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Reviewer A

The authors present a prospective single-arm trial of percutaneous microwave ablation with data on 6 patients and 7 tumors, predominantly primary lung cancer.

Major comment: The information presented suggests that the effort invested into the accurate and thorough presentation of the data generated by this already very small trial was minimized. Especially with such a small cohort, careful and detailed analysis is the only way to possibly extract meaningful information.

Based on the information presented in the ABSTRACT, the conclusion is unsubstantiated: No secondary lung neoplasms or pulmonary function testing is included in the Methods or Results.

INTRODUCTION

"MWA is a recently emerging alternative for the treatment of cancer within the lung." -> No references are provided even though MWA has been studied for almost 15 years, and the authors provide a summary of relevant studies in a table. Consider providing additional context for the reader.

Reply. Thank you, we have modified the text to reflect that this statement is meant to be comparative to SBRT, RFA or cryoablation.

Changes to text: Percutaneous microwave ablation (MWA) is a recently emerging alternative option for targeted treatment of cancer within the lung compared to the abundance of SBRT, RFA or cryoablation[6] .

p4l34, p6l12. No information about pre-procedural PFTs in METHODS, and at what time interval those were obtained in relation to the date of the ablation

Reply: Thank you for noting this omission. This has been amended

Changes to text: Additionally, all patients obtained pulmonary function testing within 3 months prior to ablation and subsequently within 3 months after ablation to assess changes in functional status.

p54. Pathologic response implies that the ablated tumors were resected. Is this correct?

Reply p54. You are correct, tumors were not corrected, and this has instead been changed to “radiographic response”.

Changes in the text: Secondary endpoints related to recurrence-free survival and overall radiographic response at 6 months and one year

p5l27, p6l3. Grade 3 CTCAE is a severe event, so the statement about the absence of severe events is incorrect
Reply: Thank you, the manuscript has been amended accordingly.
Changes in the text: Thirteen adverse events were reported (1 Grade 3, 3 Grade 2, and 9 Grade 1 events) with no Grade 4 or 5 events.

p6l20. Who and how the response assessment was performed needs to be explained in the METHODS. How many readers? Blinded? Experience level with lung ablation assessment? This assessment goes beyond everyday clinical radiology practice, especially on PET-MRI.
Reply: Thank you, the manuscript has been amended accordingly.
Changes in the text: CT related assessments including RECIST criteria were calculated by a board certified non-blinded radiologist proficient in ablation and interpretation of lung CTs. PET-MRI was independently evaluated by a non-blinded board certified nuclear medicine radiologist well versed in interpretation of chest imaging.

p6l24. "Patient did well" does not match the standard of scientific assessment required in the reporting of a clinical trial
Reply: Thank you, the manuscript has been amended accordingly.
Changes in the text: This patient underwent re-ablation with cryotherapy and subsequently experienced no complications for the next 22 months without evidence of re-occurrence.

p6l28. This paragraph pertains to MRI data. Reference to CT is out of place
Reply: Thank you, the manuscript has been amended accordingly and the term CT has been removed from this paragraph.

p7l3. Please consider reporting the actual SUV instead of a qualitative assessment
Reply. Thank you for your thoughtful comment, unfortunately this analysis was not completed and will be considered for future studies.

p8l15. Please reference existing work on the MR appearance of lung ablation zones following MWA: Roman, A., et al. The role of MRI in the early evaluation of lung microwave ablation. Int J Hyperthermia 34, 883-890 (2018).
Reply p8115. Thank you. Notably, this study evaluated contrast-enhanced MRI at 24 hours alone, and did not evaluate the combined use of PET-MRI. However, analysis regarding the peripheral rim on MRI is valuable and this has been added to the manuscript
Changes to text: The utility of contrast-enhanced MRI alone has been reported in the literature. A recent evaluation of 77 lung metastases post-microwave ablation with

MRI 24 hours later and confirmed comparable efficacy for prediction of long term recurrence and complication[16].

Reviewer B

Microwave ablation is a promising alternative to SBRT, RFA, and cryoablation in the management of non-resectable primary and metastatic lung cancer. The authors designed a prospective study evaluating the safety and efficacy of MWA in patient's with unresectable biopsy-proven lung cancers <3cm. The study results support previous data obtained from retrospective studies. However, the study has significant limitations including the very small sample size which precludes any statistical analysis, tumor heterogeneity, single institution limiting extrapolation to other populations among others. However, given the limited number of prospective studies on MWA in lung cancer, there is value to this study being published with major revision.

1) The introduction does not include any rationale for the present study and does not contain a problem statement/hypothesis. While some of this information is present in the comments section, the authors fail to properly introduce the subject, the gap in the current knowledge base, and what their study will add to the knowledge base. This could be addressed by including a succinct literature review which frames the research question behind the present study and states that question. Looking at the literature review the authors performed as well as studies not included in this literature review, the question of the safety and efficacy of MWA has been thoroughly studied questioning the significance of the present study. Furthermore, as the authors list in Table 7, there are other prospective studies that have included lesion biopsy prior to ablation, which is what the authors claim is unique about the present study. Including a comparison to SBRT or cryoablation would be much more significant.

Reply : thank you and your comments are noted. We have attempted to re-write this section to allow for better flow

Changes to the text: Despite the evolution of microwave technology in the lung, there exists a literature gap regarding the use of this particular planning software to determine the appropriate time and power to achieve an adequate ablation margin, and the safety associated with this particular technology.

The aim of this study was to conduct a prospective analysis of safety and feasibility of percutaneous microwave ablation for biopsy proven primary or secondary lung tumors. Additionally, the authors sought to determine the efficacy of the pre-planning system to predict a 5 mm margin and determine the time and power used during ablation. Finally, technical success and patient outcomes were evaluated as a secondary endpoint.

2) Methods:
- what were the technical aspects of the ablation such as planned margins, ablation duration etc. Please provide a rationale for the selection of technical parameters.
- were all of the procedures performed by the same interventional radiologist?
Reply: Thank you for your comments regarding technical aspects to the procedure – this has been added to the manuscript. All procedures were performed by ablation trained radiologists – there were 4 that participated in this study. This has been added to the text.
Changes to the text: Because the ablation zone is typically larger than the target nodule, the ablation zone size at the time of ablation was used as a proxy for lesion size in performing RECIST calculations.

3) The results section is presented poorly and seems like a copy and paste of the abstract. There are multiple grammatical errors and inconsistent placement of the Figure/Table designation in parenthesis before the period at the end of the sentence.
Reply: Thank you. This has been corrected.

4) In regards to the results on lung function, are there any data on vital capacity, total lung capacity, or reserve? It seems unlikely MWA would affect FEV1 or DLCO given the localize nature of the treatment but there may have been changes in other parameters.
Reply: Total lung capacity was not available in all patients but Vital capacity and forced vital capacity data were available with a median 0% change. This has been added.
Changes to text: . Additionally in patients 2-6, there was a median change of 0% in vital capacity and forced vital capacity.

5) Please include a discussion of relative advantages/disadvantages of MWA compared to SBRT or cryoablation.
Reply: thank you this has been added to the discussion on page 16, lines 11-20.
Changes to text: Multiple other ablative studies, with a variety of energy technologies, have established safety and efficacy of percutaneous ablation for lung cancer, as seen in Table 7. A large systematic review and pooled analysis comparing SBRT and RFA in Stage I non-operable primary lung cancer demonstrated 1 year local control rates of 77% for RFA 97% for SBRT(5) and showed that there was no difference in overall survival. RFA did have a pneumothorax in 31% of patients, and SBRT demonstrated Grade 3 pneumonitis in 2% of patients. It should be noted that cryoablation theoretically has the advantage of being resistant to the cold-sink effects of ventilation compared to RFA but there have been no direct studies to prospectively evaluate cryoablation vs RFA vs microwave ablation (7).

6) figures 5, 6, and 7 should include arrows to direct the readers' attention to important features
Reply: Arrows have been added, and figure 7 has been deleted per the next comment

7) In Figure 7, 2 of the CT images appear very blurry. Not sure what value they are adding to the figure and could probably be removed.
Reply: Thank you, we have removed Figure 7

Reviewer C
Very small trial with not much new information of what is already published.

Abstract

Objective:
Missing
Reply: Thank you. This has been added to the text
Changes to the text: Percutaneous ablation is an alternative treatment for lung cancer in non-operable patients. This is prospective clinical trial for percutaneous microwave ablation (pMWA) of biopsy-proven lung cancer to demonstrate safety and efficacy.

Introduction

The aim of the study need be indicated in introduction.
Reply: The manuscript has been amended accordingly
Changes to the text: The aim of this study was to conduct a prospective analysis of safety and feasibility of percutaneous microwave ablation for biopsy proven primary or secondary lung tumors and evaluate outcomes as a secondary endpoint.

Technical factors of MWA better placed in appendix or methods.
Reply: Thank you for your comments. We felt that given the readership, a brief discussion of the technique of MWA and how it contrasts to Cryoablation or SBRT (as requested by other reviewers) would be valuable therefore we left it in.

Methods

Terms: Efficacy, technical success, ablation zone need be defined. Compliance with the “reporting standards for ablation (Ahmed et al Radiology 2014) is desired.
Reply: Thank you, this has been added.
Changes to text: Ablation zone was defined as the region of alveolar opacity (ground

glass or consolidation) generated by the on the immediate post-ablation CT after needle removal and as the solid or cavitary opacity at the treatment site on later follow up examinations.

Technical success was defined as successful placement of the ablation probe in the planned position in the lung and the delivery of the planned dose of microwave energy.

Efficacy was defined as stability or involution of the ablation zone (i.e. lack of local tumor progression) on subsequent follow up exams to the study endpoint of 1 year.

Local tumor progression was defined as 1) growth of the ablation zone by 20% or more from the baseline post procedure measurement or from any new nadir in size established on subsequent follow up, 2) new nodularity at the margin of an ablation zone

The eligibility criteria need be defined.
Reply. Thank you, this is defined in Table 1 in the original manuscript

Were surgical patients also allowed to enroll?
Reply: Yes surgical patients were allowed to enroll. The risks and benefits of both treatments were presented to the patient by the multidisciplinary team.
Changes to the text: Additionally, patients who were candidates for surgical resection were also included in the trial after a multidisciplinary discussion.

How were RECIST applied when by default ablation zone must be larger than the target tumor?
Reply: Thank you – great suggestion. This has been amended
Changes to the text: Because the ablation zone is larger than the target nodule, the ablation zone size as measured at the time of ablation was used as a proxy for lesion size in performing RECIST calculations.

Was there an intention to treat with margins? How margins were assessed? Please refer to reference 24 for impact of margins to local tumor control.
Reply: Yes there was intent to treat for margins. 5mm margins were the target IIRC. Margins would be calculated be measuring the closest distance from lesion edge to edge of the ground glass. This has been added
Changes to the text: Primary endpoints of the study included efficacy and safety. Efficacy was defined as achieving technical success /complete ablation / ablation zone size necessary for treatment. Five mm margins were the target for adequacy of margins. Margins were calculated measuring the closest distance from lesion edge to edge of the ground glass appearance post ablation.

Comments

Reference 12 by Wolf is an older study without stratification of outcomes by margins. Not the best example of the use of MWA as it has been shown in subsequent studies.
Reply : Agree this is somewhat of an outdated study, but for historical context, the authors felt that it should be included.

References 17-26 do not seem to appear in the text
Reply: These are part of Table 7. They are present in the table and match the references- thank you.

Reviewer D
Thank you for the opportunity to review the manuscript by Reisenauer et al who report the use of CT guided percutaneous microwave ablation on 6 patients.

1. The introduction ends rather abruptly. Generally an introduction is fashioned with a brief background, impetus for the study and ends with the objective of the study. How does it stand apart from the other microwave ablation studies?

Reply. Thank you this has been added to lines 4-13 on page 6.
Changes to manuscript: Despite the evolution of microwave technology in the lung, there exists a literature gap regarding the use of this particular planning software to determine the appropriate time and power to achieve an adequate ablation margin, and the safety associated with this particular technology.
The aim of this study was to conduct a prospective analysis of safety and feasibility of percutaneous microwave ablation using the EMPRINT system for biopsy proven primary or secondary lung tumors. Additionally, the authors sought to determine the efficacy of the pre-planning system to predict a 5 mm margin and determine the time and power used during ablation. Finally, technical success and patient outcomes were evaluated as a secondary endpoint.

2. Did any patients report hemoptysis after dismissal?

Reply: no, no patients reported hemoptysis in our study.

3. Pneumonia is a well know and documented complication of microwave ablation. Can the authors please clarify if the one mortality was unrelated to ablation
Reply. Great comment. This pneumonia presented in a delayed fashion in a separate lobe from the ablation site, and was deemed unrelated. This has been added to the manuscript
Changes to text: Given that she had no symptoms or radiographic evidence of pneumonia immediately following her procedure and the original ablation site was the left upper lobe, this was deemed unrelated to her procedure.

4. Overall mortality was 4/6 over the 1 year period? one pneumonia, one metastatic disease?

Reply. At 1 year, 1 patient died from pneumonia. The second patient died from metastatic disease at 20 months. This was outside the theoretical study window which concluded at 12 months. This has been rewritten to provide clarificiation.

Changes to the text: Per study protocol, all patients completed one year follow up except one patient. At one year, 5 patients were alive. Patient 6 developed bilateral lower lobe aspiration pneumonia unrelated to the procedure and unfortunately expired 4 months after her ablation. Given that she had no symptoms or radiographic evidence of pneumonia immediately following her procedure and the original ablation site was the left upper lobe, this was deemed unrelated to her procedure. One patient expired from extra-thoracic metastatic disease outside the study window, at 20 months post-ablation.

5. One line 5, page 8 - "This current study compares favorably to the above listed trials and is unique due to 6 required biopsy-proven malignancy prior to intervention". I think this is an overstatement given only 4 patients at the end of one year survived.

Reply. Thank you for your comment. We have re-worded this sentence in the manscript. Respectfully, only one patient died at 1 year, and this was due to an event unrelated to the procedure.

Changes to the text: This current study has similar complications and efficacy profiles to the above listed trials, despite the small sample size. There are few unique studies that required biopsy-proven malignancy prior to intervention and this study additionally evaluated pulmonary testing and PET-MRI evaluation on all patients.

I think overall albeit a very small number of patients the authors' case series adds to the body of literature on microwave ablation.

Reviewer E

The authors described the results of prospective phase 1 clinical study about percutaneous lung microwave ablation.

Abstract

1. Primary endpoint of this study is unclear. In my opinion, this study was prospective phase 1 study, therefore, feasibility and safety should be more focused.

Reply to Q1. Thank you, this has been adjusted as a separate paragraph in the introduction

Changes to the text: The aim of this study was to conduct a prospective analysis of safety and feasibility of percutaneous microwave ablation for biopsy proven primary or secondary lung tumors and evaluate outcomes as a secondary endpoint.

2. What and how to evaluate in this study should be described in Methods, and Methods and Results should be one-to-one correspondence.

Reply. Thank you this has been adjusted as noted above.

Introduction

3. Purpose of this study was unclear. Hypothesis, purpose, logical reason for conducting the study should be stated in the last paragraph of Introduction.

Reply. Thank you for pointing this out. This has been added to the last paragraph of the introduction

Changes to the text: The aim of this study was to conduct a prospective analysis of safety and feasibility of percutaneous microwave ablation for biopsy proven primary or secondary lung tumors and evaluate outcomes as a secondary endpoint.

Methods

4. Page 4, Line 28–31

This study was prospective study, so there should be the determined imaging study protocol/timing. Why FDG-PET/CT or MRI was performed at random time-point?

Reply: Thank you, this was not clear in the original manuscript. This has been clarified

Change to text: Imaging with FDG PET/CT, and PET/MR was performed one day after the first 3 lesions underwent microwave ablation. Standard of care diagnostic CT was performed within 16-48 hours post-procedure and additionally at 1-2 month, 6 month and 12 month follow up. FDG PET/CT was performed within 16-48 hours post procedure and additionally at 1-2 month and 6 month follow up. FDG PET/MR was performed within 16-48 hours post procedure and at the 1-2 month follow-up visit.

5. Page 5, Line 2

Please describe the definition of technical success.

Reply: Technical success was defined as successful placement of the ablation probe in the planned position in the lung and the delivery of the planned dose of microwave energy. This has been added.

Changes to the text: Technical success was defined as successful placement of the ablation probe in the planned position in the lung and the delivery of the planned dose of microwave energy.

6. Page 6, Line 1–5,

One of advantages of using Emprint system seems to achieve predictable ablation zone. Why was planned and actual ablation zone size not compared in this study?

Reply: Thank you for this thoughtful comment. The goal was to see if the

software prescribed an adequate dosage to achieve adequate margins as measured in native lung. The lesion becomes somewhat obscured during ablation and the surrounding lung shrinks variably during treatment, so it is difficult to say how meaningful pre and post measurements would really be in assessing that -- the proof is really in the recurrence rate. We have clarified this in the manuscript.

Changes to the text: Finally, this study did not directly compared planned predicted margins to actual margins. The goal was to see if the software prescribed an adequate dosage to achieve adequate margins as measured in native lung. As the lesion becomes obscured during ablation and the surrounding tissue shrinks, direct comparisons are not only difficult, but not entirely reliable. Further investigations are needed in this area.

7. Same as abstract. What and how to evaluate the data are unclear, and Methods and Results are not on-to-one correspondence.

Reply: Thank you and please see above, this section has been re-written on pages 8 and 9, lines 18-23 and 1 – 14 as well as page 9, lines 14-19. in the methods

Results

8. Page 5, Line 11.

What was the reason of the probe becoming unavailable? The frequency of 33.3% (4/12) seems to be so high.

Reply: thank you – there was an antennae recall from the manufacturer – this has been added.

Changes to the text: An additional 6 patients were enrolled into the study but ultimately did not receive microwave ablation (one patient declined treatment, one underwent cryoablation, and four patients were withdrawn because the ablation probes became unavailable due to a voluntary antennae recall).

9. Page 5, Line 16–23.

Primary endpoint of this study was not long-time survival, therefore, this paragraph can be omitted.

Reply: We agree with the reviewer that the safety and feasibility should be the primary endpoint and have made these changes in the manuscript.

10. Page 5, Line 24-36.

This paragraph contains a lot of information and not well organized. This paragraph should be divided into several paragraph and re-united with latter paragraph. Only one thing should be described in one paragraph, i.e., one paragraph is about safety, and another is about efficacy, and so on.

Reply: Thank you, we have revised the paragraph to reflect better understand and readability.

11. Page 6, Line 12–18.
Data form patient 1 should be excluded from evaluation. % Change does not show the actual effect of MWA. And PFT data should be shown as graphs.
Reply: We agree with the reviewer and the median % change in FEV1 and DLCO was only reported in patients 2-6 in the original manuscript. We have added a graph to demonstrate the PFT change
Change in the manuscript: Added Figure 5

12. Page 6, Line 19.
How and when the ablation zone overlay was evaluated? Please describe the details.
Reply: This has been re-written to reflect better readability.
Changes to the text: The ablation zone was defined as the region of treatment-induced ground glass opacity at the target site on the immediate, post-procedure CT and as the region of solid or cavitary opacity on subsequent follow up CTs. As the index ablation target is obscured by the ablation zone after treatment, the ablation zone was measured using RECIST criteria as a proxy for the index ablation target. Local tumor progression was defined as an increase in RECIST measurements of 20% from a prior follow-up CT or as new nodularity on the margin of the ablation zone or new FDG avidity in the ablation zone on follow up exams.

13. Figure 7 should be also shown as graphs. Hard to understand with only numbers.
Reply: Per this reviewer and prior comments, we have removed Figure 7 from the manuscript

Comment
14. What is the unique point of this study? What is the difference among the past studies? Those are unclear and the authors should more focus on those.
Reply. Thank you for your comment. There are few studies that have mandated a biopsy prior to intervention, which we feel makes this study one of a few. Additionally, this study uniquely evaluates pre and post pulmonary function testing and PET-MRI to understand the evolution of lung nodules post-ablation. This has been added
Changes to manuscript: This current study has similar complications and efficacy profiles to the above listed trials, despite the small sample size. There are few unique studies that required biopsy-proven malignancy prior to intervention and this study additionally evaluated pulmonary testing and PET-MRI evaluation on all patients.

15. Same as Q1. If this was phase 1 prospective study, feasibility and safety should be the primary endpoints. The other data including efficacy and imaging findings should be the secondary endpoints.
Reply. Thank you. As mentioned above, this has been added to the manuscript.

Figures

16. Figure 1 and 2 do not show any specific information about this study. These figures should be omitted.

Reply: Thank you for your comments. We felt that Figure 1 is a pictoral demonstration of how the technology is applied and felt it to be relevant to microwave technology as a whole. Figure 2 demonstrates the 3 different probe sizes in the EMPRINT system – 15, 20 and 30 cm. Since this technology is relatively new in the lung, the authors felt this would be of interest to the readership.

17. Figure 4. It was hard to understand the time course. Easily misunderstand as interval between the ablation and 4f or 4I was same.

Reply: Thank you and we agree. This shows temporal imaging in a patient that did not recur vs a patient who did. We have redone the labeling and hope this helps with clarity and readability

18. What is the point of showing both Figure 5 and 7? Those are almost same.

Reply. This comment was also made by another reviewer. We have removed Figure 7