

Peer Review File

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Reviewer A Comments:

This is a review article that discusses technological advancements in the field of navigation bronchoscopy along with the three phases in the bronchoscopic diagnostic continuum: navigation, position confirmation, and acquisition along with a focus on the use of cone-beam CT (CBCT).

This is a well written, comprehensive review of the development of peripheral and navigational bronchoscopy with emphasis on recent technology including augmented fluoroscopy and CBCT. The authors offer a complete picture of the different challenges that have been faced in the field and the technological approaches to address such challenges. They also offer perspectives for future development. The figures/pictures are also very helpful in describing the available technology.

Reply: We thank the reviewer for these friendly comments

Changes in the text: NA

Reviewer B Comments:

Thank you for this comprehensive, insightful and amazing article from one of the world's most experienced group in this technology. There is very little that they have not covered. I have a few comments that the authors may want to discuss or share their experience with the reader.

1. At times, we have found the overlay of CBCT-AF can be useful to outline pleural edges / fissures to potentially help avoid complications such as pneumothorax.

Reply 1: We thank the reviewer for this comment, indeed we use similar markers as we use to identify the bronchi leading to the target lesion, also to mark the margins in case we are sampling very near to the pleura.

Changes in the text: We added: "In cases of sampling very near the pleura is required, it can be useful to outline the pleural edges as well as margin reference." (Page 10 line 335)

2. Another possible limiting factor in mobile 3D-CT units for guiding biopsy (and ablation) is that the software used for overlay and other software tools normally found in CBCT systems are lacking in the mobile systems.

Reply 2: Thank you for pointing out this issue, we have added a remark underlining this issue

Changes in the text: We added: "Another barrier in mobile system application is the lacking software tools for outlining the lesion and navigation trajectory intra-procedurally as well as the overlay during navigation, as are available in CBCT systems." (Page 12, line 399)

3. We have found that occasionally the overlay taken from the CBCT can be quite inaccurate. I wonder whether this group has this experience? Apart from the breath hold while acquiring the CBCT that causes the lung to be in different position, is there any other explanation?

Reply 3: Indeed, the segmented lesions and other markers placed on the CBCT made on breath hold are not continuously exact on spot. This is explained by breathing and the stress imposed on lung tissue by the catheter and sampling tools.

Changes in the text: We added: "This is explained by breathing (CBCT acquired in breath-hold and AF performed under continuous breathing) and the stress imposed on lung tissue by the catheter and sampling tools." (Page 14, line 484)

4. I wonder if the group can shed light on the different types of CBCT systems, for example, rotating arm (Siemens), spinning c-arm (Philips), as well as floor mounted and ceiling mounted systems?

Reply 4: Thank you for your comment. We indeed have the luxury of being able to work with both Siemens and Philips systems. The most important differences are that a ceiling mounted system leaves much more room for us, standing at the head of the patient. A further difference is the time needed to complete a spin and the software and interface at the workstation. We have added additional information on this topic.

Changes in the text: "The options per CBCT supplier differ on some points, so are ceiling mounted systems easier to use as these systems leave more room at the head of the patient compared to floor-mounted systems. The interface at the workstations differs in usability, in particular when it comes to outline the lesion and navigation pathway. Philips' software allows manual outlining in one slice orientation after which the lesion is visualized in 3D. In Siemens' software tools, the inner and outer margins of the lesion must be drawn in two directions to enable 3D rendering. There is minor difference in spin time, with longer spin time for Siemens CBCT systems." (Page 11 line 384)

Reviewer C Comments:

Thank you for submitting a very informative review article. The authors addressed various endobronchial biopsy techniques in the perspective of navigation, confirmation, and acquisition. The manuscript is well-written and easy to follow. However, the following issues raised my concerns.

Major issue:

1. Although the authors presented figures for rEBUS, CBCT-AF, and CBCT based navigation bronchoscopy, authors introduced other navigation tools such as ultrathin bronchoscopy, virtual bronchoscopy navigation, electromagnetic technology, multi-modality reconstruction, and robotic endoscopy. There are many limitations to understanding if readers read-only in writing. Please provide additional information to readers with specific figures or videos for these techniques

Reply 1: We would like to point out to this reviewer that our manuscript is an invited review, as part of a series of articles that focus on these other techniques. We were asked to focus on CBCT and therefore intend to keep this current focus. As we feel some introduction to the other

techniques is also needed to be able to read this practise review as a single paper and as we are aware that the vast majority of physicians will use a combination of modalities, these were also briefly highlighted.

Changes in the text: N/A

2. In addition, it will be helpful to readers to present a table that summarizes the advantages, disadvantages, and indications of the various navigation tools, confirmation tools, and sampling tools introduced by the authors.

Reply 2: We thank the reviewer for this comment. However, we do not think it possible to summarize the technology in detail in a table format. The current state of art and comprehension on navigation bronchoscopy is more than an overview on technique could provide. Because the detail is what matters in these millimeter sized nodules and there is a handful of clinical details to take into account, a more detailed understanding of the procedure and technique is needed. We hope the reviewer agrees to omit this table as this matter is more than a summation could provide, and that it is also not the focus of this article.

Changes in the text: N/A

3. In addition to specific figures of representative studies, most of the contents in the review article should be based on evidence. However, in this manuscript, there are no references to explain each technology, so the reliability seems to be low. To supplement this, add references in the technical descriptions throughout the manuscript.

Reply 3: Thank you for this comment. In this manuscript we have included all relevant and state of the art literature to our knowledge and considered relevant. We obviously disagree with this reviewers' classification that our work in this manuscript is of low reliability. For the purpose of this invitational manuscript we wanted to focus on clinical precise issues for which not always exact references are available. Based on the reviewer's comments, we have however have revised some technical descriptions and have added references where appropriate.

Changes in the text: We have added refs in the following lines: 157, 177, and 401.

Minor issue:

1. Page 2, line 59: "rapid onsite evaluation" is not clear for the readers. Please suggest more specific information in the abstract.

2. Page 2, line 62: "CBCT-AF" – Please provide the full name.

3. Page 3, line 91: Interrogative sentences are a good way to get the reader's attention, but they don't seem appropriate here. Consider translating it into a declarative text.

4. Page 7, line 253: "(i.e. (23,32,56))" is not complete. Please revise this appropriately.

Reply to minor comments:

ROSE: is very well known in this field, we have added the word: cytology for clarification
CBCT-AF: We have added (CBCT-AF) in the abstract. In the main text it is mentioned on page 10 line 325. Interrogative sentence: The sentence: 'But are the currently available approaches able to fulfil this emerging demand?' is replaced by: 'However, it must be considered whether the currently available approaches are able to fulfil this emerging demand' (Page 3, line 95).

Reference: i.e. was deleted, the used references are stated as examples. This topic will be part of a specific manuscript in this series.