

Adjuvant treatment in lung cancer

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1st Editorial decision

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Ref.: Ms. No. JCTRes-D-20-00100

ADJUVANT RADIOTHERAPY IN LUNG CANCER

Journal of Clinical and Translational Research

Dear Mrs Taboada Valladares,

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.

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 09, 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 a review article entitled „Adjuvant radiotherapy in lung cancer". However, a substantial proportion of the content of this review is dedicated to the adjuvant CHT (chemotherapy). Thus I suggest to change a title of the review on the „Adjuvant treatment in lung cancer", or , if this were not possible any longer, because this is an invited article on the predefined issue, to limit data on CHT and present it more in the context of adjuvant RT.

In general, this review needs some updating and rewording, as follows:

1. Abstract, Background: it was written: „the lack of prospective studies to determine the benefits of radiation therapy". This is a confusing statement, there were a lot of such studies.
2. Introduction, lines 27-28: In this analysis, there was no benefit of RT for pN2 patients, only in opposite to pN0-N1 there was no observed harm of RT. Please, correct.
3. For me, distinction of adjuvant RT for R0 and R1-R2 is somewhat controversial, especially, for R2, because in such indications (presence of gross disease), RT is no longer given as an adjuvant, but more as definitive treatment. Prospective studies dealing with a role of postoperative adjuvant RT were based on R0 cases. This should be clearly elucidated.
4. A chapter on role of adjuvant RT for pN2 patients in the era of adjuvant CHT should be updated and conclusions should be changed accordingly. On the ESMO 2020 congress, the preliminary results of LungART trial were presented by Cecile Le Pechoux. And these indicate, that there is no benefit of adjuvant RT for pN2 patients. This will probably change a clinical practice in this regard. Additionally, earlier in 2019, the results of the Chinese phase III trial were also against the use of postoperative RT, also in pN2 disease (Zhouguang Hui, NCT00880971, presented at 2019 World Conference on Lung Cancer, Barcelona).
5. Definition of volumes: Because you mention a problem of R1-R2 resection, a definition of volumes in such cases should be discussed (f.ex. Olszyna-Serementa, Lung Cancer, 2013)
6. Chinese NCT00880971 and LungART: please, update, as above

Reviewer #2: Thank you for this interesting work, which also in the part of the treatment with adjuvant radiotherapy at the NSCLC is completely current. Please take into account the comments included in the attached document.

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.

Authors' response

Dear Sir or Madam,

Please note the below explanations for the suggestions and indications offered on the article that your journal is currently considering for publication.

I have tried to explain how I have addressed each of them without copying the modifications verbatim.

I remain at your disposal for any further clarifications you might require.

Yours sincerely,

Begoña Taboada Valladares

Reviewer #1:

1. This is a review article entitled „Adjuvant radiotherapy in lung cancer“. However, a substantial proportion of the content of this review is dedicated to the adjuvant CHT (chemotherapy). Thus I suggest to change a title of the review on the „Adjuvant treatment in lung cancer“.

The title has been modified to *Adjuvant treatment in lung cancer*, since we aim to globally summarise adjuvant treatment in lung cancer.

1. Abstract, Background: it was written: „the lack of prospective studies to determine the benefits of radiation therapy“. This is a confusing statement there were a lot of such studies.

The sentence has been modified to make it less confusing.

2. Introduction, lines 27-28: In this analysis, there was no benefit of RT for pN2 patients, only in opposite to pN0-N1 there was no observed harm of RT. Please, correct.

The sentence has been redrafted to make results from the study more easily understandable.

3. For me, distinction of adjuvant RT for R0 and R1-R2 is somewhat controversial, especially, for R2, because in such indications (presence of gross disease), RT is no longer given as an adjuvant, but more as definitive treatment. Prospective studies dealing with a role of postoperative adjuvant RT were based on R0 cases. This should be clearly elucidated.

It is true that R2 patients are treated in a radical way when a macroscopic tumor remains after surgery. We just felt it was interesting to allude to R0 vs R-R2 given the fact that the dose varies.

4. A chapter on role of adjuvant RT for pN2 patients in the era of adjuvant CHT should be updated and conclusions should be changed accordingly. On the ESMO 2020 congress, the preliminary results of LungART trial were presented by Cecile Le Pechoux. And these indicate, that there is no benefit of adjuvant RT for pN2 patients. This will probably change a clinical practice in this regard. Additionally, earlier in 2019, the results of the Chinese phase III trial were also against the use of postoperative RT, also in pN2 disease (Zhouguang Hui, NCT00880971, presented at 2019 World Conference on Lung Cancer, Barcelona).

The abovementioned studies have been updated to include the preliminary results and conclusions presented at different conferences.

5. Definition of volumes: Because you mention a problem of R1-R2 resection, a definition of volumes in such cases should be discussed (f.ex. Olszyna-Serementa, Lung Cancer, 2013).

The abovementioned study, where volumes for incomplete resections are defined, has been introduced.

6. Chinese NCT00880971 and LungART: please, update, as above.

The abovementioned studies have been updated to include the preliminary results and conclusions presented at different conferences.

Reviewer 2:

Page 2 Line 28. Ref 4 could be omitted, since the authors coment in their paper “We did not plan to analyse the effect of postoperative radiotherapy in ANITA. Although every centre

defined its policy on radiotherapy before the beginning of the trial, more patients in the observation group than in the chemotherapy group received radiotherapy...Since the decision to give postoperative radiotherapy was not randomised, any conclusions should be drawn cautiously”

The reference has been deleted.

Page 3, Line 20. *In this paragraph it-s not clear if authors talks about the LACE study of all adjuvant trials in this setting.*

We were alluding to the same study, but we have made reference to it again in the paragraph to avoid ambiguity.

Page 2-3. *In adjuvant CT we miss the mention to 2 studies: the ANITA trial (ref 4) and the JBR.10 Trial.*

These two studies on adjuvant CT have been included.

Page 4, line 23. *Please, include HR and p value in the OS results.*

P values have been inserted for the studies mentioned in the article.

Page 5, line 2. *Please, review the sentence “ They concluded that...”*

There was a verb missing, the typo has been corrected,

Page 5, line 9. *Please consider to change “demonstrates lower survival...” to “ is associated to lower survival...”*

Replaced as indicated.

Page 5, line 20. *It’s accepted that N2 disease is associated to higher risk of recurrence and poorer survival (“may” could be avoided).*

May has been replaced by “is”.

Page 5, N2 disease. *Please introduce de HR/p value in the percentage comparisons.*

P values have been inserted for the studies mentioned in the article.

Page 6 line 29. *Corso et al don’t conduct the tratment, they just analyze the data. The “.” should be avoided after “60 Gy”.*

Duly modified.

Page 6 line 37. *The authors refer to several papers on the NCDB. To better understand the differences of each review, it would be useful to know why in the work of Mikell et al. the analysis is restricted to the period 2004-2006.*

The clarification on why the analysis is restricted to 2004-2006 has been introduced.

Page 5-8. *To help the reader, it would be useful to make a table in which the works mentioned in section N2 were discussed, including author, years analyzed, results obtained...*

Tables for the different studies have been introduced.

Page 6 line 56. *Please, consider “lower Charlson score” better than “smaller Charlson”.*

Duly modified.

Page 7 line 17. *The first sentence “Francis...” it is not clear. Please also consider if “pathological anatomy” is the best term in line 20.*

Reviewed and modified for better accuracy..

Page 8, line 51. *Introduce the number of the table you cited “Table 1 describes...”, and you have to include in the top of the table: “Table 1. Radiation limits...”*

Duly modified.

Page 9 line 33. *After sending this manuscript for evaluation, the results of the LUNG ART trial study have been presented at ESMO 2020. Although the study has not yet been published in a scientific journal, given its clinical impact, it is recommended to complete the corresponding information.*

Lung ART data have been introduced.

Page 10 line 46. *Could you comment the potential impact of the retrospective analysis on the outcome of the study? For example, the decision not to perform surgery may be related to patients with better performance status, more tumor burden... Indeed, Scriber et al point out in the discussion: “Limitations of this analysis include the lack of chemotherapy data on these patients, the inherent selection bias in retrospective reviews, the absence of central pathology review, the lack of some key pathologic variables (such as margin status), and the lack of information regarding performance status. In addition, we do not know why some patients were referred for PORT, because there may have been signs of more aggressive disease in those patients”.*

The limitations of the abovementioned study have been discussed.

Page 11 line 54. *Separate “and” and “1996”.*

Duly modified.

Page 12 line 2. Separate “and” and “2011”.

Duly modified.

Page 11-13. As in NSCLC I consider that it would be useful to make a table in which the works mentioned in section CT and PORT for SCLC were discussed.

2 tables have been introduced as required.

Page 14. Given the communication of the LUNG ART study at ESMO 2020, the authors should consider revising the discussion, which may vary in light of the study results. In addition, if this section is raised as a discussion it should be assessed to develop it further.

Preliminary results and conclusions from LUNG ART have been introduced.

Page 18. Please complete references 30 and 31, including tumor type, year of publication, access data...

Duly modified

Page 18. Complete references 34, 35, 37.

Duly modified.

2nd Editorial decision
19-Nov-2020

Ref.: Ms. No. JCTRes-D-20-00100R1
ADJUVANT TREATMENT IN 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.

The editorial board requests that an additional round of language polishing is performed to eliminate residual errors and to ensure linguistic consistency. In case of the latter, the text contains for example different notations of p-values (p: 0.05 versus $p < 0.05$, where the : should be replaced by =). Please extend this comment to a broader context. Also, given the fact that so many abbreviations are used, please provide a list of abbreviations and ensure that

all abbreviations are written out in full at first mention. Furthermore, please list the abbreviations and their meaning below each table so that readers do not have to revert to the text in order to understand the table.

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 Dec 19, 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 #2: Thank you for considering the suggestions we made. I find your work appropriate for publication.
Best,

3rd Editorial decision
13-Dec-2020

Ref.: Ms. No. JCTRes-D-20-00100R2
ADJUVANT TREATMENT IN 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 Jan 12, 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:

Dear authors,

Thank you for going through your manuscript again in an attempt to eliminate residual errors. Unfortunately, the corrections are not sufficient yet for me to accept the paper, again underscoring the authors' responsibility to raise the level of their manuscript to academic English.

Just in the last paragraph of the Introduction there are 2 evident mistakes:

- 1) ... lymph nodes, three hilars and three from the N2 mediastinal region ... -> three what from the N2 mediastinal region?
- 2) The last sentence of the paragrph does not end with a period.

Accordingly, I again ask you kindly to linguistically upgrade your paper, preferably by involving a native speaker or by engaging a paid service. If you need our help with the latter, please do not hesitate to contact the editor for assistance (m.heger@jctres.com).

Thank you,

Michal Heger
EiC

Authors' response

Authors' response

Dear Sir or Madam,

As you indicated in your e-mail, the article has been revised by a paid service to upgrade the language level.

I remain at your disposal for any further clarifications you might require.

Yours sincerely,

Begoña Taboada Valladares

4th Editorial decision
23-Jan-2021

Ref.: Ms. No. JCTRes-D-20-00100R3
ADJUVANT TREATMENT IN 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

Comments from the editors and reviewers: