Peer Review File

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Reviewer A:

This is the first case report on a patient with lung cancer who underwent bronchoscopic ablation using the new "Illumisite" electromagnetic navigation platform. For successful bronchoscopic ablation, the precise placement of the ablation catheter is essential; thus the use of the Illumisite which provides correct CT-to-body divergence during bronchoscopic ablation seems to be reasonable. This is a well-written paper, and I have a few minor comments.

Minor:

Comment 1: Please describe the short-term results (efficacy and safety) after the procedure by showing the chest CT.

Reply 1: Thank you for your advice. The post-ablation 1-month and 4-month CTs have been added.

Changes to text: Short-term results were described in Lines 145-147, while Figure 7 has been added.

Comment 2: Please describe the total procedure time.

Reply 2: The total procedure time was 171 minutes.

Changes to text: This is added to Line 142.

Comment 3: Line 119. Delete "extended working channel" and "locatable guide" as the abbreviations were shown in the Introduction Section.

Reply 3: Thank you for your kind reminder and we have deleted as suggested.

Comment 4: Figure 2 legend. Change "Figure 3A, B" to "Figure 2A, B."

Reply 4: Thank you for your kind reminder and we have corrected as suggested.

Comment 5: Figure 6 legend. Correct "figure 7B."

Reply to reviewer: Thank you for your kind reminder and we have corrected as suggested.

Reviewer B:

Thank you for allowing me to review the case report "Electromagnetic Navigation Bronchoscopy Transbronchial Lung Nodule Ablation with IllumisiteTM Platform Corrects CT-to-body Divergence with Tomosynthesis and Improves Ablation Workflow."

This is a case where Illumisite is used to correct for CT-body divergence using local registration prior to CBCT and lung nodule ablation with a microwave ablation catheter. This case is very interesting in that the authors found there is less utilization of CBCT by using the C-arm based tomosynthesis with Illumisite which improved

workflow/efficiency.

Comment 1: Could the authors comment on the reduction of radiation exposure one could expect by using Illumisite as opposed to repeated CBCT spins?
Reply 1: We agree that this is an important point to include in the case report. The average radiation dose for conventional ENB ablation was 27120μGym^2 while that in the current case is 26129μGym^2. We expect further reduction of radiation dose can be achieved by using the Illumisite platform when we are more familiarized with the system, as navigation accuracy is improved and fewer CBCTs are required to confirm entry into correct subsegmental airway.
Changes to text: Radiation dose information has been added to line 142. Discussion has been added to Lines 207-210.

Reviewer C:
The work of NG et al is important on this innovative field of endobronchial ablation: They could here present CT to body divergence which currently affects any navigation platform and even robotic which are bronchoscopes trying to take their place.
I just have a few questions for the authors

Comment 1: Could they specify their treatment indications for ground glass lesions? Patient with a history of cancer? Mixed GGO lesions? Pure groung glass opacities and if yes then on what criteria?
We know that in patients with ground glass lesions, some will lie dormant for several years and others will appear either proven to be genuine NSCLC? And at the end, what is the place of surgery in algorithm
Reply 1: Thank you for the question. We stratify lung nodules into different risk categories of malignancy using well-established criteria for example the Herder or Brock's. risk model. Family history of lung cancer, enlarging size, increasing solidity, presence of other similar GGO which were proven pre-malignant or malignancy, high FDG uptake, irregularity would suggest higher risk of malignancy. In addition, it is more prevalent in Asians to have GGOs representing early malignancy, and multiplicity may not necessarily indicate lower likelihood of cancer. We usually follow the patients up with CT over years for pure or mixed GGOs, and only offer intervention to the highest risk nodules which have progressed.
Changes to text: nil

Comment 2: On the navigation itself
Since the authors use an image correction system with the Illumisite platform and argue for it for dose radiation limitations: why don't they used the preoperative CT for planning and thus avoid a spin of CBCT in a hybrid room which also gives a lower quality image?
Reply 2: Thank you for your question. The preoperative high resolution fine cut CT is used by the ENB system for planning navigation pathway. The first spin of CBCT we

perform in the hybrid room is for assessing whether there is any change in lesion (disappearance which makes intervention unnecessary; increase in size which makes ablation unfavourable, unexpected changes eg. pneumonic changes), whether the lesion is visible (sometimes atelectasis may affect visibility of posterior lower lobe lesions, and lung recruitment by the anaesthetist is required in this case). Also, the first intra-operative CBCT provides the imaging required for augmented fluoroscopy (using 3D segmentation tools to create overlay of lesion on fluoroscopy, or to highlight preferred airway on live fluoroscopy to improve accuracy of navigation).
Changes to text: nil

Comment 3: Knowing that on this specific case, the scanner showed a sign of the bronchus as they have wrotten (which is not always present) : Could you explain to us the reason for cross country tool which is a priori only necessary in the absence of bronchi leading to the lesion ?
Reply 3: Thank you for your concern. The bronchus sign in this case shows a segmental bronchus leading to the lesion but not beyond the lesion. However, for placement of ablation catheter, the catheter tip needs to be beyond the lesion as the centre of ablation is approximately 1cm behind the tip. Therefore, the cross country tool is required: the needle is used to puncture past the lesion, dilator tunneled through to form a pathway for the subsequent insertion of ablation catheter. The ablation catheter we use has rounded soft tip and thus cannot be used for tunneling or pushed with any force through firm tissue. In fact, we use the cross country tool in almost all ablation cases except when there is bronchus through the centre of lesion and extending towards pleural surface. In our experience, the cross country tool provides a good support for laying down subsequent ablation catheter.
Changes to text: nil

Comment 4: We ourselves, users of Illumisite, have no tomosynthesis reconstruction that allows us to safely identify a 3 mm vessel without injection: can the authors explain to us if they are applying a particular protocol? And in fact we have the same results, namely a great difficulty in highlighting ground glass lesions unless there is a solid part large enough to appear.
Reply 4: We totally agree with your comment that ground glass lesions especially pure ones are difficult to visualize even with Illlumisite. Tomosynthesis reconstruction helps with lesions with some solidity, for example mixed GGO. The manufacturer's recommendation is that the limit for Illumisite tomosynthesis is 10mm GGO preferably with some solid component. Sometimes, even when the GGO is not readily seen, the surrounding pattern of vessels seen on tomosynthesis can still provide sufficient landmark for marking of the target lesion.
Differentiation between lesion and vessel on plain CBCT can be assisted by comparing pre-operative contrast CT scan with intraoperative CBCT. We may have been unclear, the 3mm vessel (Line 143-145) was seen on the cone-beam CT scan following ablation, and not by the tomosynthesis from Illumisite. We are sorry for any confusion.

Changes to text: Limitation of Illumisite for pure GGO has been added to Lines 201-203.

Comment 5: How do the authors think they can use Illumisite for this type of lesion? Won't CBCT become essential in this specific context of this type of lesion even of they want to spare radiation?
Reply 5: Thank you for your insightful comment. As mentioned above, we believe that mixed GGO visuality can be enhanced with Illumisite tomosynthesis reconstruction but pure GGO are more difficult. However, since pure GGOs have lower risk of malignancy, the need of ablation to these nodules are low. If pure GGOs indeed need to be ablated, we prefer to have proper CBCT spin after cross country needle insertion to confirm position first, because any further manipulation (eg. tunneling with dilator, laying down ablation catheter) will likely make the GGO difficult to see due to local hemorrhage or artefacts. In these cases we would not sacrifice accuracy for radiation reduction.
Changes to text: Limitation of Illumisite for pure GGO has been added to Lines 201-203.

Reviewer D:
Comment 1: This is a case report on a transbronchial lung nodule ablation procedure performed with the Medtronic Illumisite platform.
Information about the target tumor and patient characteristics are clearly presented, followed by description of the pre-procedural imaging, intra-procedural imaging and navigation, confirmation of ablation catheter positioning, ablation, and immediate assessment of the ablation zone.
Little technical detail about the Illumisite platform is provided – a summary of the platform's technical capabilities and the technology/techniques that enable these capabilities would be appreciated. This could be presented, for instance, around line 118, where the Illumisite's role in the procedure is introduced. In the article's present form, besides branding, little information is presented.
Reply 1: Thank you for your suggestion. Further description of Illumisite's role is added to the text.
Changes to text: Please see lines 124-126.

Comment 2: The primary contribution of the Illumisite platform is that it appears to provide a means to correct for predicted position of the target compared to virtual bronchoscopy. This appears to be facilitated by the tomosynthesis imaging taken with the C-arm. Please provide the difference in tumor position (e.g. center to center position) for the presented case relative to what would have been estimated on standard navigational bronchoscopy, just prior to Cross country needle deployment.
Reply 2: Thank you for your interest. We agree this is important information to be included in the case report but we do not have the exact figure. From fluoroscopy images comparing the tips of LG before and after Illumisite adjustment, the centre to centre position difference is estimated to be approximately 1-2cm.

Changes to text: No change was made to the text as we did not have the exact information on center-to-center distance.

Comment 3: Please provide an estimate of savings in procedure time (e.g. compared to range of time for other transbronchial ablations at the author's institution) and total radiation exposure that may be attributed to use of the presented platform.
Reply 3: Thank you for your question. Procedure time in the present case (first Illumisite ablation in our center) is 171 minutes, which is longer than the average of 134 minutes for conventional ENB ablation. This is likely because of the learning curve, and indeed more time is required to park the C-arm and generate Illumisite tomosynthesis. We believe with further experience, procedure time can be shortened. The average radiation dose for conventional ENB ablation was 27120μGym^2 while that in the current case is 26129μGym^2. We expect further reduction of radiation dose can be achieved by using the Illumisite platform when we are more familiarized with the system, as navigation accuracy is improved and fewer CBCTs are required to confirm entry into correct subsegmental airway.
Changes to text: Please see Line 142, and new paragraph in Lines 201-210 on the limitations of Illumisite.

Comment 4: The case report falls short of what would be anticipated for evaluation of an ablation procedure as the imaging assessment is limited to day of the procedure. Assessment of the treatment follow-up CT imaging at 30 days (or the standard protocol for the authors' institution) must be included.
Reply 4: Thank you for your kind reminder and the follow up CT has been included in the revised manuscript.
Changes to text: Please see Figure 7 for post 1-month and 4-month CT scans.

Comment 5: Please augment the description of the procedure planning presented at ~line 136. How is the predicted ablation margin calculated? By how much was the treatment margin overpredicted (please provide estimates of overprediction diameter as well as volume)? Does the prediction of the second ablation take into account changes in tissue characteristics following the first ablation?
Reply 5: Thank you for your insightful comment. The predicted margin is calculated by overlaying the size of ablation zone as provided by the manufacturer given a specific power for a specific duration. Minimal distance between the edge of lesion and the edge of ablation zone is defined as the predicted ablation margin. Treatment margin overprediction was non-uniform over different cuts of lesion, and on average by approximately 20-40% in the present case. After first ablation, we usually observe tissue contraction due to dehydration. Therefore, for second ablation margin evaluation, we also take into account tissue contraction by comparing pre-ablation CBCT with post-second-ablation CBCT. For example, if the ablation zone reached a certain vessel which was located 7mm from the edge of lesion before ablation, even if the final ablation result showed distance between vessel and lesion was only 4mm, we are confident of a 7mm margin kill.

Changes of text: Definition of predicted ablation margin was provided in Lines 136-138

Comment 6: Overall, this case report is well suited to the journal's audience, however is currently lacking important information that should be included.