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Reviewer A

I have only one commentsThe presence of a bronchus sign (or vessel sign sign) should be mentioned in the result part in the table 1 but also compared the diagnostic yield with and without this sign.

Reply: We have included data regarding presence or absence of bronchus sign to table 1, and calculations regarding diagnostic yield for positive or negative bronchus sign.

Changes in text: lines 213-227 in manuscript and table 1

Reviewer B

Your manuscript entitled "Characteristics of cone beam CT use combined with shape sensing RAB for the evaluation of pulmonary lesions: a prospective single center study" concluded that it is a safe diagnostic modality with relatively low radiation exposure comparable to other modalities. Fist, this is not a randomized controlled trial and therfore the findings are not te be concluded 'comparable to'. Second the manuscript doesn't present the diagnostic perfomance of their work in terms of diagnostic yield. This is critical in order to evaluate the value.The diagnostic yield in relation to radiation exposure could also be presented per user (n=5). Table 1 states that only in 53% rEBUS could deliver a concentric view. What happened in case an accentric view was obtained? Did the physician try to reposition the catheter in order to finally obtain a concentric image. This should be feasible but will result in higher radiation axposure. The same hold true for the 10% whch were unable to confirm. Given the current literature on RAB the rEBUS data presented should be further elaborated. Is the conclusion "relatively low radiation exposure" in line with some of the better data available (see REF Verhoven et al.)?

Reply: We thank you for your comments.

In reference to your first comment, we acknowledge that this is not a randomized controlled trial, with limited ability to draw conclusions from results.

Changes in text: In our abstract discussion we amended to state “We describe the use of ssRAB combined with CBCT to biopsy pulmonary lesions as a safe diagnostic modality with relatively low radiation exposure that is potentially comparable to other image guided sampling modalities.” Lines 51-53.

In reference to your second comment, we recognize that this manuscript will be more impactful by reporting utility of CBCT with ssRAB in terms of radiation exposure

with the addition of diagnostic yield. We included diagnostic yield as calculated from pathologic results at index bronchoscopy as we have less than 1 year follow-up available for these lesions based on study period. Given our group practice, we chose not to present per user.

Changes in text: lines 213-227

In reference to your comments on r-EBUS. We extracted this data from the procedure report as recording the optimal r-EBUS image obtained during the procedure. We did not record initial or subsequent r-EBUS imaging obtained, or maneuvers/adjustments performed by the bronchoscopist.

Changes in text: lines 139-141, lines 191-195

Our data is similar to previously described radiation dose use in bronchoscopic biopsy modalities. We have added a table 5 that summarizes studies utilizing CBCT combined with navigational bronchoscopy system for the evaluation of pulmonary lesions that reported radiation data.

Changes in text: lines 252-272, table 5

Reviewer C

This is a large, single center observational descriptive study on shape-sensing robotic assisted bronchoscopy with 3D-image confirmation using cone-beam CT. It is well written and concise manuscript. The main focus of the manuscript is radiation dose in this combination of technologies.

I have a number of remarks and comments that need revision:

Comment 1: A conflict-of-interest statement is missing.

Reply: This statement is included in the footnote per JTD's formatting guidelines: "Conflict of Interest: All authors have completed the ICMJE uniform disclosure form. Dr. Schwalk is a member of the Ambu advisory board. This role is unrelated to this study. The other authors have no conflicts of interest to declare."

Changes in text: none, lines 366-368

Comment 2:
Title / abstract:
The title and abstract are somewhat misleading. The main focus seems to be the radiation dose of CBCT use in combination with ss-RAB. But this is not immediately evident from the title nor the abstract. Based on the title I would have expect to read

more on clinical performance which is not offered. In the abstract's results, first irrelevant topics are addressed like age and nodule size, obscuring the intended key message namely DAP.

Reply: Thank you for your comments. We have edited the title to more accurately reflect the main focus of the paper.: "Radiation dose of cone beam CT combined with shape sensing robotic assisted bronchoscopy for the evaluation of pulmonary lesions: an observational single center study"

Changes in text: lines 3-4

Thank you for your comments on the Abstract Results section. We have edited to include pertinent results.

Changes in text: lines 42-49

Comment 3:
Key findings
"Technical factors" is hardly a term that is clear for readers. I take it you refer to the ALARA principles of working with radiation, and in general aim to use the lowest possible dose, and the smallest volume by active and dynamic use of collimation, and the realization that the angle of fluoroscopy greatly influences the radiation dose needed for imaging.

Reply: Yes, you are correct in our use of the term "technical factors"

Comment 4: Given the recent publication of this group on a slightly smaller cohort reporting a diagnostic yield of 91,4% [reference 4], where 200 patient procedures with 209 nodules are studied, this study now focuses on radiation dose in a cohort of 241 patients with 269 lesions. Given the reported observation periods in this, and the prior study, it is clear that a new cohort of patients is used for this current paper. But given the relative sizes of both cohorts, it is interesting to learn if the very high yield reported in the first study is maintained in this present cohort; clearly this is a high-volume center and experience with the technology has grown over time. How did this affect the yield per nodule?

Reply: You are correct in this manuscript details a new cohort.

We recognize that this manuscript will be more impactful by reporting utility of CBCT with ssRAB in terms of radiation exposure with the addition of diagnostic yield. We included diagnostic yield as calculated from pathologic results at index bronchoscopy as we have less than 1 year follow-up available for these lesions based on study period. We also clarified the methodology used to calculate yield in this manuscript compared to our recent manuscript with different methodology including

follow up and the use of diagnostic test accuracy methodology

Changes in text: lines 213-227, lines 314-320

Comment 5: Introduction:
Line 79/80: CBCT can also be used as a single tool for both navigation and confirmation of lesion access; additional navigation techniques are not mandatory when augmented fluoroscopy is used to its full potential.

Reply: Given our focus of this paper is on CBCT usage with ssRAB, we described this as an adjunct imaging modality to assist with lesion confirmation after navigation and during biopsy.

Changes in text: lines 101-102. We added in introduction that "CBCT usage has been described with guided bronchoscopy techniques such as ultrathin/thin bronchoscopy (15), manual ENB (16-18) and ssRAB. (2, 4, 19)"

Comment 6: Methods
You mention the registration / calculation / observation of CT-to-body diversion. It is unclear what is measured and how this was done.

Reply: This data was extracted data from the procedure report, and noted "if the bronchoscopist subjectively reported significant CT-to-body divergence affecting the procedure in their procedure report". This was not calculated. We added further clarification in the text.

Changes in text: lines 142-144, lines 207-209, lines 302-305

Comment 7: My assumption is that ssRAB was used to navigate, and when the system told you that the target was reached a CBCT spin was obtained and showed a difference. Was this the routine protocol? Please clarify what your protocol was and how you did measure the differences?
But more importantly, in the discussion you already indicate that no fixed protocol was used, and multiple bronchoscopists all used their personal preference, CBCT TIL was not mandatorty, radiation dose was not routinely stored let alone, the choice of scanning protocol was not standardized.
This makes it very difficult to interpret the results of this study.

Reply: Yes, we previously described our procedural technique in Styrvoky Lung 2022; in routine practice, yes most of the bronchoscopists would navigate to the target lesion using ssRAB and when in acceptable position, use adjunct imaging such as r-EBUS, or CBCT to visualize catheter to lesion positioning, and make adjustments. We did not measure any CT to body divergence.

Changes in text: lines 298-305

You are correct that we have no fixed protocol for these procedures. We are describing our experiences and outcomes in a group setting with varying practice patterns among the bronchoscopists using this combination of technologies that may represent post-marketing adoption and usage of ssRAB.

Changes in text: none

Reviewer D

The manuscript describes the technical factors associated with the use of cone beam CT (CBCT) combined with shape sensing robotic assisted bronchoscopy (ssRAB) to biopsy pulmonary nodules. The combination of CBCT and ssRAB used in pulmonary nodule biopsy is a new hot topic in the field of interventional pulmonology and research in this field should be highly encouraged. It is important to determine whether this combination truly results in a higher diagnostic yield and whether it is safe for the operators given radiation concerns.

Major concerns
1. Could the authors please explain better the clinical significance of the data reported in the manuscript? If the fluoroscopy time and radiation dose are considered “low and safe”, it is important to compare CBCT data with regular fluoroscopy data. I would recommend the authors go back to previous cases when ssRAB was used in combination with the c-arm and use that as a historical control.

Reply: The clinical significance is that there is limited data describing radiation use not only in ssRAB in conjunction with CBCT but with standard 2D fluoroscopy. Recently published data describing diagnostic yield with ssRAB including Oberg Lung 2022, Styrvoky Lung 2022, and Kalchiem-Dekel Chest 2022 did not report radiation use. The bronchoscopy literature has not routinely reported radiation use in manuscripts; for example, the NAVIGATE trial only listed if fluoroscopy or CBCT used during the procedure without additional information.

Our procedural room has a fixed CBCT, so every patient who is scheduled for a ssRAB has access to CBCT use during their procedure. We do not have data regarding ssRAB use with traditional c-arm for historical comparison.

Changes in test: lines 331-334. We added table 5 listing studies reporting radiation data in CBCT combined with navigational bronchoscopy systems; there is high variability in reporting metrics.

2. The technical factors, such as number of spins, total fluoroscopy time, and radiation dose, are important clinical information. However, unfortunately, the data itself seems

to be not comprehensive enough for a full manuscript worth publishing.

Reply: As described above, given the limited data available with this combination of techniques, we felt reporting our technical factors of CBCT use with ssRAB and providing radiation data on other diagnostic modalities is an important addition to the literature.

3. In methods, the authors mentioned the body-to-CT divergence. They described it as being measured subjectively, where the bronchoscopists were asked if there was significant CT-to-body divergence that affected the procedure. For research purposes, I think it is too vague as different people probably have difference definitions of such divergence. Did the divergence change how the bronchoscopist navigated to the nodule? Why did the bronchoscopist think there was a divergence? How much change was there when the CBCT spin was compared with the CT scan obtained prior to the procedure? Can the difference be measured using the imagine studies to confirmed the divergence?

Reply: Given this is a prospective observational study reporting outcomes from our institution with no set protocol for the procedure, we were only able to determine CT to body divergence as a subjective factor based on limited extracted data from the procedure report. Given variability in how the CBCT spins were performed, we did not do any calculation or measurements between pre-procedure and intra-procedure CT imaging. We recognize the limitation and agree that you bring up excellent questions for future research projects.
Changes in text: lines 142-144, lines 207-209, lines 302-305

4. In methods, the authors claimed that this was a prospective study. Can the authors explain what the inclusion and exclusion criteria were, please? The description in the manuscript is more consistent with a retrospective review study.

Reply: This was a prospective observational study of all consecutive patients who underwent ssRAB procedures using the Ion endoluminal system to sample pulmonary lesions between February 25, 2022 and March 8, 2023 at the University of Texas Southwestern Medical Center (UTSW).

We cited that we previously described our procedural technique in Styrvoky Lung 2022: “Patients with lung nodules or lesions were evaluated as inpatient or outpatient; the clinical judgment of the pulmonologist determined if the patient was scheduled for ssRAB or underwent other evaluation”

5. Can the authors further clarify when the CBCT spins were performed? Was there always an initial spin to see the nodule and eliminate the effect of atelectasis as much as possible? Was there always a spin to see “tool in the lesion”? What was the research protocol?

Reply: Most spins were performed after navigation, with subsequent spins after additional catheter adjustment or to provide tool in lesion confirmation if ROSE non-diagnostic. We did not have a set procedural protocol with no requirement for tool in lesion. We are describing our experiences and outcomes in a group setting with varying practice patterns among the bronchoscopists using this combination of technologies that may represent post-marketing adopation and usage of ssRAB.

Changes in text: lines 298-305

6. In the results, the authors reported that 24.2% of nodules were visible under fluoroscopy, and only <50% nodules were considered as peripheral. Can the authors please justify why those patients were recruited in this study instead of using regular C-arm/fluoroscopy?

Reply: Our procedural room has a fixed CBCT, so every patient who is scheduled for a ssRAB has access for CBCT use during their procedure. During this study period, we performed 282 ssRAB procedures, with ~89% utilizing CBCT. It has become routine and standard of care for our patients during these procedures to utilize these technologies. Per preference of bronchoscopist, CBCT performed even if lesion visible on 2D fluoroscopy to view catheter to lesion or other structures, assist in making adjustments or for augmented fluoroscopy.

Changes in text: lines 290-293

Minor problems
1. Can the authors share the ventilator settings for the procedure in the methods please?
Reply: We cited that we previously described our procedural technique in Styrvoky Lung 2022: “All procedures were performed under general anesthesia with specific ventilation settings at the discretion of the bronchoscopist, usually including higher level of positive end expiratory pressure (PEEP) and a tidal volume in the range of 8–10 mL/kg of ideal body weight.”

2. Given this is a prospective study, were the patients consented for the study?

Reply: Our IRB approved a waiver of informed consent under 45 CFR 46.116(c):

1. This research involves no more than minimal risk to subjects. No new data are being generated. Only existing standard medical data is being used. The nature of the data does not in itself pose financial, social, or reputational risk to the subjects if released.

2. No subject rights or welfare will be adversely affected by the fact that their data will exist in a research database.

3. It is not appropriate to provide the subjects with data regarding the study, as study databases will be de-identified for analysis.

Changes in text: lines 113-114

3. In results, the authors reported that EBUS was performed in 63.1% procedures. Can the authors explain the main reasons why EBUS was not performed in the rest of the procedures?

Reply: The choice of performing linear EBUS was at the discretion of the bronchoscopist if concern for primary pulmonary malignancy needed for staging. As detailed in our results and our prior publication (Styrvoky Lung 2022), we diagnosed non-pulmonary malignancies / metastatic disease, and non-malignant disease, where linear EBUS may not be required

Changes in text: lines 195-197

Reviewer E

I think this study has good value in reporting radiation dose, timing, feasibility in fixed CBCT and shape sensing robotic bronchoscopy.
Here are some feedbacks:
- In the introduction, first 2 paragraphs (on robotic bronch/ct body diversion) can be shortened but instead, it would be helpful for reader to understand the differences of different CT modalities (for example: fixed CBCT, mobile CT scan, conventional CT : time of each spin and dosing of each standard spin , safety dose for human etc)

Reply: Given the focus on CBCT, we further elaborated on differences in fixed vs mobile CBCT including acquisition time, portability, image quality and cost. As discussed later, doses vary based on system and setting, so we did not include in this section. Given conventional CT is not discussed as an adjunct imaging for bronchoscopic biopsy, we did not include further discussion in this section.

Changes in text: lines 90-100

- Method: Suggest mention about whether or not needle in lesion is confirmed for all the procedures or not. This would affect the timing and radiation dose in total. Also does this system allow updating the location of lesion on 2D fluoroscopy ?

Reply: We did not require tool in lesion confirmation. Yes, the Philips Allura Clarity system with Xperguide allows for segmentation of the nodule, then superimposing on 2D fluoroscopy for visualization. Subsequent CBCT spins and segmentation can adjust positioning.

Changes in text: lines 95-97, 127-130,

- Results: Do you have data on diagnostic yield for these procedures (6months-1 year?)? How many patients need another procedure? We can use CBCT anyway that we want but what the effectiveness of this method is? If not, I think you should list it in the limitation

Reply: We recognize that this manuscript will be more impactful by reporting utility of CBCT with ssRAB in terms of radiation exposure with the addition of diagnostic yield. We included diagnostic yield as calculated from pathologic results at index bronchoscopy as we have less than 1 year follow-up available for all lesions based on study period.

Changes in text: lines 213-22

- Complications: the pneumothorax rate for your study seems higher than other center (for example: 1.5% in the study at MSKCC. In our center, the pneumothorax rate is almost <0.5% when we use CBCT, same for the study by Reisenauer. Do you have an explanation for a relatively higher pneumothorax rate in your study?

Reply: We have included Table 5, which lists studies that detail radiation use with cone beam CT and navigational bronchoscopy systems; our pneumothorax rate is comparable.

Changes in text: table 5

Reviewer F

In this prospective single center study, the authors describe radiation exposure, overall safety data, and other procedural characteristics during the use of ssRAB with fixed CBCT in the largest cohort to date. The manuscript is generally well-written and easy to follow and provides interesting figures. The data that is presented will be informative to many clinicians, especially since the data for radiation safety in the setting of RAB with CBCT for lung nodule sampling is scare. I have only a few comments to strengthen the manuscript.

1. On lines 124-127, the authors make mention of how 282 ssRAB procedures were performed during the study period. Of these, 245 procedures used ssRAB with CBCT, however only 241 ssRAB with CBCT procedures were included due to available radiological data. Would the authors please comment on why 4 of these procedures did not have radiological data. The authors may consider including a figure to show the selection criteria used for the 282 procedures, and how they arrived at 241 procedures which met criteria for their analysis.

Reply: We have included a flow chart showing study inclusion. During the study period, radiation data was not routinely stored in the EMR, and required manual recording on data sheets; thus, for four cases this was inadvertently not performed. We have since subsequently been able to work with our institution to ensure this data is recorded in EMR (dose report automatically sent to PACS).

Changes in text: figure 3

2. To strengthen their discussion of the importance of radiation safety, the authors may consider mentioning what is the upper limit of safe radiation dose for a patient, and also what is the annual occupational radiation exposure limit for the operator and staff set by the national council on radiation protection and measurement (NRCP) and international commission on radiological protection (IRCP).

Reply: We agree; we have added information regarding annual occupation exposure limits and elaborated on the radiation safety paragraph.

Changes in text: lines 335-348

3. On lines 104-105, the authors make mention of precautions taken to minimize radiation exposure to the patients and staff per standard radiation safety protocols. Could the authors elaborate on their safety protocol and measures used to minimize radiation to the patient and staff? (e.g. other than the CBCT spin, was pulse vs continuous fluoroscopy used, was high vs low dose fluoroscopy used?)

Reply: While we did not record individual settings for procedures, the RTR would use clinical judgment to select pre-set system parameters, which often included low dose fluoroscopy and minimizing radiation on the CBCT. When sampling or adjusting catheter, we minimized use of fluoroscopy with pulse or continuous.

Changes in text: lines 345-348

4. It is very impactful that the authors compare the radiation exposure dose of their cohort with the radiation exposure dose of other lung nodule sampling techniques. Similarly, could the authors comment on the relative radiation exposure time of their cohort in comparison with other lung nodule sampling techniques?
a. Salahuddin M, Bashour SI, Khan A, Chintalapani G, Kleinszig G, Casal RF. Mobile Cone-Beam CT-Assisted Bronchoscopy for Peripheral Lung Lesions. Diagnostics (Basel). 2023 Feb 21;13(5):827.
b. Pritchett MA, Schampaert S, de Groot JAH, Schirmer CC, van der Bom I. Cone-Beam CT With Augmented Fluoroscopy Combined With Electromagnetic Navigation Bronchoscopy for Biopsy of Pulmonary Nodules. J Bronchology Interv Pulmonol. 2018 Oct;25(4):274-282.

Reply: We added further discussion on these two sources and added table 5 listing radiation exposure use in studies utilizing CBCT with navigational bronchoscopy systems.

Changes in text: lines 252-272, table 5

5. While DAP and CAK may be a good surrogate measurement for the amount of radiation delivered to a patient, it may not accurately represent the radiation dose the operator and the staff are exposed to. Is the radiation dose exposure measured by individual dosimeters available? If so, the authors may consider including this in their results and discussion, since this may be more relevant when considering radiation safety in the setting of annual occupational radiation exposure limits.

Reply: Yes, per our institutional guidelines, all employees wear radiation dosimeters to monitor occupational radiation exposure limits. We agree that this would be insightful information. Given we wear our badges for all procedures that utilize fluoroscopy/CBCT, this encompasses many additional procedures other than ssRAB, and thus may misrepresent radiation exposure.

Changes in text: lines 339-343

6. Although the focus of this manuscript is the radiation exposure data provided by their cohort of ssRAB combined with CBCT for lung nodule sampling, it may still be worthwhile for the authors to mention their diagnostic yield, diagnostic accuracy, localization success, percentage of tool-in-lesion if that data is available (I assume localization success was at least 89.6% based on the r-EBUS view data provided). Per their previous retrospective analysis, 200 procedures were evaluated. Since this is a larger cohort of the ssRAB with fixed CBCT analyzed, this data may benefit the readers and future investigators, who may want to reference this data in future studies.

Reply: We recognize that this manuscript will be more impactful by reporting utility of CBCT with ssRAB in terms of radiation exposure with the addition of diagnostic yield. We included diagnostic yield as calculated from pathologic results at index bronchoscopy as we have less than 1 year follow-up available for these lesions based on study period.

Changes in text: lines 213-227

Reviewer G

Thank you for the opportunity to review this manuscript from Styrvoky et al regarding characteristics of cone beam CT use during shape sensing robotic bronchoscopy. The manuscript contains interesting data and is well-written. However, I have several comments that may serve to improve it:

1) The title does not completely capture the essence of the work. The manuscript is primarily about radiation exposure during CBCT in these procedures. Therefore, the title should have some mention of this.

Reply: Thank you; yes, we have edited our title.

Changes in text: lines 3-4

2) The work contains a unique dataset capturing radiation exposure as well as the presence of CT to body divergence. Would it be possible to look for patient or lesion factors associated with 1) CT to body divergence (BMI, lesion location, etc) as well as 2) RT exposure. This might be interesting to see and might provide pre-procedural data to inform a more difficult procedure and potentially allow for interventions to minimize these effects in the high-risk population.

Reply: We added table 5, which compares patients with no or significant CT to body divergence, we included significant patient factors and radiation differences between these two groups.

Changes in text: lines 209-211

3) The authors recommend that bronchoscopists be mindful of RT dosing during these procedures and work to reach “as low as reasonably achievable” doses. While this is certainly worth emphasizing, the manuscript might have more utility if it contained specific suggestions for achieving this.

Reply: We have added an additional section on recommendations for ALARA best practices.

Changes in text: lines 344-348

4) One significant limitation of the study is lack of a uniform workflow for imaging during these procedures. This information would be helpful to allow proceduralists to relate the study data to their own practice. Is it possible to provide even a general overview? With a mean number of 1.5 spins, it should mean that some do 1 and some do 2. Would be interesting to know when the first spin is performed at least. After navigation is finished? Needle out vs. catheter alone?

Reply: Although we had no set procedural protocol, we did further elaborate in the text in regards to general workflow for the reader.

Changes in text: lines 298-302

Reviewer H

Overall, a well written large cohort prospective study that outlines radiation exposure of fixed CBCT usage along with ssRAB, which have not been well published in the past.

To further strengthen the paper, consider the following:
1) Compare fluoroscopy associated radiation exposure with ssRAB, as most institutions with robotic bronchoscopy still use fluoroscopy rather than CBCT.

Reply: We did not record this information prospectively, and during the study period the radiation dose report was not routinely stored in the EMR. Unfortunately, this data is unavailable.

2) Clarify if any variability in radiation exposure and procedural duration between bronchoscopists?

Reply: Given our group practice, we chose not to analyze data individually among bronchoscopists.

Minor
Line 30 – Methods: We conducted a single center, prospective study of patients undergoing ssRAB combined with fixed CBCT for the pulmonary lesion biopsy. We report our patient demographics and pulmonary lesion and procedural characteristics.

Reply: Thank you; we have edited.

Line 57 – under direct visualization (this only applies to Monarch) with easy catheter.

Reply: Both Monarch and Ion allow for navigation under direct vision; Monarch allows for direct vision during biopsy.

Reviewer I

The authors main outcome was technical aspects of combined CBCT and RAB.
I would suggest the following:
1-A table summarizing all studies using CBCT and navigational bronchoscopy with radiation dosages as a comparison

Reply: We have added table 5, which lists studies using CBCT and navigational bronchoscopy systems that reported radiation doses.

2-Outcomes of tool in lesion, diagnostic yield following procedure along with sensitivity of malignancy, prevalence of malignancy. these are important as it can

confirm the additional use of CBCT in RAB

Reply: We recognize that this manuscript will be more impactful by reporting utility of CBCT with ssRAB in terms of radiation exposure with the addition of diagnostic yield. We included diagnostic yield as calculated from pathologic results at index bronchoscopy as we have less than 1 year follow-up available for these lesions based on study period.

Changes in text: lines 213-227