Peer Review File

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Reviewer A:

Comment 1: I had a lot of pleasure to read your paper and so going back to our practice over the last years. Your paper is a good summary of the impact of PET in radiotherapy planning and treatment delivery and you have well updated the information available. I have no major problems except when using PET-CT directly for treatment planning. This is possible but must be done with a lot of safeties. You are pointed some of the problems but there are many more including the right set-up for the patients (nuclear medicine and radiotherapy are not using the same table or device to immobilize the patient). There is also the issue of the quality of the CT acquisition but also the use of not of IV contrast a plus for our contouring. One another problem when using PET-CT is the false negative but also the false positive especially for lymph nodes in countries with granulamatouse disease.

Reply 1: Thank you for your kind comments and for your feedback. We greatly appreciate your time in reviewing the article. We do agree that there are problems with using PET-CT directly for treatment planning as you noted. We included your comments regarding these challenges in the paper as noted below. The text below reflects the changes as well as some of the previously noted text which does highlight some of your comments. Additionally, we recognize that PET-CT can lead to false positive results and have made that clear with the change as noted below.

Changes in the text:

Line 140-144: *"Of note, if the PET/CT is used as the primary planning image the CT component must be a high-quality diagnostic CT for accurate treatment calculations. Furthermore, the same table and immobilization devices should be used. When completing a separate PET/CT scan for radiation planning, it is critical to use the same position and immobilization methods that will be used during treatment."*

Line 188-191: "*Radiotracer uptake can occur nonspecifically and can be taken up by tissues through normal physiologic processes or non-malignant pathologic processes. This can lead to false positive findings. This can commonly be seen in lymph nodes on FDG PET in patients with infection or granulomatous disease."*

Comment 2: To use radiotracers for an adaptative radiotherapy is certainly a huge problem as your review is telling us but the problem is the PET-CT regardless of the tracers used is only an image at one moment and the key issue is to be able to adapt the treatment daily or weekly. In your paper you are focusing on PET-CT but to-day another issue is the used of MR

Reply 2: Thank you for your feedback. We agree that the imaging does reflect one moment and that adaptation at some interval whether daily or weekly is critical. We highlight these challenges in adaptation with changes to the manuscript as noted below.

Changes in the text:

Line 307-308: “These adaptive treatments have already been explored with combined MRI linear accelerators.”
Line 344-347: “Adaptive radiotherapy is in its infancy, however, its utilization can potentially improve the therapeutic ratio. The difficulty of adaptive therapy is replanning treatment weekly or daily to account for these changes. The novel combined PET/CT scanner which will be discussed next provides a solution to this problem.”

Reviewer B:

Comment 1: These authors have provided a comprehensive review on the state of the PET applications in radiation therapy planning based on FDG-PET imaging. They have done an excellent job of summarizing the standards that relate to this discipline which have evolved significantly over the past two decades. The authors accurately describe how this technology has improved the efficacy of radiation therapy and prevention of serious complications due to this very important intervention. Therefore, the paper as written is quite comprehensive and also accurate.
Reply 1: Thank you for your kind words. We greatly appreciate the time you have taken to review the manuscript.
Changes in the text: None needed for comments above.

Comment 2: However, the authors have failed to describe the evolving role of PET for assessing vascular complications as well as inflammation in organs that are in the field of view of radiation therapy. In particular, vascular complications have serious consequences and are potentially life-threatening. Radiation to head and neck region results in inflammation and atherosclerosis in the carotid arteries. By now, it is well established that such complications lead to dementia and strokes in this population. Similarly, radiation to the heart for treating patients with left breast cancer and left lower lung cancer also leads to significant coronary artery disease and heart attacks. While FDG is of value in detecting vasculitis in the carotids and myocarditis in the heart, Sodium Fluoride (NaF)-PET is a very effective modality for detecting atherosclerosis in both domains. Therefore, the authors should emphasize this new domain for PET in detecting and preventing such serious complications. Also, the authors should emphasize that proton therapy, in contrast to photon therapy, is associated with minimal complications in patients who have been treated with this form of radiation therapy. Similarly, the authors should emphasize the effects of radiation in salivary glands as well as other structures in the head and neck region which can be assessed by FDG-PET. Similarly, inflammation in the lung can be fatal and also lead to chronic disability in the treated population as a side effect of photon therapy.
Reply 2: Thank you for your feedback. We agree that the evolution of PET to assess radiation complications is an important new domain for PET in detecting and preventing treatment related complications. We have included your comments as

noted below and highlighted this new domain for PET.

Changes in the text:

Line 330-342: :Adaptive planning could also be of used to reduce dose to normal tissue should it show significant radiation effect. The use of PET is evolving to help detect acute and long-term complications of radiation. These side effects can have significant effects on patients. Not much research has been completed to assess radiation toxicity using PET during the course of radiotherapy. However, a few studies have evaluated radiation toxicity in the months following radiation. These studies were able to use PET following radiation to assess carotid vasculitis in head and neck cancer patients, parotid gland inflammation in head and neck cancer patients, and pulmonary inflammation in esophageal cancer patients.(61–63) Further studies should occur to evaluate the use of PET during radiotherapy to assess, treat, and prevent radiation induced toxicity. Such research should incorporate additional radiotracers which may be more selective at detecting inflammation in certain organs. For example, sodium fluoride (NaF)-PET is effective at detecting atherosclerosis and could be used to evaluate carotid atherosclerosis in head and neck patients or coronary artery atherosclerosis in breast cancer patients.(64) Furthermore, new radiation modalities such as proton therapy attempt to reduce radiation to normal tissue relative to photon-based radiotherapy. Use of PET could assist in evaluating toxicity differences between photons and protons."