Peer Review File
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Reviewer A:

Comment 1: The authors carry out an excellent review of the current technology used in the diagnosis of pulmonary nodules, technology that is increasingly advanced and complex but whose real reliability is difficult to assess.

As described to the authors, there is still a significant disparity in analytical criteria and selection biases that allow the different techniques to be accurately compared. However, there is no current prospective comparative literature
between RANB and CBCT, AF, EMN or a combination of technologies.

The increase in technology usually leads to an increase in the economic cost of such tests, sometimes hardly justifiable in relation to the improvement generated. This improvement should be justifiable by a significant increase in reliability or patient safety.

The description of their hybrid technique is accurate and provides a great structural advantage by having all the necessary apparatus available in a single scenario. In future studies, it would be interesting to have the results available on a sufficient sample of patients acquired prospectively and which eliminates selection bias. Similarly, it would be very interesting to know the cost of each procedure in comparison with the basic standard technique (e.g. TTNB) and thus compare the diagnostic accuracy of both techniques, since not all centers have sufficient resources or budgets to have this technology available.

Congratulations to the authors for the excellent review and for the refined description of their own technique.

Reply 1:
The authors would agree that future studies looking at the cost-effectiveness analysis by technique would aid medical centers and health systems in the decision making process when considering which technology to purchase. Discussion added page 12, lines 637-638.

Reviewer B:

Comment 2:
In the section “Cone Beam CT and Augmented Fluoroscopy”, page 6/line 191 , add reference (Kheir F, Thakore SR, Uribe Becerra JP, Tahboub M, Kamat R, Abdelghani R, Fernandez-Bussy S, Kaphle UR, Majid A. Cone-Beam Computed Tomography-Guided Electromagnetic Navigation for Peripheral Lung Nodules. Respiration. 2021;100(1):44-51) which showed increased diagnostic yield when EMN/CBCT was compared to EMN alone using strict definition.

Reply 2: This citation has been added to the section aforementioned. It can now be found on page 7 line 410-411. Table 2 has also been updated to reflect the addition as has the references list.

“A retrospective comparison study of EMN and CBCT versus EMN found increased diagnostic yield of 74.2% with EMN+CBCT compared to 51.6% with EMN alone using a strict definition of DY.”

Comment 3:

The authors specified in search strategy until 04/01/2023. However, they need to discuss a relevant meta-analysis to their submitted manuscript, reference (Kops SEP, Heus P, Korevaar DA, Damen JAA, Idema DL, Verhoeven RLJ, Annema JT, Hooft L, van der Heijden EHFM. Diagnostic yield and safety of navigation bronchoscopy: A systematic review and meta-analysis. Lung Cancer. 2023 Jun;180:107196)

Reply 3:
A discussion of this metanalysis has been added to the manuscript. It can be found on page 4-5 lines 191-223.

"Two systematic review and meta-analyses have been published on this topic. Nadig et al. found an overall DY for guided bronchoscopy of pulmonary lesions to be 69.4%. They found no difference in DY in studies prior to 2012 compared to after 2012, suggesting no improvement in DY with advances in technology.[16] In subgroup analysis there was no difference in DY when newer technology was added, though the limitation of this study is that all new technologies such as CBCT, RANB, and augmented fluoroscopy (AF) were grouped into a single category in subgroup analysis. Kops et al. published a similar meta-analysis using different study selection criteria, and found an overall DY of 70.9%. This study did do subgroup analysis of technologies used and found that newer techniques, including CBCT, RANB, and tomosynthesis based EMN have a statistically higher DY than older techniques, suggesting that there has been some improvement in DY when evaluating the newest technology.[17] Kops et al. also categorized studies by the definition used by Vachani et al. but found no statistical difference in DY when comparing studies that used a liberal definition of DY to those that used a strict definition. However, both of these studies comment on the significant study heterogeneity, which is primarily due to the variation in study design and DY definition."

Comment 4:
The body of manuscript referred to Table 1 but there is a typo error as the Table on page 9 was titled Table2!

Reply 4:
The table has been appropriately updated with the addition of another table.

Comment 5:
Add a paragraph discussing different biopsy modality treatment including cryobiopsy for peripheral lung nodules

Reply 5:
The scope of this review is to enhance the understanding of new technologies used to reach peripheral nodules and the relative diagnostic yield of each technique. While the authors agree that various biopsy modalities may have different yields, there is very little literature conducted to directly compare biopsy tools in the periphery. While there has been a suggestion of added yield with transbronchial needle aspiration, this has not been studied experimentally (Ost DE. Reply: Quantifying the Benefits of Peripheral Transbronchial Needle Aspiration. Am J Respir Crit Care Med. 2016 Jul 1;194(1):122-3). Ongoing clinical trials should help clarify the questions surrounding cryobiopsy in the periphery for nodules (NCT05751278). For completeness, we will includes a few comments about this data. A discussion on biopsy technique has been added on page 5 lines 225-233

"Another area of variation in bronchoscopic literature has been the type of biopsy tool used in diagnosing PPNs. The AQuIRE registry showed the marginal benefit of peripheral transbronchial needle aspiration (TBNA) when added to transbronchial biopsy with forceps, broncheoalveolar lavage, and brushings to be 6.3%, but that must be weighed against the marginal risk incurred by performing needle

aspiration.[18] The added benefit of TBNA remains to be studied in a prospective randomized fashion. The author in this response notes a significant amount of resources would have to be used to answer this question appropriately. More recently, cryobiopsy is being considered for the diagnosis of peripheral pulmonary nodules. It has not been prospectively evaluated, however, ongoing clinical trials should help clarify the utility of this emerging technology (NCT05751278)."

Comment 6:
Discuss radiation effect of CBCT with references

Reply 6:
Paragraph of the dose of radiation exposure from CBCT on page 7, lines 417-427.

"One of the concerns of CBCT has been added radiation exposure to patients. Various studies have evaluated the dose of radiation exposure using CBCT and the most important factor is the number of image acquisitions. Radiation exposure varies by device and number of images per spin. A phantom study in 2014 demonstrated radiation doses of 0.98-1.15mSv from CBCT without AF.[38] More recent literature has demonstrated the learning effect associated with the use of CBCT with AF. In one study radiation doses decreased from 14.3mSv per case to 5.8mSv per case over a 3 year period as bronchoscopists became more adept at using the technology.[39] For comparison, the radiation dose for a low dose CT in the National Lung Cancer Screening Trial (NLST) was 1.4mSv.[40] While the radiation exposure of a single CBCT spin is similar to that of a low dose CT, the risk of higher exposure with more image acquisition brings up the importance of having more data to determine if a tool-in-lesion spin increases DY enough to justify a higher radiation dose."

Reviewer C:

Comment 7:
This is review on the growing body of evidence showing the increased diagnostic yield and safety of advanced guided bronchoscopy for the diagnoses of peripheral pulmonary nodules.
In the recent years, many reviews have been published, underlining the interest in this field and need for direction in the multitude of studies, technologies and outcomes. Likely, this need for direction is based on the wide variety of definitions used to present diagnostic outcomes. Vachani etal [ref 12 in this manuscript] have published on the massive effect of definition on outcome as the authors also underline and discuss. However, the impact thereof is not presented clearly in this manuscript.
But whereas recent studies like the systematic review published by Kops in Lung Cancer [https://doi.org/10.1016/j.lungcan.2023.107196] have used this to show the impact thereof, this manuscript does not. Also another recent review by Nadig in Chest 2023 is not included in this manuscript. Compared to these reviews this narrative review does not have the same level of completeness.
Regretfully, therefore this manuscript does not really add new insight to the current body of evidence, it's narrative nature lacks reference to the most recent publications that do support their conclusion that newer technology and the integration of high-end 3D imaging with cone-beam CT in navigation bronchoscopy procedures is of added value.

Reply 7:
A discussion of the two meta analysis mentioned has been added (page 4-5 lines 191-223). This narrative review has different objectives than those studies. While their objective was to understand the overall diagnostic yield of navigational bronchoscopy and in one case variation by technique, the objective of this study is to discuss each technique in further detail, including discussions on the technological basis of the

techniques, the data that exists for each technique, and a discussion on the limitations and strengths of that data. This review also provides a practical approach to the application of these techniques as used by the authors currently.

Reviewer D:

Comment 8:
maybe on other method should be added on this manuscript (VB planner+ r-EBUS), which is very useful and cheaper : Lachkar S, Perrot L, Gervereau D, De Marchi M, Morisse Pradier H, Dantoing E, Piton N, Thiberville L, Guisier F, Salaün M. Radial-EBUS and virtual bronchoscopy planner for peripheral lung cancer diagnosis: How it became the first-line endoscopic procedure. Thorac Cancer. 2022 Oct;13(20):2854-2860. doi: 10.1111/1759-7714.14629. Epub 2022 Aug 29. PMID: 36054681; PMCID: PMC9575082.

Reply 8:
While the above listed study provides value in understanding the utility of preprocedural navigational planning, this review intends to specifically highlight new technology's attempts to reduce historical barriers to higher diagnostic yields (specifically CT to body variation). The technique and technology listed above does not use intraprocedural imaging. The authors do note that the above study does highlight the importance of identifying the cost effectiveness of these new technologies but that is not the objective of this narrative review. A discussion of this study has been added to page 5-6, lines 345-348.

"As the initial navigational technology has emerged, it is worth mentioning that VBN offers a more cost-effective option. VBN does not consume disposables or require the purchase of extensive hardware beyond the traditional guidance of r-EBUS. VBN has performed well when combined with r-EBUS even in the prospective setting.[1,21–23] However, this technology, as well as other virtual and EMN based techniques are limited by CT-to-body divergence, differences between the pre-procedure CT mapping and the true anatomy of the PPN during bronchoscopy.[24]"

Comment 9:
maybe citation should be avoided in abstract and conclusion

Reply 9:
Citations removed from abstract and conclusion.

Reviewer E:

Comment 10:
In "Our hybrid approach": can you clarify what EMN or RAB system and CBCT system you are utilizing? (Based on photo is Philips – Allura or Azurion?)

Reply:
Please see page 10 rows 529-530.

"The authors have access to both the Monarch and Ion RANB systems that we have combined each with the Phillips Azurion ceiling mounted fixed CBCT system."

Comment 11: Please elaborate on why endotracheal tube is shortened.

Reply: See page 11, line 568-574

"This is to further assist the C-arm clearance with the endotracheal tube during image acquisition, as well as optimize the robotic platform's interface with the patient"

Comment 12:
Do you use a scope holder when performing the CBCT spin during navigational bronchoscopy, or is someone holding the bronchoscope in place? Ask as this may affect bronchoscopic motion or exposure of staff to additional radiation during spin.

Reply: See page 11 lines 598-600

"If RANB is not available and a nodule is reached using navigational bronchoscopy, a scope holder is utilized during any further CBCT image acquisition to avoid radiation exposure to operators."

Comment 13:
I understand the patient wrapping as we perform at our institution as well, but for proceduralists unfamiliar, may clarify how patients are wrapped, so they can use this if starting their own CBCT/ navigational bronchoscopy programs.

Reply 13:
See page 11 lines 571-574

"To do this, two operating room staff place the patient's arms against their sides and secure bedding under one arm. Then the staff cross the bedding over the anterior surface of the patient and place the patient in a semi-lateral decubitus position to tightly wrap the bedding under the patient's opposite side. The patient is then returned to the supine position."

Comment 14: In Hybrid OR flow sheet: third box is "RANB EMN leads placed on patient and patient wrapped tightly with ***" appears incomplete.

Reply 14:
See updated OR Flow figure with "bedding" in place of "***"

Comment 15:
can you clarify what EMN or RAB system and CBCT system you are utilizing? (Based on photo is Philips – Allura or Azurion?)

Reply 15:
Please see page 10 rows 529-530.

Comment 16:
After reading the flow sheet and paragraph, I am unclear as to timing of the CBCT spin: is it immediately after intubation prior to or after navigation OR both?

Reply 16:
Figure 1. has been updated to be consistent with the paragraph. Currently the authors perform a CBCT spin after navigation to the nodule using RANB, then a spin is performed with a r-EBUS probe in place to perform segmentation for AF. However, the authors note there is no good data to suggest that a CBCT spin performed after navigation is superior to a CBCT spin performed immediately after intubation.

Comment 17:
On C: “Segmentation of PPN”: why did you select mediastinal views rather than lung to visualize nodule being segmented?

Reply 17:
The image has been updated with lung windows. There is no preferred windowing for segmentation used by the authors.

Comment 18:
On D: “Augmented fluoroscopy overlay in active navigation”: I do not see this image included.

Reply 18:
Image added to figure OR Flow.

Reviewer F:

Comment 19:
This narrative review describes the different navigation modalities and ends with a clear description on how the authors' utilize robot assisted navigation bronchoscopy with CBCT navigation bronchoscopy. Earlier this year two comprehensive meta-analyses were published by Nadig et al en Kops et al. these meta-analyses showed a more comprehensive review of the literature. These reviews also focused on the strictness of definition proposed by Vachani et al. Additionally a multitude of narrative reviews have been published in the past 2 years, also covering robotic bronchoscopy and CBCT guided bronchoscopy quite extensively. Unfortunately, based on this body of recent literature I do not see the added scientific value of this paper although it is well written.

Reply 19:
While this narrative review follows two systematic metanalysis the objective of this review is different from that of the two metanalyses. While those two reviews sought to understand the study heterogeneity and bias that affects diagnostic yield, this review is aimed to provide a synopsis of current literature and how the authors interpret that literature to directly apply it to their bronchoscopic method. Neither of the aforementioned metanalyses are aimed at providing practical guidance for thinking through available new technology and employing it. Our goal is to summarize the newest technology and helped readers understand key differences between them as well as rationale for their development. This is particularly important as community based health care systems have increasing access to the available technology, but must decide which techniques to practically implement and how to go about building their navigational bronchoscopy platform.

Reviewer G:

Comment:
Three robotic platform is available in US.
Please add comparison table of those three platform performance strong and week points.

Reply: This table has been added as “Table 1.” in the manuscript

Reviewer H:

Comment:

Recently, thanks to a rapid increase in technology available for the biopsy of pulmonary nodules, the diagnostic yield for the peripheral pulmonary nodules has seemed to be improved. In our institution, we utilize ENB with CBCT under general anesthesia. RANB is also an emerging navigational bronchoscopy. This review to consider the difference of diagnostic accuracy using navigation tools currently available is important. This narrative review seems to be well structured.

Reply: The authors appreciate the reviewers comments on this manuscript.