PET/CT in the Evaluation of Relapsed or Refractory Hodgkin Lymphoma

Shekeab Jauhari, MD, and Sunita D. Nasta, MD

Abstract

18F-fluorodeoxyglucose-positron emission tomography (FDG-PET) has been the most important advance in the assessment of Hodgkin lymphoma (HL) since the introduction of computed tomography (CT). In the frontline management of HL, FDG-PET combined with low-dose CT has emerged as the modality of choice for staging and treatment response assessment. Substantial data have accumulated over the past several years supporting the use of PET/CT in the evaluation and management of relapsed or refractory HL, as well. In this article, we review the role of PET/CT after the frontline treatment of HL, as well as the prognostic utility of PET/CT before autologous and allogeneic stem cell transplantation. We also review the use of PET/CT as a part of response-adapted treatment strategies in relapsed or refractory HL and implications for current and future clinical practice.

Key words: computed tomography, positron emission tomography, relapsed or refractory Hodgkin lymphoma, Deuville score, extranodal sites, response-adapted treatment strategies, staging.

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Introduction

Imaging has long been utilized by clinicians for the assessment, treatment, and surveillance of Hodgkin lymphoma (HL). Computed tomography (CT) was first incorporated into the Ann Arbor Classification in the 1980s for staging; it remained the imaging modality of choice in HL for several decades.[1,2] Positron emission tomography (PET) using the radiopharmaceutical 18F-fluorodeoxyglucose (FDG), and, subsequently, hybrid PET/CT, have been the most important advances in the assessment of HL since the introduction of CT. Hodgkin lymphoma and other non-Hodgkin lymphomas are routinely FDG-avid, with a sensitivity of more than 80% and a specificity of approximately 90%, exceeding that of CT.[3] This derives from the improved ability of FDG-PET to detect involvement in subcentimeter lymph nodes and extranodal sites, including liver, lungs, bone, and marrow, compared with CT.

Over the past several years, FDG-PET combined with low-dose CT has gained traction as the imaging technique of choice in HL. PET/CT improves on the sensitivity and specificity of either modality alone, provides better anatomic localization of FDG-avid lesions, and obviates the need for contrast-enhanced CT.[4,5] The National Comprehensive Cancer Network (NCCN) guidelines currently recommend the use of PET/CT for pretreatment evaluation and posttreatment response assessment in HL.[6]

Among patients with HL, treatment responses on PET are graded using the Deauville criteria score, or 5-point scale.[7] In this scoring system, FDG uptake in the mediastinal blood pool and liver serve as controls. Sites of lymphoma visualized on PET are graded based on FDG uptake as follows: 1 = no uptake, 2 = uptake less than the mediastinal blood pool, 3 = uptake between the mediastinal blood pool and liver, 4 = uptake moderately more than liver, and 5 = uptake markedly higher than liver or new sites of disease. A score of 1 or 2 corresponds to complete responses (CRs) and a score of 4 or 5 represents residual disease. Importantly, the Deauville score permits for the standardized evaluation of treatment responses, allowing for the incorporation of PET/CT in clinical trial protocols.

PET/CT has been extensively studied in the frontline management of HL. The role of PET/CT at the start and end of therapy is well described. In addition, interim PET/CT following 2 or 4 cycles of chemotherapy serves as an important prognostic marker. In patients with advanced HL, negative interim PET/CT after 2 cycles of multi-agent chemotherapy was associated with a 2-year progression-free survival (PFS) of 95%, whereas positive interim PET/CT was associated with a 2-year PFS of 16% to 27%.[8]

Approximately 15% of patients with HL have refractory disease at the end of initial treatment, and up to 40% of patients with advanced disease eventually relapse. Although relapsed or refractory HL remains curable, it poses

significant diagnostic and therapeutic challenges for physicians. As in the frontline management of HL, PET/CT is frequently utilized for staging, prognostication, and treatment-related decision making in relapsed or refractory HL.

We provide here a series of clinical vignettes along with a review of existing data supporting the use of PET/CT in this context.

Following Frontline Therapy

Assessment of Residual Masses

Clinical Vignette 1: A 23-year-old man with stage IIIb classical HL has recently completed 6 cycles of doxorubicin-bleomycin-vinblastine-dacarbazine chemotherapy. PET/CT performed at the end of treatment demonstrates a near CR. However, there remain a 2 x 1-cm subcarinal lymph node (standardized uptake value [SUV] = 3, corresponding to a Deauville score of 3) and a 1 x 1-cm right hilar lymph node (SUV = 4, corresponding to a Deauville score of 4). The mediastinal blood pool has an SUV of 2.5, and the liver has an SUV of 3.5. What are the next best steps?

PET/CT is highly predictive of PFS and overall survival (OS) at the end of frontline therapy in HL, and remains the standard for remission assessment.[9,10] Whereas most patients achieve complete metabolic responses with frontline therapy, many will have PET-negative residual masses. The results of most studies suggest that metabolically inert masses at the end of treatment do not influence PFS or OS and should not alter management.[11,12] In the German Hodgkin Study Group (GHSG) HD 15 trial, patients with advanced HL were randomized to receive standard bleomycin-etoposide-doxorubicin-cyclophosphamide-vincristine-procarbazine-prednisone (BEACOPP) in 8 cycles or dose-escalated BEACOPP in 6 or 8 cycles.[11] Patients with PET-negative residual masses greater than 2.5 cm at the end of treatment had no difference in 4-year PFS compared with patients who had a radiographic CR.

Residual metabolically active lesions on PET/CT scan present more of a challenge for clinicians. Although these may represent active disease in some cases, they may also represent posttherapy inflammatory changes, other infectious or inflammatory processes, or brown fat. Up to 40% of patients with positive PET/CT scans after frontline therapy will not relapse. Data supporting particular diagnostic or management strategies around residual PET-avid lesions are limited. Some clinicians favor administering radiation therapy (RT), especially in cases of bulky or advanced disease, as was done in the GHSG HD 15 trial. There is no evidence to suggest any benefit with this approach, and it may expose patients to overtreatment. One approach is to perform surveillance imaging to better confirm suspicions for refractory disease before proceeding with biopsy or additional therapies. In general, biopsy is recommended to confirm residual disease before proceeding with therapy. This is even more important in the case of late relapses, which may represent other tumor types.

Surveillance for Disease Relapse

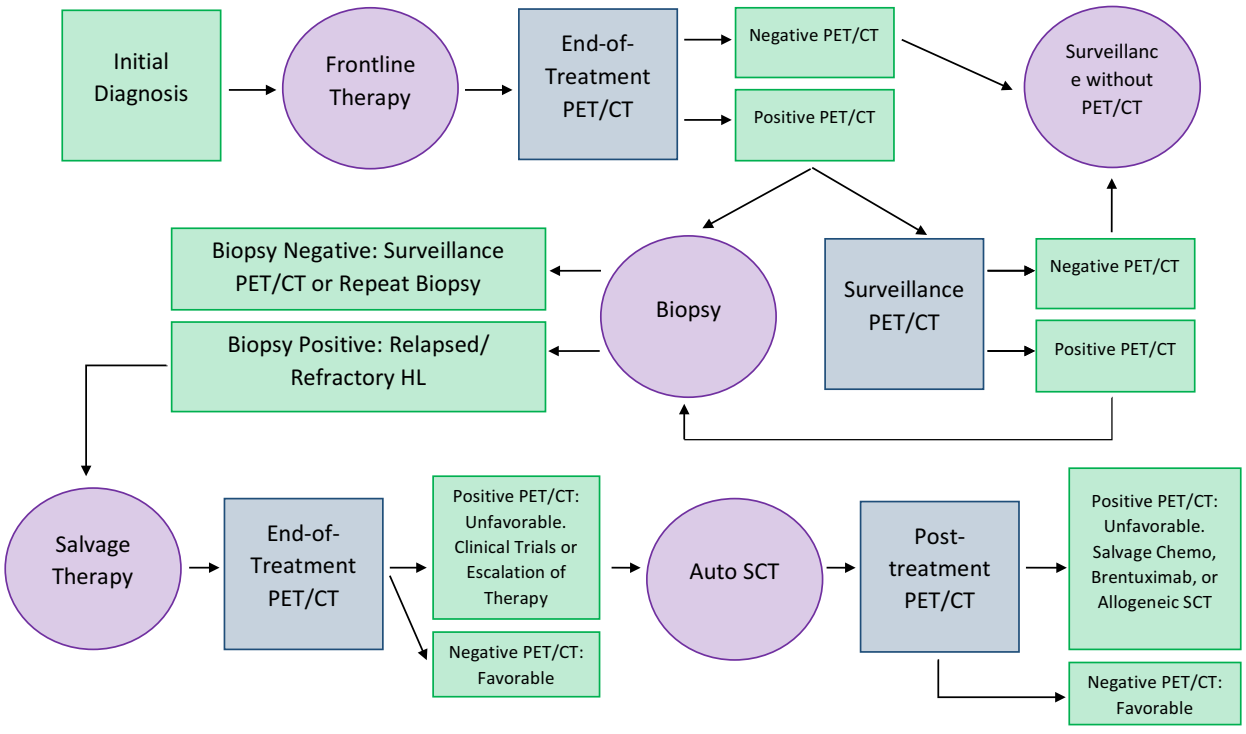
Clinical Vignette 2: A 60-year-old man with stage IIb classical HL has completed frontline chemotherapy and RT. His posttreatment PET/CT scan demonstrates complete metabolic and radiographic response, corresponding to a Deauville score of 1. For reference, the mediastinal blood pool has an SUV of 2.5 and the liver has an SUV of 3.5. As a part of surveillance, how frequently should PET/CT be performed?

Approximately 10% to 20% of patients with early-stage HL and 30% to 40% of patients with advanced-stage HL develop relapsed disease following frontline chemo-RT. Relapse usually occurs within 5 years after treatment. Patients are seen for follow-up visits in the months to years following treatment as a part of routine surveillance for disease recurrence, although without clear consensus regarding the optimal strategy. The role of imaging in posttreatment surveillance remains controversial: the NCCN recommends CT scans every 6 to 12 months for 3 years following treatment for HL, but retrospective studies and cost-effectiveness analyses have argued against the use of CT in the absence of symptoms.

FDG-PET is more sensitive than CT in detecting HL as a part of surveillance strategies. In a prospective study, 36 patients were assigned to receive FDG-PET scans at 4-to-6-month intervals over 2 to 3 years and to have confirmatory scans performed 4 to 6 weeks after any positive findings.[13] Five patients were found to have relapsed or refractory disease by FDG-PET in the follow-up period that was otherwise missed by CT alone or clinical evaluation, and 6 patients were noted to have false-positive findings. These findings are corroborated by several studies that also describe the high number of false-positives, elevated cost, and limited overall value with the use of PET/CT for surveillance.[14] A retrospective analysis of 192 patients with HL in first remission who underwent PET/CT and CT alone for surveillance demonstrated that PET/CT had a positive predictive value for disease recurrence of only 22.9% compared with 28.6% for CT alone.[15] The cost of detecting a single event was $100,000.

Thus, PET/CT should not be used for routine surveillance in patients previously treated for HL. These recommendations apply only to asymptomatic patients without evidence of relapse. Clinical judgment should inform the use of advanced imaging based on suspicion for disease recurrence.

FIGURE. Evidence-Based Uses of PET/CT in Relapsed or Refractory Hodgkin Lymphoma



Prognostic Utility

Before or After Autologous Stem Cell Transplantation

Clinical Vignette 3: A 32-year-old woman with relapsed classical HL has completed salvage chemotherapy. Prior to high-dose chemotherapy (HDC) and autologous stem cell transplantation (SCT), a PET/CT is performed, which demonstrates a good partial response, but residual right supraclavicular adenopathy with PET avidity (SUV = 5). What are the chances for long-term disease remission?

Multiple studies suggest that FDG-PET provides important prognostic information when performed after salvage chemotherapy and before HDC and autologous SCT among patients with relapsed or refractory HL.[16-18] In a retrospective review of 46 patients receiving FDG-PET following salvage chemotherapy and before autologous SCT, FDG-PET–negative patients had a 3-year event-free survival (EFS) of 82% and OS of 91%, whereas FDG-PET–positive patients had a 3-year EFS of 41% and OS of 64%.[16] The median time interval from the completion of salvage chemotherapy and FDG-PET was 3 weeks (range, 1-10) and was not statistically different between PET-positive and -negative patients.

These findings reiterate the role of FDG-PET as a predictive marker for survival outcomes following salvage chemotherapy and before autologous SCT. FDG-PET status is probably the most predictive of outcome relative to other markers in the relapsed or refractory setting, including extranodal disease, B-symptoms, length of initial remission, and conditioning regimen.[18] Although it is predictive, positive FDG-PET status prior to autologous SCT should not preclude the possibility of transplant. These patients may benefit from modified conditioning regimens, posttransplant management, or consideration of clinical trials. Importantly, PET/CT should be performed at least several weeks following salvage therapy to limit the detection of false-positives.

FDG-PET and CT together may better predict outcomes than FDG-PET alone in this setting. In a retrospective analysis of 50 patients with relapsed or refractory lymphomas, of which 19 were HL, FDG-PET and CT were both predictive of PFS and OS following autologous SCT; however, the combination provided superior predictive power for relapse (hazard ratio of 4.2 for both compared with 1.5 for CT and 3.4 for FDG-PET).[19] Other studies have also demonstrated

the predictive power of combined PET/CT around autologous SCT.[20] PET/CT will remain the modality of preference for pretransplant evaluations.

PET/CT following autologous SCT may also provide prognostic information. In a retrospective study of 43 patients with relapsed or refractory HL, patients with positive PET/CT scans within 6 weeks following autologous SCT had significantly worse PFS and OS compared with patients with positive PET/CT before the transplant.[21] These findings suggest that posttransplant PET/CT may be better predictive of survival outcomes compared with pretransplant PET/CT. Positive PET/CT following autologous SCT can more easily and immediately guide clinicians in their medical decision making, as well.

Before Allogeneic Stem Cell Transplantation

Data regarding the prognostic utility of FDG-PET after second relapses following autologous SCT in HL are limited. Most studies performed on the topic have evaluated the prognostic utility of FDG-PET before reduced-intensity allogeneic SCT in relapsed or refractory lymphomas as a general category; they have not focused on HL in particular. Their findings regarding the prognostic utility of FDG-PET before allogeneic SCT also are often discordant.[22-24] In the largest retrospective analysis to date assessing the prognostic utility of FDG-PET prior to allogeneic SCT, the survival outcomes of 160 patients with HL across 4 treatment centers in the United Kingdom were evaluated.[25] The Deauville criteria 5-point scale (D1–D5) was used to grade FDG-PET status before allogeneic SCT. Patients with the highest burden of disease on FDG-PET (D5) and those with progressive disease had worse OS. Although an early survival advantage was seen among patients with limited disease by FDG-PET (D1 and D2) compared with those who had higher burden of disease (D3–D5), there was no significant difference in PFS or OS at 4 years. These findings suggest that FDG-PET prior to allogeneic SCT may have more limited utility in predicting responsiveness to a graft-versus-tumor effect in the context of allogeneic SCT.

Additional prospective studies with larger cohorts of patients with HL are warranted to determine the predictive utility of FDG-PET prior to allogeneic SCT, although these may be practically challenging to organize. Alternative clinical and laboratory measures, either with or without pretransplant FDG-PET, may serve as better markers of response.

Response-Adapted Treatment Strategies

Clinical Vignette 4: A 19-year-old woman with refractory classical HL has completed 2 cycles of salvage chemotherapy. An interim PET/CT scan is performed and demonstrates stable supraclavicular, axillary, mediastinal, and inguinal lymphadenopathy by size and FDG avidity. How should her therapy be modified?

Response-adapted treatment strategies in HL seek to preserve the efficacy of chemo-RT while minimizing harm and incorporate the use of advanced diagnostic modalities that include PET/CT. As a part of these response-adapted treatment strategies, positive interim PET/CT scans may prompt a switch from standard regimens to more-intensive therapies, while negative scans may allow for continued standard therapies or de-escalation. Many clinical trials in the frontline setting are evaluating whether interim PET/CT can be used to adjust therapies and improve treatment outcomes or limit overall toxicity. Some results have suggested significant improvement in survival outcomes with this approach.[26]

The same approaches also are being evaluated in the relapsed and refractory settings.[27-30] In a single-center prospective study, 96 patients with relapsed or refractory HL received 2 cycles of salvage chemotherapy with ifosfamide-carboplatin-etoposide (ICE) or augmented ICE. This was followed by interim FDG-PET to document PET-negative status before autologous SCT.[27] Fifty-eight patients (60%) achieved negative interim FDG-PET status after receiving salvage chemotherapy. Thirty-eight patients (40%) had positive interim FDG-PET status after salvage therapy and 33 went on to receive biweekly gemcitabine-vinorelbine-liposomal doxorubicin (GVD) for 4 cycles. Of those receiving GVD, 17 achieved PET-negative status. All patients with PET-negative status before autologous SCT had an EFS near 80% at 51 months, whereas those with PET-positive status after salvage chemotherapy had an EFS near 30%. These findings suggest that escalating salvage therapies in response to positive interim FDG-PET may substantially improve patient outcomes.

Other studies have incorporated novel therapies and approaches. In a retrospective analysis of 111 patients with relapsed or refractory HL, individuals underwent PET/CT scanning before autologous SCT and after salvage therapy with rituximab plus dexamethasone-cytarabine-cisplatin (R-DHAP), ICE, etoposide-ifosfamide-doxorubicin, or ifosfamide-gemcitabine-vinorelbine-prednisolone. They were then randomized to receive single or tandem autologous SCTs.[28] Patients with positive PET/CT scans also had improved 5-year PFS with tandem autologous SCTs compared with single autologous SCTs (43% vs 0%), and to a greater degree than patients with negative PET/CT scans.

In an ongoing prospective study, 45 patients with relapsed or refractory HL received brentuximab vedotin for two 28-day cycles, with 3 doses per cycle, followed by PET/CT.[29] Approximately 27% of patients had negative PET/CT and

went on to receive autologous SCT, while the remainder received augmented ICE followed by autologous SCT. While these strategies are promising and confirm the importance of achieving negative FDG-PET status, additional prospective and multicenter studies are warranted before PET/CT can be reliably used to guide treatment-related decision making outside of the context of clinical trials.

Discussion

In the past decade, PET/CT has emerged as the imaging modality of choice for staging, prognostication, and response assessment in HL. The use of PET/CT has evolved significantly over this time and has substantially influenced the evaluation and management of relapsed or refractory HL. The prognostic role of PET/CT status prior to autologous SCT has been clearly demonstrated. Clinical studies are demonstrating that PET-negative status should be targeted prior to autologous SCT. There are no guidelines at present recommending the use of interim PET/CT or response-adapted treatment strategies in relapsed or refractory HL. Until there is sufficient evidence to suggest improved outcomes associated with these approaches, they should not be used routinely in clinical settings.

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Affiliations: Shekeab Jauhari, MD, is with the Division of Hematology/Oncology, Duke University Medical Center, Durham, NC; Sunita D. Nasta, MD, is with the Division of Hematology/Oncology, Hospital of the University of Pennsylvania, Philadelphia.

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Address correspondence to: Shekeab Jauhari, MD, 428 Morcroft Lane, Durham, NC, 27705; Email: shekeab@gmail.com.

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