

## **Brain metastases: Single dose radiosurgery versus hypofractionated stereotactic radiotherapy: a retrospective study**

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Handeling editor:

Michal Heger

*Department of Pharmaceutics, Utrecht University, the Netherlands*

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

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Received: 7 March, 2020

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1<sup>st</sup> editorial decision

1-Apr-2020

Ref.: Ms. No. JCTRes-D-20-00011

Brain metastases: Single dose radiosurgery versus hypofractionated stereotactic radiotherapy.  
A retrospective study.

Journal of Clinical and Translational Research

Dear Ms De la Pinta,

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.

Please place particular emphasis on addressing the following in addition to the reviewer comments. The result do not seem to add much to the current knowledge in the field. Numerous groups have investigated this approach and reported the outcome data. Consequently, reporting about the overall results for single dose radiosurgery (SRS) in a small series does not make sense since SRS has already been evaluated in thousands of

patients around the world. Moreover, recommendations for hypofractionated stereotactic radiotherapy of brain metastases have already been incorporated into the NCCN guidelines. We therefore like you to address the novelty of the work, or otherwise comment why a validation study should have been performed. This may be useful when the outcomes in other published trials are contrasting.

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 May 01, 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 paper reports about a series of patients with brain metastases located in critical areas or large-sized that have been treated by hypofractionated rather than single dose radiosurgery.

General:

- Please state clearly your hypothesis and the measures to prove or falsify it
- take care to use proper text formatting, use of the English language, use of abbreviations, reference to Figures, style of arguing and citations

Special:

Many groups (>20) have reported about the outcome of hypofractionated stereotactic radiotherapy for brain metastases.

Please try to compile these e.g. in a table and show your results in conjunction with them.

One way to render this paper more interesting would be to compare the outcome of 3 groups:

- A) SRS without dose reduction
- B) SRS with dose reduction with the reasons for reduction properly stated
- C) Hypofractionated stereotactic radiotherapy with reasons properly stated

- please arrange the discussion for arguing in some direction rather than enumerating results

Reviewer #2: This is an interesting analysis based on clinical experience and which focuses

on an aspect as relevant as the treatment of brain metastases with radical intention.

Despite its interest and timeliness, the work presents many formal aspects that the authors must correct before even considering a possible publication:

Page 2 line 29: Clarify the text meaning of "RS" and "SRS". Do they represent the same? Are they used interchangeably?

Page 2 and following: Substitute the comma in the percentages per point, according to the English notation (i.e. 53.6% instead of 53,6%)

Page 4, line 32: Clarify the use of the term "Biological Dose Equivalent" when perhaps they are referring to "Biologically Effective Dose" (see: Fowler JF. 21 years of biologically effective dose. Br J Radiol. 2010 Jul; 83 (991) : 554-68. Doi: 10.1259 / bjr / 31372149)

Page 5 line 13: define meaning of acronyms RPA, GPA, PS

In table 1 define acronyms: SRS, hFSRT, NSCLC, KPS, WBRT, etc.

In Table 1, with respect to the KPS section in hFSRT patients, 28 and 11 patients are counted, with 2 to the 41 included.

Thoroughly review grammar, syntax and writing of the entire text

Finally, the study is interesting and well conceived, provides useful information and is well structured. Tables and figures provide non-redundant information and the bibliography is updated

Reviewer #3: This is a retrospective study analyzing single-fraction vs. multi-fraction SRS for brain metastases.

There are no page #s so I cannot be more precise in describing the location of text.

Specific comments are as follows:

The paper should be reviewed for spelling and grammar as well as abbreviations that are not defined. Some specific examples are:

Abbreviation that should be defined or not used: CL, TSH-FSR, TSFEH, LQ

"6 patients for which" should be "6 patients for whom"

"Despite of" (in abstract and paper) is not correct grammar

"Treatment of brain metastases is not defined" makes no sense

I am unfamiliar with the word "cristaline": in this context.

The abstract (and text) use "p" to abbreviate for patients. This is not standard. The abstract also has unusual use of spaces and hyphens - presumably to cut back word counts, but make difficult to read. Other means can be used to reduce word counts (hyphenate Kaplan-Meier, reduce superfluous wording change  $p = 0.93$  to  $p=0.93$  ...)

In the Introduction (1st paragraph) "... 5-10 metastases without differences from patients ..." What differences are the authors referring to ?

Was a V12 of 10 cc a strict constraint ?

In the methods the authors describe the volumes of lesions treated with SRS and hFSRT. Why were only 43 patients chosen for this analysis ? Also the authors state 43 patients then state 43 lesions. Which is it. This entire paragraph is actually results and not methods and should be moved.

What is mean by 30Gy was associated with a better LQ ? This makes no sense.

The 3rd paragraph of the discussion lists study after study. This would be best described in a table. Perhaps the authors can describe why they selected these studies (of many). Notably there are many studies of fractionated SRS for brain metastases.

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Author's rebuttal

Reviewer #1: This paper reports about a series of patients with brain metastases located in critical areas or large-sized that have been treated by hypofractionated rather than single dose radiosurgery.

General:

- Please state clearly your hypothesis and the measures to prove or falsify it. **This has been added.**

- take care to use proper text formatting, use of the English language, use of abbreviations, reference to Figures, style of arguing and citations. **This has been checked.**

Special:

Many groups (>20) have reported about the outcome of hypofractionated stereotactic radiotherapy for brain metastases. Please try to compile these e.g. in a table and show your results in conjunction with them. **This has been added in table 2.**

One way to render this paper more interesting would be to compare the outcome of 3 groups:

A) SRS without dose reduction.

B) SRS with dose reduction with the reasons for reduction properly stated

C) Hypofractionated stereotactic radiotherapy with reasons properly stated

**Modified, we are compared three groups in results.**

- please arrange the discussion for arguing in some direction rather than enumerating results. **This has been added.**

Reviewer #2: This is an interesting analysis based on clinical experience and which focuses on an aspect as relevant as the treatment of brain metastases with radical intention.

Despite its interest and timeliness, the work presents many formal aspects that the authors must correct before even considering a possible publication:

Page 2 line 29: Clarify the text meaning of "RS" and "SRS". Do they represent the same? Are they used interchangeably? **This has been modified. We are difference between SRS by general concept and single dose SRS by one dose treatment.**

Page 2 and following: Substitute the comma in the percentages per point, according to the English notation (i.e. 53.6% instead of 53,6%). **This has been modified.**

Page 5 line 13: define meaning of acronyms RPA, GPA, PS  
In table 1 define acronyms: SRS, hFSRT, NSCLC, KPS, WBRT, etc.  
Thoroughly review grammar, syntax and writing of the entire text. **This has been added.**

Finally, the study is interesting and well conceived, provides useful information and is well structured. Tables and figures provide non-redundant information and the bibliography is updated. **Thank you for your comment.**

Reviewer #3: This is a retrospective study analyzing single-fraction vs. multi-fraction SRS for brain metastases.

There are no page #s so I cannot be more precise in describing the location of text.

Specific comments are as follows:

The paper should be reviewed for spelling and grammar as well as abbreviations that are not defined. **This has been added.** Some specific examples are:

"Despite of" (in abstract and paper") is not correct grammar. **This has been changed.**

The abstract (and text) use "p" to abbreviate for patients. This is not standard. The abstract also has unusual use of spaces and hyphens - presumably to cut back word counts, but make difficult to read. Other means can be used to reduce word counts (hyphenate Kaplan-Meier, reduce superfluous wording change  $p = 0.93$  to  $p=0.93$  ...) **This has been changed.**

Was a V12 of 10 cc a strict constraint? **Yes, V12 is a strict constraint.**

In the methods the authors describe the volumes of lesions treated with SRS and hFSRT. Why were only 43 patients chosen for this analysis? Also the authors state 43 patients then state 43 lesions. Which is it. This entire paragraph is actually results and not methods and should be moved. **We had missing in this data, we have eliminated this section from the text.**

The 3rd paragraph of the discussion lists study after study. This would be best described in a table. Perhaps the authors can describe why they selected these studies (of many). Notably there are many studies of fractionated SRS for brain metastases. **We include a table with studies, table 2. We include these studies because of published recently and include comparisons between single dose SRS and hFSRT. We have also modified the discussion of toxicity to make it simpler**

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2<sup>nd</sup> editorial decision

7-May-2020

Ref.: Ms. No. JCTRes-D-20-00011R1

Brain metastases: Single dose radiosurgery versus hypofractionated stereotactic radiotherapy. A retrospective study.

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 Jun 06, 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: Most of the recommendations have been applied.

Reviewer #2: Thank you for your response and for the modifications made to the manuscript, which clarify and improve it.

However, I still believe that the manuscript would benefit from an in-depth review of language and grammar by a native English speaker.

Reviewer #3: There remains some issues with grammar and flow, too many to list. Some are listed below however. This needs to be resubmitted after a thorough review by a primary English speaking editor or authors.

"LPFS was not inferior than SRS." Should be "LPFS was not inferior compared to lesions treated with SRS."

"Acute and late toxicities were more frequently in the hFSRT-group ..." should be "Acute and late toxicities were more frequently observed in ..."

Confusingly, the results and conclusions in the abstract do not match --- "hFSRT exhibited similar survival rates and LPFS rates with a lower risk of toxicity in comparison to those treated with single-dose SRS"

The rates are only slightly higher in the hFSRT group (well within errors), and not enough to say "more frequently observed" especially if the authors conclude that they are similar.

"Of these patients, 56 patients ..." who are these patients ???

"Although hFSRT was used for large lesions and in adverse locations. LPFS was not inferior to SRS." Should be a comma and not period between these.

"10 patients previously SRS and 1 patient after SRS" should be "10 patients prior to SRS and 1 patient after SRS"

There is still no hypothesis explicitly stated as suggested by reviewer 1.

A PTV of 3mm is quite large. This should be discussed in the limitations section.

What is "chronic crisis"

The following does not make sense "Number of metastases is controversial in the series, age is not a criteria for SRS"

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Author's rebuttal

Reviewers' comments:

Reviewer #1: Most of the recommendations have been applied. **Thank you for the comment**

Reviewer #2: Thank you for your response and for the modifications made to the manuscript, which clarify and improve it.

However, I still believe that the manuscript would benefit from an in-depth review of language and grammar by a native English speaker. **Changed accordingly, thank you.**

Reviewer #3: There remains some issues with grammar and flow, too many to list. Some are listed below however. This needs to resubmitted after a thorough review by a primary English speaking editor or authors. **Changed accordingly, thank you.**

"LPFS was not inferior than SRS." Should be "LPFS was not inferior compared to lesions treated with SRS." **Changed accordingly, thank you.**

"Acute and late toxicities were more frequently in the hFSRT-group ..." should be "Acute and late toxicities were more frequently observed in ..." **Changed accordingly, thank you.**

Confusingly, the results and conclusions in the abstract do not match --- "hFSRT exhibited similar survival rates and LPFS rates with a lower risk of toxicity in comparison to those treated with single-dose SRS" **Changed accordingly, thank you.**

The rates are only slightly higher in the hFSRT group (well within errors), and not enough to say "more frequently observed" especially if the authors conclude that they are similar. **Changed accordingly, thank you.**

"Of these patients, 56 patients ..." who are these patients ??? **Changed accordingly, thank you.**

"Although hFSRT was used for large lesions and in adverse locations. LPFS was not inferior to SRS." Should be a comma and not period between these. **Changed accordingly, thank you.**

"10 patients previously SRS and 1 patient after SRS" should be "10 patients prior to SRS and 1 patient after SRS" **Changed accordingly, thank you.**

There is still no hypothesis explicitly stated as suggested by reviewer 1. **Changed accordingly, thank you.**

A PTV of 3mm is quite large. This should be discussed in the limitations section. **Changed accordingly, thank you.**

What is "chronic crisis" **Long-term seizure is the correct term. Changed accordingly, thank you.**

The following does not make sense "Number of metastases is controversial in the series, age is not a criteria for SRS" **Changed accordingly, thank you.**

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3<sup>rd</sup> Editorial decision

23-May-2020

Ref.: Ms. No. JCTRes-D-20-00011R2

Brain metastases: Single dose radiosurgery versus hypofractionated stereotactic radiotherapy.  
A retrospective study.

Journal of Clinical and Translational Research

Dear author(s),

Thank you for resubmitting a revised version of your manuscript, which has been reviewed by the editor-in-chief. The editor's comments are appended below. Based on his comments, 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 Jun 22, 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:

The manuscript is replete with grammatical, spelling, and formatting errors. Please correct in line with the attached manuscript in which I have corrected the first page. Thank you.

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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4<sup>th</sup> Editorial decision

27-May-2020

Ref.: Ms. No. JCTRes-D-20-00011R3

Brain metastases: Single dose radiosurgery versus hypofractionated stereotactic radiotherapy: a retrospective study.

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 Jun 26, 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 #4: Dear authors,

The linguistic corrections you had made in revision 3 were still far from adequate. I have therefore corrected the manuscript myself. Please use the attached version when addressing my last two concerns:

1. Please indicate which statistical analysis was performed.
2. The overall survival reporting in the Results section lists 4 percentages for the SRS group. This should be 2 values (for 6 months and 1 year). Please correct.

Thank you,

Michal Heger  
Editor-in-chief

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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5<sup>th</sup> editorial decision

28-May-2020

Ref.: Ms. No. JCTRes-D-20-00011R4

Brain metastases: Single dose radiosurgery versus hypofractionated stereotactic radiotherapy: a retrospective study.

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