

## Peer Review File

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### **Reviewer A:**

Comment 1: Thanks to the authors for this review of the broad topic of the effect of radiation on the heart. The authors are trying to cover a lot of material and therefore they are only able to cover the different topics very superficially. I would recommend putting the breast and lymphoma sections next to each other as these are patients with longer term survival; as opposed to the esophageal and lung patients who have more comorbidities and tend not to live as long following radiotherapy. There is no section on pediatric radiotherapy and long-term toxicities, which may add further depth.

Reply 1: Thank you for the thoughtful comments. We have moved the breast and lymphoma sections next to each other. We aimed to write a review primarily on radiotherapy for adults for which there is abundant data. While we agree that the effects of radiotherapy on children is a topic worthwhile of further study, it could easily stand alone as a separate paper and is outside the precise scope of this one, especially as the reviewer has noted that we did try to cover a lot of material on radiotherapy for adults and therefore could only cover them very superficially.

Changes in the text: We have moved the Hodgkin's Lymphoma section (now section 4.2 in pages 11-14, lines 218-285) to right after the Breast Cancer section (section 4.1).

Comment 2: The section on using RT as a treatment for cardiac problems is introduced very abruptly. Having read up to that point, I was not expecting the authors to cover this. It might be useful to signpost a bit more in the introduction what topics will be covered in the article and why. The article would also be enhanced by a bringing together all the disparate threads in the conclusion.

Reply 2: We greatly appreciate the reviewer's feedback. As recommended by the reviewer, we have elaborated on the introduction and brought together the disparate threads in the conclusion.

Changes in the text:

- We added and elaborated upon these sentences in the introduction: "Counterintuitively, radiotherapy may also be used to target select cardiac regions to treat recurrent in-stent restenosis and cardiac arrhythmias. In this review, we provide an overview of radiotherapy-induced cardiac toxicities, with an emphasis on the clinical implications for therapeutic radiotherapy planning and treatment for cancers of the breast, esophagus, lung, and lymph nodes and for select cardiac-directed management" (page 1, lines 63-67).
- We added and elaborated upon these sentences in the discussion: "In recent decades, the attempts to lower the administered cardiac radiation dose during cancer-directed treatments have broadly been successful. Recently, cardiac-directed radiotherapy has been utilized to treat recurrent in-stent restenosis and cardiac arrhythmias by leveraging the effect of radiotherapy on abnormally functioning, non-cancerous cells. More work remains to be done to further minimize the risks to patients while maximizing the benefits of radiotherapy" (page 26-27, lines 552-557).

#### **Reviewer B:**

Comment 1: Thank you for an opportunity to review your paper. It was educational for me.

Reply 1: Thank you very much for this comment.

Changes in the text: none.

Comment 2: My only comment is to give you some additional publications on cardiac toxicity in NSCLC published by our group. Do note that I am not asking you to cite these papers, but I think it would be useful for you to know of their existence, given your effort to provide a comprehensive review. The upshot of these papers is that fairly strong cardiac toxicity can be associated with doses above 50Gy, particularly in the right-superior quadrant of the heart.

Impact of Cardiac Dose on Overall Survival in Lung Stereotactic Body Radiotherapy (SBRT) Compared to Conventionally Fractionated Radiotherapy for Locally Advanced Non-Small Cell Lung Cancer (LA-NSCLC).

<https://pubmed.ncbi.nlm.nih.gov/34367717/>

Detecting spatial susceptibility to cardiac toxicity of radiation therapy for lung cancer.

<https://pubmed.ncbi.nlm.nih.gov/33506164/>

Using Novel Statistical Techniques to Accurately Determine the Predictive Dose Range in a Study of Overall Survival after Definitive Radiotherapy for Stage III Non-Small Cell Lung Cancer in Association with Heart Dose.

<https://pubmed.ncbi.nlm.nih.gov/34804634/>

Reply 2: We thank the reviewer for sharing these three articles and cited two of them. We did not cite the third article, “Impact of Cardiac Dose on Overall Survival in Lung Stereotactic Body Radiotherapy (SBRT) Compared to Conventionally Fractionated Radiotherapy for Locally Advanced Non-Small Cell Lung Cancer (LA-NSCLC),” given we did not discuss the role of SBRT for patients with locally advanced NSCLC.

Changes in the text:

- We referenced one article in “A commonly used cardiac dose constraint is the mean heart dose, although the percentage of cardiac volume receiving a particular dose of radiotherapy has also been utilized as a treatment optimization constraint” (page 15, lines 312-314).
- We referenced another article in “Additionally, subregions of the heart may be susceptible to radiotherapy, thus protective strategies for them could be warranted” (page 17, lines 337-340).