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## Evaluating Lymphoma with PET and PET/CT

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

### LEARNING OBJECTIVES

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

- Describe the role of PET in evaluating disease stage in lymphoma
- Discuss the role of PET in predicting overall response and duration of response after standard therapy
- Outline the role of PET in predicting response and long-term outcome after high-dose therapy
- Summarize the role of PET in evaluating persistent mediastinal masses

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Dr. Rizzieri and Dr. Goggins have no significant financial arrangement or affiliation with any manufacturer of any pharmaceutical or medical device and are not affiliated in any manner with any provider of any commercial medical or healthcare professional service.

Fluorodeoxyglucose PET is a metabolic imaging tool that detects foci of increased glycolysis, a common feature of tumor tissue.<sup>1</sup> A study by Wagner et al<sup>2</sup> using a murine model confirmed fluorodeoxythymidine as another suitable tracer for PET, enabling imaging of human lymphoma cells in vivo. The trial found a close correlation between the fluorodeoxythymidine and fluorodeoxyglucose in determining malignant lesions and noted similarities to values of the Ki67-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 in an effort to better understand prognosis and guide therapies. The clinical trials supporting its use are often difficult to interpret because of differences between machines, scan interpretations, and inclusion of mixed disease types (e.g., non-Hodgkin's lymphoma, Hodgkin's disease). Taken as whole, however, the published clinical trial data support the use of PET scans in lymphoma.

Many of these trials 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 patients with lymphoma can 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 lymphoma. 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 1).<sup>3</sup>

Most of these studies incorporate diffuse B-cell large cell lymphoma or Hodgkin's disease. It is important to keep in mind that the sensitivity of PET differs among the 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.<sup>4,5</sup> Similarly, detection of small lymphocytic lymphoma on FDG-PET is only about 50%.<sup>6,7</sup>

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

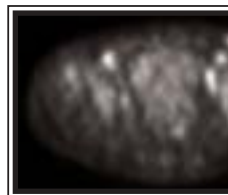


Figure 1. FDG-PET scan shows activity (bright areas) in multiple areas of lymphoma in abdominopelvic region.

FDG uptake in grade 2 or 3 follicular NHL over grade 1.<sup>8,9</sup> Maximum SUV for indolent lymphomas appears to be around 6, with more aggressive lymphoma or lymphomas in transformation between 8 and 11.<sup>10</sup> Hubner et al<sup>11</sup> found a correlation between SUV and DNA proliferation in carcinoma patients, and Bares et al<sup>12</sup> found a high SUV uptake in 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 tissue remains an active area of investigation.

PET imaging is highly sensitive in patients with more aggressive lymphomas, and the actual amount of uptake of the labeling agent may have implications for grade of disease, transformation, and degree of disease response.

**STAGING**

With the use of multimodal therapy and the likelihood, in some instances, of minimizing therapies based on stage of disease, accurate staging is essential to the optimal management of NHL. Multiple studies have supported the use of PET for accurate staging and restaging of NHL. One of the first trials to evaluate the impact of FDG-PET on initial staging and management of NHL and HD compared 129 sites of disease, of which 88 were concordant.<sup>13</sup> In evaluating 45 patients for initial staging, FDG-PET correctly upstaged or downstaged 16% of patients, leading to a change of therapy in 13%. It understaged three patients who were correctly staged by conventional modalities. Discordant lesions were verified by biopsy or clinical follow-up.

These data correlated with previous studies of a mixed lymphoma population that compared PET with CT imaging. One study found no positive lesion on CT that was a false negative on PET.<sup>14</sup> Jerusalem et al<sup>15</sup> reported a high concordance between PET and CT for evaluation of the spleen, liver, and digestive tract, though bone marrow infiltration based on PET scan was discordant in 12 patients.

Detection of lymphoma in bone marrow with PET imaging has been documented. One trial directly correlated PET activity with bone marrow biopsies and found correlation between PET scans and marrow histology in 39 of 50 patients: concordant positive in 13 patients and concordant negative in 26.<sup>16</sup>

Primary intestinal lymphoma is a rare clinical condition. A study of eight patients with varying tumor grade attempted to stage patients with duodenal positive follicular

lymphoma. None of the patients with primary duodenal FL showed pathologic elevated FDG uptake. The findings were not influenced by tumor grade or proliferative activity.<sup>17</sup>

Case reports of varying locations of lymphomas have supported the use of FDG-PET in head and neck lymphomas, primary breast NHL, and primary thyroid lymphoma. An anecdotal case report of four patients illustrates the clinical evaluation of head and neck lymphomas.<sup>18</sup> 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 lymph nodes.

Data supporting PET imaging in the diagnosis of central nervous system lymphoma are inadequate at this time. PET cannot reliably differentiate CNS lymphoma from infection or other CNS malignancies.<sup>19</sup>

Foo et al<sup>20</sup> published a retrospective trial of 38 lymphoma patients, which involved multiple lymphoma subtypes of NHL. 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<sup>21</sup> evaluated a prospective group of 88 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.

**MEDIASTINAL MASS**

Residual mediastinal masses may occur with various types of lymphoma. Many patients with residual mediastinal masses are actually cured, as the masses may represent benign fibrotic tissue.<sup>22-24</sup>

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. Panizo et al<sup>25</sup> studied 29 patients with HD who had a residual mass of at least 2 cm documented by CT one month after completion of therapy. Patients underwent PET scanning 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-treatment. Residual masses in other areas may also be followed in a similar manner.<sup>26</sup>

**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.<sup>22</sup> Figure 2 shows the value of assessing response with PET as a comple-

**SELECTED STUDIES INDICATING THE VALUE OF FDG-PET FOR ASSESSING RESPONSE AND PREDICTING SURVIVAL IN LYMPHOMA PATIENTS**

Study	Patients	Result
Foo <sup>20</sup>	38	PET positive predictive value 100%; CT 33%
Jerusalem <sup>34</sup>	54	PET-negative patients had only 10% relapse rate
Spaepen <sup>37</sup>	60	PET-negative pretransplant patients have better overall and progression-free survival than those with positive test
Cremerius <sup>38</sup>	22	PET-negative patients have better survival than PET-positive patients
Becherer <sup>39</sup>	16	PET-negative pretransplant patients live longer than PET-positive patients

mentary study to CT. With large masses, shrinkage is often noted with 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 2B and 2D).

Patients who relapse after initial therapy for lymphoma are often retreated with conventional chemotherapy prior to an autologous 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.

Foo et al<sup>20</sup> noted a PPD of 100% for PET imaging at the completion of treatment. The PPD value of CT was only 33% at the time of relapse. PET imaging changed treatment management in 50% of the cases in this trial.

Schot et al<sup>27</sup> studied 68 relapsed lymphoma patients, 46 of whom had chemosensitive disease (33 NHL, 13 HD). Disappearance of greater than 90% reduction of intensity of FDG uptake (SUV) after two reinduction chemotherapy courses correlated with a favorable outcome. Two-year progression-free survival was 62% for PET-negative patients versus 32% for PET-positive patients.

## PROGNOSIS

Most studies support the correlation of FDG-PET results with patient outcome. The major factors of PET imaging in determining prognosis are sensitivity and specificity of detecting residual disease and the detection of metabolic activity in residual tissue.<sup>28</sup>

Romer et al<sup>29</sup> noted the ability of PET to differentiate responders from nonresponders as early as one week after therapy. The authors noted a correlation between the lower SUV uptake and increased remission rate at one year.

High-risk patients appear to have the best correlation between positive PET imaging and relapse of lymphoma. Mikhael et al<sup>30</sup> analyzed 49 adult patients with aggressive biopsy-proven 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 positive scans was 100%, versus 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.<sup>15,30,31</sup> Despite the negative predictive value of PET imaging, 10% of patients will likely recur, due to undetectable minimal residual disease. Spaepen et al<sup>32</sup> supported the high probability for mini-

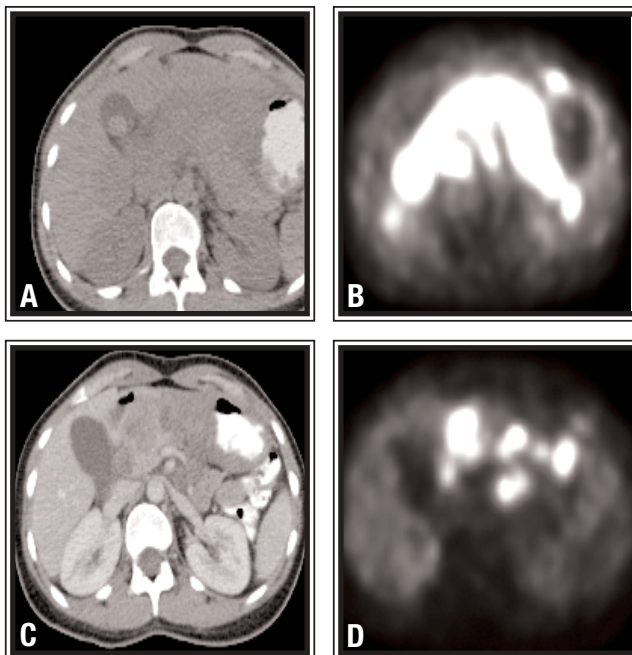


Figure 2. Large cell lymphoma. Abdominal mass is seen on CT (A) and PET (B). Following chemotherapy, the mass has shrunk (C), but PET shows activity (D), demonstrating that active lymphoma is still present.

mal residual disease or recurrent disease for persistently abnormal FDG-PET scans post-treatment. Naumann et al<sup>33</sup> prospectively 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 the 39 HD patients with negative PET scans, for a negative predictive value of 100%. The small number of patients with positive PET scans all 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.<sup>34-36</sup> Jerusalem et al<sup>34</sup> 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 neg-

ative PET scans relapsed, and 80% of relapses occurred outside the residual mass on CT.

Spaepen et al<sup>37</sup> noted in a recent trial of 60 patients that F-18 FDG-PET has an important prognostic role in the pretransplant evaluation of aggressive lymphoma. Patient eligibility included those undergoing transplantation for diffuse large B-cell lymphoma, anaplastic lymphoma, or mantle cell lymphoma. The study excluded patients with refractory disease and those with less aggressive pathologic lymphoma variants such as follicular lymphoma. The authors demonstrated a statistically significant difference between pretransplant negative PET scan results in improving overall survival (OS) ( $p < 0.00002$ ) and progression-free survival (PFS) ( $p < 0.000001$ ). The number of events ( $n = 5$ ) in the PET-negative group limited the trial, 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 Hodgkin's disease patients showed a statistically significant difference in PFS ( $p = 0.0025$ ), but not in OS ( $p = 0.13$ ). This trial did not control for stage, which, as we have demonstrated, confounds the effects of the PET results on prognosis. Spaepen found no association in predicting PFS and OS when controlling for International Prognostic Index score ( $p = 0.78$  and  $p = 0.65$ ).

Cremerius et al<sup>38</sup> prospectively investigated the prognostic role of pre- and post-ASCT in 22 patients with NHL. The major limitation of this study was the use of ASCT as initial therapy, which is not considered standard of 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. Becherer et al<sup>39</sup> studied 16 patients with HD and NHL and found longer OS and PFS in the pretransplant PET-negative group ( $p = 0.001$ ). The authors did not control for stage. This study incorporated patients with chemorefractory disease and patients with low- to high-grade lymphomas.

In summary, PET imaging results may be predictive of outcome in patients undergoing

high-dose therapy. It remains unclear how to most appropriately factor in the results both pre- and post-high-dose therapy, although persistent disease based on PET results may suggest 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 randomized, 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 masses

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 lymphoma; and
- PET appears to be of prognostic value pre- and post-high-dose therapy.

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