PET–Computed Tomography for Radiation Treatment Planning of Lymphoma and Hematologic Malignancies

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KEYWORDS

• FDG-PET • Radiation treatment • Lymphoma
• Hematologic malignancy

Metabolically active tumor cells are functionally distinct because of their increased glycolytic activity relative to normal cells. Whole-body imaging using PET uses the radiolabeled glucose analogue, fludeoxyglucose F 18 (FDG), which is preferentially taken up by malignant cells. Tumor cells are characterized by the upregulation of glucose transport as well as hexokinase activity. The phosphorylation of hexokinase leads to the accumulation of FDG in malignant relative to nonmalignant cells. PET imaging complements computed tomographic (CT) scan anatomic information by localizing metabolically active cells within the anatomic tumor volume. FDG uptake is seen not only in malignant processes but also in inflammatory and infectious processes. Nevertheless, the sensitivity and specificity of PET relative to CT and magnetic resonance (MR) imaging is increased for malignancies, such as lymphoma, and thus these techniques play a critical role in diagnostic workup and treatment response evaluation. As a result of the utility of PET in the evaluation of lymphoma, interest in incorporating PET into radiation planning has grown.[1–7]

Radiation oncology has made substantial progress in technology with the development of conformal radiation treatment techniques, such as intensity-modulated radiotherapy, stereotactic radiotherapy, and stereotactic radiosurgery. These systems deliver radiation with high precision and leave little room for errors in targeting the tumor (**Fig. 1**). Diagnostic imaging is used to aid the radiation oncologist in target volume definition (**Fig. 2**). Three-dimensional tumor volumes are routinely developed using CT scan treatment planning or simulation based on standard definitions defined by the International Commission on Radiation Units and Measurements, ICRU50. Lymphoma disease extent is assessed with physical examination; tissue biopsy, including bone marrow biopsy; and imaging modalities. Although CT provides important anatomic definition, it has its limitations. Small-volume nodal disease that can have significant implications on radiation treatment field design can be missed (**Fig. 3**). Residual masses after chemotherapy that may represent scar tissue can also be difficult to interpret in the absence of functional imaging. PET contributes

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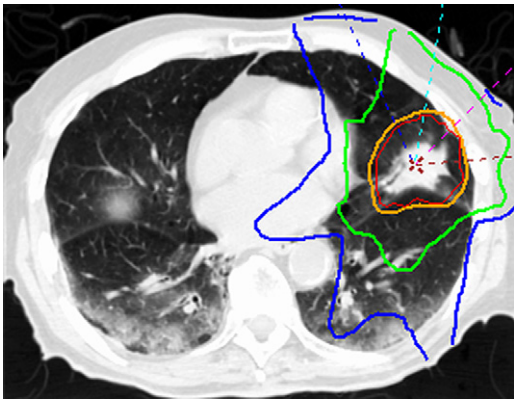

Fig. 1. Example of radiation plan created using intensity-modulated radiotherapy (IMRT) in a patient who presented with a peripheral lung mass contoured on a CT treatment-planning scan. With IMRT, a concave dose distribution can be accomplished to deliver prescription dose to the tumor volume while protecting normal structures, including surrounding normal lung. The surrounding multicolored lines represent isodose distributions. Each color represents a percentage of the prescribed dose received by the given volume encompassed within the curve. Precision in target volume delineation is essential when the radiation dose is prescribed with highly conformal techniques.

complementary information and can aid in disease assessment for the purpose of delineating anatomic areas at risk. Therefore, PET has been integrated into radiation treatment planning and contributes functional information to the design of the tumor volume to help create a biologic target volume (BTV). The BTV is a concept proposed by Ling and colleagues[8] that takes into account the tumor as depicted on functional imaging, such as PET.

Although radiation treatment is integral to the management of lymphoma, extended fields (extended field radiotherapy [EFRT]) are no longer commonly treated because of significant normal-tissue exposure. Most patients with early-stage lymphoma are now treated with combined-modality therapy using chemotherapy followed by involved field radiation therapy (IFRT), which includes the involved site and immediately adjacent lymph node regions in the treatment field.[9] Thus, lymphoma radiation treatment field design has undergone an evolution from EFRT to IFRT.[9] Involved node radiotherapy (INRT) shrinks fields further so that only the involved lymph nodes with a margin is included in the radiation treatment field. INRT is now under active investigation. Initial studies suggest that relapse rates with INRT are equivalent to those with IFRT and EFRT for patients with early-stage Hodgkin disease (HD) and early-stage follicular lymphoma.[10,11] However, the application of INRT and conformal techniques requires a higher level of precision in identifying involved disease because of the greater potential for a marginal miss.

FDG-PET RADIATION PLANNING FOR LYMPHOMA

PET scan has become an integral aspect of the diagnostic workup for lymphoma because its utility in staging has been demonstrated in multiple studies.[12–18] Stumpe and colleagues[19] demonstrated a specificity of 96% for PET compared with 41% for the staging of patients with HD and a specificity of 100% compared with 67% for patients with non-Hodgkin lymphoma (NHL). However, FDG avidity varies widely depending on lymphoma subtype. Aggressive NHLs, such as diffuse large B cell lymphoma, and HD are more likely to be FDG avid than low-grade NHLs, such as follicular and marginal zone lymphomas.[15,20–23] FDG avidity in low-grade lymphomas can also be inconsistent, and thus, PET may not be as useful for target delineation in these cases in which FDG distribution could be variable.[12,24–26] However, staging conclusions can sometimes be difficult to derive because it is often not feasible to obtain pathologic proof of lymphoma at each FDG-avid site, given the systemic nature of the disease. Because inflammation, reactivity, and infection can also cause uptake on PET, the physician must use all available clinical information, including physical examination, imaging, and pathology, to delineate the target in the absence of pathologic confirmation.

Given the usefulness of PET in defining disease extent, it has been increasingly incorporated into radiotherapy planning to help in the definition of radiation treatment fields. An FDG-PET scan obtained in a nuclear medicine department can be coregistered to a CT treatment-planning scan obtained in a radiation oncology department. The patient should be placed in the treatment-planning position using an appropriate individualized immobilization device for the PET scan as well as for the CT treatment-planning scan. The PET scan is then transferred and fused with the CT treatment-planning scan. However, if the patient's position varies between the 2 independently performed scans, it may be more difficult to confidently delineate the target. Dedicated PET/CT scanners for simulation can minimize this error by acquiring both the PET and CT scans in the same session so that the scans can be immediately coregistered for radiation planning. For