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# Peer Review File

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**Reviewer A**

The authors report a retrospective, single center case series on their use of navigation bronchoscopy guided microwave ablation for patients with early stage lung cancer. This is a descriptive analysis of 15 patients undergoing this procedure.

**General comments:**

Comment 1: Minor language editing for syntax and grammar will improve the reader's understanding of the authors' message.

Reply 1: Thank you for your kind reminder. We have asked a native speaker to polish the language. Hope it goes well for understanding.

Changes in the text: We have the text revised for syntax and grammar. All revision and modification have been marked in the manuscript.

Comment 2: While the title reflects use of MWA for early lung cancers, the authors describe 10 patients undergoing simultaneous surgical resection for concomitant lung nodules. This is very confusing and requires clarification. Presumably the authors feel that the ground glass nodules undergoing MWA represent separate malignant processes from those resected, otherwise this would represent higher stage disease.

Reply 2: Thank you for your comment. Indeed, it is important to consider and clarify the stage of those 10 patients with multiple pulmonary nodules. According to IASLC's Staging Manual, tumors should be considered multifocal ground glass lung adenocarcinoma if there are multiple sub-solid nodules (either pure ground glass or part-solid), with at least one suspected or proven to be cancer. And this applies whether or not a biopsy has been performed. All nodules in our study were either pure GGO or sub-solid therefore met the criteria so nodules undergoing MWA represented synchronous primary as those resected.

Change in the text: We added the following sentences in the manuscript to clarify this question.

According to IASLC's Staging Manual (18), tumors should be considered multifocal ground glass lung adenocarcinoma if there are multiple sub-solid nodules (either pure ground glass or part-solid), with at least one suspected or proven to be cancer. And this applies whether or not a biopsy has been performed. All nodules in our study were either pGGO or sub-solid therefore met the criteria so nodules undergoing MWA represented synchronous primary as those resected. (see Page 11, line 11-20).

Comment 3: Based on the description, it is not entirely clear when the diagnosis of the ablated


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ground glass nodules was made - presumably at the time of bronchoscopy based solely on the use of ROSE. Please clarify the diagnostic timeline versus the ablation procedure which per the description appeared to follow immediately after the bronchoscopy.

Reply 3: Thank you for your comment. For 13 nodules, ablation was offered immediately after biopsied tissues were proved to be malignant by ROSE. For the two nodules which did not have a malignant histology by ROSE possibly due to failed biopsy, ablation was still offered with patients' informed consent because they were radiologically suspicious on a series of CT images. All biopsied tissues were further examined by histology examination.

Changes in the text: We have added the details on the diagnostic timeline and the ablation procedure in the manuscript.

1) Ablation was carried out immediately after malignancy was confirmed by ROSE. For nodules which ROSE showed no sign of malignancy, MWA was still given with patients' informed consent prior to the procedure because the nodules were radiologically suspicious on a series of follow-up CT scans (see Page 9, line 1-4).

2) For 13 nodules, ablation was offered immediately after biopsied tissues were proved to be malignant by ROSE. For two nodules which ROSE showed no signs of malignancy, MWA was still given with patients' informed consent prior to the procedure because the nodules were radiologically suspicious on a series of follow-up CT scans (see Page 12, line 3-7).

**Specific Comments:**

Comment 1: The authors refer to local therapies such as RFA and MWA as recommended alternative treatments. These are not currently recommended alternative treatments and are generally still used as part of investigational protocols.

Reply 1: Thank you for your correction. According to NCCN guideline, image-guided thermal ablation may be an option for selected patients, not receiving SBRT or definitive radiotherapy. We should have been more precise. Therefore, we made changes accordingly

Changes in the text: We have modified the text as advised.

1). Non-surgical ablative procedures are thus investigated as therapeutic alternatives in early-stage lung cancer for patients not suitable for surgery (see Page 5, line 13-15)

2). Ablation treatments have been investigated as alternative options for patients unsuitable for surgery (see Page 13, line 9-10)

Comment 2: Use of the term "early lung cancer" in the title would be better served to reflect that they were all ground glass as this suggests a specific subset of cancer types and may influence the response to MWA.

Reply 2: Thanks for your advice. Since all of the lesions treated by MWA were ground glass nodules, the title should include GGN accordingly.

Changes in the text: The title has been changed to "Electromagnetic Bronchoscopy Guided Microwave Ablation for Early-Stage Lung Cancer Presenting as Ground Glass Nodule".

Comment 3: Recommend listing cancer types of treated nodules in Table 1.

Reply 3: Thanks for your suggestion. Cancer type is an important piece of information that should not be omitted.

Changes in the text: We added the data of histology in Table 4 which listed the procedure outcomes of ENB-guided MWA. Thirteen of the ablated nodules were biopsy-proven adenocarcinoma; 2 of them had no histologic proof of malignancy. (see Table 4).

Comment 4: The authors use reference 2 to suggest that 80% of early stage lung cancers cannot be removed surgically. This seems to be an inordinately high number, and upon review of the reference, this value does not seem to be supported by data. This seems to be at odds with other reports suggesting a much lower number. e.g. <5% (Bryant, et al. Thorac Surg 2018, PMID 29198624. Puri, et al. J Thorac Oncol 2015, PMID 26334753) though it could be higher in select populations (Lee, BMC Pulm Med 2018, PMID 30075770). At best, the reference the authors use may be very region-specific but not necessarily generalizable.

Reply 4: Thank you for your suggestion. Data on the proportion of early-stage lung cancers that cannot be removed surgically vary from study to study. We agree that our choice of reference might not be generalizable and might undermine the points we were making. We appreciate the references you provided and have made adjustments accordingly.

Changes in the text: As advised, the statement has been changed into the follwoing statements:

1). “approximately 5-25% of early-stage lung cancers cannot be removed surgically”. (see Page 5, line 6-7)

2) “about 5-25% of early-stage lung cancers cannot be treated by surgery” (see Page 13, line 1-2)

Comment 5: The authors conclude that the procedure is "safe". Given the low number of patients, it is difficult to conclude this and would recommend removal or softening of this conclusion. It should also be followed by comment that larger, prospective, randomized, multi-center studies are needed.

Reply 5: Thank you for your input. We agree it is too early to conclude its safety and indeed larger, prospective, randomized, multicenter studies are needed as for any new procedures and treatments. Therefore, to emphasize on our preliminary experience we use more precise expressions, among which the word safe is better defined or softened across the manuscript.

Changes in the text:

1). We have modified the conclusion in the main text to the following statement. “For medically inoperable patients with simple GGN manifesting early stage lung cancer, and patients with multiple GGN manifesting primary lung cancers which cannot be resected at the same time, ENB-guide MWA could be a potentially safe, feasible and technically effective

alternative for local treatment whether in combination or not with surgical resection, but large prospective randomized multicenter studies are still needed to further confirm its role in the management of early-stage lung cancer".(see Page 17, line 5-11).

2). The conclusion in the abstract was also modified to "For medically inoperable patients with a single GGN manifesting early-stage lung cancer and patients with multiple primary early-stage lung cancers which cannot be resected at the same time, ENB-guided MWA might be a relatively safe and feasible alternative local treatment with high technical success rate, whether combined with surgical resection or not. However, large, prospective, randomized, multicenter studies are needed to confirm its role in the treatment of early-stage lung cancer". (see Page 4, line 7-13)

Comment 6: Methods, "Procedure" section (page 4), line 128. Midazolam and fentanyl are used for sedation to achieve general anesthesia via LMA. This medication combination is more typical of MAC anesthesia rather than general anesthesia. Please clarify.

Reply 6: Thank you for your comment. We should have made it clearer. Patients were put under monitored anesthesia care with midazolam and fentanyl and intubated with laryngeal mask throughout the ENB procedure. And if the patient had other concomitant pulmonary nodules which required further surgical resection after ENB procedure, general anesthesia was further achieved by propofol and fentanyl. They were then intubated with a double-lumen endotracheal tube.

Changes in the text: The statements on anesthesia have been changed to "patients were put under monitored anesthesia care with midazolam and fentanyl and intubated with laryngeal mask throughout the ENB procedure (see Page 8, line 13-15)" and "If the patient had other concomitant pulmonary nodules which required further surgical resection, general anesthesia was further achieved by propofol and fentanyl (see Page 9, line 9-10)".

Comment 7: The study is listed as having IRB approval but was retrospective in nature. Is bronchoscopic MWA a routine clinical procedure that does not require investigational protocols at the study institution?

Reply 7: Thanks for your correction. Retrospective was misused in the original submission. This study was focused on the preliminary experience of ENB-MWA and investigated the safety and feasibility of ENB-MWA. Because of its nature, IRB approval was needed and acquired.

Changes in the text: the word 'retrospective' was deleted. Instead, we substituted it with more precise expression to define the nature of our study: it was a nonrandomized, single-arm study with a small patient pool. (see Page 16, line 12-13).

Comment 8: Table 1: need definitions for pGGO vs. mGGO

Reply 8: Thank you again for your reminder.

Changes in the text: definitions of pGGO and mGGO (pGGN: pure ground glass nodule; mGGN: mixed ground glass nodule) were added below Table 1.

Comment 9: Table 1: Comorbidity is listed as present in 7 but not in 8 patients. This seems disparate from the usual use of ablation therapies as alternatives for patients unable to tolerate surgery. Also, please define comorbidity as used in this table.

Reply 9: Thank you for your input. Indeed, it is better to define comorbidity to avoid any ambiguity. Seven out of eight patients that were listed without comorbidities in Table 1 were enrolled according to the third indication listed in Method: patients with synchronous multiple primary tumors, resections of which might require bilateral surgery, lobectomy plus segmentectomy, multiple lobectomies, or even pneumonectomy. We used MWA in combination with surgery to preserve more pulmonary function for these patients (case 2, 3, 4, 5, 6, 9 and 10 in Table 2). One patient of a single lesion had no comorbidity but refused to receive surgery therefore MWA was used.

Changes in the text: We have added the definition of comorbidity in the manuscript.
"Comorbidity here is defined as the co-existence of disorders other than lung cancer in the same individual, for example, cardiovascular disease, other types of concomitant cancers and so on". (see Page 7, line 16-18)

Comment 10: Table 2: patient 6 is listed as having two lung nodules measuring 3.2 and 3.1 cm. This contradicts Table 1 where all 15 lesions are listed as less than or equal to 3 cm.

Reply 10: Again, your comment is much appreciated. The title of Table 1 was misleading. Patient 6 had three lesions in total, two of which, measuring 3.1 and 3.2 cm respectively, were treated by surgical resection. Only the 1.5 cm lesion was treated by MWA. Table 1 showed only lesions treated by MWA and those treated by surgical resection were not included.

Changes in the text: We have changed the title of Table 1 to "Demographic characteristics of patients and nodules treated for MWA". (see the title of Table 1). We have also added a sentence in *Result*. "All lesions indicated for ENB-guided MWA were no more than 3cm and were air-rich lesions (GGN)". (see Page 10, line 14-16)

**Reviewer B**

The treatment of choice in early stage lung cancer both small cell and non-small cell lung cancer is complete surgical resection. However, the best local therapy for medically inoperable patients, those with multiple lung tumors, or those who refuse surgery is not clearly established.
Bao and colleagues report their experience with an electromagnetic bronchoscopy-guides-microwave ablation (ENB-MWA) in 15 patients with lung tumors, in

which a large proportion of patients underwent additional surgery. This is a small pilot clinical study demonstrating the feasibility of ENB-guides MWA and potential advantages of ENB-guides MWA over CT-guided transcutaneous RFA otherwise commonly performed in this nonsurgical patient population.
I take the liberty of making the following comments:

Comment 1: Throughout the manuscript, the authors refer to lung cancer and ground glass opacity. The authors should clarify which histology is being referred to. Also, exact histology information is missing in the table

Reply 1: Thank you for your comment. Histology information is important for reader's understanding of our message. Thirteen of the 15 nodules were biopsy-proven adenocarcinoma, while the biopsy results for the other two came back negative for malignancy; however, the two nodules were still considered to be malignant based on follow-up CT scans.

Change in the text:

1). We have added more detailed histology information in Table 3.

2). In order to include the characteristics of the lesions treated by MWA, the title has been modified into “Electromagnetic Bronchoscopy Guided Microwave Ablation for Early-Stage Lung Cancer Presenting as Ground Glass Nodule”.

3). Meanwhile, in the *Result*, we have added the sentence “For 13 nodules, ablation was offered immediately after biopsied tissues were proved to be malignant by ROSE. For two nodules which ROSE showed no signs of malignancy, MWA was still given with patients’ informed consent prior to the procedure because the nodules were radiologically suspicious on a series of follow-up CT scans” to describe the information about the histology of the nodules. (see Page 12, line 3-7).

Comment 2: for example, lines 187-189. the authors do not demonstrate histologic images that would demonstrate ablation of the tumor sites and base their assumption that necrosis would be present only on computed tomography and also not on PET positivity at several months postintervention. this limitation should be mentioned

Reply 2: Thanks for your comment. We should have been more specific. A major challenge of ablation has been the lack of a reliable postprocedural assessment of the response to treatment. No standard imaging protocol for post-ablation follow-up has been established yet. Unlike surgical resection, in which a tumor is removed and then processed for histopathologic analysis, the ablated tumor is left in situ, and thus direct histopathologic verification of complete tumor ablation is difficult to perform. Histologic assessment of the ablation zone margins by fine-needle aspiration biopsy has been proved to be unreliable because it is frequently associated with both high false-negative rate and high false-positive rate due to sampling error. Although core-needle biopsy may increase diagnostic value, it is associated with increased risks and still subject to false-negative results caused by sampling error.

Therefore, biopsy was not routinely used for assessment of postintervention change. Since PET is inadequate at detecting metabolism of early-stage lung cancer presenting GGN, it does not seem cost-efficient to use PET for post-intervention assessment.

Changes in the text: We have added more information in both *Method* and *Limitation* to clarify the problem of post-ablation assessment.

1). "It should be noted that a major challenge of ablation has been the lack of reliable postprocedural assessment of the response to treatment. No standard imaging protocol for post-ablation follow-up has been established. Postprocedural imaging is only a rough guide to the success of ablation therapy, since microscopic foci of residual tumor is impossible to identify on imaging and can only be confirmed by re-biopsy" (see Page 10, line 4-7)

2). "Thirdly, no reliable postprocedural assessment of the response to treatment has been established, meanwhile, the long-term oncologic effect has not been collected" (see Page 16, line 19-21).

Comment 4: Line 203-204 (ref 16-18) is not correct in my opinion. The literature cited is very controversial and cannot be cited in this form. Chang and colleagues presented the results of two discontinued randomized trials comparing good SBRT with poor surgical performance. The surgical complications reported in the publication by Chang and colleagues are not acceptable. I am not aware of any prospective comparative study that has shown comparable oncologic outcomes between surgery and SBRT. The sentence in lines 203-204 may be confusing to the reader and should be deleted. For the same reason, I would also delete the sentence in lines 49-50, because without further explanation it could suggest as a sole statement that the non-surgical ablative procedures are also therapeutic options in early stage lung cancer.

Reply 4: Thanks for your advice. As we have mentioned in the introduction, we strongly believe surgical resection is the standard treatment of early-stage lung cancer. It is not our intention to oversell the role of SBRT or for that matter, the role of ablation. The message should be clear that ablation is only used as alternative for medically inoperable patients or patients with multiple primary lesions not suitable for surgery.

Change in the text: We have deleted the two sentences, and statements for ablative procedures were added in the text as follows:

1). Non-surgical ablative procedures are thus investigated as therapeutic alternatives in early-stage lung cancer for patients not suitable for surgery. (see Page 5, line 13-15)

2). Ablation treatments have been investigated as alternative options for patients unsuitable for surgery. (see Page 13, line 9-10)

Comment 5: The authors repeatedly refer to early-stage lung cancer, which is not the case when multiple foci are present. In the latter case, a T3, T4 or M1a (PUL) situation would be present, which does not represent early stage. Therefore, the title of the paper alone is

misleading. I ask for clairification here.

Reply 5: Thank you for your comment. Indeed, it is important to consider and clarify the stage of those 10 patients with multiple pulmonary nodules. According to IASLC's Staging Manual, tumors should be considered multifocal ground glass lung adenocarcinoma if there are multiple sub-solid nodules (either pure ground glass or part-solid), with at least one suspected (or proven) to be cancer. And this applies whether or not a biopsy has been performed. All nodules in our study were either pGGO or sub-solid therefore met the criteria so nodules undergoing MWA represented synchronous primary as those resected.

Changes in the text: We added the following sentences in the manuscript to clarify this question.

According to IASLC's Staging Manual (18), tumors should be considered multifocal ground glass lung adenocarcinoma if there are multiple sub-solid nodules (either pure ground glass or part-solid), with at least one suspected or proven to be cancer. And this applies whether or not a biopsy has been performed. All nodules in our study were either pGGO or sub-solid therefore met the criteria so nodules undergoing MWA represented synchronous primary as those resected. (see Page 11, line 11-20).

Comment 6: Were the cases discussed in a multidisciplinary tumor board and was the therapy determined there?

Reply 6: We appreciate your comment. Indeed, all cases included in this study were discussed in a multidisciplinary board including thoracic surgeons, radiologists and medical oncologists. The decision to proceed with MWA therapy was made collectively by all board members based on patients' best interests.

Changes in the text: "A multidisciplinary team including thoracic surgeons, radiologists and medical oncologists carefully evaluated patients' medical operability and technical achievability of successful ablation before granting the procedure". The above sentence was added in *Method*.(see Page 7, line 1-3).

**Reviewer C**

I agree with the premise of the article that there is a progressing need for development of minimally invasive ablation modalities for NSCLC/lung tumours. I applaud the authors for completing this study and demonstrating the technical ability to deliver ENB in a safe & accurate way.

Comment 1: However, with follow-up consisting solely of CT performed 1 week, it is not possible at all to comment on effectiveness of the technique in controlling pulmonary cancers. At best, the CT can confirm that the MWA was accurately targeted to the tumour, but the efficacy/effectiveness in oncologic control cannot be inferred. I prefer the term (as used by the

authors in Table 4) “technical success, and recommend the abstract/conclusion be adjusted. (Given the latest ablation treatment was Dec 2020, I do not believe presentation of even local disease-free survival would be appropriate yet).

Reply 1: Thanks for your comment and suggestion. The oncological effectiveness of the procedure was hard to conclude here due to the short follow-up time period. Distinction between “technical success” and “effectiveness” should be made here. A major challenge of ablation has been the lack of a reliable postprocedural assessment of the response to treatment. No standard imaging protocol for post-ablation follow-up has been established yet. As you mentioned, postprocedural imaging findings are only a rough reflection to the success of ablation therapy, since microscopic foci of residual tumor is impossible to identify. According to “Standardization of Terminology and Reporting Criteria for Image-Guided Tumor Ablation (J Vasc Interv Radiol 2009;20:S377-90. DOI:10.1016/j.jvir.2009.04.011)”, “technique effectiveness” means that complete ablation of macroscopic tumor is achieved as evidenced by follow-up images after a given period of time (i.e., one week or one month after treatment) while technical success is defined as the correct placement of MWA antenna and completion of ablation according to plan. Therefore, the term “technique effectiveness” is more appropriate for this article.

Changes in the text: We abandoned the use of “complete ablation” as advised and replaced it with the more appropriate term “ technique effectiveness” to indicate the complete ablation of macroscopic tumor evidenced by imaging. The following statement was added in the manuscript: “technique effectiveness” refers to a “complete ablation” of macroscopic tumor as evidenced by the imaging of a tumor covered by a larger solid or ground-glass opacity area (see Page 9, line 21, Page 10, line 1-2).

Comment 2: In particular “MWA effectiveness was evaluated by CT scan within the first week after treatment” I think is compromised by the existence of likely inflammation – it is almost certain that not all opacity would be ablation, and viable tumour will be persisting. On this note, I think the sentence “CT scan by the first postoperative week showed complete ablation for 11 nodules indicated for ENB guided MWA” (line 188) would be more accurate if ‘complete ablation’ were replaced by ‘technical success’. To illustrate my concern, A recently published study on bronchoscopic thermal vapor ablation (Respiration. 2021;100(5):432-442. doi: 10.1159/000514109) noted small amounts of viable tumour in a minority of patients. I believe this study should be cited to illustrate this issue.

Reply 2: Thank you for comment and the reference you provided. Indeed, complete ablation is not the most appropriate term for many reasons. First, one week was rather too short to tell the long term effective of ablation. Second, even though a complete ablation zone is achieved on CT scan, microscopic foci of residual tumor can still remain. Therefore, we have made changes accordingly.

Changes in the text: We adopted the term of “technique effectiveness” to replace “complete ablation”, The following statment was added in the manuscript: “technique effectiveness” refers to a “complete ablation” of macroscopic tumor as evidenced by the imaging of a tumor covered by a larger solid or ground-glass opacity area (see Page 9, line 21, Page 10, line 1-2).

Meanwhile, the reference which state viable tumor left in a minority of patients was also cited in the following sentence: “Postprocedural imaging is only a rough guide to the success of ablation therapy, since microscopic foci of residual tumor is impossible to identify on imaging and can only be confirmed by re-biopsy” (see Page 10, Line 7-9).

Comment 3: Of note, I think the images presented in Figure 5 are promising, however the imaging in Figure 4 is far from convincing regarding the absence of malignancy. I would recommend use of images form another patient.
Reply 3: Thank you for your input. In hindsight, we totally agree that images from Figure 4 might not be the perfect example to present. And as you mentioned before, CT images were indicator of technique effectiveness rather than complete histological ablation therefore we feel the original expression “the lesion was replaced by parenchyma bands” was not appropriate either.

Changes in text: We have updated Figure 4 as well as made adjustment to the description. In order to be more precise we changed the notes in Figure 4 as follows : the ablation zone was replaced by parenchymal changes different from the original nodule. However, further follow-up CT scans are needed to confirm the effectiveness of ablation. (see legends for Figure 4)

Comment 4: I suspect size will be important – can the authors please comment specifically on the technical success for the three lesions sized 2-3cm.

Reply 4: Thank you for your comment. Indeed, size is an important factor for technical success. Larger lesions are easier to target and reach theoretically and biopsy results of all three nodules sized 2-3cm came back positive for malignancy. And for ablation effectiveness, larger energy output and longer duration of MWA treatment were used for these three lesions of larger size. Post-ablation images showed two of them get technique effectiveness of ablation.

Changes in the text: In the manuscript, we added the following comment on size:

1). Lesions of larger sizes or with bronchus signs would be easier to reach successfully (9,28,29). In this study, all the three nodules sized 2-3cm get biopsy-proven malignant diagnosis. (see Page 15, line 4-6).

2). Larger energy output and longer duration of MWA treatment were used for three lesions of larger size (2-3cm).Post-ablation images showed that technique effectiveness was achieved in two of them.(see Page 12, line 16-18)

Comment 5: What was the size of the ablation zone achieved on CT chest? Did this correlate well with energy delivered?

Reply 5: Again, your comment is much appreciated. The ablation zone was defined as radiological region of the post-ablation change characterized by a solid or ground-glass opacity area around the tumor. In some circumstances, it was difficult to evaluate whether ablation zones completely covered tumors because both tumors and ablation zones had ground glass characteristics. In such cases, it could be evaluated by referencing the anatomic landmark such

as vessels. The ablation zone is dependent on both the energy output and duration of MWA treatment.

Changes in the text: We have modified the manuscript as advised:

1). The ablation zone was the radiological region of the post-ablation change characterized by a solid or ground-glass opacity area around the tumor. (see Page 9, line 18-19)

2). MWA generates higher temperature in a shorter period of time and is less subject to high impedance from high temperature and heat sink effect, thus producing larger and more homogeneous ablation zone which is dependent on both the power output and duration of MWA treatment. (see Page 13, line 15-19)

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Comment 6: For the two patients experiencing hemoptysis, how long after the MWA procedure was this noted?
Reply 6: Hemoptysis in both patients was noticed on postoperative day one.

Changes in the text: we have specified in our text: hemoptysis of both patients was noticed on postoperative day one and they recovered swiftly after intravenous antibiotics and coagulation treatment. (see Page 12, line 11-12)

Comment 7: Line 264 – typographic error “antenna location cha”

Reply 7: Sorry. It was a typo.

Changes in the text: We have corrected the typo in the text. (see Page 16, line 9)