

Peer Review File

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Reviewer A Comments:

I think the paper is appropriate for the journal's readers and fit the scope of the journal. The core theme of the article is relevant to the field. There are currently some previous reviews on the subject (e.g. DOI: 10.3390/life13020254). The appropriate structure of the paper has been used. The abstract is reflective and gives a complete idea about the whole article.

1. The introduction is clear, effective and well organized. Please consider discussing and citing the recent work by Altorki et al (DOI: 10.1056/NEJMoa2212083) while approaching gold standard therapies for NSCLC (line 71 to 94).

Reply: Thank you very much for the insightful suggestion.

Changes in text: This is inserted in Lines 104-108. "This is further supported by a recent randomized controlled trial by Altorki et al, reporting similar 5-year disease-free survival (63.6% vs 64.1%) and 5-year overall survival (80.3% vs 78.9%) between groups treated with sublobar and lobar resection, for stage I lung cancers less than 2cm in size." The reference has been inserted in reference section.

2. Transbronchial microwave ablation section:

1) Line 104: consider citing and commenting on the paper by Steinfort et al. (DOI: 10.1159/000529167).

Reply: Thank you for your suggestion.

Changes in text: The following has been inserted in Lines 129-132 : "More recently, a first-in-human dose escalation study involving 8 patients using an external cooled bronchoscopic RFA catheter revealed adequate ablation zone coverage in all cases, with more uniform necrosis observed at higher energy levels."

2) Line 197-212: consider adding and commenting on General Electric OEC 3D and Ziehm Vision RFD 3D technology.

Reply: Thank you for providing the latest mobile C-arm machine models. Unfortunately these are relatively new and there are minimal papers published with regard to lung reconstruction, and we have not had the opportunity to try these machines, thus it is difficult for us to provide any specific insights.

Changes to text: The two machines has been added as examples of mobile C-arm devices in Lines 234-235.

3. Robotic bronchoscopy section:

Line 240: add and comment on the Galaxy system and the MATCH study (DOI: 10.1097/LBR.0000000000000923)

Reply: Thank you for reminding us on the latest player in the field.

Changes to text: The following has been added to Lines 293-298. “There are other new players joining the market. The Galaxy System™ by Noah Medical(45) provides a single-use bronchoscope with 4.0mm outer diameter and 2.1mm working channel, and uses proprietary digital tomosynthesis (TiLT+ Technology™) via augmented fluoroscopy to confirm tool-in-lesion(46). Their recent animal MATCH study had up to 95% tool-in-lesion rate. Vision during biopsy can be maintained(47)”.

4. Other sections are presented in an optimal manner. The conclusion is valid and mainly justified. Consider citing the paper by Fantin et al. (DOI: 10.3390/life13020254)

Reply: Thank you for your kind comments. The paper you suggested provides a very good overview of latest local ablation technologies.

Changes to text: The paper has been cited at Line 120.

5. The references are mainly updated. The supplementary material is appropriate and well represents the workflow of the authors. There is no evidence of ethical breaches. Minor English language revision is needed.

Reply: Thank you for your kind comments. The manuscript has been subjected to basic grammar check prior to submission.

Reviewer B Comments:

This is a well written, elaborate yet concise and uptodate review of the current field of minimal invasive transbronchial treatment options. This is a rapidly evolving field, and I concur with the author’s conclusion that this is field of importance in changing field of lung cancer treatment. It is evident that this team of authors have personal experience with a number of these treatments.

I have a number of remarks and comments that need revision:

1. In general, for each and every one of these treatments, 3D-imaging is an essential part, and paramount for the correct positioning of tools used for delivering energy or other forms of treatment. Given the importance of that factor, I would therefore strongly suggest to address this point explicitly, and also add that for those colleagues who want to start in this field, investing in proper equipment is important and that mobile systems are to be used with caution, especially in subsolid lesions, and do not support augmented fluoroscopy. So please rephrase the paragraph starting in line 197.

Reply: We certainly agree that proper and high resolution equipment is crucial to the success of ablation. We have expressed the limitation of mobile C-arm machine in visualizing sub-centimeter pure ground glass lesions in Lines 239-241.

Changes in text: We have inserted the following text in Lines 246-250. “We would like to stress the importance of high resolution 3D imaging for determining the ablation success, and mobile systems currently available suffer from lower resolution than floor-mounted systems. While augmented fluoroscopy can help operators reach the lesion, confirmation of catheter location by 3D imaging is still necessary before ablation.”

2. To further emphasize this subject on the best possible imaging, please clarify in relation to the remark relating to the navablate trial on line 142 “the average ablative margin was 9.9mm”: how was this assessed? Using the CBCT directly following treatment or on day 3 or day 30? This study has not been published in full, so it is impossible for interested readers to interpret this remark.

Reply: Thank you for your interest and suggestions. The ablative margin is measured between the edge of ablation zone and the nodule periphery, on day 0 cone beam CT.

Changes to text: The above is added to Line 168.

3. In the section on EMN, the authors are very laudative on the accuracy of this technology. I would like to advice to significantly rephrase this entire section. EMN valid and very useful tool, but from a technological perspective the technique has an inherent error-margin that is often larger than the target nodule. Further, as a means of navigation, it largely depends on the quality of the pre-procedural CT and the algorithm to extract the airway anatomy from that, airways that have a parallel route and are therefore also subject to the inherent error-margins. Using EMI is very intuitive and easy accessible, but users should be aware that the ‘green ball’ is not the absolute truth and is influenced by a number of technical and environmental issues like for instance changing the position of a C-arm or CBCT device or even wearing mobile phones near the electromagnetic field.

Reply: Thank you for pointing out the limitations of EMN and we totally agree that the accuracy of EMN is highly dependent on the quality of input (pre-procedural CT), and has inherent errors.

Changes to text: The following has been added to lines 187-193. “Despite the success of reported ENB ablation series, ENB itself carries inherent error margins that can at times be larger than the target nodule. The accuracy of ENB can be affected by nearby interference, for example the position of CBCT or certain electronic devices close to the field. Therefore, in practice another modality of imaging, either CBCT or EBUS, should be used in adjunct with ENB to provide double confirmation of catheter location before ablating nodule.”

4. Line 275 cryoablation: CO2 is used to cool down probes for cryo-treatment. Argon is used for elektrocautery.

Reply: Thank you for your correction.

Changes to text: Please see Line 319.

5. Line 343: Please add reference(s) for these observations.

Reply: Thank you for your kind reminder.

Changes to text: Reference has been added to Line 385.