

Lymphoma

Although lymphoma accounts for only 4% of cancers diagnosed annually, its diagnosis, staging, and management requires frequent imaging such that lymphoma may account for more than approximately 50% of the PET scans performed at a referral institution. However, imaging of lymphoma is challenging because its appearances are diverse with potential involvement of almost all organs. Additionally, lymphoma can mimic the appearance of almost all other neoplasms. Finally, the glucose uptake of a lymphoma within a given patient may be heterogeneous, presumably representing different clones of cells with different patterns of glucose metabolism; however, significant heterogeneity may suggest important differences in biologic behavior.

Initial Staging

Routine staging of lymphoma, including both Hodgkin and non-Hodgkin's lymphoma, involves a CT scan with contrast to the neck and pelvis and a PET scan. Although a gallium scan was typically part of the pretreatment workup of lymphoma, gallium scans have been largely replaced by PET scans. Various studies have reported that a PET scan can contribute to staging by upstaging disease, but this rarely results in a treatment change. Although the actual impact on treatment might be uncertain, particularly if disease is upstaged from stage III to stage IV, the consistent message from these studies is that PET scan more typically upstages disease rather than downstages. PET scans may also help identify extranodal disease. For example, PET may identify bone involvement not detected with CT scan, typically upstaging disease from stage III to stage IV.

Although a clinical role of the initial PET scan is to provide a baseline for subsequent evaluation, controversy is ongoing about this indication. For some types of lymphoma, such as Hodgkin disease, the initial PET scan is almost always positive, and if treatment response is based on a normal PET scan, then an initial PET scan is not routinely needed. Additionally, unlike other malignancies, a high correlation exists between the CT scan (i.e., anatomic image) and PET scan (i.e., functional image), and therefore the interpretation of a positive PET scan in the setting of a negative CT scan is uncertain. Thus, if a CT scan after therapy is negative, residual FDG uptake in a site of initial disease is of uncertain significance. The need for a baseline PET scan may also vary with histologic subtype and stage of disease. For example, a baseline PET scan may not be required for advanced stage follicular lymphoma if the recommended treatment was observation, whereas it would be recommended if treatment was recommended.

PET scan also has been evaluated as a technique to assess bone marrow involvement. A meta analysis including 587 patients with lymphoma pooled from 13 studies showed that, compared with biopsy, PET had a moderate sensitivity of 51% and a specificity of 91%. These results suggest that PET cannot replace bone marrow biopsies. In general, PET is not commonly used to assess bone marrow involvement, although its results will be reported as an incidental finding potentially used to direct biopsy.

Limited data are available on PET as a routine method of surveillance. Although no survival advantage has been documented, PET scan may be helpful in the small subset of patients with unusual sites of disease, such as bone, subcutaneous tissue, or skin, in which follow-up with other imaging techniques is limited.

PET Scans and Lymphoma Histology

Several studies have shown that the intensity of FDG uptake is associated with aggressive disease. In one study of 97 patients with non-Hodgkin's lymphoma who were either treatment-naïve or undergoing initial evaluation for relapsed disease, all cases of indolent lymphoma that had an SUV less than or equal to 13 and an SUV greater than 10 excluded indolent lymphoma with a specificity of 81%. The authors concluded that this information may be helpful if discordance is seen between biopsy and clinical behavior. Because of the overlap in SUV values across the histologies, a PET scan cannot replace a biopsy but may be particularly useful in guiding biopsies. For example, unless otherwise instructed, a surgeon may biopsy the most convenient node available, but a PET scan can specifically target a lymph node with the highest SUV.

PET scans also have been investigated as a technique to detect malignant transformation of chronic lymphocytic lymphoma, such as Richter's transformation. For example, an SUV greater than 5 has been considered highly suggestive of Richter's transformation. In a retrospective study of 37 patients with CLL, 10 of 11 (91%) with Richter's transformation had an SUV uptake greater than 5.

Response Criteria and Prognosis

In 1999, an international workshop developed standard response criteria for lymphoma based on clinical radiologic and pathologic (i.e., bone marrow criteria) findings. The radiologic response was typically evaluated with CT scan. One category of response was complete response uncertain (CRu), which reflects the inability of CT to distinguish among viable tumor, necrosis, or fibrosis in residual masses.

Because studies have reported that PET scan results have prognostic value, interest was shown in incorporating PET imaging into response criteria. For example, Juweid et al. assessed response using the international criteria in conjunction with PET scan results in 54 patients with aggressive non-Hodgkin's lymphoma after 4 to 6 cycles of chemotherapy and compared response with progression-free survival. PET scans were considered positive or negative based on visual assessment; in the lung, scans were considered positive if the uptake exceeded that of the mediastinal blood pool structures. Using the CT-based international criteria alone, 17 patients experienced a complete response and 7 a CRu. In contrast, when PET results were incorporated, 35 patients experienced a complete response and no patients experienced a CRu. Therefore, a negative PET scan even in the presence of a residual mass is interpreted as a complete response. In this study, results of the PET scan recategorized patients with a CRu to either a complete response or partial response, essentially eliminating the CRu category except for the small subset of patients with indeterminate bone marrow.

In 2007, the International Working Group for non-Hodgkin's lymphoma published 2 documents establishing the role of PET scans in assessing lymphoma tumor response. One document developed guidelines for performing and interpreting PET imaging to assess treatment response, whereas the second proposed revised response criteria. Specifically, the revised response criteria have eliminated the category of CRu, and the categories of complete response, partial response, and stable disease are based partly on the results of PET scans.

Interim Restaging

As an interim restaging technique, a PET scan after a few cycles of chemotherapy could provide early detection of treatment failure, prompting a switch to more aggressive therapy. For example, in patients whose tumors respond to chemotherapy, an estimated 80% to 90% of the effect of chemotherapy on tumor FDG uptake occurs within the first 7 days after initiation of therapy. Various studies have examined interim PET as a prognostic indicator, concluding that the results of an interim PET scan are strong and independent predictors of progression-free survival in Hodgkin disease and non-Hodgkin's lymphoma.

Study results suggest that therapy does not need to be changed when the PET scan is negative, but a separate trial is needed to determine whether a positive PET scan should prompt an alternative therapy and whether this alternative therapy can improve outcomes. A trial design to test these outcomes would include a PET scan as an interim staging technique. Patients with a negative PET scan would continue on therapy, whereas those with a positive PET scan may undergo biopsy confirmation considering the rate of false-positive PET scan results. Patients with a positive biopsy can then be randomized to either continue initial therapy or be switched to an alternate therapy. Ideally, treatment outcomes would be improved in patients switching to alternative therapy.

Summary of Recommendations

In staging, PET scans serve as a baseline for lymphomas that are potentially curative (i.e., diffuse large B-cell lymphoma [DLBCL], Hodgkin disease). The PET scan serves as a baseline when assessing treatment response. Scans rule out systemic disease in clinically localized lymphoma (i.e., early-stage Hodgkin lymphoma, DLBCL, Hodgkin disease, follicular lymphoma, and mantle zone lymphoma), and are used to assess lymphoma when transformation is suspected.

PET scans can be useful for evaluating residual masses. At the end of therapy, a positive PET scan is associated with a poor disease-free survival. However, because of false-positives, biopsy is necessary for deciding on aggressive therapeutic interventions. For evaluating treatment response, PET scans have a limited role if the diagnostic CT is normal. PET scans have been incorporated into treatment for aggressive non-Hodgkin's lymphoma and Hodgkin lymphoma, and PET scans also are used to direct biopsy of most suspicious areas based on SUV. Because of the high false-positive rate (outside of a clinical trial), PET scans are not routinely indicated in the interim evaluation for prognostication and are not used for routine follow-up of node-based disease. However, PET may be beneficial in selecting patients with unusual sites of disease, such as bone, where PET is superior to CT, and for distinguishing between indolent and aggressive non-Hodgkin's lymphoma based on SUV value.