

REVIEW

# Utility of Positron Emission Tomography Imaging in Lymphoma: A Clinician's Point of View

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**KEY WORDS:** *positron emission tomography; fluorodeoxyglucose; lymphoma; Hodgkin's disease*

**ABBREVIATIONS**

ASCT = autologous stem cell transplantation  
CR = complete remission  
CRu = complete remission unconfirmed  
CT = computed tomography  
DLBCL = diffuse large B-cell lymphoma  
FDG = fluorodeoxyglucose (<sup>18</sup>F)  
HL = Hodgkin's lymphoma  
PET = positron emission tomography  
PFS = progression-free survival  
PR = partial response

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ABSTRACT

Positron emission tomography (PET) using fluorodeoxyglucose (<sup>18</sup>F) (FDG) is increasingly used in the staging of lymphoma. Results of the use of PET during and after completion of therapy for staging of Hodgkin's lymphoma and aggressive non-Hodgkin's lymphoma demonstrate a highly predictive value for outcome. Based on recommendations of the International Harmonization Project, FDG-PET has been incorporated into the revised response criteria of lymphoma. There is currently no evidence to support the use of FDG-PET in indolent lymphoma, nor for its routine use during follow-up. Evidence also lacks on the impact of FDG-PET on treatment outcome. Clearly, well designed clinical trials are warranted to determine the subsets of patients who will benefit from this modality.

INTRODUCTION

Positron emission tomography (PET) using fluorodeoxyglucose (FDG), a glucose analog, with the positron-emitting radioactive isotope fluorine-18 substituted for the normal hydroxyl group at the 2' position in the glucose molecule, is a functional imaging technique that is widely used in the management of patients with lymphoma. FDG-PET is based on the principle that malignant cells have increased rates of glucose uptake and metabolism compared with normal tissues. There has been considerable progress in investigating the value of FDG-PET in lymphoma since the first report back in 1987,<sup>1</sup> but its precise role in disease management has not been well defined because it has been introduced into clinical practice without well designed prospective randomized trials. In lymphomas, FDG-PET imaging has been evaluated in all the time points of management. In this article we will review from a clinical point of interest, the evidence for the use of FDG-PET in monitoring the treatment of lymphoma, including initial staging, interim and post-treatment response evaluation, follow-up, and finally the issue of response-adapted therapy.

FDG-PET IN INITIAL STAGING OF LYMPHOMA

Staging of lymphoma is usually performed using computed tomography (CT). However, CT lacks functional information, which can impede the identification of

disease in normal-sized tissue. FDG-PET has become an established imaging modality to stage lymphoma and over the past decade its reliability has dramatically improved, with technological advances including three-dimensional acquisition, and image fusion between PET and CT. Integration of both modalities may outperform both FDG-PET alone and CT alone in staging of malignant lymphoma.

Clinical staging of both Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma is critical for determining the treatment strategy and prognosis. The Ann Arbor staging system is used for staging, initially traditionally based on physical examination and bone marrow evaluation, but subsequently CT scans have been incorporated.<sup>2</sup> It is questionable whether PET should be incorporated into the Ann Arbor staging system. PET is highly sensitive in detecting nodal and extranodal involvement by most histological subtypes of lymphoma and may provide complementary information to conventional staging methods.<sup>3</sup>

Lymphomas differ with regard to their glucose metabolic activity. Systemic studies show that indolent lymphomas exhibit lower glucose metabolic activity (FDG uptake) than more aggressive lymphomas.<sup>4</sup> Most types of lymphoma are FDG-avid with a sensitivity that exceeds 80% and a specificity of about 90%, which is superior to CT.<sup>5</sup> Positron emission tomography and CT are 80% to 90% concordant in staging of patients who have diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, and mantle cell lymphoma. In patients with discordant results, PET results in upstaging due to detection of additional nodal, hepatic, or splenic disease. In contrast, concordance of PET and CT in determining clinical stage occurs in only 60% to 80% of patients with HL, with comparable discordant findings in both directions.<sup>6</sup> A meta-analysis of FDG-PET in staging of lymphoma demonstrated a pooled sensitivity for 14 studies of 90.9% (95% CI, 88.0 to 93.4) with a false-positive rate of 10.3% (95% CI, 7.4 to 13.8) with an apparently higher sensitivity and false-positive rate in patients who had HL.<sup>7</sup> Although PET can detect bone or bone marrow involvement, PET alone is unreliable in detecting limited bone marrow involvement and cannot substitute for bone marrow biopsy in lymphoma staging.<sup>8</sup>

The revised guidelines for the staging and the response criteria of HL and non-Hodgkin's lymphoma were recently published to include the expanding role of PET/CT. The two major summary points of the International Harmonization Project were the standardization of performance and interpretation of PET in lymphoma<sup>9</sup> and new response criteria incorporating PET and bone marrow immunohistochemistry.<sup>10</sup> One important outcome of the Project was the elimination of the term complete remission unconfirmed (CRu) that provides a better separation of the progression-free survival (PFS) curves between complete remission (CR) and partial response (PR) patients. Despite the superior sensitivity and specificity compared with CT, PET is currently not required

as part of standard lymphoma staging, although the expert panel recommends pretreatment PET in patients with HL or DLBCL enrolled in a clinical trial. The reasons for not being incorporated in standard staging of lymphoma are the cost, the small percentage of patients (15% to 20%) in whom PET detects additional disease sites that modify clinical stage, and more importantly the even fewer patients for whom this modification alters management and outcome. The lack of evidence to suggest an impact of initial FDG-PET staging and modified disease management on patient outcome remains a crucial issue that needs to be addressed in well designed prospective trials. The expert panel also does not recommend the use of PET in initial staging of the routinely FDG-avid follicular and mantle cell lymphomas and the variably FDG-avid other indolent and aggressive lymphomas, unless patients are participating in a clinical trial and overall response rate /complete remission is a primary study end point.

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#### FDG-PET IN INTERIM RESPONSE EVALUATION OF LYMPHOMA

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Conventional methods for treatment response monitoring are based on morphological criteria, and a reduction in tumor size on CT as the most important determinant. However, the rate of tumor regression may not be an accurate predictor of outcome. Functional imaging with FDG-PET enables evaluation of early metabolic changes rather than morphological changes. A considerable number of studies of FDG-PET after 1-3 cycles of chemotherapy for aggressive non-Hodgkin's lymphoma<sup>11-14</sup> and HL<sup>15,16</sup> demonstrate that early metabolic changes are highly predictive of treatment response and outcome.

In a large retrospectively studied cohort of 121 patients with high-grade non-Hodgkin's lymphoma, the response on FDG-PET following 2 or 3 cycles of treatment was highly predictive of PFS and overall survival.<sup>17</sup> The estimated 5-year PFS rate was 89% for patients with PET-negative results, 59% for patients with minimal residual FDG uptake, and 16% for patients with PET-positive results. Interim FDG-PET has also been compared with the International Prognostic Index (IPI), a score that is currently used to prognosticate lymphoma. In a multivariate analysis, interim FDG-PET was more predictive than the IPI for PFS ( $P < 0.058$ ) and overall survival ( $P < 0.03$ ).<sup>12</sup>

Interim PET after 2 or 3 cycles of ABVD chemotherapy has also a highly predictive value in HL, with 5-year PFS rates of 39% for patients with PET-positive results and 92% for patients with PET-negative results.<sup>18</sup> A study including only patients with advanced stage HL and scanned after 2 cycles of ABVD found 2-year PFS rates of 0% for patients with early PET-positive results and 94% for patients with PET-negative results.<sup>19</sup> Concerns have been recently raised regarding the

positive predictive value of interim PET in patients treated with the more dose-intense BEACOPPesc regimen.<sup>20</sup> Although several studies demonstrate a highly predictive value, the expert panel of the International Harmonization Project does not recommend interim PET in routine clinical practice. Currently there are no available data to demonstrate improvement in results by altering treatment based on this information, and interim PET is recommended in patients enrolled in clinical trials.

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**INTERIM PET RESPONSE-ADAPTED THERAPY**

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Currently ongoing clinical trials are addressing the issue of treatment modification based on the result of interim PET. The hypothesis tested in these trials is that some patients may benefit from the recognition of treatment failure early during first line treatment and from initiation of more aggressive second line treatment as soon as possible. Trials are investigating whether patients with interim PET-positive scans for DLBCL will benefit from early modification to a more intensive regimen or high dose therapy and autologous stem cell transplantation (ASCT).<sup>21,22</sup> Ongoing trials are also assessing the value of interim PET in HL. A large number of patients with early stage HL are overtreated, and efforts are focusing on identifying those who will benefit from less intensive therapy, reducing the long-term risk of secondary cancers and cardiopulmonary disease. The U.K. RAPID trial and the GHLSG HD16 trial are evaluating the effect of omitting radiotherapy in patients with early stage HL and interim PET-negative results.<sup>23</sup> Several trials are also evaluating early treatment intensification with BEACOPPesc or even ASCT in patients with advanced stage HL and a PET-positive result after 2 cycles of ABVD.<sup>24,25</sup>

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**POST-TREATMENT PET FOR RESPONSE EVALUATION IN LYMPHOMA**

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A number of studies have demonstrated that FDG-PET performed after treatment is highly predictive of PFS and overall survival in HL and aggressive non-Hodgkin's lymphomas.<sup>26-28</sup> FDG-PET demonstrates the ability, at least to some extent, to distinguish between viable disease and necrosis or fibrotic tissue in residual masses following treatment. These observations led to the development of new recommendations for response criteria, incorporating FDG-PET into the definitions of end-of-treatment responses for FDG-avid lymphomas.<sup>10</sup> Based on the recommendations of the expert panel of the International Harmonization Project patients with the routinely FDG avid HL and DLBCL should have a FDG-PET performed for response assessment following

completion of treatment. A negative FDG-PET scan does not exclude the presence of undetectable disease, but overall with the new response criteria one expects the false-negative results will be much fewer than the false-positive, with a overall benefit and sparing a considerable number of patients from unnecessary treatment.

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**PET FOR FOLLOW-UP OF LYMPHOMA**

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There are limited studies evaluating the role of PET during follow-up. A large retrospective study evaluated 151 patients with mediastinal lymphoma (HL and aggressive non-Hodgkin's lymphoma) with follow-up PET every 6 months for the first 2 years and then every 12 months for a further 3 years.<sup>29</sup> A positive surveillance PET was documented in 30 patients at a median of 22 months following treatment completion. A biopsy was performed in all cases, confirming recurrence of the original disease in 17 (57%) cases, while a benign condition (fibrosis [n=9] or sarcoid-like granulomatosis [n=3]) and a case of thymoma were documented in the remaining 13 (43%) cases. Although early detection of disease relapse and early salvage therapy in a minimal disease status is desirable, further prospective studies are warranted to evaluate if there is a role of surveillance PET in the follow-up of patients with lymphoma.

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**PET BEFORE HIGH-DOSE SALVAGE THERAPY IN LYMPHOMA**

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PET is also predictive of outcome following high-dose therapy and autologous stem cell transplantation (ASCT) for relapsed lymphoma. Several studies have shown that PET performed following induction therapy and prior to ASCT is highly predictive of outcome. In a large retrospective study of 60 patients, 30 had a negative PET before ASCT; 25 of those patients remained in remission and only three patients had disease progression following ASCT.<sup>30</sup> Persistent abnormal PET was documented in 30 patients, and 26 of those developed disease progression. The predictive value of PET in this setting was superior to that of conventional staging and the International Prognostic Index for non-Hodgkin's lymphoma.<sup>31</sup> However, these studies also demonstrated that there is a high rate of false-positive results in this setting, disproportionate to that seen when FDG-PET is performed early during first-line therapy.

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**ISSUES WITH PET IN LYMPHOMA**

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There are some important limitations in the use of FDG-PET, and these issues need to be resolved in future studies.

The differences in equipment, techniques, and variability in interpretation between readers limit the value of comparisons among studies. New technology such as PET/CT also limits comparisons with older data. Histologic subtypes of lymphomas also differ with regard to their glucose metabolic activity, with implications for both staging of disease and treatment monitoring.<sup>4</sup> False-positive FDG uptake is also an important variable that must be taken into account when interpreting results. Nonmalignant conditions such as inflammation, infection, and granulomatosis (sarcoidosis or sarcoid-like lesions) and physiologic FDG uptake such as brown fat tissue, activated muscle, and hyperplasia of thymus can lead to false-positive results.<sup>32</sup> Abnormal FDG uptake can also be observed in the bone marrow and the spleen following chemotherapy or in patients receiving granulocyte colony-stimulating factor (G-CSF) after chemotherapy.<sup>33</sup>

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### CONCLUSION

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The integration of PET in the revised clinical staging guidelines and the elimination of CRu represents progress in the staging and management of patients with lymphoma. One must emphasize that PET does by no means replace the need for biopsy. PET response-adapted therapy is experimental and is the subject of ongoing appropriately designed clinical trials. There are still limitations in the guidelines of the International Harmonization Project that need to be addressed through prospective trials.

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