In patients with lymphoma, positron emission tomographic (PET) scans show abnormalities at diagnosis. Normal findings on the scan after therapy is highly predictive of a good prognosis, particularly in patients with diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, and Hodgkin lymphoma. However, the optimal application of PET scans to the management of all patients with lymphoma remains problematic. The major controversies include the optimal timing of PET scans (for staging, during therapy, after completion of therapy, surveillance in remission), standardization of PET scan interpretation (visual interpretation compared with standard uptake value [SUV] calculation), what constitutes a positive PET scan result, and whether PET scans should be used to direct therapy (eg, does changing therapy in patients with positive findings on PET change outcome, should biopsies of sites with positive PET results be done routinely before a management change). Although a large body of literature addressing these topics exists, the studies are often difficult to compare, making definitive conclusions on all these issues difficult. The previously published studies often used different designs and variable reporting, making interpretation and comparison of the results difficult. In the early studies particularly, heterogeneous populations with different stages of disease and different histologic subtypes were included, making the clinical applicability of the studies’ results difficult. More recent studies focusing on efforts to standardize the conduct and interpretation of PET scans and on risk-adapted therapies based on interim PET scan results will, it is hoped, improve the management and outcome of patients with lymphoma. A literature search of PubMed from 1999 to 2011 was performed using the following keywords: PET scan, FDG-PET, PET/CT, lymphoma. We highlight the current standard use of PET scans in patients with lymphoma as well as the areas of controversy regarding their use.

TYPES OF PET SCANS
Fluorine 18 fluorodeoxyglucose (FDG)-PET is a metabolic imaging technique that uses a radiopharmaceutical to target glucose metabolism. The radio-labeled glucose analogue FDG is transported into metabolically active cells and phosphorylated in a manner similar to glucose. Phosphorylated FDG is typically not dephosphorylated in tumor cells, and because it is not metabolized, it becomes trapped in the cell. The PET scanner then detects the positron-emitting fluorine 18 (\(^{18}\)F) isotope that is linked to FDG. Although FDG-PET provides useful functional information when used alone, additional anatomic and structural information is added when FDG-PET is used in combination with low-dose or full-dose computed tomographic (CT) scanning. PET/CT has virtually become the standard and has largely replaced PET-only scanning. It is not clear, however, whether the resolution of the CT part of the scan is important. There is a strong correlation between unenhanced low-dose PET/CT scans and contrast-enhanced full-dose PET/CT scans for both lymph node involvement and extranodal disease in lymphomas, suggesting that unenhanced low-dose PET/CT scans might be sufficient in most patients as the only imaging technique for the initial staging of lymphomas.

Abstract
The use of sensitive and specific imaging techniques for accurate initial staging and evaluation of response to therapy in patients with lymphoma is essential for their optimal management. Fluorine 18 fluorodeoxyglucose (FDG) positron emission tomography (PET) integrated with computed tomography (CT) has emerged as a powerful imaging tool and is being routinely used in staging, response evaluation, and posttreatment surveillance in patients with non-Hodgkin lymphoma and Hodgkin lymphoma. PET/CT is currently widely used in clinical practice, but the established clinical benefit is currently restricted to the posttreatment evaluation of Hodgkin lymphoma, diffuse large B-cell lymphoma, and follicular lymphoma. Although used in other histologic subtypes and in other clinical situations including response assessment, its impact on patient outcome remains to be demonstrated. We performed a literature search of PubMed from 1999 to 2011 using the following keywords: PET scan, FDG-PET, PET/CT, lymphoma. This review addresses the challenges and controversies in the use of PET/CT scans in the management of patients with lymphoma.
Positron emission tomography (PET) has become standard in managing patients with lymphoma.

The most appropriate method of interpreting PET scans remains uncertain, but objective approaches are being developed.

PET scanning as part of staging and therapy evaluation should be routine for patients with Hodgkin lymphoma, diffuse large B-cell lymphoma, and follicular lymphoma.

Interim PET scanning to direct therapy shows promise.

PET scans should not be used for surveillance for relapse in patients in remission.

Alternative tracers to improve imaging are being explored. Although FDG has been widely studied and appears to have broad utility as a PET tracer in lymphoma, there are several situations in which alternative tracers may have an advantage. The first is to facilitate imaging of regions of the body with high FDG background, such as the central nervous system, where the high cerebral uptake of FDG may compromise detection of lymphoma. Alternative tracers that measure proliferation, including fluorodeoxyglucose (FDG) or the amino acid analogue fluorothyrosine, appear to have a higher sensitivity and specificity than FDG.

Fluoroethyltyrosine and FLT may also be useful alternatives when high FDG uptake could be the result of inflammatory, infectious, or granulomatous processes. The most important alternative tracers in routine practice in other malignancies are \(^{11}\)C-choline and \(^{18}\)F-choline, mainly for the evaluation of prostate cancer; \(^{11}\)C-methionine for brain tumors; \(^{18}\)F-DOPA (\(^{18}\)F-deoxyglucose) for neuroendocrine tumors and movement disorders; \(^{68}\)Ga-DOTANOC (tetrazaaclycloclodetetraacetic acid-[1-Nal3]-octreotide) and other somatostatin analogues for neuroendocrine tumors; and \(^{11}\)C-acetate for prostate cancer and hepatic masses.

To enhance the role of PET scans in measuring disease activity and response, tracers such as \(^{18}\)F-FLT (3-deoxy-3-fluorothymidine) that measure proliferation are also being evaluated, and 3\(^{-}\)-deoxy-3\(^{\prime}\)-[\(^{18}\)F]fluorothymidine PET may be useful in monitoring and/or predicting therapeutic response. This is supported by initial studies that found that administration of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) or CHOP was associated with an early decrease in lymphoma FLT uptake. Of note, however, there was no reduction of FLT uptake after use of rituximab alone, indicating no early antiproliferative effect of immunotherapy.

Although FDG-PET has emerged as an important advance in the assessment of patients with lymphoma, the intensity of the PET signal can vary because of various factors that should be considered when reviewing the scan. In addition to technical issues (Table 1), the number and proliferation of malignant cells in the tumor can affect the FDG uptake. In classic Hodgkin lymphoma, Reed-Sternberg cells represent less than 1% of the cells within the malignant lymph node. They are surrounded by a large number of normal mononuclear cells that are metabolically active and that contribute to the FDG uptake. The metabolic activity of the tumor microenvironment works to amplify the FDG-PET signal but may also become negative despite the persistence of a large residual mass. In contrast, neoplastic cells in non-Hodgkin lymphoma account for most of the lymph node population. Fluorine 18 fluorodeoxyglucose-PET interpretation, therefore, might differ between Hodgkin lymphoma and non-Hodgkin lymphoma because of different biologic behavior and response profiles.

Furthermore, biologic changes in tumor cells, including changes in proliferation rates, can be useful in identifying sites of lymphoma transformation, particularly if FDG uptake in one area is discordant with others.

The immune competence of the patient may also affect the results of the FDG-PET scan. Recent research suggests that PET may be of limited value in AIDS-related lymphoma. Although the negative predictive value of 31 interim PET scans in patients positive for human immunodeficiency virus was 91%, the positive predictive value was only 15%. The positive predictive value was even lower for posttreatment PET at 7%; the negative predictive value was 87%. Notably, of 13 patients who had positive PET findings after therapy, 12 had achieved disease remission. Thus, although the negative predictive value of interim and end-of-treatment PET in these patients was high, the positive predictive value of PET was extremely low, with

### TABLE 1. Factors That Can Influence Results of Positron Emission Tomography

<table>
<thead>
<tr>
<th>Variable</th>
<th>Influence</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammation</td>
<td>Inflammaion</td>
<td></td>
</tr>
<tr>
<td>Blood glucose level</td>
<td>Blood glucose level</td>
<td></td>
</tr>
<tr>
<td>Tumor size</td>
<td>Tumor size</td>
<td></td>
</tr>
<tr>
<td>Patient diet, hydration, exercise, medication</td>
<td>Patient diet, hydration, exercise, medication</td>
<td></td>
</tr>
<tr>
<td>Time from last treatment</td>
<td>Time from last treatment</td>
<td></td>
</tr>
<tr>
<td>Method of calculating the standardized uptake value</td>
<td>Method of calculating the standardized uptake value</td>
<td></td>
</tr>
<tr>
<td>Time from injection to measurement</td>
<td>Time from injection to measurement</td>
<td></td>
</tr>
<tr>
<td>Scanner quality control</td>
<td>Scanner quality control</td>
<td></td>
</tr>
<tr>
<td>Region of interest determination</td>
<td>Region of interest determination</td>
<td></td>
</tr>
</tbody>
</table>
46% of patients in remission after having a positive PET scan result. In this population, the potential for confounding disease processes associated with high FDG avidity is likely to have contributed to the low positive predictive value.

The type of chemotherapy given may affect PET results, in that dose-intense therapy may negate the prognostic significance of interim PET results. In a phase 2 study of dose-dense, sequential immunochemo therapy, 98 patients received induction therapy with 4 cycles of accelerated R-CHOP followed by an interim FDG-PET scan. Thirty-eight patients with FDG-PET–positive disease underwent another biopsy; 33 had a negative result, and 26 remained progression-free after ICE (ifosfamide, carboplatin, etoposide) consolidation therapy. Progression-free survival of patients with a positive interim FDG-PET scan result and a negative biopsy finding was identical to that in patients with a negative result interim FDG-PET scan. In this study, interim or posttreatment FDG-PET evaluation did not predict outcome.7 Furthermore, novel biologic agents that target pathways within the lymphoma cell may inhibit glucose metabolism and may decrease FDG avidity, thereby making the FDG-PET scan more difficult to interpret. The context in which the patient is being assessed should therefore always be considered when interpreting the PET scan.

INTERPRETATION OF PET SCANS

There is variability in interpretation of PET scans among centers and even among those interpreting the scan at the same institution. Although some institutions report the results on the basis of visual assessment, others report an SUV. Current guidelines suggest that a visual assessment of PET scans is adequate for a positive or negative decision at the end of therapy. Assessments during treatment or in clinical trials, however, may require quantification of attenuation-corrected PET scans. Although protocols have been established to standardize the interpretation of PET scans,11 the quantitative assessment of tumor responses and the comparison among studies require rigorous quality control.12 In 2007, on the basis of the collective expertise of its members, the International Harmonization Project (IHP) subcommittee developed consensus recommendations for the use of FDG-PET in lymphoma.8 Visual assessment alone was considered adequate for reading FDG-PET scans at the completion of therapy. The mediastinal blood pool uptake was recommended as the reference background activity to define FDG-PET positivity for a residual mass of 2 cm or greater, regardless of location. It was recommended that smaller residual masses or normal-sized lymph nodes be considered positive if the activity was greater than the surrounding background. The subcommittee also proposed specific criteria for defining FDG-PET positivity in the liver, spleen, lung, and bone marrow and strongly encouraged the use of attenuation-corrected PET scans.

Although the IHP criteria are useful for FDG-PET analysis at completion of therapy, there are limitations when using them for interim FDG-PET. As discussed earlier in this article, the IHP criteria use lymph node size as the cutoff for reference background (mediastinal blood pool activity when ≥2 cm and the surrounding background when <2 cm). However, it is generally felt that for assessment of early response, particularly in risk-adapted therapeutic trials, it is preferable to refer to a background tissue (such as the liver) with a higher level of uptake than that of current international criteria that were designed for end-of-treatment evaluation.13 As recently shown, the reproducibility of lymph node measurements is poorest below 20 mm, which leads to major discrepancies in FDG-PET interpretation14 as the reference background changes. In 2009, an international workshop on interim FDG-PET15 took place to reach a consensus on criteria for interim FDG-PET scans. It was proposed that a baseline CT/PET scan be performed before treatment and that a visual analysis using a 5-point scale be performed (Table 2).5 When a therapeutic decision is to be

---

**TABLE 2. Visual Analysis of FDG-PET Scans According to Deauville 5-Point Scale**

1. No uptake.
2. Uptake less than or equal to mediastinal uptake.
3. Uptake greater than mediastinal uptake but less than or equal to liver uptake.
4. Uptake moderately more than liver uptake, at any site.
5. Markedly increased uptake at any site and new site of disease.

FDG-PET = fluorodeoxyglucose positron emission tomography.

Data from Leuk Lymphoma.15
made, the cutoff should be modified according to the end point of the study. A score of 3 in localized classic Hodgkin lymphoma, for example, might be considered as FDG-PET–positive when a decrease in therapy is planned. In contrast, a score of 3 in advanced Hodgkin lymphoma might be considered positive when treatment intensification is planned. An international validation study for this strategy is currently in progress.

**WHICH LYMPHOMAS YIELD ABNORMAL RESULTS ON PET SCAN?**

Most lymphomas demonstrate FDG uptake, and FDG-PET is useful for most histologic subtypes of lymphoma; Hodgkin lymphoma, DLBCL, follicular lymphoma and, probably, mantle cell lymphoma are PET-avid in nearly 100% of cases. However, the intensity of uptake (ie, a higher SUV) is typically highest in DLBCL and lower in follicular lymphoma and mantle cell lymphoma. Indolent lymphomas such as small lymphocytic lymphoma and splenic marginal zone lymphoma are less FDG-avid, and FDG-PET may be less likely to detect sites of active disease. Less is known about FDG-PET in T-cell lymphomas, but FDG-PET results are positive in most T-cell lymphomas except indolent cutaneous T-cell lymphoma. Although PET scans may be useful in identifying sites of disease, some studies have suggested that FDG-PET may not be predictive of outcome in certain histologic subtypes. Studies in NK/T-cell lymphomas, for example, have failed to show that negative findings on an interim PET scan correlates with a better progression-free survival.

Further studies will therefore be necessary to clearly define the prognostic role of PET scans in T-cell lymphomas.

PET scan results may differ by disease site, and lymphomas that localize to those sites may be less reliably assessed. Fluorine 18 fluorodeoxyglucose PET may not be reliable for identifying bone marrow involvement and, perhaps, involvement of the small or large bowel. Comparison with bone marrow biopsies showed that FDG-PET was not reliable for detection of bone marrow involvement in any lymphoma subtype. In one study, negative PET scan results did not rule out colonic involvement in lymphoma patients.

**CURRENT USE OF PET SCANS IN MANAGING LYMPHOMA**

**Staging**

Fluorine 18 fluorodeoxyglucose-PET has become an important component of staging in lymphoma patients. Combining FDG-PET with a CT scan (PET/CT) improves the interpretation of PET scans, and PET/CT has become the standard. It has been suggested that the addition of contrast-enhanced CT may further increase the benefit. Other authors have challenged this view by reporting that a diagnostic CT scan with intravenous contrast does not add useful information regarding extent of lymphoma in patients undergoing PET/CT for staging if the low-dose CT scan is interpreted individually. Fluorine 18 fluorodeoxyglucose-PET is important in staging of lymphoma; FDG-PET leads to a change in stage of disease in up to 20% to 40% of patients, and in 5% to 15% of patients, this changes the treatment choice. At present, the use of FDG-PET scans in the staging of lymphoma is the standard of care in most patients.

**Posttreatment Scans (To Document Remission)**

The use of PET scans in patients with lymphoma after therapy to document remission is standard practice. PET/CT has become a standard of care in both Hodgkin lymphoma and non-Hodgkin lymphoma as part of the restaging assessment. Patients with a negative PET scan result have an excellent outcome, and multiple studies have shown that FDG-PET performed after treatment is highly predictive of progression-free survival and overall survival in aggressive non-Hodgkin lymphoma and follicular lymphoma.

PET scans can also be particularly useful in patients with lymphoma who have a residual mass at the completion of therapy. In a large pooled analysis by the German Hodgkin Study Group, 728 Hodgkin lymphoma patients with a mass greater than 2.5 cm after 6 to 8 cycles of BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) were analyzed. Patients with PET-negative results were observed. Those with positive findings on PET received consolidation radiotherapy (RT). The freedom from progression at 3 years was 92% for patients with negative PET results and 86% for those with positive results. In fact, patients with a residual mass who have negative results on PET should be considered to be in complete remission.

Furthermore, PET may also be useful to determine whether consolidation RT is necessary. There is continued interest in using PET scans to identify which patients may benefit from consolidative involved-field radiotherapy (IFRT) after systemic chemotherapy. As with chemotherapy treatment modification, there is potential for overtreatment (PET false-positive) as well as the risk of inferior outcome with omission of IFRT (PET false-negative). In an analysis of patients with Hodgkin lymphoma who had residual masses after BEACOPP chemotherapy, PET scans were used to restrict RT to those with positive scan results. Only 11% needed RT, compared with 71% who received RT in prior trials.
when PET was not used. A similar algorithm to limit treatment has been applied at the British Columbia Cancer Agency for limited-stage DLBCL. Patients who have negative PET results after 3 cycles of R-CHOP receive one further cycle of R-CHOP, whereas those with positive findings also receive RT. Of the 65 initial patients treated, 49 (75%) had negative PET results, and 47 received one additional cycle of R-CHOP; only one relapse was observed. Of 16 patients with positive findings on an interim PET, 3 relapsed after combined-modality treatment. In a recent study from Norway, patients with DLBCL who had an indeterminate or positive findings on PET after chemoinmunotherapy had a good prognosis, but RT may have been the reason in some patients. These results are preliminary and encourage further similar studies and longer clinical follow-up to confirm the utility of such an approach.

Interim Scans (To Direct Treatment)

Early interim FDG-PET is a strong and independent predictor of progression-free survival in Hodgkin lymphoma. A positive result on early interim FDG-PET is predictive of progression in patients with advanced-stage or extranodal disease. For patients with advanced-stage Hodgkin lymphoma, positive findings on an interim FDG-PET performed after a few cycles of standard chemotherapy identifies poorly responding patients and is associated with a poorer prognosis. This has led to prospective studies to assess PET-based treatment strategies. In contrast, due to heterogeneity in DLBCL, no reliable conclusions can be drawn, and interim PET scans remain investigational in this disease. Interim PET scans in patients with DLBCL should therefore be reserved for research studies in which treatment regimens and image interpretation are standardized. Initial retrospective studies in DLBCL suggested a dramatic difference in outcome for patients with positive and negative findings on interim PET. Subsequent prospective studies have not found such a dramatic difference, and some patients with a positive interim PET result may still have a favorable outcome.

One approach under investigation for patients with negative early interim PET findings, particularly those with Hodgkin lymphoma, is to employ chemotherapy-reduction strategies. In advanced-stage disease, in which higher doses of chemotherapy are indicated, omitting chemotherapy cycles or changing to less intensive chemotherapy could potentially spare treatment-related toxicity with the goal of maintaining efficacy. However, the major risk of treatment modification is the potential for inferior outcomes as a result of less intensive therapy in good responders or from changing the treatment regimen in slow responders. The latter is because some slow responders will achieve a remission and these complete responses are usually durable. It is not certain that the alternative therapies will have a result that is better or as good. Trials in Hodgkin lymphoma using this approach are in progress, and some of these studies are highlighted in Table 3.

<table>
<thead>
<tr>
<th>TABLE 3. Partial List of Clinical Trials Evaluating PET-Directed Therapy in Hodgkin Lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study group</strong></td>
</tr>
<tr>
<td>EORTC-GELA-IIL</td>
</tr>
<tr>
<td>UK NCRI lymphoma group</td>
</tr>
<tr>
<td>GHSG</td>
</tr>
<tr>
<td>GITIL</td>
</tr>
<tr>
<td>UK NCRI lymphoma group</td>
</tr>
<tr>
<td>IIL</td>
</tr>
<tr>
<td>GHSG</td>
</tr>
<tr>
<td>GELA</td>
</tr>
</tbody>
</table>

BVD = doxorubicin, bleomycin, vinblastine, dacarbazine; EORTC = European Organisation for Research and Treatment of Cancer; escBEACOPP = escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; GELA = Groupe d’Etude des Lymphomes de l’Adulte; GHSG = German Hodgkin Study Group; GITIL = Gruppo Italiano Terapie Innovative nei Linfomi; IIL = Intergruppo Italiano Linfomi; PET = positron emission tomography; RT = radiotherapy; UK NCRI = United Kingdom National Cancer Research Institute.
Screening for Relapse

Although it is appealing to potentially use FDG-PET to identify patients with subclinical disease, it is not clear that screening for relapse by PET scanning achieves that.52 Particularly in aggressive lymphomas and those patients with extranodal involvement, most relapses are diagnosed clinically. Only in selected patients with Hodgkin lymphoma were relapses more commonly detected by routine imaging. However, imaging-detected relapse was not associated with improved survival.53 An important issue related to the use of FDG-PET to screen for relapse is the high number of false-positive results54 and the expense.55 Furthermore, repeated PET scans increase the radiation exposure and thereby increase the risk for malignancy.56 The high rate of false-positive results highlights the importance of a confirmatory tissue biopsy. Even in patients with positive findings on interim PET, histologic confirmation plays an important role in identifying true relapse. In a study of patients receiving PET-scan-directed therapy for DLBCL, only 5 of 38 patients with positive results on PET had positive biopsy finding.7 In a recent report in Hodgkin lymphoma surveillance, PET results were abnormal in 18 patients and in 3 of these patients represented the first evidence of relapse. In 14 patients (78%), the abnormal findings were false-positive but required additional images or biopsies.55

Searching for Transformation or to Direct Biopsies

Initial studies of the use of FDG-PET in lymphoma showed that PET scans could predict the histologic grade.57 Like de novo aggressive lymphomas, most transformations have a high SUV, and transformation should be suspected in indolent lymphoma with high SUVs on FDG-PET. Biopsies to confirm this should be directed to the site of greatest FDG avidity.58 PET can also be helpful in identifying sites of lymphoma that are not clinically evident or clearly appreciated with use of other imaging modalities. For example, FDG PET/CT is helpful in diagnosing malignant involvement of the peripheral nerves, especially when findings from anatomic imaging (magnetic resonance imaging or CT) are negative.59

Fever of Unknown Origin or Bone Marrow Involvement

In a patient with a persistent fever, PET scans can play an important role. Fluorine 18 fluorodeoxyglucose-PET is a valuable imaging technique as part of a diagnostic protocol in the general patient population with a fever of unknown origin (FUO) and also in patients with an elevated sedimentation rate or C-reactive protein in the serum60. In patients with an FUO, PET scans should be used as a second-line test after initial testing has failed to identify a source.61 In contrast, PET has been relatively unreliable in diagnosing bone marrow involvement. Diffuse bone marrow uptake at initial staging of Hodgkin lymphoma could be due to bone marrow involvement but more likely is due to bone marrow inflammatory change.62 In patients with non-Hodgkin lymphoma with bone marrow involvement, bone marrow FDG uptake depends on whether the infiltrate comprises small or large cells, large cells being more likely to be FDG-avid. This may explain the apparent low sensitivity of FDG-PET previously reported for detecting bone marrow involvement.53

CONTROVERSIES IN THE USE OF PET SCANS

What Constitutes a Positive PET Result?

Despite the efforts at standardization, interpretation of PET scans has not been consistent and difficulties often arise, particularly when minimal FDG uptake is present. Interpretation of FDG-PET remains subjective and often depends on the experience of the reader. Therefore, even when blinded, readers may often disagree. In a study by Zijlstra et al,64 the scoring of PET scans by 11 nuclear medicine physicians was compared with the interpretation by an expert. When the expert interpretation was that the PET scan result was positive, the agreement was 82% to 94%, but when the expert interpretation was that the PET findings were negative, the concordance was only 45%. The investigators also found that more experienced PET readers tended to have fewer false-positive results.64 This raises the question of whether all PET scans need expert review. Particularly in the context of clinical trials, it may be desirable to have the opinion of several experts to reduce interobserver variability. A major limitation of this central review is the need to do it in a clinically relevant time frame rather than in a retrospective fashion. A real-time approach is being adopted by a number of cooperative groups, including the Groupe d’Etude des Lymphomes de l’Adulte (GELA) group.65 In an initial analysis, FDG-PET scans from 166 consecutive patients included in the H10 study were reviewed. Discordant findings between the local site and the central review panel were observed in 6% of the scans, and most of the results, which were revised from negative to positive. The investigators found a significantly higher interobserver agreement when the readers interpreted the subsequent PET scan in conjunction with the baseline FDG-PET scan. A similar network established in the United Kingdom for clinical trials in classic Hodgkin lymphoma has found good concordance in PET in—
interpretation in patients with advanced-stage classic Hodgkin lymphoma treated with ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine). Although it may not be possible for every PET scan to be reviewed by a central panel of experts, these findings suggest that scans should be reported by experienced readers and equivocal scans possibly shared with other expert readers. Furthermore, the previous PET scans should always be accessed for comparison.

**Should a Negative or Positive PET Scan Be Used to Direct Therapy?**

As discussed earlier in this article, the value of the interim PET scan results may differ by the patient’s diagnosis. In patients with classic Hodgkin lymphoma, the initial retrospective analyses of PET scans suggested a dramatic difference in outcome between those with positive and negative results. Subsequent prospective studies have largely supported the initial findings.

However, the identification of patients who have a worse outcome on the basis of positive interim PET findings does not necessarily mean that changing treatment will improve their outcome. Many of these patients will still achieve a complete remission, and those complete remissions will usually translate into cure. For example, in one series of 46 patients who underwent interim PET scanning, 20 had positive interim results but 13 of these 20 patients had negative findings after treatment was completed. Patients who achieved a negative interim PET result had a 96% 2-year failure-free survival, in contrast to a 92% 2-year failure-free survival in those who had a positive interim PET findings but achieved a negative result after treatment was completed. In another series of patients treated with ABVD, positive interim PET findings were in association with a progression-free survival rate of 71%, compared with 90% for patients with a negative interim PET result. However, once again, the patients with positive interim PET findings who achieved a negative result after completing treatment had as good an outlook as those with an early negative PET result. For changing therapy on the basis of positive interim PET findings to be beneficial, the new therapy will need to cure all of the patients destined to be cured with the initial treatment and also cure some of the patients in whom therapy would otherwise fail. This may turn out to be true, but it needs to be proved.

In DLBCL, the initially reported difference in prognosis based on interim PET scans has been less dramatic in prospective studies, particularly in studies in which intensive chemotherapy was given. In studies in which repeat biopsies have been obtained in patients with DLBCL who have positive findings on PET, most have not shown persistent disease. Despite this, many current trials either stratify patients by PET scan result or change treatment in patients with positive findings on PET. Whether this is an effective strategy or not is the subject of multiple clinical trials.

It is not clear, however, whether a PET-directed therapeutic approach is the best for these clinical trials. A case could be made for including all patients in randomized studies that randomize between PET-directed therapy and assigned therapy that remains unchanged unless there is evidence of progression. Some recent data suggest that the results of a PET scan may add little in determining outcome when response is being assessed by CT scan. In a clinical trial of 1712 pediatric patients with Hodgkin lymphoma, all patients received ABVE-PC (doxorubicin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide) chemotherapy for 2 cycles and the response was assessed by CT scan. Rapid responders by CT scan were randomized between IFRT and observation. Slow responders by CT scan were randomized between an intensified chemotherapy regimen plus IFRT vs standard therapy plus IFRT. A secondary analysis based on PET response after 2 cycles was also performed, but the randomization was based on CT scans only and not on the PET scan results. In patients classified as rapid responders by CT scan, there was no difference between those with PET-positive and PET-negative results regardless of therapy. In those called slow responders by CT scan, there was also no difference except for a trend toward a better outcome with intensified therapy in patients with positive findings on PET. At present, PET-directed therapy is still investigational, and changes in therapy based on PET scan are best made within the context of clinical trials.

**TABLE 4. Recommendations for Use of FDG-PET in Patients With Lymphoma**

<table>
<thead>
<tr>
<th>FDG-PET definitely recommended</th>
<th>FDG-PET probably indicated (but more data needed)</th>
<th>FDG-PET not recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial staging in patients with HL, DLBCL, and FL</td>
<td>Initial staging in patients with PTCL and MCL</td>
<td>Monitoring of patients for relapse</td>
</tr>
<tr>
<td>Restaging at completion of therapy in HL, DLBCL, and FL</td>
<td>Interim response assessment in patients with HL and DLBCL</td>
<td>Detection of potential sites of transformation</td>
</tr>
<tr>
<td>Restaging at completion of therapy in PTCL and MCL</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DLBCL = diffuse large B-cell lymphoma; FDG-PET = fluorodeoxyglucose positron emission tomography; FL = follicular lymphoma; HL = Hodgkin lymphoma; MCL = mantle cell lymphoma; PTCL = peripheral T-cell lymphoma.
Should a PET Scan Be Used to Monitor Patients for Relapse?

Although detecting disease progression early is an attractive goal and PET scans may allow earlier detection than other imaging modalities or clinical examination, it is not proven that early detection improves the outcome of patients with lymphoma. In addition to making care more costly without any proven benefit, harm can come from interim imaging studies such as PET/CT. We are not willing to treat patients who achieve a complete remission without biopsy proof of recurrence. If the true-positive rate for PET scans in asymptomatic patients is only 20%, 80% of the patients will have unnecessary biopsies. There is also a real risk of second malignancies related to the radiation from frequent scans, particularly in younger patients. 70 In women younger than 30 years, there will be a significant risk for inducing breast cancer.

PET scans detect any cells that are metabolically active, and when used to monitor patients in remission, they are likely to yield an increased rate of false-positive results. Positive findings on PET scan need to be evaluated with biopsies, and false-positive PET results may lead to multiple, possibly unnecessary, extra biopsies. 55 Furthermore, active lymphoma is likely to lead to accumulation of cells and increasing lymphadenopathy; therefore, increasing size rather than increased FDG uptake may be a better determinant of which lesion needs to be biopsied. If an imaging modality is indicated to assess relapse, a CT scan may be sufficient, and if a node or mass is no bigger, the patient can be observed without a biopsy. Although we believe it is unlikely, surveillance PET or CT scans might improve outcome by identifying early relapse in some patients. This could be possible if salvage therapy would be more effective when administered a few weeks earlier and the biopsies done in patients with abnormal results but no relapse did not worsen their outcome. However, it will take a prospective trial to prove this is the case before routine scans in remission should be standard care.

CONCLUSION

PET scans have become an integral part of the management of patients with lymphoma. Recommendations for the use of FDG-PET scans are listed in Table 4. They are currently standard practice as part of the staging work-up and to confirm remission at the end of therapy. They may also be useful in detecting sites of lymphoma transformation and the source of an FUO. While an interim PET scan is commonly performed, its role in directing therapy remains investigational. Outside of a clinical trial, any positivity on an interim PET scan requires a biopsy of that site, and therapy should only be changed if biopsy-proven persistent or progressive disease is documented. As regards the use of PET scans in monitoring patients for relapse, it is the view of the authors that this is not indicated.

Abbreviations and Acronyms: ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine; BEACOPP = bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; CT = computed tomography; DLBCL = diffuse large B-cell lymphoma; FDG = fluorine 18 fluorodeoxyglucose; FLT = fluoro-l-thymidine; FUO = fever of unknown origin; IFRT = involved-field radiotherapy; IHP = International Harmonization Project; PET = positron emission tomography; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; RT = radiotherapy; SUV = standardized uptake value.

Potential Competing Interests: Dr Armitage reports consultant or advisory boards roles with Zelpharm, Seattle Genetics, Genentech, Allos, and Roche. Dr Ansell reports research funding from Seattle Genetics.

Correspondence: Address to James O. Armitage, MD, Department of Internal Medicine, Division of Hematology/Oncology, University of Nebraska Medical Center; 987580 Nebraska Medical Center; Omaha, NE 68198-7680 (joarmita@unmc.edu).

REFERENCES

10. Shankar LK, Hoffman JM, Bacharach S, et al. Consensus recommendations for the use of 18F-FDG PET as an indicator of


47. Holte H, Bogrud T, Leppa S, et al. 18FDG PET/CT after intensified chemoimmunotherapy in diffuse large B-cell lymphoma (DLBCL), aged 18-65 years with AAIP 2-3: Positive or indeterminate lesions have a low positive predictive value; A Nordic phase II substudy. Ann Oncol. 2011;22(suppl 4):152. (abstract 224).