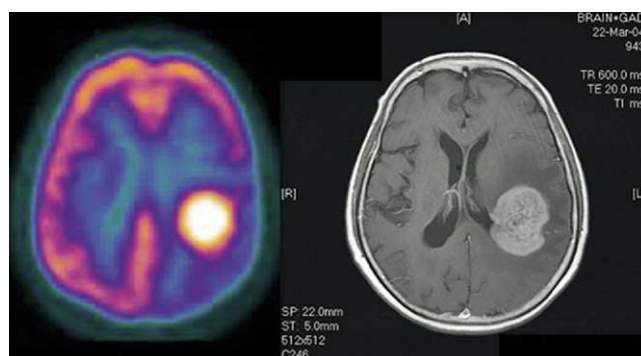


Figure 9 Despite relatively high uptake of FDG in the normal brain, very intense FDG uptake in most primary cerebral lymphomas renders PET a useful technique for therapeutic monitoring. New tracers like FLT that have low uptake in the normal brain may be more sensitive for small lesions and possibly for leptomeningeal disease. (Color version of figure is available online.)

some change in treatment as a result of PET, than appreciated from earlier studies involving patients who were part of a prospective trial. These results may reflect referral biases related to clinical use of PET, particularly toward cases where the clinician is uncertain regarding optimal treatment. Using similar methodology of referring physician surveys, a French group found a relatively high impact of 42 FDG PET studies performed in childhood lymphoma with management changed in 23% of cases.⁴³ From many other studies, it is difficult to ascertain how often changes in stage were associated with change in management and vice versa. These figures will also depend on the population studied because if predominantly advanced-stage patients on conventional staging were studied, it would be anticipated that PET would have a much lower likelihood of changing management and therefore a lower impact. We recently reported⁴⁴ our experience with FDG PET in patients with “indolent” NHL in a study of 47 patients, although this included only 12 a primary staging. The latter patients were chosen primarily because they were being considered for local radiotherapy. PET upstaged 58%. In all 47 patients, the case sensitivity of FDG PET was 98% and of discordant results between FDG PET and conventional staging techniques on follow-up or biopsy, 95% ($P < 0.0001$) were confirmed to be correct on PET.

Future Perspectives

Given the excellent performance of FDG PET, it is relatively unlikely that it will be supplanted in the near future by other imaging techniques. New PET tracers may be useful in providing more specific information regarding tumor characteristics. In particular, ¹⁸F-fluorothymidine (FLT)⁴⁵ may provide useful information regarding cellular proliferation and hence may provide grading and prognostic information. Low uptake of FLT in the brain may provide an advantage over FDG, which is actively concentrated in normal cortex, may yield superior sensitivity for detection of cerebral involvement. However, most primary cerebral lymphoma has relatively high metabolic activity in our experience (Fig. 9). Un-

fortunately, high uptake in normal bone marrow and the liver may limit the sensitivity of FLT PET for detection of extranodal involvement.

It is more likely that the current rapid dissemination of hybrid PET/CT scanners will have a significant impact on the staging of lymphoma, with the possibility that this will become the initial staging tool of choice. Preliminary evidence exists that PET/CT is more accurate than stand-alone PET, with a comparison in 73 patients demonstrating an accuracy of 93% versus 84% ($P = 0.03$).⁴⁶ On the basis of similar results, other groups have questioned whether diagnostic CT is routinely required when PET/CT is available.³ It is our opinion that the role of diagnostic CT will change more to that of specific problem solving.

Conclusion

Recognition of the patient groups most likely to benefit from the generally superior diagnostic performance of PET compared with conventional investigation paradigms is important. FDG PET already is becoming the first rather than the last test performed for staging patients with newly diagnosed lymphoma. The major advantage of PET over conventional imaging in the staging setting is its ability to detect disease in structures without morphological abnormality. Hence upstaging of disease is the most common result of integrating PET into the staging paradigm. This may have both prognostic and therapeutic implications depending on the clinical practices and preferences of managing clinicians. Where radiotherapy is part of the management of lymphoma patients it is likely that PET will have a greater impact than in settings where only chemotherapy is used. This ignores the potential utility of FDG PET as a baseline for therapeutic monitoring studies, a topic beyond the scope of this review.

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