

## **Hypofractionation and stereotactic body radiation therapy in inoperable locally advanced non-small cell lung cancer**

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Handling editor:

Michal Heger

*Department of Pharmaceutics, Utrecht University, the Netherlands*

*Department of Pharmaceutics, Jiaxing University Medical College, Zhejiang, China*

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1<sup>st</sup> Editorial decision

19-Oct-2020

Ref.: Ms. No. JCTRes-D-20-00104

Hypofractionation and SBRT in Inoperable Locally Advanced Non-Small Cell Lung Cancer  
Journal of Clinical and Translational Research

Dear Dr Rico,

Reviewers have now commented on your paper. You will see that they are advising that you revise your manuscript. If you are prepared to undertake the work required, I would be pleased to reconsider my decision.

For your guidance, reviewers' comments are appended below and attached to this email.

If you decide to revise the work, please submit a list of changes or a rebuttal against each point which is being raised when you submit the revised manuscript. Also, please ensure that the track changes function is switched on when implementing the revisions. This enables the reviewers to rapidly verify all changes made.

Your revision is due by Nov 18, 2020.

To submit a revision, go to <https://www.editorialmanager.com/jctres/> and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely

Michal Heger  
Editor-in-Chief  
Journal of Clinical and Translational Research

Reviewers' comments:

Reviewer #1:

- This is a comprehensive and generally well-written narrative review that effectively describes the various studies on moderate hypofractionation and SBRT boost for Stage III NSCLC.
- A summary table of all the described studies with a few data points for each could help the reader reference individual articles.
- There are grammatical / spelling errors throughout the manuscript that should be addressed. Examples include page 2, line 49; page 3, line 35; page 5, paragraph 6, etc. Authors also at several points refer to "mean" toxicity rates (eg page 5, line 55) which is the incorrect term, as these toxicity rates are proportions.
- Page 2, line 29: It is not correct that the majority of recurrences are locoregional after treatment of Stage III NSCLC, and the given reference only distinguishes between local and regional nodal relapses. Many (probably most) patients with Stage III NSCLC recur distantly. Today, effective treatment of Stage III lung cancer should balance efforts at local control without exceeding what any individual patient can tolerate, to avoid compromising their ability to receive immunotherapy as well. This balance (and caveat to the net benefit of any fractionation change, which could increase toxicity) should be further explored in the discussion/conclusion.
- Though the authors mention BED and convenience as advantages to hypofractionation, there needs to be a greater discussion on implications of hypofractionation on normal tissue toxicity (that could be mitigated with the careful use of IMRT/SBRT to spare esophagus, etc). For instance, the section on hypofractionation could start by introducing the concept of SBRT for Stage I as an example of the ideal use of (ultra)hypofractionation that can produce exceptional local control. However, central structure tolerances (eg, proximal bronchial tree, esophagus, maybe heart) limit ultrahypofractionation, thus moderate hypofractionation, etc. The section on personalized hypofractionation illustrates the use of some of these concepts to design trials in which doses can be personalized by proximity to OAR's, etc.
- Page 5, line 53: should clarify that the authors are discussing a previously-referenced review article, thus the large ranges in the reported OS / toxicity data.
- For toxicity data, at several points where the grade of toxicity is not given (eg, example above) the authors should clarify whether they are referring to "any" toxicity vs high-grade toxicity.
- The section on hyperfractionation contains some interesting historical data but is more or less irrelevant to current practice. I don't feel strongly about its inclusion but feel that the article could be better focused by cutting this section.

Reviewer #2: This work provides an overview of altered radical radiotherapy fractionation schedules with a focus on hypofractionated schedules for locally advanced NSCLC in light of a paradigm shift in the management due to immunotherapy. This topic is also topical with the ongoing pandemic.

The manuscript provides a synopsis of most of the published evidence. However, there are some major concerns with this work which are outlined below that needs to be addressed. This would enhance the impact of this work.

1. Specific aim(s) for the conduct of this work needs to be clarified given other recent papers published in this topic as quoted.
2. The title of the work states hypofractionation but there is a major section dedicated to hyper fractionation. Suggest either shorten the hyperfractionated section (preferred) or alter the title to altered fractionations.
3. This work aims to explore studies exploiting some of 5Rs of radiobiology. However, as we know the main issue with hypofractionation schedules is normal tissue toxicities. Suggest adding/discussing mitigation strategies eg. technological advances that could help to deliver these schedules, particularly SABR schedules safely by minimising toxicities.
4. Suggest adding a paragraph describing SABR in the context of this paper.
5. There is emerging preclinical evidence of varying immunomodulatory effect of different radiotherapy fractionation schedules. Given rapid developments with immunotherapy coming into the concurrent chemoRT setting, how this approach is going to shape the future of radiotherapy fractionation schedules, particularly for hypofractionated/SABR schedules?
6. Suggest outline potential future directions for hypofractionation/SABR in this setting.

Few other minor specific points in the manuscript that needs to be addressed:

1. P1, L1 - 'uneven' results - would be better with mixed results?
2. P1, Ref 1 - 4yr outcome data presented at ESMO2020. Suggest add and discuss ESMO Ref as this is the most recent update.
3. P1, L57 - debate of what's the best management for operable N2 disease, especially single N2 station node hasn't been settled. Note PACIFIC study captures inoperable disease only so there may be a role for surgery in some patients with mediastinal involvement. This point needs to be brought in here.
4. P3, L30 - please quote which studies are referred here.

There is additional documentation related to this decision letter. To access the file(s), please click the link below. You may also login to the system and click the 'View Attachments' link in the Action column.

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#### Authors' response

This work provides an overview of altered radical radiotherapy fractionation schedules with a focus on hypofractionated schedules for locally advanced NSCLC in light of a paradigm shift in the management due to immunotherapy. This topic is also topical with the ongoing pandemic.

The manuscript provides a synopsis of most of the published evidence. However, there are some major concerns with this work which are outlined below that needs to be addressed. This would enhance the impact of this work.

1. Specific aim(s) for the conduct of this work needs to be clarified given other recent papers published in this topic as quoted.

We have added a paragraph in the *abstract* and in the *introduction* pointing out that this review focuses on analyzing the role of SBRT and hypoRT in the current context, taking into account the pandemic situation and the emergence of immunotherapy.

2. The title of the work states *hypofractionation* but there is a major section dedicated to *hyper fractionation*. Suggest either shorten the *hyperfractionated* section (preferred) or alter the title to altered fractionations.

Following the reviewer's recommendations, we have shortened the section *hyperfractionation*

3. This work aims to explore studies exploiting some of 5Rs of radiobiology. However, as we know the main issue with hypofractionation schedules is normal tissue toxicities. Suggest adding/discussing mitigation strategies eg. technological advances that could help to deliver these schedules, particularly SABR schedules safely by minimising toxicities.

In the first four paragraphs of the *SBRT* section we have added comments trying to respond to the reviewers' recommendations.

4. Suggest adding a paragraph describing SABR in the context of this paper.

In the third paragraph of the *SBRT* section, we have added a comment describing the SBRT in the context of the paper.

5. There is emerging preclinical evidence of varying immunomodulatory effect of different radiotherapy fractionation schedules. Given rapid developments with immunotherapy coming into the concurrent chemoRT setting, how this approach is going to shape the future of radiotherapy fractionation schedules, particularly for hypofractionated/SABR schedules?

We have completed the last paragraph of the *SBRT* section with comments on the role of RT in its combination with immunotherapy given its immunomodulatory role.

6. Suggest outline potential future directions for hypofractionation/SABR in this setting.

We have added a last sentence to the conclusion pointing out potential future directions.

Few other minor specific points in the manuscript that needs to be addressed:

1. P1, L1 – ‘uneven’ results – would be better with mixed results?  
*Modified.*
2. P1, Ref 1 – 4yr outcome data presented at ESMO2020. Suggest add and discuss ESMO Ref as this is the most recent update. (Ref 8)  
*We have added the reference and commented on the results in the second paragraph of the section *Results and discussion*.*
3. P1, L57 – debate of what’s the best management for operable N2 disease, especially single N2 station node hasn’t been settled. Note PACIFIC study captures inoperable disease only so there may be a role for surgery in some patients with mediastinal involvement. This point needs to be brought in here.  
*We have added a comment about it the in the first paragraph of the section *Results and discussion*.*
4. P3, L30 – please quote which studies are referred here.  
*We have not been able to identify the references that are claiming us. We have reviewed the entire text to try to ensure that nothing was left without the proper references.*

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2<sup>nd</sup> Editorial decision  
24-Mar-2021

Ref.: Ms. No. JCTRes-D-20-00104R1  
Hypofractionation and SBRT in Inoperable Locally Advanced Non-Small Cell Lung Cancer  
Journal of Clinical and Translational Research

Dear author(s),

Reviewers have submitted their critical appraisal of your paper. The reviewers' comments are appended below. Based on their comments and evaluation by the editorial board, your work was FOUND SUITABLE FOR PUBLICATION AFTER MINOR REVISION.

If you decide to revise the work, please itemize the reviewers' comments and provide a point-by-point response to every comment. An exemplary rebuttal letter can be found on at <http://www.jctres.com/en/author-guidelines/> under "Manuscript preparation." Also, please use the track changes function in the original document so that the reviewers can easily verify your responses.

Your revision is due by Apr 23, 2021.

To submit a revision, go to <https://www.editorialmanager.com/jctres/> and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely,

Michal Heger  
Editor-in-Chief  
Journal of Clinical and Translational Research

Reviewers' comments:

Reviewer #1: Comments have been addressed and I do not have any further concerns.

Reviewer #2: Thank you for addressing my comments. My only suggestion is to add the results of RTOG 1106 (WCLC 2021) and PET-BOOST (ESTRO 2020) to the paragraph, just above SABR section (results available since the original submission).

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Authors' response

Reviewer #1: Comments have been addressed and I do not have any further concerns.

Reviewer #2: Thank you for addressing my comments. My only suggestion is to add the results of RTOG 1106 (WCLC 2021) and PET-BOOST (ESTRO 2020) to the paragraph, just above SABR section (results available since the original submission).

[I have added the results of the studies suggested in the previous paragraphs to the SBRT chapters.](#)

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3<sup>rd</sup> Editorial decision  
29-Mar-2021

Ref.: Ms. No. JCTRes-D-20-00104R2  
Hypofractionation and SBRT in Inoperable Locally Advanced Non-Small Cell Lung Cancer  
Journal of Clinical and Translational Research

Dear authors,

I am pleased to inform you that your manuscript has been accepted for publication in the Journal of Clinical and Translational Research.

You will receive the proofs of your article shortly, which we kindly ask you to thoroughly review for any errors.

Thank you for submitting your work to JCTR.

Kindest regards,

Michal Heger  
Editor-in-Chief

Journal of Clinical and Translational Research  
Peer review process file 07.202102.017



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Comments from the editors and reviewers: