

Quality of life after stereotactic body radiation therapy versus video-assisted thoracic surgery in early stage non-small cell lung cancer. Is there enough data to make a recommendation?

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Quality of life after SBRT vs VATS in early stage NSCLC. Is there enough data to make a recommendation?

Journal of Clinical and Translational Research

Dear Dr. Navarro-Martin,

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. The authors should note that at this point the review add little to existing literature. As we do not want to regurgitate that which is already known and that which has been adequately summarized by others, the acceptance of your paper will be predicated on your successful introduction of novelty in the manuscript. This will require you to have complete awareness of what has been published on the subject matter as well as a thorough understanding of knowledge gaps and the newest trends in the clinical management of early stage NSCLC. Us giving you a chance to revise should be interpreted as confidence in your ability to improve the manuscript accordingly.

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 Jan 09, 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: 1. In your introduction you write about a high median age, what is it exactly? You mention a 'tumor-specific long survival' This is wrong!!! Lung cancer has a high mortality. What do you mean? What is the median OS in early stage NSCLC. Be more specific.

2. You describe papers about surgery alone, SBRT alone. (exception is the study of Wolff et al.) In the review of Pompili there is 1 study of Louie et al who compares SBRT and Surgery. Why is this study not included in your review?

3. It seems obvious, as a clinician, that SBRT has little impact on QoL compared to surgery in the first 6 to 12 months. What is the impact on QoL 1 year later? As the review of Pompili states : it seems the same for SBRT and Surgery. This is an interesting conclusion.

What is the added value of your review compared to the review of Pompili?

Authors' response

Reviewer A: Major Revision.

Comments:

Comment 1: Introduction. "In your introduction you write about a high median age, what is it exactly? You mention a 'tumor-specific long survival' This is wrong!!! Lung cancer has a high mortality. What do you mean? What is the median OS in early stage NSCLC. Be more specific".

Reply to comment 1:

Thank you for your comment.

#1a _A high median age. Line 14 page 2. We agree with the reviewer that we can be more specific regarding the high median age.

#1b_ Tumor-specific long survival Line 16 page 2. Regarding the tumor specific long survival, depends on which cancer or stage are comparing with. In the context of our article, we are talking about early stage lung cancer, and compared to locally advanced NSCLC or metastatic NSCLC, the survival is much longer (see <https://seer.cancer.gov/statfacts/html/lungb.html> OS at 5 years in early stage 59% vs 31.7% locally advanced or 5.8% in metastatic disease).

To be more specific, we have modified the text (blinded version) as follow: Page 2 line 14: *In the scenario of early stage NSCLC, at diagnosis 51.5% of patients are 67 years old or older (5). HRQOL measures are thought to be fundamental due to the survival in early stage, 59% at 5 years (6).*

Comment 2: General. “You describe papers about surgery alone, SBRT alone. (exception is the study of Wolff et al.) In the review of Pompili there is 1 study of Louie et al who compares SBRT and Surgery. Why is this study not included in your review?”

Reply 2:

Thank you for your question. The study of Louie et al. was included in table 2 page 17. Moreover, we speak about this paper on **page 11 line 15 to 24** in the **original pdf**. In this **new version on page 14 line 29. (blinded version)**

Comment 3: General.

It seems obvious, as a clinician, that SBRT has little impact on QoL compared to surgery in the first 6 to 12 months. What is the impact on QoL 1 year later? As the review of Pompilli states: it seems the same for SBRT and Surgery. This is an interesting conclusion. What is the added value of your review compared to the review of Pompili?

Reply 3:

What is the impact on QoL 1 year later? As the review of Pompilli states: it seems the same for SBRT and Surgery. This is an interesting conclusion.

Thank you for pointing out this issue. As, we will explain later, the number of patients who underwent VATS as a surgical procedure in the Pompilli review were 123, and in our review, there were 328. To our knowledge, there is only one paper published by Avery et al 2020 (table 1) with at least 1year follow up postVATS. This study reported that HRQL had not recovered at 12 months with a reduction in physical role, social function and persistent fatigue and dyspnoea. Instead, 8 papers have been published with at least 1year of follow up after lung SBRT: Mathieu et al 2015 found no significant changes in QoL over the time, Ubels et al 2015 found that QoL punctuation remained stable over the time, Wolff and Alberts 2019 measured no differences over the time, Lagerwaard et al 2012 saw a significant deterioration in PF scores, Van der Voort van Zyp et al. 2010 found no significant changes but with did measure an improvement in emotional functioning score, Louie et al (Netherlands), 2015 saw more global health events in the surgery arm, Widder et al. (Netherlands), 2011 found stability in global quality of life and physical functioning and Nestle et al 2020 study found out that for frail patients with poor baseline QoL/GHS scores (<50), a significant improvement could be seen after SBRT. In conclusion, we don't agree with the conclusion drawn in the Pompilli review. However, data comparing the impact on QoL at 1year between one study in VATS against 8 studies in SBRT has to be taken with caution. In this regard, we

express our concerns on **page 27 blinded version** in the conclusion section:

“..making a recommendation in terms of QoL impact between VATS and SBRT is not prudent” . Moreover, we identify the ECOG and cardiovascular comorbidities as factors to identify patients who benefit most from lung SBRT in terms of quality of life (page 27 line 19-20).

#What is the added value of your review compared to the review of Pompili?

Thank you for your comment. We agree with the reviewer about the value of the review published by Pompilli et al. However, in our review we try to be more specific about the impact of QLQ after treatment at different time points, and on the other hand, as a systematic review, we offer new evidence published after the publication of the Pompilli paper.

Regarding the specificity on the quality of life measures, we included in the criteria for inclusion of the studies: Quality of life had to be measured at least twice after treatment (box page 3). There is one exception mention, the papers published by Swartz et al. in 2017 and 2019, who only have one time point measure after treatment. The reason for including this study was that it was the study with the largest number of patients.

Regarding the value of our review compared to new papers recently published: In the last year some articles on the surgery field have been published, such as Avery et al (17) 2020 with 110 patients enrolled prospectively , Xu et al 2020 with 115 patients prospectively included, the paper of Schwartz et al (19) 2019 with 184 patients. On the other hand, SBRT articles recently published: Alberts et al. (Netherlands), 2019 and Wolff et al study with 261 patients prospectively included and Adebahr et al. 2018 and Nestle et al. 2020 with 97 patients prospectively included.

All these mentioned studies were not in the review by Pompilli and include data on 200 prospectively recruited patients that received either modality treatment. In summary, we believe that our manuscript can offer a better quality of knowledge on this topic.

In addition, the Pompilly review was not conceptually focused only in VATS, as it states on page 7056 in the Search strategy and study selection: “Studies with less than 20% video-assisted thoracoscopic surgical procedures were excluded”. This condition allowed for a high number of open surgeries (at least 80% of open surgeries) and therefore, affected the final results. From the 7 papers reported in the Pompilli review, only two (Handy et al 2010, and Rizk et al 2014) reported the number of VATS vs open surgery. The percentage of VATS was 25.5 % for the Handy manuscript and 56% for Rizk mannuscript. This means that the confirmed number of patients treated with VATS in the Pompilli review was 123 in comparison to 328 in our review.

To conclude, to our knowledge we add 3 important messages in our review that are not present in the Pompili review: First, the comparison of QoL measures is done between lung SBRT and VATS, excluding open surgery that would favor SBRT QoL outcomes. Second, the number of manuscripts with prospectively included patients is higher in our review. And third and last, our conclusions differ and we add the identification of a subset of patients that could benefit most of SBRT due to their comorbidities.

Ref.: Ms. No. JCTRes-D-20-00091R1
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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:

Reviewer #1: All questions are properly answered.