Peer Review File

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Reviewer A

Congratulations to write about an upcoming future in minimal invasive diagnostically and therapeutical lung approaches - Interventional Pulmonology and Thoracic Surgery will meet in hybrid rooms for sure.

Some comments:

a) COPD IV was excluded. Chronic lung diseases like COPD or IPF are drivers of incidental small pulmonary nodules below 10mm - of them the majority to be benign ! However looking into the real clinical challenge is the fact that we find up to 50times more incidental nodules in these kind of chronic diseases in comparison to patients without lung disease but only every 10th-20th is malignant. In absolute numbers according to different mathematical models (like Brock University Model) COPD IV is one of the major risk factors for malignant incidental malignant nodules. Therefore this exclusion makes your study weaker - biased- and a bit of unrealistic in regards to complication rates. Could you comment on this in your article? COPD IV is one of the major groups in my hospital for iSPN work-up including microwave ablation.

Author's reply: Thank you for your suggestions. While we acknowledge that GOPD IV is a major risk factor for incidental malignant nodules, the decision for this exclusion criteria is due to the higher general anaesthesia risk and procedural risks associated with this patient group, coupled along with our early experience and initial learning curve of this novel technique. Indeed as we gain more experience, this exclusion criteria may be changed and COPD IV patients can be included.

Changes in text:
Line 40-41
"in view of higher general anaesthesia risk and procedural risks,"
Line 41-43
"In the future, with more safety data and experience, patients with COPD IV can be included as well as it stands as one of the major risk factors for malignant incidental malignant nodules."

b) Suspicious nodules were excluded by histology. Do you perform this rule in N1 lymph nodes peritumoral as well - which can be very demanding? Pure thermal ablation will not treat any N1 lymph node which occur in up to 10% postoperative in comparison to PETCT clinical stages - even in stage IA cancers.

Another problem is the fact that a small amount of adenocarcinomas show initially an endobronchial spreading - which can especially be seen in some cases with broncus sign. There are a few case reports that even after RO resection of an early adenocarcinoma there is very early relapse exactly at the border of the resected ground. However - burning while pulling back the ablation catheter should be part of a protocol. Could you comment on these 2 points?

Author's reply: Thank you for your comments and suggestions.

All suspicious nodal involvement were excluded by histology i.e via endobronchial ultrasound biopsy, if such lymph nodes were large or hypermetabolic on imaging. Eligible nodules for bronchoscopic microwave ablation are effectively T1N0M0.

Regarding the issue of endobronchial spread, although this is relatively more likely in cancers with bronchus sign, it is still relatively uncommon. After ablation, the ablation catheter is retracted within the extended working channel before removing, thereby reducing the risk of iatrogenically-induced endobronchial spread.

Changes in text"
Line 45-46
"so that eligible nodules for bronchoscopic microwave ablation are effectively T1N0M0."

c) You did exclude pacemakers. Pacemakers are pretty common in lung diseased patients due to the overlap of chronic cardiac diseases. This again is a bias with respect to safety issues as pacemaker patients are hemodynamically ill. I can accept this for S7 lesions - but in regards to physics microwave generators induce heat without electric currency which is one of the major advantages in comparison to RFA. I do not understand why you did exclude these patients for physical aspects. Could you comment on this?
Author's reply: Thank you for your comment. The manufacturer of the ablation system we use currently do no recommend its use in patients with pacemaker. We look forward to newer designs that are pacemaker compatible.

Changes in text:
Line 52
"based on manufacturer's current recommendation"

d) According to your protocol NOAC can be restarted 1 day postoperatively ! Well - this can be done, however we have seen severe bleeding even with a delay of 4 weeks after biopsying: Bleeding is not only a function of NOAC - it is as well a function of peritumoral inflammation, pulmonary hypertension and tumor anatomy like cavitation or cyst. In my institution we tend to put NOACs in full dosage off 4 weeks pi in case this is possible in regards to heart function: For example with LVEF < 30% we clearly emphasize towards the patient the risk of embolism vs. bleeding locally. In all cases the patient has to sign thorough consent. Many times we reduce NOACs for 50% of the preinterventional dosage. This seems to work very well. On the other side we have seen strokes after EBUS-TBNA in mediastinal adenocarcinoma without any NOAC pre- and post interventional - even under sinus rhythm.
Author's reply: Thank you for your insightful comment and for sharing your experience with peri-operative anticoagulation management. Fortunately, with our limited experience thus far, we have not encountered any serious bleeding complications with our current peri-operative anticoagulation regime but this is of course subject to change with further experience and potentially more complicated cases in the future.
Changes in text: nil

e) You restricted your treatment to 30mm diameter in size and 5 mm away from major vessel. In regards to size even 30mm is really challenging - and I expect that in future we will do much more overlapping ablation zones - or add another local treatment. The majority of cases with early relapse I have seen in cases with around 30mm despite good technical performance! In regards to vessel size - what is a major vessel ? You should define this. One solution could be measurement of local temperature with sensors in the site of ablative target during a ,,pre-ablation" round, then adjust your protocol to the accomplished temperatures - and redo it in a second step. There are sensors available even for endobronchial use - or even antennas with temperature sensing to adjust ablation algorithm during the procedure (medwave). It is highly problematic to control the efficacy of a thermal ablation alone along the post-procedural GGO around the tumor - overestimation of the dead zone of more than 50% is easily possible. All this is mentioned in my review.
Author's reply: Thank you for your insightful suggestions and sharing your experience. We would agree that lesions up to 30mm become quite challenging and would likely need double ablation, with a higher risk for recurrence. With regard to the size of a "major" vessel, we would define this as >3mm in diameter. We also acknowledge that temperature sensors would improve the effectiveness of ablation and will consider utilizing these in future cases.

Changes in text:
Line 148-149
"double ablations tend to be for larger lesions , and higher vigilance for recurrence is needed in these ablated lesions during post-ablation serial imaging"

Line 62-63
"(>3mm in diameter)."

f) For your final publication including FU you should mention in regards to results:
How many cases with Broncus sign?
How many TBATs in this group?
How many "unfavorable nodules" in the whole study group? In my opinion you should only treat patients with "favorable" nodules as we have SBRT as another option.
Author's reply: Thank you for your comment. In line with the editor's preference for this particular paper, we wanted to introduce our technique with respect to procedural and clinical pearls, rather the detailed results have been reported in another publication as referenced both in this paper, and below;

Chan JWY, Lau RWH, Ngai JCL et al. Transbronchial microwave ablation of lung nodules with electromagnetic navigation bronchoscopy guidance-a novel technique and initial experience with 30 cases. Transl Lung Cancer Res. 2021 Apr;10(4):1608-1622.

Changes in text: nil

g) Pneumothorax is not only a question of ablation effect - it is as well a question of ventilation over time and pressure effects. You should clarify what ventilation maneuvers were used over x time and y pressure influence.
Author's reply: Thank you for your comment. We use standard ventilation techniques and have no particular ventilation requirement during the ablation procedure. Pneumothorax as a consequence of the procedure is often related to inadvertent pleura puncture as described, as opposed to the ablation zone reaching the pleura. After ablation, high PEEP pressures should be avoided and patients are usually extubated promptly.
Changes in text: nil

h) In seldom cases as a bail-out you claim that ablation without biopsy can be considered. You can state this in a clinical daily all-comers decision - but not in one of the first prospective trials in endo-mwa. This again is a bias to possible more favorable results as explained above.
Author's reply: Thank you for your comment. As with a previous comment, this is an introduction of technique and clinical decision making to our usual clinical practice in patients receiving bronchoscopic microwave ablation. We definitely agree that future prospective trials should only perform ablation for histologically confirmed malignancies.

I would love to review the results of your study which will be pending due to FU.

Review B

This manuscript reports on clinical experience bronchoscopic ablation of lung tumors. The authors describe their experience performing ablation with the Emprint ablation catheter guided by Superdimension ENB and cone beam CT. The topic of the article is well suited to the "Innovations in robotic VATS and bronchoscopic procedures" section.

Introduction, second paragraph, "theoretical advantages are seen…" – please amend sentence. Does this mean the theoretical advantages anticipated with MWA have been observed in the clinical setting (not sure this is accurate)?. Suggest rephrasing to indicate MWA has theoretical advantages.
Author's reply: Thank you for your comment. We agree to indicate MWA has theoretical advantages instead of having been observed.

Changes in text:
Line 24-25
"The theoretical advantages of microwave ablation compared with radiofrequency ablation include;"

Second to last paragraph of techniques section discusses margin. How is margin defined? What is

the recommended margin size for a successful treatment? What method is employed to identify device position and energy delivered to achieve the desired margin?
Author's reply: Thank you for your comments
CBCT just prior to ablation is used to confirm catheter position with regard to the target lesion. A minimum of 5mm margin was planned for each nodule and the expected ablation zone border was drawn using PURE® platform (Siemens Heathineers, Germany) software, with the minimum predicted margin measured. Successful treatment was defined as inclusion of lesion into the ablation zone with adequate margin based on post-ablation CBCT scan.

Changes in text:
Line 115-116
"in order to plan the predicted ablation zone using the PURE® platform (Siemens Heathineers, Germany) software, with adequate margin, defined as a minimum of 5mm "

***Please elaborate on the post-ablation evaluation of the treatment zone on CT imaging. How is the ablation border identified and compared against the tumor volume to determine margin? This seems a departure from established methods for percutaneous ablation where margin is often assessed at a few weeks post-ablation.
Author's reply: The pre- and post-ablation CBCTs were overlayed upon each other, such that the pre-ablation tumour border can be compared to the post-ablation ablation border to determine margin. We routinely perform CT at 1 month after ablation, and most of the ablation zones enlarge and become more well-defined that the CBCT done immediately post-operatively. However, the original lesion tends to become less obvious on 1-month CT, in addition of significant tissue contraction, making margin determination difficult at 1 month.

Changes in text:
Lines 123-124
"If the lesion is not well seen after ablation, pre- and post-ablation CBCT are overlayed to determine the actual margin achieved."

Please comment on challenges with positioning the catheter. In fig 11 the predicted ablation zone is substantially larger than the tumor, yet an inadequate ablation was achieved. This suggests that the targeting with the presented technique may be quite limited.
Author's reply: Thank you for your comments. In fact in Fig11 we demonstrate the challenges that are sometimes faced with certain nodules, whereby it is indeed difficult to reach the target lesion leading to an inadequate ablation zone that would cover the entire lesion - thus, as described in the paper, the techniques or double ablation/bracket ablation would need to be adopted to provide adequate coverage. This is also demonstrated in Fig11. Careful case selection is therefore important.

Changes in text:
Line 152-153
"due to the limitation in exact positioning of the ablation catheter to achieve an adequate margin with a single ablation zone in large lesions"

**Challenges – elaborate on risk of pneumothorax when ablating in proximity to the pleural wall. What is the critical dimension here? Closest distance from catheter tip to the pleural wall? Distance from some other point along the catheter to the wall? Is energy dose for a tumor based purely on size of tumor, or does distance to pleural wall play a role?
Author's reply: Thank you for the comment.
In fact the ablation zone reached the pleura in more than half of our cases, but pneumothorax was encountered only in 2 cases (one due to inadvertent advancement of catheter leading to pleural puncture, and another due to rupture of a rapidly enlarging cavity post ablation on postoperative day 1, rather than intraoperatively). We have also performed VATS wedge resection of other nodules after ablating the primary nodule, and intraoperatively found that the ablated visceral pleura appears thickened and scarred down rather than becoming thin and prone to rupture. Thus even if the ablation zone reaches the pleura, the rate of pneumothorax is low. The risk of pneumothorax theoretically is higher when a large surface area of pleura is ablated, thus in general

we would choose the energy level where as little pleura is ablated while leaving as much ablation margin to the nodule.

Changes in text
Line 132
"In our experience however, as long as…"

Figs 4 and 8 depict the bronchoscope position secured by taping to a box lodged on the CT table/arm. This does not appear to be a very robust approach and raises potential safety concerns.
Author's reply: Thank you for your comment. The bronchoscope position and its tools within are in fact primarily stabilized/fixed by internal "locks" within the bronchoscope system, and the "lock" between bronchoscope and the endotracheal tube. The box only served as a supporting structure. We would agree that the positioning of the bronchoscope with tape and a box is a less than sophisticated method, especially with the emergence of more robust and established bronchoscope stabilisations systems now available on the market. In fact we are too, in the process of securing such stabilisation systems/bronchoscope holders for our centre as our experience with bronchoscopic ablation increases. In the meantime however, this is a safe and reproducible method that has served us well thus far.

Changes in text:
Line 102-104
"Some bronchoscope stabilization systems are also now commercially available which would, likewise provide security to the entire apparatus without the operator."

Fig 9 – what do the blue and green ellipsoid contours represent? What lead to the pneumothorax, advancement of the ablation catheter, or the preceding advancement of the needle?
Author's reply: Thank you for your question. For Fig 9, the advancement of the catheter led to pleural puncture, resulting in pneumothorax as stipulated in the figure legend.

Regarding to the blue and green ellipsoid contours, perhaps with reference to Fig 8, they represent the predicted ablation zones in different axes.

Overall, an interesting article describing a single center's experience with transbronchial ablation. While interesting, more detail needs to be added to describe how treatment parameters are selected and how post-treatment imaging is

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Reviewer C

The article titled "Bronchoscopic ablation of lung tumours: patient selection and technique" by Ng et al. describes the pre-procedural and intraoperative approach to electromagnetic navigational bronchoscopy in the treatment of non-surgically resectable lung cancer. Overall the review is timely and relevant to clinicians managing these patients, especially in the era of imaged guided interventions. The article is well written and the figures appropriate for demonstrating key intra-operative execution. Recommend acceptance with minor grammatical corrections.
1) please move the period to after the references at the end of the sentence
Author's reply: Thank you for the suggestion.
Changes in text: as suggested by the reviewer

2) please clarify whether microwave ablation is effective in patients with sternal wires. You state in the patient selection section that "microwave is limited" in these patients but then go on to say that ENB is still effective.
Author's reply: Thank you for your comment
We would clarify that microwave ablation is feasible and that despite the presence of sternal wires, localisation using ENB is not affected.

Changes in text:

Line 50-51
"the accuracy of ENB for localisation of the target lesion is not affected (18), and bronchoscopic microwave ablation would still be feasible "

Reviewer D

1) This is very novel and comes from the center with the largest experience with this modality

2) This is more of a technique paper, with tips and tricks, so we don't need detailed information on Dr Ng's series. That will be addressed in another manuscript that he will likely be submitting elsewhere (and was only recently presented at another meeting)

3) The first reviewer has opinions about

a. Not excluding COPD IV
b. Pacemaker patients
x
Dr. Ng should address the comments as he feels best, however I do feel that this is a very preliminary experience - few centers are embarking on this, and so strict safety and inclusion/exclusion criteria as they are applying are reasonable. As centers start to develop similar programs , I'm sure the exclusion/inclusion criteria will be modified.

Questions for the authors:

2) How important is it for the ablation catheter to be placed centrally within the target lesion? Meaning, if there are issues with probe placement for small lesions, can the probe be placed alongside the lesion, and a larger ablation zone planned that might include a small tumor?

Author's reply: Thank you for your question. It would be favourable if the catheter can be placed centrally within the lesion, but this is not always possible due to lesion location / patient anatomy. If the ablation catheter cannot be placed centrally within the target lesion, the probe can be placed alongside the lesion and a larger ablation zone be planned, as long as the predicted margin is more than 5mm.

2) Were there any cases where ablation was planned and then they simply were not able to navigate in a satisfactory way to the target

Author's reply: Thank you for your question. In most cases we were able to navigate to the lesion as planned, but in around 5% of cases we had difficulty navigating to the desired location. In these circumstances, unplanned double ablation via 2 different navigation routes may be required to adequately include the lesion within ablation zone. Case selection is therefore important.
