Peer Review File

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<mark>Reviewer A</mark>

1) You compared some anatomical parameters between two cohorts without making any intra-patient comparison, as would have been more correct given that this work is a mere dosimetric and non-clinical study. Each patient has unique anatomical characteristics and could hardly be perfectly matched to another. A more appropriate investigation design would be like that in PMID: 36601278 and PMID: 33788746. These two are important studies, which you should have cited. The comparison should have been made between the DIBH simul CT and that one in FB for each patient and not between different patients.

Response : Thank you for your better suggestions. It can well design a comparison between two respiratory controls in prospective study. These two studies are indeed worth learning from. We have written our shortcomings in the discussion and will consider using similar research methods as (PMID: 36601278 and PMID: 33788746) in future studies. We added reference and re-updated the reference list. The investigation of comparing those parameters from FB and DIBH scans in some patients worthy of further study.

Changes in the text: we have modified our text as advised (see Page8, line239-243).

2) Pictures for illustrating investigated anatomical parameters are necessary, rather than referring to other references.

Response : Thank you very much for the comment. We revised Figure 1 again and uploaded the revised picture as suggested.

Changes in the text: we have modified our text as advised (see Page 5, line 144-150, figure 1).

3) You advocated using Δ HH as a reliable parameter for predicting patients who are more likely to benefit from DIBH use. You provided no reference for a HH value working as a safety threshold based on which the prediction of DIBH beneficiaries is possible. How can I compute the Δ value in my daily clinical practice if I perform just one CT simulation? If the answer would be to do two CTs (FB vs DIBH) in the same patient, why did you extrapolate the Δ HH value from different patients? It's misleading.

Response : Thank you very much for the comment. As a retrospective study, we conducted a preliminary analysis of the parameters that may benefit patients in DIBH. However, since this

study was not designed as an RCT, we were unable to perform two CT scans on each patient. If this parameter is to be applied clinically, we must calculate the threshold for the HH parameter. From our preliminary findings, we can only conclude that changes in HH values do affect the dose of radiation received by the heart and that this value can indeed predict the level of radiation exposure to the heart. We will need to investigate this further in our next study.We also discussed our shortcomings and issues in the study.

4) To worsen even more the matter, there is the fact that each cohort comprises very different patients, not only for any divergence in anatomical features but also because some of them were treated on the chest wall (whose dorsal limit in delineating CTV can be nearer to the heart) rather than on the residual breast. I assume that not all patients received a boost, whose omission obviously may reduce the heart dose. Lastly, the inclusion of the internal mammary chain in CTV among some patients notoriously increases heart exposure to radiation.

Response : Thank you for giving so much detailed suggestions. It was indeed better to divide into chest wall irradiation and breast groups, but due to insufficient sample size, we could not analyzed it separately. However, there was no difference in statistics between DIBH and FB groups in the irradiation techniques. Similar studies have also analyzed the breast and chest wall field together (showed in Ref1).

1. Reference : 1. Yeung R, Conroy L, Long K, Walrath D, Li H, Smith W, Hudson A, Phan T. Cardiac dose reduction with deep inspiration breath hold for left-sided breast cancer radiotherapy patients with and without regional nodal irradiation. Radiat Oncol. 2015 Sep 22;10:200. doi: 10.1186/s13014-015-0511-8. PMID: 26391237; PMCID: PMC4578779.

5) Most of the information in Table 1 is useless since this is a dosimetric study. Why should I concern about the histopathological grade, vascular invasion, molecular subtype, et cetera if these do not alter my dosimetric goals in daily planning? The report of these characteristics has no sense at all.

Response : I think your suggestion is very helpful. We initially included these parameters as basic information based on the diagnosis and treatment standards for breast cancer, but they were not actually used in subsequent analysis. Therefore, we can consider removing these parameters.

Changes in the text: we have modified our text as advised (see Table 1).

Reviewer B

L69 Highlight box for Original Article

The authors need to highlight originality/novelty of their study In What is known and what is new? and in the Discussion section.

Responses: Thank you very much for the comment. We have add the novelty of our study in Discussion section.

Changes in the text: we have modified our text as advised (see Page7, line212-221).

L78 Please define the abbreviation OS.

Responses: Thank you for your suggestion. We have defined the abbreviation for OS. Changes in the text: we have modified our text as advised (see Page3, line79).

L94-96 References with description of the DIBH and IBH techniques are needed. Responses: Thank you for your suggestion. Two references that provide detailed descriptions of the DIBH and IBH techniques (ref 14,15) are attached and re-updated the reference list. Changes in the text: Changes in the text: we have modified our text as advised (see Page4, line96).

L110 "We retrospectively analyzed the data..." Please add text about what data were analysed (e.g. CT planning scan images).

Responses: Thank you for your suggestion. Changes have been made. Changes in the text: we have modified our text as advised (see Page4, line110-113).

L135-136 Please write about how reproducible was the patient position as estimated by "the weekly cone-beam computed tomography"?

Responses: Thank you for your suggestion. This sentence in Line 136-137 have explained that weekly cone-beam computed tomography was performed to verify position and examine the treatment reproducibility.

L143 "We previously described anatomic variables from the treatment scan fields (18)". Probably the wrong reference is cited here. Reference 18 does not contain the names of the authors of the manuscript.

Responses: We check ref 18. We apologize for the misunderstand about this reference. In this field, we referenced the anatomic variables from the treatment scan fields reported by other researchers.

Changes in the text: we have modified our text as advised (see Page5, line144-150).

Please provide a figure 1 showing the HH, DBIB, HCWL, HCWD. Responses: Thank you for your suggestion. We have modified the figure 1. Changes in the text: we have modified our figure 1 and text as advised(see Page 5,line148-149). L164-169 I would suggest moving this text into the Methods section.

Responses: Thank you for your input. After discussing it among our authors, we believe it would be best to keep this section in the Results section.

L 190 "In turn, DIBH markedly decreased the heart volume" Please rephrase "decreased the heart volume".

Response: Thank you for your suggestion. Changes have been made. Change in text : we have modified our text as advised (see Page7, line194).

L 207 The discussion is not strong enough. It has to highlight novelty/ originality of the study. Response:Thank you for your suggestion. We have explained the originality of study and novelty in our discussion.

Change in text : We have modified our text as advised (see Page7, line212-221).

L209 "In this study, DIBH allowed better separation of the heart and LAD..." The "separation of the heart and LAD." requires rephrasing. Response: Thank you for your suggestion. Changes have been made. Change in text: We have modified our text as advised (see Page7, line217).

L209-212 Why do you consider references 19 and 20 relevant to the present study? Reference 20 discusses the effect of the audio-visual guidance, but the present study does not do it. Response: Thank you for your suggestion. We removed those Reference.

L233-235 "Currently, advanced RT techniques, such as intensity-modulated RT and volumetric-modulated arc therapy, have been employed in DIBH planning." How is this sentence related to the limitations of the study?

Response: Thank you very much for the comment. We used this sentence to explain the development of the DIBH technology. It is not contain in the limitations of our study.

In Figure 1. Should be "breath hold time" instead of "breath holed time". Response: Thank you for your suggestion. Changes have been made. Change in text : we have modified our figure1 as advised.

<mark>Reviewer C</mark>

1. Highlight Box

Two points are needed for this item, please clarify "what is known" and "what is new" respectively.

* The box should be concise with NO more than 150 words.

What is known and what is new?

• We confirmed the <u>dosimetric</u> benefits of DIBH for the heart and cardiac substructures. We showed that anatomic characteristics correlate with heart doses and may inform patient selection for DIBH.

Response : Thank you for your comments. We have modified the Highlight Box.

2. Figure 1

Please provide an editable version of the flow chart (figure 1) in DOC/PPT. DO NOT just copy the figure to DOC, editable format is needed for copy editing.

Response : Thank you for your comments. We have sent editable version of the flow chart (figure 1) in PPT.

3. Table 1 Please explain RT, IMC in the table footnote. Response : Thank you for your comments. We have add the RT and IMC's footnote.

4. DBIB

Please unify the explanation of DBIB. Main text:

54 heart height (HH), heart chest wall length (HCWL), the mean distance between the

ipsilateral lung and breast (DBIB), and the heart-chest wall distance (HCWD) (P<0.05).

Table footnotes:

*, significant differences. CT, computed tomography; HH, heart height; DBIB, the

distance between ipsilung and breast; CD, Chest depth; HCWL, heart chest wall length;

Response : Thank you for your comments. We have unify the explanation of DBIB.

5. References/Citations

Reference 22 and 23 are not cited in the main text, please revise. Please note that 22 and 23 should be cited between reference 21 and 24.

Response : Thank you for your comments. We check the reference, 22 and 23 and re-updated the reference list.