Peer Review File
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Reviewer A

In this article, authors compared the difference in treatment outcome depending on the CyberKnife SBRT tracking method.
Although there are many reports comparing dose distributions by the CyberKnife SBRT tracking method, there are few that compare treatment outcomes, so this article is highly useful. The manuscript is well structured and the English is easy to read. However, there are some concerns in this paper.

Comment 1:
The description in the introduction that X sight lung was omitted from the analysis should be described in the method.
Reply 1:
We thank the reviewer for this comment. Change have been made accordingly.
Changes in the text:
We added a new paragraph explaining why it was omitted from the analysis.
See Page 9, Line 179-185)

Comment 2:
With a median follow-up of 31.6 months, it is not appropriate to assess the 5-year survival curve.
Reply 2:
We agree with this point. The 2 years overall survival was the main point here and was already report in the article, 5-year survival curve was reported as it's the most used in published studies even if it's clearly is underpowered.
Changes in the text:
See those data Page 14; Line 281-282.

Comment 3:
LC is statistically correct with competing risks of death and distant recurrence.
However, it would be better to add dose fractionation as a factor for LC in subgroup analyses.
Many publications have reported the association between BED and LC in both primary lung cancer and metastatic lung tumor. (https://doi.org/10.1016/j.ijrobp.2016.01.065, https://doi.org/10.1016/j.ijrobp.2015.04.004)
Reply 3: We thank the reviewer for this comment. The aim of this study was to assess the difference in LC according to fiducial implantation; we agree this would be a great way to improve our next studies.
Changes in the text:

We added this comment on our discussion.
See Page 19; Line 395-400

Comment 4:
Is there a rationale for Lung dose cutoffs in Table 2?
Reply 4: We chose to report the usual dose constraint of our institution, those are mostly based on RTOG0618(Timmerman et al. 2018), RECORAD (Noël et al. 2016) and ROSEL trial (Louie et al. 2015) dose constraints.
Changes in the text:
None.

Comment 5:
Wouldn't it be better to write down the median and range for comparison? (Table 2)
Reply 5: We thank the reviewer for this comment. Change have been made accordingly.
Changes in the text:
We added the median data and range in Table 2.

Comment 6:
Marker less irradiation is certainly a good noninvasive treatment, but it cannot be performed in
all cases.Intravascular marker placement is highly safe (https://doi.org/10.1259/bjr.20160560),
and incases where X sight Spine cannot be used, markers should be placed intravascularly.
Reply 6:
We thank the reviewer for this comment.
Changes in the text:
We added this point in the discussion and the reference in the text.
See Page 19, Line 379-381

Reviewer B

This is a well written manuscript addressing an important question of whether implanting gold seeds/ coils are critical for treatment of patients with stage I lung cancer or lung metastases. The larger cohort of patients with reasonable follow-up ensures that these estimates provided are reliable. The statistics used is sound and there are no major or minor language concerns.

Comment 1: I would like to sought only 1 clarification from the authors on line 183 page 9 - For the SBRT typically most patients would complete their planned therapy within a week. How was weekly review done in this cohort.
Reply 1:
Patients were assessed during a consultation once a week during treatment and after the final fraction, in our institution, not all treatments starts on a Monday, this results in

patients getting treated sometimes on 2 consecutive weeks even when treated with 3 fractions since we usually respect a 24-48h window between two fraction.
All patients are assessed for toxicities during the treatment by their radiation oncologist on the last day of treatment.

Changes in the text:

None

Reviewer C

Overall, this seemed to be a well thought out and well written paper. It also serves to help improve the knowledge base of outcomes between these techniques.
Strengths: Good number of patients included, good length of follow-up for lung cancer & metastatic patients (nearly 3 years), and a detailed/thorough statistical analysis and comparison.

Comment 1:

- Limitations: Retrospective nature (with its inherent biases), amount of missing data, many tumor types were not histologically confirmed. Addition major limitations included:
- There were significant differences between the tumor characteristics between the 2 groups. This is important as local control and survival outcomes could vary based on tumor histology or based on whether the patient had primary vs. metastatic disease being treated.
- Additionally, the dose/fractionation differed between the groups. Dose/fraction differences could affect locoregional control and survival.

Reply 1:

We thank the reviewer for this comment.

Changes in the text:

Some precisions about those limits have been added to the manuscript (See page 18, Line 370-372) and we reported the fact that a minimal BED of 100Gy was respected for all treatment. (See page 19, Line 395-400)

Comment 2:

Based on the limitations above, I would be careful with the strength of the conclusion. While it does seem that fiducial-less CK results in similar outcomes to fiducial-based CK, this study does not prove that. However, it does provide a decent suggestion to that point.

Reply 2:

We thank the reviewer for this comment. Manuscript will be changed accordingly.

Changes in the text:

We added some precision about our study limits, See Page 19, Line 395-400
We corrected our conclusion to be more careful about the limitation of this study, See Page 20, Line 404-407

Reviewer D

This article is a retrospective review of the outcomes at a single center of lung SBRT for primary or oligometastatic cancer in the lungs using robotic radiosurgery, comparing the outcomes of fiducial-based respiratory motion management to planning with an ITV on 4D-CT using spine setup. It includes a decent number of patients for a single center study. The authors conclude that local control and survival outcomes are not significantly different between the 2 different respiratory motion management strategies on CyberKnife. I believe that this article would be of sufficient interest with the readers of your journal, and would contribute to the body of literature supporting fiducialless SBRT. However, I would recommend the following changes to be implemented before publication of this article:

Comment 1: Abstract line 44: Since there are studies that on the near accelerator based SBRT without fiducials, and it should be clarified that the paucity of data regarding outcomes refer specifically to robotic SBRT.

Reply 1:

We thank the reviewer for this comment. Manuscript will be changed accordingly.

Changes in the text:

We added precision on the type of SBRT used. See Page 3, Line 44 and Page 6, Line 96-97.

Comment 2: Introduction 114: A brief explanation as to why Xsight motion management was not widely used in your center may be useful to give context to your audience, since this is advertised by the company as a viable alternative to spine tracking with an ITV.

Reply 2:

Only a few patients have been treated with Xsight® Lung in our center during this period mostly because the majority of our data comes from the early uses of lung SBRT in our institution, Xsight® lung was not as effective as it is now and resulted in a lot of tumor detection failure in the early settings, we chose to use preferentially the other methods available as it also reduced the treatment volumes and the workflow on our simulation scanner.

Changes in the text:

We added a new paragraph explaining why it was omitted from the analysis.
See Page 9, Line 180-185

Comment 3: Introduction 119: An explanation needs to be given in the introduction as to why the analysis separates the outcomes between those tracked with gold seeds versus coils versus the spine. Most readers would assume that the seeds and the coils would be sufficiently similar regarding the technical aspects of tracking that this should be analyzed together as a single group and then compared to those treated with spine tracking, rather than a three-way analysis, the rationale behind this structure of analysis needs to be clarified early on in the paper.

Reply 3:
We made the choice to separate those 2 techniques for homogeneity reasons, in our experience, coils tend to be a little less accurately implemented and further from the lesions than the gold seeds, it also seems to result in more tracking failure, we feared that pooling the two techniques would weaken our data.
Changes in the text:
We added some context to explain why those two types of markers were separated in the analysis.
See Page 7, Line 120-123.

Comment 4: Materials and methods 146: it would be useful for readers not as familiar with the CyberKnife to describe the tracking vest with infrared emitters used in the system.
Reply 4:
We thank the reviewer for this comment. Manuscript will be changed accordingly.
Changes in the text:
We added some precisions about the tracking method.
See Page 8, Line 149-156.

Comment 5: Materials and methods 147: It should be clarified that the recommendation is for 4-6 fiducials to be placed, not necessarily tracked during treatment.
Reply 5:
We thank the reviewer for this comment. Manuscript will be changed accordingly.
Changes in the text:
We added some context on the real-life use of fiducials and the possibility to track only the most relevant fiducials.
See Page8, Line 157-158.

Comment 6: Materials and methods 151: The statement here that the rate of pneumothorax that is clinically significant is low contradicts the data later presented in the paper. Most institutions would consider a mandatory overnight hospitalization to be by itself a clinically significant issue with fiducial placement. Literature needs to be cited to support the statement that the rate is "low ". Also needs to be a discussion here with relevant literature cited regarding the lower rate of pneumothorax noted in fiducials placed using navigational bronchoscopy.
Reply 6:
We thank the reviewer for this comment. This article will be included to support our statement: doi:10.1186/s13014-019-1373-2 and the subgroup analysis of the NAVIGATE study will be included to document the lower pneumothorax rate with the navigational bronchoscopy: doi : 10.1177/1753466619841234.
Changes in the text:
We cited an article about the incidence of pneumothorax in fiducials implantation procedure for SBRT.

See Page 8, Line 161.
We added a discussion about the safety of navigational bronchoscopy and the possibility to perform biopsy if needed when the technique is available and cited the NAVIGATE study.
See Page 9, Line 168-171.

Comment 7: Materials and methods 153: The description of "unfit patients "is somewhat vague, since there is discussion earlier in the behavior regarding those unfit for surgery. It should be clarified that these are patients who are unfit for CT-guided biopsy and fiducial placement.
Reply 7:
We thank the reviewer for this comment. Manuscript will be changed accordingly.
Changes in the text:
We added some date on the patient qualified as “unfit” and for which procedures.
See Page 8, Line 163-165.

Comment 8: Materials and methods 153: Intravascular coil placement is not be used very often at other institutions, a reference describing this approach would be helpful for most readers.
Reply 8: We thank the reviewer for this comment. Usually, endovascular embolization coils are placed via the femoral vein into subsegmental pulmonary artery branches near the tumor under biplane angiography guidance Manuscript will be changed accordingly.
+ citer un article
Changes in the text:
We added an article and some explanation to clarify the coils placement procedure.
See Page 9, Line 166-168.

Comment 9: Materials and methods 167: Details regarding the method of 4DCT acquisition including the model of the scanner as well as the model and manufacturer of the system generating the 4DCT is needed
Reply 9:
We thank the reviewer for this comment. We added the requested data.
Changes in the text:
See Page 9-10, Line 191-194

Comment 10: Materials and methods 169: It should be clarified whether the manufacturer recommendation of that free-breathing CT being and end-expiratory CT was followed at your institution
Reply 10:
In our institution to limit motion blur during the scan, we perform a free breathing CT and ask the patient to block his breathing mid cycle, without forced inspiration or expiration to avoid motion blur, manuscript will be changed to clarify this.
Changes in the text:
We added some text to clarify clinical practice in our institution

See Page 9, Line 192-193.

Comment 11: Materials and methods 169: The second half of that sentence appears to describe the clinical rationale of including patients without a biopsy, if that is the case this belongs in the earlier section regarding "Patients". However, if the intent of this part of the sentence is to clarify that a fused PET scan is used for GTV delineation and treatment planning, then that should be stated.
Reply 11:
We thank the reviewer for this comment. Manuscript will be changed accordingly.
Changes in the text:
As the FDG avidity question was already described in the Patients section (Page 7, Line 137-138), we removed it from this paragraph.
See Page 9, Line 189-190

Comment 12: - Materials and methods 170: Further clarification is needed on how the ITV is generated for patients treated using spine tracking. Was the ITV generated on a MIP? Was a contoured in the lung windows on all available phases of the 4DCT if the latter is the case, how many phases were used? Also, regarding the next sentence, some more details regarding the expansions used in patients treated with spine tracking is needed since this is a central subject of the paper. Were tumors that were farther away from the spine treated using a larger margin of 5 mm? How far away was considered too far? was the tumor excursion on the 4-dimensional CT use as a factor in determining ITV to PTV margins? Were these margins trimmed down to a smaller value close to critical structures such as the chest wall or proximal bronchial tree?
Reply 12: GTV was delineated by the physicians on the pulmonary window, on one CT in case of Synchrony ®, for Xsight® spine, an ITV was obtained after delineating the GTV on the 0%, 30%, 50% and 80% phase of the 4D-scan, merged together as an ITV and then checked on the 4D cinema mode. We cited on “Treatment method”(Page 9, line 168-169) That Xsight® spine is used for tumor located less than 50mm from the middle of the posterior wall of the vertebra. Usually, margins were not trimmed down to a closer value close to critical structures, however PTV coverage was reduced if needed to respect dose constraints on those critical structures.
Changes in the text:
We added some clarifications in the text to explain deeper how ITV and PTV were generated.
Page 10, Line 200-207

Comment 13: Statistical methods 204: Regarding confirmation on CT PET, was this based on radiology interpretation or based on PERCIST (PET-specific RECIST) criteria?
Reply 13: As this is a retrospective study, PERCIST criteria were used by the nuclearist physician in our center however there was no centralized review using those criteria for the PET CT performed outside of our institution.
Changes in the text:
None.

Comment 14: Results 222: "ware" should be spelled "were ". In the next sentence, it should be "months ".
Reply 14:
We thank the reviewer for this comment. Manuscript will be changed accordingly.
Changes in the text:
The mistake was corrected.
See Page 12, Line 255

Comment 15: Results 251: A) is missing at the end
Reply 15:
We thank the reviewer for this comment. Manuscript will be changed accordingly.
Changes in the text:
Correction has been made
See Page 13, Line 281

Comment 16: Toxicities: Most SBRT publications report the rate of rib fracture and chest wall pain, this needs to be included in your paper, particularly since many lesions that are closer to the spine will also be closer to the chest wall and ribs.
Reply 16:
Being a retrospective study, we didn't found any rib fracture or chest wall pain in our patient's file despite there were most likely some which weren't reported.
Changes in the text:
We clarified in the discussion the fact that rib fractures and chest pain were not found in patients files some have probably occurred but were reported neither by the patient or the physician.
See Page 17, Line 333-335

Comment 17: Discussion 279: To be emphasized that spine tracking is safe and effective in appropriately selected patients (tumors 5 cm from the spine)
Reply 17:
We thank the reviewer for this comment. Manuscript will be changed accordingly.
Changes in the text:
We added the precision that patient must be appropriately selected.
See Page 16, Line 13

Comment 18: Discussion 280: If the authors wish to cite their own work, in particular reference 27, it should be made clear whether the patients described in this study are included in that prior publication.
Reply 18:
We thank the reviewer for this comment. Manuscript will be changed accordingly.
Changes in the text:
We precise in the discussion the fact that this study includes patients from our previous published study.
See Page 19, Line 388-389

Comment 19: Discussion 304: There needs to be a discussion with the relevant literature cited regarding the fact that navigational bronchoscopy is a safer approach regarding the rate of pneumothorax compared to CT based biopsy and fiducial placement.

Reply 19:

We'll include that discussion with the result of subgroup analysis of the NAVIGATE study (doi : 10.1177/1753466619841234.)

Changes in the text:

Discussion was added about this procedure performance.

See Page 17, Line 342-344

Comment 20: Discussion 329: A discussion regarding any potential concerns regarding the lower BED in the 4 fractions regimen is a concern, and this would also be a good place to have a discussion regarding any potential differences in the risk of chest wall pain or rib fracture given the PTV with spine tracking

Reply 20:

We thank the reviewer for this comment, the four-fraction regimen conserve a ≥100Gy BED ratio (113Gy) and is safe to use.

Changes in the text:

We added some data regarding the regimens BED that need to be respected and cited an article to justify it.

See Page 18, Line 370-372

Comment 21: Table 1: Since there are significant differences between the cohorts regarding the lesion type, primary, and location, this needs to be described in the results, and also addressed the discussion. Is there a particular reason for example why more spine tracking patients had tumors in the right upper lobe? Is there any concern regarding any bias in the analysis given the fact that the coil cohort has a particularly high percentage of patients with unknown histology? Why are the patients treated with spine tracking, which is also a noninvasive approach, more likely to have known histology compared to the coil cohort?

Reply 21:

There are no known reasons why spine tracking patients had more tumors in the right upper lobe, however since the pulmonary diameter in the upper lobes is smaller, the treated lesions are maybe more likely to be close to the spine and patients in this setup accessible for spine tracking. The coil cohort has a particularly high percentage of patients with unknown histology because those were more likely unfit patient who couldn't get a transthoracic biopsy and therefore couldn't get coils implantation who share the same contraindication. (See page 18, Line 356-358)

Patients treated with spine tracking are probably more likely to have known histology because even if the patient is fit for gold seeds implantation, if spine tracking is reasonably feasible, the trend in our practice was to favorize this approach.

Changes in the text:

We added some explanation in the discussion about these differences.

See Page 18, Line 354-356