EVALUATING LYMPHOMA WITH PET AND PET/CT

high-dose therapy. It remains unclear how to most appropriately treat patients both pre- and post-high-dose therapy, although persistent disease based on PET predicts a worse outcome. Further studies that further consolidation is warranted.

CONCLUSIONS

Several conclusions can be drawn from the current data on PET imaging, although they are limited by the lack of randomization, prospective, and adequately powered trials evaluating the change in overall survival or disease-free survival. The data support the following conclusions:

• PET is of high sensitivity and specificity compared with CT.
• PET is a good study for evaluating stage of disease.
• FDG uptake on PET of residual mass seen on CT is a strong indicator of outcome for both relapse and survival.
• PET results correlate with patient outcome.
• Histology may influence the specificity, sensitivity, and accuracy of PET.
• High SUV appears to correlate with recurrent lymphomas, and PET appears to be of prognostic value pre- and post-high-dose therapy.

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LEARNING OBJECTIVES

Upon completion of this activity, participants should be able to:

• Describe the role of PET in evaluating lymphoma stage in lymphoma.
• Discuss the role of PET in predicting overall survival and duration of response using standard imaging techniques.
• Define the role of PET in predicting response and long-term outcome after high-dose therapy.
• Summarize the role of PET in evaluating persistent mediastinal mass.

By David Rizzieri, M.D., and Timothy Goggins, M.D.

Evaluating Lymphoma with PET and PET/CT

In this activity, Dr. Rizzieri and Dr. Goggins evaluate the role of 18F-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) in the staging and treatment monitoring of non-Hodgkin's lymphoma (NHL) and Hodgkin's disease (HD). Taken as whole, however, the published clinical trial data support the use of PET in malignant lymphomas, including malignant lymphomas and Hodgkin's disease. FDG-PET is a metabolic imaging tool that detects areas of increased metabolic activity, a common feature of tumor tissue. A study by Wagner et al. using a murine model confirmed fluorothymidine-fluorodeoxyglucose as another suitable tracer for PET, enabling imaging of human lymphoma cells in vivo. The trial found a close correlation between fluorothymidine-fluorodeoxyglucose and fluorodeoxyglucose uptake in determining malignant lymphomas and noted similarities to values of the Ki-67-labeling index of tissue biopsies.

Over the last decade, PET imaging has become a commonly used tool to distinguish the nature of tumors both before and after treatment to assist the clinical evaluation system. As one study has noted, PET/CT imaging is more accurate compared with standard lymphoma scans in lymphoma.

Most of these studies are retrospective and incorporate a mixed lymphoma population that includes multiple subtypes of non-Hodgkin's lymphoma (NHL) and Hodgkin's disease (HD). The studies are often performed without blinded scan readers, indicating that a systematic bias may occur. Despite these limitations, the benefits of PET imaging for lymphomas appear to have the potential to be illustrated in terms of histology, stage, residual mediastinal masses, relapse, and prognosis.

HISTOLOGY OF LYMPHOMA

The accompanying table lists the results of five trials that included patients with various types of lymphomas. FDG-PET scanning has been shown to accurately detect lymphoma subtypes of diffuse large B cell NHL, mantle cell lymphoma, indolent follicular lymphoma, and Hodgkin's disease. In a retrospective analysis of 172 patients at the University of Pennsylvania, only 6% of patients had no evidence of disease on FDG-PET imaging (Figure 11).

Most of these studies incorporate diffuse B-Cell large cell lymphoma and Hodgkin's disease. It is important to keep in mind that the sensitivity of PET differs among lymphoma subtypes, and data derived from one group are not completely transferable to another. Indolent lymphomas such as marginal zone lymphomas appear to have less reliable positive FDG-PET findings. Similarly, detection of small lymphocytic lymphoma on FDG-PET is only about 50%.
FDG uptake in grade 2 or 3 follicular NHL over grade 1.17 Maximum SUV for indolent lymphomas appears to be around 6, with more aggressive lymphomas or lymphomas in transformation having SUVs >11.18,19 Hubner et al.20 found a correlation between SUV and DNA proliferation in carcinoma patients, and Barac et al.21 demonstrated that SUVs correlate with recurrent lymphomas. Necrotic tissue shows significantly lower uptake values; the role of specific SUV correlation in FDG-PET scans for histological subtype or necrotic versus live specific SUV correlation in FDG-PET scans and restaging of NHL. One of the first trials was inadequate at this time. PET cannot reliably differentiate CNS lymphomas from infection or other CNS malignancies.19

Data-supporting PET imaging in the diagnosis of central nervous system lymphoma is insufficient at this time. In evaluating 45 patients, it was noted that PET was able to distinguish between tumor and necrosis with a sensitivity of 83% and a specificity of 89%. The authors did not control for stage. This may account for some of the sensitivity.18

FDG-PET imaging has been documented in the initial evaluation of NHL; however, the number of patients was small. FDG-PET imaging in the evaluation of the CNS may play a larger role in the near future.22,23

DISCUSSIONS IN PET IMAGING

Primary intestinal lymphoma is a rare condition. A study of eight patients with duodenal lymphoma, who had their stage changed as a result of PET imaging, revealed that the greatest impact in patients with early-stage disease; nine of 44 patients had treatment intensification as a result of their PET scans.24

MEDIASTINAL MASS

Residual masses of primary lymphomas may occur with various types of lymphomas. Many patients with residual mediastinal masses are actual- ly cured, as the masses may represent benign fibrotic tissue.25,26

It has been shown, however, that a positive PET scan in patients with mediastinal masses in both Hodgkin’s lymphoma and NHL indicates a significantly higher risk of relapse.27-29 Foon et al.30 evaluated 29 patients with HD who had a residual mass of at least 2 cm documented by CT one month after comple- tion of treatment. PET scans were obtained within one week of the CT scan. The positive predictive value (PPV) of PET-positive scans was 75% and the negative predictive value was 100% at one year. Additional anecdotal reports support the use of PET for mediastinal masses post-treat- ment. Residual masses in other areas may also be followed in a similar manner.31

RELAPSE

Numerous studies noting the ability of PET to predict relapse have been reported (see table). Residual masses are noted in up to 60% of patients with lymphoma after completion of treatment, and fewer than 20% will relapse.32 Figure 2 shows the value of assessing response with PET as a comple- mentary study to CT. With large masses, shrinkage of the imaging therapy, though it is unclear with conventional CT whether there is residual disease in the remaining mass (compare Figures 2A and 2C). PET imaging provides a reliable, non-invasive measure for persistence of disease (compare Figures 2A and 2D). Patients who relapse after initial therapy for lymphoma are often retreated with con- ventional chemotherapy in an attempt to stem cell transplant (ASCT). The cost and potential toxicity of this procedure underscores the importance of adequate staging and documentation of recurrent disease prior to its initiation.33

Schol et al.34 studied 68 relapsed lymphoma patients, 46 of whom had chemosensitive disease (33 NHL, 13 HD). Disappearance of greater than 90% of the SUV of intensity of FDG uptake (SUV) after two reinduction chemother- apy courses correlated with a favorable outcome. Two-year progression-free survival was 62% for PET-negative patients versus 32% for PET-positive patients.35

PROGNOSIS

Several trials have supported a 90% rate of long-term remission for individuals with neg- ative PET scans post-treatment.36-38 The authors did not control for stage. This may account for some of the sensitivity.18

Foon et al.39 evaluated a prospective group of 88 PET-negative pretransplant patients who had chemosensitive NHL. All patients had had pretreatment PET scans, and 45 had had post-treatment PET. The post-treatment PET appeared to predict outcome. The relapse rate for patients with negative PET scans was 10%, whereas patients with positive PET scans had a relapse rate of 19%. This difference between pretransplant negativity and positivity was significant (p = 0.00001). The number of events (n = 5) in the PET-negative group was small and two of these patients who died were censored from the analysis for OS and PFS at the time of their death, due to postmortem examinations negative for residual lymphoma. The 19 HD patients who failed to achieve a complete response at post-ASCT, which, as we have demonstrat- ed, confounds the effects of the PET scan, is not considered standard care in the U.S. Six of seven patients who did not achieve some response on FDG-PET developed lymphoma progression with a median PFS of nine months and OS of 29 months. The author found significantly shorter survival among patients who failed to achieve some response on FDG-PET. Borch- erer et al.40 studied 16 patients with HD and NHL and found longer OS and PFS in the PET-negative patients (p = 0.001). The authors did not control for stage. This study incorporated a higher proportion of che- moradiotherapy and patients with low- to high-grade lymphomas. In summary, PET imaging results may be predictive of outcome in patients undergoing
FDG uptake in grade 2 or 3 follicular NHL over 8.2. Maximum SUV for indolent lymphomas appears to be around 6, with more aggressive lymphomas or lymphomas in transformation having SUVs above 8.2. Hubner et al.11 found a correlation between SUV and DNA proliferation in carcinoma patients, and Baraz et al.12 found a high SUV uptake in metastatic prostate cancer, suggesting a possible correlation between SUV and DNA proliferation.

Case reports of varying locations of lymphomas have supported the use of FDG-PET in head and neck lymphomas, including tonsil, nasopharynx, and base of the tongue. An anecdotal case report of four patients illustrates the clinical evaluation of head and neck lymphomas.22-24 The four cases demonstrated the importance of FDG-PET in determining a benign etiology, focusing excisional biopsy on the lymph node with highest SUV uptake, and illustrating the activity within residual lymphoma.

Data supporting PET imaging in the diagnosis of central nervous system lymphoma are inadequate at this time. Patients undergoing (PFS) ablation can have detected CNS lymphoma from infection or other CNS malignancies.25 Foo et al. published a retrospective trial of 38 lymphoma patients, which involved multiple lymphoma subtypes of PET identified additional sites of disease in 29% of patients. The sensitivity of initial PET imaging was 96% as compared with only 71% for CT imaging. PET imaging has an impact on Hodgkin’s disease as well. A trial published by Naumann et al. showed a 90% abnormality of PET when PET was positive in patients with varying stages of Hodgkin’s disease based on CT imaging. PET images changed the stage of HD in 20% of the patients. Management of the disease would have been changed in 16 of the 18 patients who had their stage changed as a result of PET imaging. PET appeared to have the greatest impact in patients with early-stage disease; nine of 44 patients had treatment intensification as a result of their PET scans.

MEGISITATIONAL MASS
Residual medullary masses may occur with various types of lymphomas. Many patients with residual mediastinal masses are actually lymphoma patients who may have had chemosensitive disease (33 NHL, 13 HD). Disappearance of greater than 90% of SUV and 100% of intensity of FDG uptake (SCV) after two reinduction chemotherapy regimens may be an excellent PET marker for persistent disease. Two-year progression-free survival was 62% for PET-positive patients versus 32% for PET-negative patients.

PROGNOSTIC STUDIES
Several trials have supported a 90% rate of long-term remission for individuals with negative PET scans post-treatment. Naumann et al.33 prospectively followed 58 patients with HD who had post-treatment PET scans, and 45 had pretreatment PET scans. Three patients had persistent PET lesions; 45 had had post-treatment PET. The post-treatment PET appeared to predict outcome. The relapse rate for post-positively treated tumor stages in patients was 20% compared with only 17% for negative FDG-PET imaging. The trial also compared PET with CT; positive-CT scans correlated to residual disease in only 41% of patients. Several trials have supported a 90% rate of long-term remission for individuals with negative PET scans post-treatment.32,33 Despite the negative predictive value of PET imaging, 10% of patients will likely recur, due to undetectable minimal residual disease. Spasen et al. supported the high probability for mini-

mal residual disease or recurrent disease for persistently abnormal FDG-PET scans post-treatment. Naumann et al.33 followed 58 patients with HD or NHL who had post-treatment complete remission with residual masses found on CT scans. No recurrence was noted in any patients with positive PET scans, for a negative predictive value of 100%. The small number of patients with positive PET all scans developed relapse lymphoma.

AUTOLOGOUS STEM CELL TRANSPLANTATION
The prognostic value of FDG-PET after first-line therapy for HD and aggressive NHL is well supported.12-14 Jerusalem et al. found in 54 patients that a positive PET scan involving a residual lesion indicated relapsed disease. The relapse rate was only 10% among patients with negative PET scans and negative CT scans. Only 26% of patients with residual mass on CT and negative PET scans relapsed, and 80% of lesions were cured outside the residual mass on CT.

Spasen et al. noted in a recent trial of 60 patients that post-ASCT PET has an important prognostic role in the pretransplant evaluation of aggressive lymphoma. Patient eligibility was high-risk disease, defined as an implanta-

tion for diffuse large B-cell lymphoma, anaplastic lymphoma, or mantle cell lymphoma. The included patients with refractory disease and those with less aggressive pathologic lymphoma variants such as follicular lymphoma. The authors demonstrated a statistically significant difference between posttransplant negative PET scan results in improving overall survival (OS) (p = 0.00002) and progression-free survival (PFS) (p = 0.00001). The number of events (n = 5) in the PET-negative patients was too small to allow a separate analysis of events in these patients who died censored from the analysis for OS and PFS at the time of their deaths, due to postmortem examinations negative for residual lymphoma. The 19 HD patients who were positive in the PET stage, which, as we have demonstrated, confounds the effects of the PET results, will be included in a separate study with no association in predicting PFS and OS when controlling for Internation- al Prognostic Index score (p = 0.78 and p = 0.65).

Cremerius et al. prospectively investigated the prognostic role of pre- and post-ASCT PET in 22 patients with NHL. The major limitation of this study was the use of ASCT as initial therapy, which is not considered standard care in the U.S. Six of seven patients who did not achieve some response on FDG-PET developed lymphoma progression with a median PFS of nine months and OS of 29 months. The authors found significantly shorter survival among patients who failed to achieve some response on FDG-PET. Becker et al32 studied 16 patients with HD and NHL and found longer OS and PFS in the PET-negative PET group (p = 0.001). The authors did not control for stage. This study incorporated patients with chemotherapy and patients with low- to high-grade lymphomas. In summary, PET imaging results may be predictive of outcome in patients undergoing
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• PET results correlate with patient outcome.
• Histology may influence the specificity, sensitivity, and accuracy of PET.
• High SUV appears to correlate with recurrent lymphoma, and
• PET appears to be of prognostic value pre- and post-high-dose therapy.

Following these conclusions:

• Outline the role of PET in evaluating persistent mediastinal masses.

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HISTOLOGY OF LYMPHOMA

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Other trials have correlated transformation to a more aggressive lymphoma with increased standard uptake value (SUV). Some suggest increased

REFERENCES