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Review Article

The Role of PET/CT in the Evaluation and Management of Relapsed or Refractory Hodgkin Lymphoma

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Abstract

FDG-PET has been the most important advance in the assessment of Hodgkin lymphoma (HL) since the introduction of 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 last 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 and the prognostic utility of PET/CT before autologous and allogeneic stem cell transplantation. We also review the use of PET/CT as part of response-adapted treatment strategies in relapsed or refractory HL and implications for current and future clinical practice.

Keywords: Hodgkin lymphoma; Relapsed or refractory lymphoma; PET; Autologous stem cell transplant; Allogeneic stem cell transplant

Abbreviations

HL: Hodgkin Lymphoma; CT: Computed Tomography; SPECT: Single Photon Emission Computed Tomography; PET: Positron Emission Tomography; FDG: 2-Deoxy-2[F-18] Fluoro-D-Glucose; NCCN: National Comprehensive Cancer Network; 5-PS: 5 Point Scale; ABVD: Adriamycin, Bleomycin, Vinblastine, Dacarbazine; BEACOPP: Bleomycin, Etoposide, Adriamycin, Cyclophosphamide, Vincristine, Procarbazine, Prednisone; SCT: Stem Cell Transplant; CR: Complete Response; PPV: Positive-Predictive Value; PFS: Progression-Free Survival; OS: Overall Survival; EFS: Event-Free Survival; ICE: Ifosfamide, Carboplatin, Etoposide; DLI: Donor-Lymphocyte Infusion; GVD: Gemcitabine, Vinorelbine, Doxil

Introduction

Imaging has long been utilized by clinicians in the assessment, treatment and surveillance of Hodgkin lymphoma (HL). These techniques have evolved substantially over the last fifty years. Prior to the 1980s, disease staging relied primarily on techniques that had limited sensitivity or were invasive, including lymphangiography and laparotomy. Computed tomography (CT) was first incorporated into the Ann Arbor Classification for staging and remained the imaging modality of choice in HL for several decades [1,2]. Since then, novel techniques in functional imaging have attempted to improve on the sensitivity and specificity of CT, including Gallium-67 and Thallium-201 planar and single photon emission computed tomography (SPECT) imaging, but these have not provided enough of an advantage to serve as practical alternatives.

Positron emission tomography (PET) using the radiopharmaceutical ^{18}F-fluorodeoxyglucose (FDG), and subsequently hybrid PET/CT, have been the most important advances in the assessment of HL since the introduction of CT. The technology relies on FDG, a positron-emitting glucose analogue that is absorbed by cells and phosphorylated but cannot undergo further steps in glucose metabolism, thereby becoming trapped within cells.^{18}F subsequently decays and generates annihilation photons which are detected by the PET scanner. HL and other non-Hodgkin's lymphomas are routinely FDG-avid with a sensitivity of ~80% and a specificity of ~90%, exceeding that of CT [3]. This derives in part from the improved ability of PET/CT to detect involvement in sub-centimeter lymph nodes and extra-nodal sites, including liver, lungs, bone and marrow, and to exclude involvement in enlarged lymph nodes or other concerning sites on CT.

Concordance of FDG-PET and CT in determining clinical stage occurs in only 60% to 80% of cases of HL. While upstaging occurs more often with FDG-PET, the degree of discordance highlights why FDG-PET alone has not replaced CT in the evaluation of HL. Over the last several years, however, a single hybrid imaging session combining FDG-PET 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]. National Comprehensive Cancer Network (NCCN) guidelines currently recommend the use of PET/CT for pre-treatment evaluation and post-treatment response assessment in HL [6]. PET/CT is also increasingly utilized in multi-center clinical trials on HL. Important metrics, like the 5-Point Scale (5-PS), have helped standardize how treatment responses can be graded by visual inspection and communicated between clinicians [7].

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 two or four cycles of chemotherapy serves as an important prognostic marker in HL, outperforming the International Prognostic Score and International Prognostic Index [8]. In patients with advanced disease, negative interim PET/CT after two cycles of ABVD was associated with a 2-y PFS of 95%, whereas positive interim PET/CT was associated with a 2-y PFS of 16 to 27%. This informs the rationale for PET-adapted

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therapy in multiple clinical trials, where therapies may be escalated after positive interim PET/CT to improve treatment response or deescalated after negative interim PET/CT to reduce toxicity.

The majority of patients with HL achieve a complete response (CR) with frontline chemo-radiotherapy. Approximately 15% of patients have refractory disease at the end of initial treatment, however, and up to 40% of patients with advanced disease initially go on to relapse in the months to years thereafter. While relapsed or refractory HL remains curable, it poses significant diagnostic and therapeutic challenges for physicians and has remained an important area of clinical investigation for several decades. Substantial data has accumulated over the last several years regarding the utility of PET/CT in relapsed or refractory HL. As in frontline management, PET/CT is used for staging, prognostication, and guiding decision-making about treatment in relapsed or refractory HL. We provide here a review of these practices and the evidence that supports them to date.

Following Frontline Therapy

Assessment of residual masses

PET/CT is more sensitive, specific and cost-effective than CT alone in the assessment of disease status at the end of frontline therapy in HL [9]. PET/CT performed at the end of therapy with ABVD or BEACOPP in advanced-stage HL is also highly predictive of progression-free survival (PFS) and overall survival (OS) [9,10]. For these reasons, PET/CT is the standard of care for remission assessment in HL. While most patients will achieve complete metabolic and radiographic responses with frontline therapy, many will have PET-negative residual masses. Most studies suggest that metabolically-inert masses at the end of treatment do not influence PFS or OS and therefore should not alter management or surveillance strategies [11,12]. In the GHSG HD 15 trial, patients with advanced stage HL were randomized to receive BEACOPP in 6 cycles, dose-escalated BEACOPP in 6 cycles, or dose escalated BEACOPP in 8 cycles [11]. Patients with FDG-PET negative residual masses greater than 2.5 cm in size at the end of BEACOPP had no difference in 4-year PFS compared with patients who achieved complete metabolic and radiographic CR. Similar findings were noted in a prospective study of 163 patients with advanced stage HL receiving ABVD who had residual masses greater than 2 cm in size at the end of therapy [12]. FDG-PET was used to characterize these lesions as metabolically active or inactive. PET-negative patients received no additional therapies and had a 3-year PFS of 89%, comparable to patients in the GHSG HD 15 trial.

Residual metabolically-active lesions on PET/CT present more of a challenge for clinicians, however. While these may represent active disease in some cases, they may also represent post-therapy inflammatory changes, other infectious or inflammatory processes, or brown fat. Up to 40% of patients with positive PET/CT 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, especially in cases of bulky or advanced disease. The GHSG HD 15 trial incorporated this approach as part of their treatment paradigm, although there is no evidence to suggest any benefit; this approach may expose patients to over-treatment. Many clinicians favor surveillance imaging or the use of CT to better ascertain the presence of refractory disease before proceeding with biopsy or additional therapies. It is important to demonstrate the presence of residual disease by biopsy before proceeding with therapy, but the negative predictive value of these biopsies remains low.

Thus, if a residual mass is found after completing frontline therapy, a PET/CT can be performed and, if negative, confers an excellent prognosis and eliminates the need for further evaluation. In this setting, a positive PET/CT offers a more limited predictive value and generally warrants further evaluation before second-line therapies can be initiated.

Surveillance for disease relapse

Approximately 10% to 20% of early-stage patients with HL and 30% to 40% of advanced-stage patients with HL develop relapsed disease following frontline chemo-radiotherapy. Relapse usually occurs within the first five years after treatment. Still, second or third-line salvage therapies can yield long term responses in approximately 50% of these cases. For these reasons, patients are seen for follow-up visits in the months to years following treatment as part of routine surveillance for disease recurrence, though without clear consensus regarding the optimal strategy. The role of imaging in post-treatment surveillance remains controversial. While the NCCN recommends CT every 6 to 12 months for three years following the treatment of HL, retrospective studies and cost-effectiveness analyses have argued against the use of CT in the absence of symptoms.

FDG-PET is well-recognized as being more sensitive than CT in detecting HL as part of surveillance strategies. In a prospective study, 36 patients were assigned to receive FDG-PET scans at 4-6 month intervals for a three year period and to have confirmatory scans performed 1 month after any positive findings [13]. Of these patients, 5 were noted to have relapsed or refractory disease in the follow-up period that were otherwise not detected by clinical evaluation, laboratory parameters, or CT. Six patients were noted to have false-positive findings that later resolved on confirmatory scans. The frequency of scans and high number of false positives noted here highlight the challenges of using PET/CT as part of a routine surveillance strategy.

These findings are corroborated by several studies, which also describe the high number of false-positives, high cost, and limited overall value with the use of PET/CT for the surveillance of patients in clinical remission [14]. A retrospective analysis of 192 patients with HL in first remission who underwent PET/CT and CT for surveillance demonstrated that PET/CT had a positive-predictive value (PPV) for disease recurrence of only 22.9% as compared with CT (28.6%) [15]. The approximate cost of detecting a single event was $100,000. For these reasons, there is no role for the routine use of PET/CT for surveillance in patients previously treated for HL. It is important to note that these recommendations only apply to asymptomatic patients without evidence of relapse. Clinical judgment should inform the use of advanced imaging based on suspicion for disease recurrence.

Prognostic Utility

Before or after autologous stem cell transplantation (SCT)

Multiple studies suggest FDG-PET provides important prognostic information when performed after salvage chemotherapy and before high-dose chemotherapy and autologous SCT among patients with

relapsed or refractory HL [16-18]. In a retrospective review of 46 patients who underwent FDG-PET following salvage chemotherapy and prior to 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]. In a prospective study of 153 patients who underwent either gallium or FDG-PET imaging prior to autologous SCT, patients with negative scans had a 5-year EFS of 75% versus 31% among those with positive scans [17]. While only 42 patients underwent FDG-PET compared with 111 who underwent gallium as part of the study, there were no significant differences in outcomes observed between the two groups, allowing for combined analysis. These findings demonstrate the role of FDG-PET as a predictive marker for important survival outcomes following salvage chemotherapy and prior to autologous SCT. Importantly, FDG-PET status provides independent prognostic information and is probably the most predictive of outcome relative to other markers in the relapsed or refractory setting, including presence of extra-nodal disease, receipt of adjuvant radiotherapy, presence of B-symptoms, length of initial remission, and conditioning regimen [18]. These findings also demonstrate that while predictive, positive FDG-PET status prior to autologous SCT should not preclude the possibility of transplant, but that these patients may benefit from modified conditioning regimens, post-transplant management, or consideration of clinical trials.

Most studies to date have commented on the prognostic utility of FDG-PET prior to autologous SCT, but FDG-PET and CT together may better predict outcomes than FDG-PET alone. In a retrospective analysis of 50 patients with relapsed or refractory lymphomas of whom 19 were HL, FDG-PET and CT were both predictive of PFS and OS following autologous SCT [19]. Patients with positive findings by CT had a hazard ratio for progression of 1.5 while those with positive findings by FDG-PET had a hazard ratio of 3.4. Patients with both positive CT and FDG-PET findings had a hazard ratio of 4.2, suggesting superior predictive power to either modality alone. Some studies have re-demonstrated the predictive power of combined PET/CT around autologous SCT [20]. PET/CT will remain the modality of preference for pre-transplant 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 within 6 weeks following autologous SCT had a significantly worse PFS and OS compared with patients with positive PET/CT before autologous SCT. Notably, a subset of patients with positive PET/CT before transplant and negative PET/CT after transplant had no significant difference in PFS or OS compared with patients who had negative PET/CT before transplant [21]. These findings suggest that post-transplant PET/CT may be better predictive of survival outcomes compared with pre-transplant PET/CT, although this has not been well-studied. 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 and have not focused on HL in particular. Their findings regarding the prognostic utility of FDG-PET before allogeneic SCT are also often discordant. In a prospective study of 80 patients with relapsed lymphomas who underwent PET/CT before reduced-intensity allogeneic SCT, 42 patients were PET/CT positive prior to transplant [22]. No significant difference was observed in PFS or OS between patients on the basis of pre-transplant PET/CT status. Of note, only 22 patients carried diagnoses of HL and no sub-group analyses were performed, limiting interpretation with regards to HL. Other studies suggest FDG-PET performed in this setting may provide important prognostic information [23,24]. In a retrospective study of 42 patients with HL who underwent FDG-PET scans prior to reduced-intensity allogeneic SCT, 17 patients were FDG-PET negative prior to transplant. FDG-PET negative patients had a 3-year OS of 100% and PFS of 76% whereas FDG-PET positive patients had a 3-year OS of 51% and PFS of 17% [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 four treatment centers in the UK were evaluated [25]. The 5-PS, or Deauville criteria, was used to grade FDG-PET status before allogeneic SCT on a scale of 1 to 5. Patients with the highest burden of disease on FDG-PET (D5) and who also had progressive disease had worse OS compared with the rest of the patients. Although there was an early survival advantage 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 while FDG-PET status before autologous SCT is predictive of chemo-responsiveness and future survival, it 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 better 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 pre-transplant FDG-PET, may serve as better markers of response.

Response-adapted Treatment Strategies

While most patients with HL can achieve long-term cures with frontline therapy, there is substantial risk for developing toxicities and infections in the short-term and secondary malignancies in the long-term. Response-adapted treatment strategies seek to preserve the efficacy of chemo-radiotherapy while minimizing harm to patients and incorporate the use of advanced diagnostic modalities, including PET/CT. Interim PET/CT performed after two cycles of chemotherapy has been shown to be highly predictive of end-of-treatment response and PFS in the frontline management of HL [26]. In this context, negative interim PET/CT corresponds with improved PFS while positive interim PET/CT corresponds with worse PFS. Multiple clinical trials are currently evaluating whether this strategy can be used to adjust therapies in real-time to improve treatment outcomes or limit overall toxicity [27]. As part of these response adapted treatment strategies in advanced stage HL, positive interim PET/CT scans may prompt a switch from standard regimens to more intensive therapies. In the RATHL UK study, newly diagnosed

patients with advanced HL were initiated on ABVD. Interim PET/CT after two cycles of therapy would guide further management, with negative PET/CT leading to de-escalation to AVD and positive PET/CT leading to escalation to eBEACOPP or BEACOPP-14. Interim PET/CT was positive in 16% of patients, who then underwent therapy escalation and achieved CR in 76% of cases. While long-term results are pending for multiple studies, preliminary findings suggest PET-adapted treatment strategies may lead to improved outcomes. Currently, however, interim PET/CT is not recommended in any guidelines for the routine diagnostic or therapeutic management of HL.

Building on current investigational approaches in the frontline management of HL and recognizing the prognostic utility of PET/CT prior to transplant, many studies have sought to evaluate whether alternative response adapted treatment strategies may improve outcomes in relapsed or refractory HL as well [28-31]. These approaches also rely on interim PET/CT and many have demonstrated improved outcomes for patients, although in the context of limited study. In a single-center prospective study, 82 patients with relapsed or refractory HL received two cycles of salvage chemotherapy with ICE or augmented ICE followed by interim FDG-PET to determine whether additional therapies were warranted before auto SCT [28]. 58 patients (60%)achieved negative interim FDG-PET status and received high-dose chemotherapy and auto SCT thereafter. 33 patients with positive interim FDG-PET status went on to receive biweekly gemcitabine, vinorelbine, and liposomal doxorubicin (GVD) for four cycles, of whom 17 patients (52%) achieved negative FDG-PET status prior to auto SCT. Patients who achieved negative FDG-PET status with and without GVD had EFS of 80% at 51 months whereas patients with positive FDG-PET status at the end of therapy had EFS of 29%. These findings suggest that escalating salvage therapies in response to positive interim FDG-PET may improve the likelihood of achieving CR prior to auto SCT and thereby improve patient outcomes.

Other studies have also evaluated the utility of PET/CT in guiding treatment-related decision-making before auto SCT, many of which incorporate novel approaches and therapies. In a retrospective analysis of 111 patients with relapsed or refractory HL, individuals underwent PET/CT after salvage therapy and before auto SCT and were then randomized to receive single or tandem auto SCTs [29]. Patients with negative PET/CT scans had improved 5-year PFS with tandem auto SCTs compared with single auto SCTs (87 *vs.* 75%). Patients with positive PET/CT scans also had improved 5-year PFS with tandem auto SCTs compared with single auto SCTs (43% v. 0%) and to a greater degree than patients with negative PET/CT. In an ongoing prospective study that is pending accrual of data for survival outcomes, 45 patients with relapsed or refractory HL received brentuximab vedotin for several cycles followed by PET/CT [30]. Approximately 27% of patients had negative PET/CT and went on to receive auto SCT, while the remainder received augmented ICE followed by auto SCT. PET-adapted strategies have also been used around allogeneic SCT, as in one study which used surveillance FDG-PET to guide the administration of donor-lymphocyte infusion (DLI) [31]. While these strategies are promising and confirm the importance of achieving negative FDG-PET status, additional prospective and multi-center studies are warranted before PET/CT can be reliably used to guide treatment-related decision-making in relapsed or refractory HL.

Conclusion

In the last 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. Grading criteria have emerged that allow for standardization in reporting treatment responses in PET/CT. Increasingly, PET/CT is being used in clinical trials as part of response-adapted treatment strategies, and although clinical practice has not yet changed, the results from these studies are promising.

PET/CT has also substantially influenced the evaluation and management of relapsed or refractory HL. The prognostic role of PET/CT status prior to autologous SCT has been repeatedly demonstrated and has been suggested in allogeneic SCT, although this must be better characterized. As in the frontline management of HL, clinical studies are demonstrating that targeting PET-negative status prior to transplantation should be a therapeutic goal in order to meaningfully improve survival outcomes. Importantly, 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 as positive PET/CT scans may prompt over-treatment.

A key challenge in developing large, prospective trials utilizing PET/CT in relapsed or refractory HL are relatively small numbers of patients and a limited number of centers which specialize in their treatment. With the emergence of targeted therapies that have demonstrated efficacy in multiply-treatment refractory HL, there is greater reason to pursue multicenter, prospective trials that use PET/CT for response assessment and as part of adaptive treatment strategies. This work is crucial in order to allow novel therapies and treatment approaches to be effectively utilized in this population.

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