Advancing Precision Nuclear Medicine and Molecular Imaging for Lymphoma

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KEYWORDS

• Lymphoma • Position emission tomography • Fluorodeoxyglucose • Biomarker • Molecular imaging • Precision medicine

KEY POINTS

- Fluorodeoxyglucose F 18 (^{18}F FDG) is a PET imaging radiopharmaceutical that is evolving into an imaging biomarker for the detection and therapeutic response assessment of lymphomas.
- There are current challenges and opportunities for advancing the role and capabilities of ^{18}F FDG-PET in lymphoma.
- ^{18}F FDG-PET contributions will expand owing to new emerging technologies, clinical trial utilization, standardization, and its role in radiomics and big data analysis of lymphoma.
- Precision nuclear medicine and advanced molecular imaging approaches are poised to fundamentally adapt lymphoma management for the upcoming era of personalized medicine and precision medicine.

CLINICAL EVOLUTION OF PET WITH FLUORODEOXYGLUCOSE F 18 AS A BIOMARKER FOR LYMPHOMA

As our understanding of cancer expands, physicians are searching for new and improved tools to more precisely guide medical decision making as well as to accurately stratify each patient's risk at diagnosis and throughout the disease course. Many disciplines of medicine have contributed in this effort, but specifically regarding the diagnosis of lymphoma and its clinical management, PET with fluorodeoxyglucose F 18 (^{18}F FDG-PET) imaging has made a tremendous clinical impact. ^{18}F FDG-PET imaging is evolving into a standard of care modality for the majority of

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lymphoma subtypes and its value in the molecular and functional characterization of lymphoma has overtaken more traditional anatomic imaging approaches. Additionally, in comparison to the nonimaging risk stratification tools (eg, molecular profile, International Prognostic Index [IPI], and International Prognostic Score) only ^{18}F FDG-PET has demonstrated real-time comprehensive disease evaluation, assessment of individual disease risk, likelihood of response to therapy, and survival, and therefore represents an emerging and important precision medicine tool to guide patient treatment.

Diagnostic Initial Staging

Initial diagnostic risk scoring systems for nearly every lymphoma subtype include Ann Arbor Stage[1] within its reference criteria: the IPI,[2,3] revised IPI (R-IPI),[4] Follicular Lymphoma IPI (FLIPI),[5] and International Prognostic Score.[6] In this regard, ^{18}F FDG-PET has been shown to improve diagnostic stage accuracy compared with other standard imaging modalities and staging tools and have, in some cases, led to change in therapeutic management in both Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL).[7–14] Interestingly, the improved salvage treatment options at relapse as well as the similarities in management of stage I versus stage II and stage III versus stage IV disease have probably limited this improved staging accuracy from contributing to an overall survival (OS) benefit. However, the improved staging accuracy of ^{18}F FDG-PET has led to the elimination of unnecessary consolidative radiation therapy and toxicity at diagnosis. For example, ^{18}F FDG-PET in follicular lymphoma (FL) has resulted in 11% to 31% upstaging from stage I and II (early stage) to stage III and IV (advanced stage).[15,16] The pretreatment ^{18}F FDG-PET also performed better than the FLIPI prognostic scoring system in identifying those patients who would have an incomplete therapeutic response or early relapse.[15] For the relatively common NHL subtype diffuse large B-cell lymphoma (DLBCL),[17] ^{18}F FDG-PET has demonstrated increased sensitivity for identifying both nodal[8,12,18–22] and extranodal[15,21] disease sites when compared with conventional computed tomography (CT) imaging at diagnosis and subsequently guides therapeutic management. ^{18}F FDG-PET is not only useful at complementing the assessment of the bone marrow involvement,[20,23] but is able to identify otherwise asymptomatic but high-risk/nonmarrow skeletal lesions,[24] providing an opportunity for involved field radiation therapy (IF-XRT) to improve event-free survival in such patients.

In addition to identifying disease sites at diagnosis, the semiquantitative assessment using standardized uptake value (SUV) with ^{18}F FDG-PET has also been shown to correlate with disease histology in lymphoma.[25] There are many instances in which this can be used to guide differentiation of indolent and aggressive lymphoma subtypes[26–28] and this diagnostic functionality becomes critically important when there is clinical suspicion for de novo or midtreatment transformation events. It is often the lesion with the highest ^{18}F FDG uptake (ie, highest SUV) on the ^{18}F FDG-PET that guides targeted biopsy for histopathologic confirmation.[29–31]

Interim Staging

The performance of ^{18}F FDG-PET during induction therapy has emerged as a treatment-defining diagnostic test for many lymphoma subtypes because its real-time insight into therapeutic response has improved the prognostic ability for ^{18}F FDG–avid lymphomas.[32,33] In particular, the subtype of lymphoma that has demonstrated the greatest usefulness from interim ^{18}F FDG-PET is HL. Studies have confirmed a negative interim ^{18}F FDG-PET scan after 1 to 3 cycles of induction chemotherapy[12,34,35] is a strong predictor of progression-free survival (PFS) and has also been shown to perform better than the International Prognostic Score for prediction of prognosis.[35] Conversely, a positive interim ^{18}F FDG-PET at the same treatment interval not only correlates with classically associated high-risk features of disease,[12,35] but has also been shown to predict either refractory disease or early disease relapse.[36] These data have driven the clinical use of interim ^{18}F FDG-PET to better evaluate, inform, and guide the course of treatment for HL patients. For example, the historical standard of care for patients with early stage HL has been IF-XRT at the completion of systemic induction chemotherapy. However, it was recently demonstrated that early stage HL patients with a negative ^{18}F FDG-PET scan after 4 systemic chemotherapy cycles of adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) regardless of risk factors had similar and in some cases better outcomes if they did not undergo the previously considered standard IF-XRT.[37] Conflicting data using this approach have been published in which an increased progression/relapse rate was observed after the preplanned 1-year interim analysis in the cohort of early stage favorable and unfavorable HL patients in which radiation was eliminated.[38] However, the relatively short period for this interim analysis, which led to it being discontinued per the