Editorial

Overcoming the hurdles of using PET/CT for target volume delineation in curative intent radiotherapy of non-small cell lung cancer

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PET/CT imaging has proven to be an invaluable tool for target volume delineation in radiation treatment planning of non-small cell lung cancer. However, as with any technological advancement, it has its limitations. In their recent review article published in Radiotherapy and Oncology, Konert *et al*. (1) eloquently summarize many of the challenges encountered by radiation oncologists when using PET/CT-based planning in radical intent radiotherapy. The authors go further to describe evidence-based recommendations to provide clear guidance on the use of PET/CT in target volume delineation in order to overcome some of these challenges and standardize clinical practice.

^{18}F-fluorodeoxyglose (FDG) positron emission tomography (PET) capitalizes on the increased uptake of glucose in metabolically active tissues, including malignant tumors. In FDG-PET imaging, a radioactive analog of glucose is injected into the patient. As it decays, photons are ultimately produced and detected by the PET scanner. When acquired with a CT scan, the combined PET/CT can be registered with the CT acquired during patient simulation to identify FDG-avid areas for inclusion in the treatment volume. In cases where it may be difficult to distinguish tumor from atelectasis or pulmonary edema, PET/CT fusion with a planning CT is of particular benefit. PET/CT also has the potential to decrease inter-observer variability in target volume delineation, as sighted by Ashamalla *et al*. and others (1,2). Indeed, the advantages of using PET/CT for target volume delineation in not only early stage NSCLC, but in locally advanced disease and for other body sites as well, has been widely published (3-6). Despite its feasibility and widespread application in radiation treatment planning, PET/CT can be challenging to use and a standardized method of applying it to target volume delineation is needed.

The first set of challenges encountered when attempting to use a PET/CT to contour a target volume as identified by Konert *et al*. (1) is the acquisition of the image. PET/CT scans obtained for diagnostic purposes are usually acquired in a different position than the CT scans used for treatment planning, making an accurate registration of the two images difficult. The authors caution against the co-registration of diagnostic PET/CT with planning CTs. Instead, they suggest either obtaining a second PET/CT once distant metastatic disease is ruled out, or, requesting that the diagnostic PET/CT be obtained in the treatment planning position. In an era in which controlling costs is paramount and obtaining insurance authorization can be challenging, the former option is generally not financially feasible. The latter option is not only more cost-effective, but, highlights the need for early coordination of patient care to minimize unnecessary expenditures, which our current healthcare system is emphasizing. The challenges of co-registration between PET/CT and planning CT, however, should not be minimized. Given that the goal of using PET/CT is to accurately delineate the target when its location on the planning CT is ambiguous, being able to accurately co-register these two images is crucial. Another means of facilitating accurate co-registration which the authors do not comment on is the use of an immobilization device during PET/CT acquisition, which our group has implemented in past publications (2,7,8). This same device

can then be used for the planning CT to further improve co-registration accuracy.

Next, the authors describe the challenges faced in image interpretation and respiratory motion management and describe the methods by which treatment planning volumes should be generated based on the PET/CT. They highlight the need for a multi-disciplinary approach to target volume delineation including consultation with a nuclear medicine physician. This is a commendable recommendation because it allows the radiation oncologist to benefit from the expertise of the nuclear medicine physician skilled in interpreting PET/CT and to clarify any ambiguities on the PET/CT itself. The authors also make recommendations for target volume delineation based on whether respiratory compensation is utilized, highlighting the fact that PET/CTs are acquired during free breathing and therefore inherently account for tumor motion by averaging the tumor location during the breathing cycle. In order to take advantage of this aspect of the PET, however, the importance of accurately co-registering the PET/CT and planning CT is once again emphasized. To conclude this section of their manuscript, the authors comment on the difficulty with standardizing PET contouring secondary to variations in the window/level (W/L) settings and biological factors which may affect the levels of background PET activity. One way to standardize the use of PET in target volume delineation is by utilizing the "halo" to define the GTV. We have previously defined an anatomic biologic contour(ABC)-based GTV as the region encompassed by the distinct "halo" around areas of maximal SUV uptake and shown that its use in target volume delineation significantly decreases inter-observer variability in radiation treatment planning (2,7,8). This "halo" not only aids in increasing concordance among observers, but, can also increase the accuracy of target volume delineation as shown by Lin *et al.* (9).

Another challenge posed by the authors is the identification of which lymph nodes to include in the delineation of the target volume given that lymph nodes harboring disease require inclusion within the treatment field. Identification of pathologic lymph nodes is complicated by their oftentimes lower standard-uptake value (SUV) as compared to the primary tumor. Use of PET/CT for predicting nodal involvement is associated with a variable false positive rate (10), especially in the case of small sub-centimeter lymph nodes (11). Some authors have attempted to identify an SUV cut-off in order to improve the accuracy of the test, however, the choice of which cut-off value to use remains a subject of debate and the false positive rate cannot be completely eliminated (12,13). Another means of increasing the accuracy of PET/CT in identifying pathologic lymph nodes which has been proposed is using the ratio of lymph node to primary tumor SUV (14). This is a novel parameter which still needs to be validated in other studies but has shown promising results.

The authors conclude by addressing the future of PET fusion technology with a discussion of the combination between functional MR and PET information. Another compelling imaging modality which may become useful for target volume delineation is hypoxia imaging (15-17). Hypoxia PET combines a variety of 2-nitroimidazoles, labeled with fluor-18 (^{18}F), as the radiotracer. These compounds are able to identify regions of tumor hypoxia. Use of hypoxia PET for contouring target volumes will allow us to go one step further by varying radiation dose levels within the target volume to target radio-resistant hypoxic regions. While more research is needed before this can be applied to a clinical setting, it holds promise as an imaging modality to aid in target volume delineation.

In conclusion, the use of PET/CT for target volume delineation in curative intent radiation therapy of NSCLC has allowed for significant improvement in contouring accuracy and decrease in inter-observer variability. However, there are several practical limitations to its use that need to be strongly considered. Konert *et al.* (1) provide a comprehensive analysis of the challenges presented by the use of PET/CT in target delineation in NSCLC. Their recommendations to improve the application of PET are essential given that it is currently the standard method for delineating treatment volumes. Their publication also highlights the need for improving methods of imaging acquisition and target volume determination to guide practice as we move forward.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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