

## Peer Review File

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### Reviewer Comments

#### Reviewer A

**Comment 1:** I would like to recommend a small change to the title of the work to define the target of subjects who can benefit from these procedures

**Reply 1:** We have changed the title to ‘Endoscopic Treatment for Lung Cancer in Medically Inoperable Patients’ to more accurately reflect that the majority of the treatment modalities in this manuscript are performed on medically inoperable patients.

#### Reviewer B

**Comment 1:** In line 61, a reference from 1999 is used to state that 25% of patients forego surgical options, but since then, many things have changed. Does the 25% still hold? At least in our country, we think it is more than 30%.

**Reply 1:** We have examined prior publications. Following the publication in 1999 from the New England Journal, several studies have provided data on surgical resection rates for lung cancer: According to a paper in Thorax in 2006, these rates varied from 46% to 83% within the European population. A 2014 Australian study reported a range of 38-43%, and a 2020 paper concentrating on New Zealand's population indicated a rate of 47%. Consequently, I have revised the pertinent section of the manuscript as follows.

**Comment 2:** In line 74, stabilization of the probe through cumulative resistance during transthoracic methods is stated, but would the authors not say that the probe is less stabilized compared to bronchoscopic techniques by such a technique as it is performed under continuous breathing?

**Reply 2:** Nodules situated at the lung apex exhibit minimal movement during respiration, while those at the lung base move significantly as shown by Alexander Chen et al. (CHEST 2015;147:1275-1281). Even in the case of nodules with significant movement during continuous breathing, we do not consider the transbronchial approach advantageous since the bronchoscope remains fixed during ablation. Instead, as we described in the manuscript, we believe that the transthoracic approach is more favorable from a stability perspective due to a higher cumulative resistance with muscles and skin. However, there is no conclusive evidence regarding our opinion. We have rephrased the text as follows.

**Comment 3:** In line 95, we would recommend that the authors state that ‘a review of published literature in 2013 reports that...’

**Reply 3:** We have changed it as suggested by the reviewer.

**Comment 4:** In line 99, one fatal incident is mentioned, but there are two cases named afterward – intraprocedural respiratory arrest and hemothorax – referenced by [7] and [8]. The wording is correct, as you state only one patient died from intraprocedural

respiratory arrest, but since this comes after the overall pneumothorax rate in MWA, it can be confusing. We would advise to split the sentence in two.

**Reply 4:** We have changed the sentence as follows:

Original: “In comparison; in a large retrospective single-center study with 108 transthoracic MWA cases, pneumothorax occurred in 32%, and 19% of all cases required chest tube insertion, including one fatal incident complicated with intraprocedural respiratory arrest due to an expanding pneumothorax.”

Revised: “In comparison; in a large retrospective single-center study with 108 transthoracic MWA cases, pneumothorax occurred in 32%, and chest tube insertions were required in 19% of the cases. This study reported one fatal incident complicated with intraprocedural respiratory arrest due to an expanding pneumothorax.”

**Comment 5:** In line 109, fields are not plural, so they should be fields.

**Reply 5:** Thank you for pointing out the typo. We have corrected it.

**Comment 6:** In all lines where authors are mentioned, like in line 128, 137, and so on, the year in which the article was published could be added to put them into the correct perspective regarding technology timelines.

**Reply 6:** We have included the publication year of the article or the year of the study throughout the manuscript.

**Comment 7:** In line 244, oppose should be in the past tense, so opposed.

**Reply 7:** Thank you for pointing out the typo. We have corrected it.

**Comment 8:** In this paragraph, the order in which information is stated is different from the first two paragraphs. This is not necessarily bothering but could be improved upon.

**Reply 8:** The flow in this paragraph differs from that of RFA and MWA because we combined the summaries of RFA and MWA for a comparative analysis, given their similar treatment concepts. Nevertheless, to improve the flow as suggested by the reviewer, we have made some changes to the paragraph. We believe the flow has become clearer (The flow of this paragraph: ‘What is cryoablation’ --> ‘Efficacy and complications of transthoracic cryoablation’ --> ‘recent attempt for transbronchial cryoablation to mitigate transthoracic complications’).

**Comment 9:** In line 267-268, it might be interesting to add that bronchoscopic cryoablation might be technically more difficult, from a 'getting there and performing perspective'. A 2.2. mm cryoprobe is technically feasible, but the 'volume' over which it will ablate in lung tissue is significantly lower with current designs than that of percutaneous or transthoracic methods. furthermore, due to the high rigidity of these probes, they will likely dislocate the device with which access to the lesion was obtained (personal experience).

**Reply 9:** We agree with the need to improve the flexibility of probes. We have added the following sentences to demonstrate the potential inferiority of transthoracic cryoablation and the necessity for future devices with greater flexibility.

**Comment 10:** Also here, the order of the information in the paragraph differs from other paragraphs, which could be improved upon we believe. It would subsequently be best if clinical studies and references on transbronchial PDT in humans were stated based on the time of publishing to put it in perspective.

**Reply 10:** We have added the publication year of each article. We think that the order of the information presented may not disrupt the flow for readers. PDT differs from other modalities regarding the initial targeted location (PDT was initially applied for central early-stage lung cancer). In this paragraph, the flow is as follows: ‘How does PDT work?’, ‘PDT for centrally located early-stage lung cancer’, ‘PDT has been attempted recently for peripheral early-stage lung cancer’, and finally ‘Complications of PDT’. To address another comment from the reviewer, the last paragraph related to the enhancement of immune response has been moved to another section.

**Comment 11:** In line 346, can a section be added on how sensitive this therapy is for lesions? I.e. will lesions only with a slight contact with the bronchus be treated entirely as the laser light penetrates >1 cm in tissue with sufficient energy, or does it mean a subset of patients can be targeted that have a concentric sign? Would be an interesting addition, as we're all looking for the therapeutic effect combined with the workability of performing the therapy.

**Reply 11:** We have created a new paragraph to discuss the penetration depth of PDT, starting at line 330.

**Comment 12:** In line 351 and/or 355, for the more experienced reader, it would be good to add which radionuclide (Iridium-192) is used for these seeds in the mentioned research.

**Reply 12:** We have added information of the radioactive source (Iridium-192) in each previous study.

**Comment 13:** Could the authors give a reason as to why most studies on this subject are retrospectively performed?

**Reply 13:** We do not have a clear answer for this question. One reason might be the low number of patients receiving brachytherapy. As Aumont-le Guilcher et al. and Soror et al. summarized, even in high-volume centers, they have only 6-17 patients per year. However, this is not a definitive reason for not performing a prospective study. Since the reason is still no better than a conjecture, we won't include this discussion in the manuscript.

**Comment 14:** In line 368, we believe roentgenographically could be replaced by the more commonly used word radiographically.

**Reply 14:** We have corrected it accordingly.

**Comment 15:** In line 373, endobronchial can be omitted, as lung cancer cannot necessarily be classified as endobronchial. If peripheral is meant, then this word should

be used since it is different but we would propose to exclude the specification.

**Reply 15:** We agree with this. We have changed the sentence accordingly.

**Comment 16:** In line 395, can the numbers on radiation complications be compared to SABR for example? We believe that local treatment would theoretically still produce a lower complication rate based on a lower radiation dose to healthy tissue.

**Reply 16:** We have added a summary of previous complication data about external beam radiotherapy for central airway obstruction, starting at line 393.

**Comment 17:** Pulsed electric field (PEF)

The sentence in line 403-405 is incorrectly worded.

**Reply 17:** We have changed the sentence as follows.

**Comment 18:** In line 425, 'the' absopal effect should be 'an' absopal effect.

**Reply 18:** We have corrected it accordingly.

**Comment 19:** In line 426, in mouse model should be in mouse models or in a mouse model, depending on the number of mice used.

**Reply 19:** We have corrected it.

**Comment 20:** While indeed PEF seems to focus on the immunogenic effect as a 'sales point' for their technology, it might be interesting to put this into perspective with an additional comment. Cryoablation has indeed also for long been associated with absopal and immunogenic effects, but so did MWA and so on. It seems all of them can potentially induce an immune effect, but we don't seem able to predict when it will happen and in which patient (and we know it will not happen in all, indeed). I.e. Radiotherapy in combination with immunotherapy is also a significant field of interest.

**Reply 20:** We agree with the reviewer's comment here. To discuss the immunogenic effect of each modality, we have created a new section on page 23 and summarized the evidence.

**Comment 21:** In line 449, what do the authors mean by 'a longer time from the anesthesia induction', is that the procedure to sedate the patient itself or the navigation bronchoscopy procedure? Please clarify.

**Reply 21:** We have changed the sentence to make it clearer.

**Comment 22:** In line 455, we think confirmation should be confirmation.

**Reply 22:** We did not get what the reviewer mentioned here. We assume the word of 'confirmation' should be emphasized.

**Comment 23:** In line 456, would the authors not say that RP-EBUS would allow for more localized positioning of the probe, as nearby vessels can be more clearly visualized compared to fluoroscopy and sometimes even (low-dose) CBCT?

**Reply 23:** We do not believe that RP-EBUS is superior to CBCT in terms of

confirmation. As explained in the preceding text, one reason is that when atelectasis occurs, it becomes challenging to determine the precise location of the target using only RP-EBUS. Another reason is that, with RP-EBUS, even if it confirms that the probe has reached the inside or adjacent to the tumor, the three-dimensional understanding of whether it is positioned at the center of the tumor is inferior to CBCT. When considering the curative treatment of lung tumors, it is necessary to determine the ablation area with appropriate margins. Therefore, we believe that CBCT, which allows three-dimensional positional understanding, is superior as a confirmation and localization modality.

**Comment 24:** In line 483-485, the number of patients in both groups should be added by (n=...) to put the 1-2 and 9 lesions that were obscured into perspective.

**Reply 24:** We have added the number of patients in each group in the study.

**Comment 25:** In line 500, we think that as experienced users of non-robotic; the friction of a bronchoscope + catheter-based approach is seemingly as stable as the robotic approach, or even more so as some of the robotic platforms (which we also have experience with) tend to move around in more central airways, whereas the catheter-based approach is less affected. The active steerability for angulation into the lesion, however, is indeed a 'plus' factor.

**Reply 25:** We intended to highlight the advantage of robotic bronchoscopy, wherein the position and angle of the bronchoscope's tip remain unchanged unless adjusted by the procedure. However, as the reviewer pointed out, experienced bronchoscopists may achieve similar performance using non-robotic tools, especially in terms of stability when employing fixation tools during ablation. There have been no published studies demonstrating the superior stability of robotic bronchoscopes compared to conventional bronchoscopes. Therefore, we have decided to remove the sentence discussing stabilization here.

**Comment 26:** In line 511, we think 'sections of' ... should be 'sections on'.

**Reply 26:** We have changed the words in line 570 as follows:

Original: "As described in the sections of cryotherapy, PDT, and PEF,"

Revised: "As described previously,"

**Comment 27:** In line 514, as stated earlier, it would be interesting to lengthen this part slightly and provide some context. It seems all of these modalities see abscopal effects in some patients, etc. Only limiting it to cryo/pdt/pef would perhaps not do full justice. This should also be included in the conclusion.

**Reply 27:** Please refer to the response to Comment 20. We have added the section discussing the abscopal effect and synergistic immune effects. Additionally, sentences have been added to illustrate this in the conclusion.

**Comment 28:** Could the authors give a reason for the fact that most patients in the mentioned trials were presented with two lung nodules that were treated? It seems as though this could be important to determine the (future) place of this technique in our

current work-up.

**Reply 28:** We believe that insights from the reviewer here are important. In considering the future positioning of transbronchial treatment, it is essential to discuss which cases have appropriate indications. As the reviewer pointed out, many previous studies cited in this manuscript had patients with multiple lung nodules treated with transbronchial treatment. Therefore, we have decided to create a new paragraph in the "Future direction of endoscopic treatment" section to discuss this aspect further.

### **Reviewer C**

**Comment 1:** If the number of characters in the text is permissible, I think it would be interesting to add if there is anything known about the background lung conditions that are permissible when performing these treatments. For example, whether these treatments are currently acceptable for patients with interstitial pneumonia or lung cancer after radiation therapy.

**Reply 1:** We believe that insights from the reviewer here are crucial. In considering the future positioning of transbronchial treatment, it is important to discuss which cases have appropriate indications. We have added a new paragraph in the "Future direction of endoscopic treatment" section to discuss the safety of transbronchial treatment in patients with underlying lung disease further.