Personalized Management Approaches in Lymphoma

Utility of Fluorodeoxyglucose-PET Imaging

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KEYWORDS

• Lymphoma • PET imaging • Response-adaptive treatment • PET-directed therapy

KEY POINTS

- Response-adaptive therapy for lymphoma using guidance by PET/CT imaging provides a way to minimize treatment toxicity and radiation exposure for patients with malignant lymphoma.
- Interim PET/CT imaging can be used to tailor radiation therapy in patients with Hodgkin lymphoma.
- Escalation of treatment in patients with positive interim PET/CT imaging leads to better outcomes than historically recorded.
- New computer software improves accuracy and sensitivity of PET imaging to calculate a corrected total disease activity level.

Although an abundance of literature over the past decade addresses the use and relevance of PET/computed tomography (CT) imaging in the diagnosis and staging of lymphoma, a more recent area of immense clinical importance has been to evaluate the role of this imaging modality in risk-adaptive treatment approaches. This article focuses on the most recent literature surrounding the topic of PET/CT-guided therapy including a summary of the evidence on the use of PET/CT imaging as a prognostic indicator in certain lymphoma subtypes, most up-to-date evidence on therapeutic adjustment based on PET/CT results, evidence supporting the use of PET/CT imaging to optimize the use radiation therapy (RT) in lymphoma management, and ongoing research on using PET/CT to escalate or deintensify lymphoma-directed treatment.

HODGKIN LYMPHOMA

Hodgkin lymphoma (HL) occurs with an incidence of roughly 9000 cases per year in the United States. Over the course of the last few decades, standard of care in HL has improved dramatically such that cure is achieved in 75% to 90% of patients depending on stage and risk factors. Major efforts have been made over the last decade to minimize toxicity while maintaining the efficacy of treatment. Within this movement, fluorodeoxyglucose (FDG)-PET imaging has emerged as a promising tool.

Current guidelines recognize the use of PET/CT in the diagnosis and staging of HL.[1] The inclusion of combined PET/CT imaging in the primary evaluation of HL has led to higher diagnostic accuracy with consequentially more frequent upstaging compared with CT scan alone.[2,3] This increased

Disclosure Statement: The authors have nothing to disclose.

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PET Clin 11 (2016) 209–218
http://dx.doi.org/10.1016/j.cpet.2016.02.001
1556-8598/16/$ – see front matter

sensitivity in initial staging has had a valuable impact on treatment selection for these patients.

PET/CT has also been well validated as a prognostic tool in HL. Literature supports the use of interim and posttherapy PET/CT to prognosticate progression-free survival (PFS) and overall survival (OS), with a very high negative predictive value upward of 94%.[4] A positive mid-treatment PET/CT is associated with decreased PFS and OS.[5] However, positive predictive value of interim PET/CT is markedly lower than the negative predictive value (53.8% vs 100%, respectively).[5]

Perhaps most exciting over the last decade, however, has been investigation into the role of PET/CT in driving management decisions for HL. Active exploration seeks to address whether chemotherapy should be de-escalated based on negative interim scans or intensified in response to positive interim scans. Additionally, there is much interest to identify a subset of patients who benefit most from adjuvant RT based on PET/CT imaging.

Given that HL is a disease of younger patients with long life expectancies, optimizing exposure to RT is of utmost importance. Lower total doses of RT and minimized fields may result in fewer toxicities, which include coronary angiopathy, secondary malignancies, thyroid abnormalities, and pulmonary toxicities.[6]

In 2013, Girinsky and colleagues[7] demonstrated that the addition of PET to CT imaging improved delineation of involved node RT with increased clinical target volumes but without increased volume of radiation delivered. Therefore, the addition of PET identified, with higher precision and sensitivity, targetable lymph nodes for RT without necessitating larger radiation volumes.

Others have addressed the possibility of eliminating the need for RT entirely. For example, Radford and colleagues[8] described the UK RAPID study, in which 602 patients with negative PET/CT (defined by the International Harmonization Project [IHP] criteria)[9] after three cycles of adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) were randomized to RT versus no RT. The 3-year PFS was 94.6% and 90.8% in the RT and no-RT groups, respectively. Although the study did not show noninferiority in terms of PFS, the authors concluded that patients with a negative PET/CT have an excellent prognosis with and without consolidative RT following chemotherapy.[8]

In contrast, Raemaekers and colleagues[10] demonstrated early treatment failure without RT in patients with negative PET/CT. This study enrolled 1137 patients with stage I/II HL and omitted involved-node RT in patients with a negative PET/CT after two cycles of ABVD. A preplanned interim futility analysis with the goal to stop recruitment in the case of inferiority in the investigational arm demonstrated futility in the favorable and unfavorable subgroups who did not receive RT ($P = .017$ and 0.026, respectively). In light of this analysis, the study was terminated, because the data predicted that the group was unlikely to observe efficacy between the standard and experimental arms.

Additionally, in the RATHL study, Engert and colleagues[11] investigated PET-directed RT following six cycles of escalated bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine and prednisone (eBEACOPP) in advanced HL. In this study, only 11% of patients ultimately received RT for mass lesions measuring greater than or equal to 2.5 cm on PET/CT imaging. The group concluded that six cycles of BEACOPP followed by PET-directed RT interpreted according to the London criteria was more effective in terms of freedom from treatment failure with less toxicity than eight cycles of escalated BEACOPP.[12] Thus, there are promising data suggesting that PET-directed RT is effective and safe in HL but, because data are still somewhat conflicting, further investigation is warranted before the use of PET/CT to determine the need for consolidative RT is incorporated into standard practice.

Several groups have tested the hypothesis that escalation of therapy based on PET/CT imaging after one to three cycles of initial chemotherapy may salvage patients predicted to have a poor prognosis with standard-dose chemotherapy based on positive PET/CT results.

Gallamini and colleagues[13] in 2011 published results from 219 patients who received response-adapted treatment based on PET/CT performed after two cycles of ABVD. Patients who were PET/CT positive according to the London Criteria after two cycles of ABVD were escalated to BEACOPP.[13] The 2-year PFS was 91% for the entire cohort. PFS was 95% for PET-negative and 62% for PET-positive patients. These results were believed to be better than historic ABVD control subjects who would have continued this therapy in the setting of a positive interim PET/CT scan, leading the authors to conclude that escalation of therapy based on interim PET/CT imaging can lead to improved outcomes without exposing all patients to increased toxicity of more intense chemotherapeutic regimens, such as BEACOPP.

Several other clinical trials are currently ongoing to investigate the role of PET/CT in response-adapted therapy, which are discussed next. The RATHL study used PET/CT to investigate the role of prolonged bleomycin exposure in patients with HL undergoing combination chemotherapy with ABVD. Patients with negative PET/CT according to the London criteria after two cycles of ABVD