

Article information: <https://dx.doi.org/10.21037/jtd-23-681>

Reviewer A

I have minor comments to make:

Lines 20-21: and metastases from extrathoracic malignancies (instead "and extrathoracci lesions").

Response: Thank you for your comment. We have made changes as per your suggestion. (revised manuscript, page 2, line 32-33)

Lines 66-67: incur in higher cost for the two treatments, as well as potentially longer and more difficult diagnostic sessions.

Response: Thank you for your comment. We have made changes as per your suggestions. (revised manuscript, page 4, line 81-82)

Lines 68: I won't say EUIS-B is a novel technique, the studies of Herth and Wangboo were published almost 10 years ago.

Response: We agree in part. However, in medicine, we feel it is a relatively new technique if it has been in practice for roughly the last decade.

Line 91-92: Moreover, this technique...this sentence is redundant.

Response: Thank you for your comment. We have deleted this sentence as per your suggestion.

Line 128; and station 1...and station 3P.

Response: Thank you for your comment. We have made changes as per your suggestion. (revised manuscript, page 6, line 140-141)

Line 142-143: centrally rather than near the main airway...this sentence is confusing, please consider rewrite.

Response: We have reevaluated the sentence in question. After thorough proofreading, we've concluded that the sentence does not contain any major errors and do not feel that it is

confusing.

Line 152: For mediastinal staging of lung cancer.

Response: Thank you for your comment. We have made changes as per your suggestion. (revised manuscript, page 7, line 166)

Line 156-157: "inaccessible to bronchoscopic samplit via the airways" What does it mean? Were they out of the reach of conventional bronchoscopy?

Response: Yes, this means they were out of the reach of conventional bronchoscopy.

Reviewer B

In this narrative review, the authors have provided a concise and comprehensive overview of EUS-B-FNA for diagnostic and staging purposes, covering the literature from the past to the present. The topics covered are essential for the clinical implementation of EUS-B-FNA and are likely to be of interest to many readers. The authors' efforts are commendable. I have a few minor comments:

In the transbronchial approach, mediastinal cryobiopsy and EBUS-IFB have become new topics of interest. It would be helpful for readers to know the authors' opinion as experts in this field on when to use these new techniques versus EUS-B, which would provide valuable information.

Response: Thank you for your comments. Mediastinal cryobiopsy and EBUS-IFB are considered to be complementary to EBUS-TBNA for patients with intrathoracic lymphadenopathy either when additional tissue is requested for comprehensive molecular testing or for suspected lymphoma and sarcoidosis. However, there are some reports that the complication rates of the combined approach are higher than with EBUS-TBNA alone. Finally, considering the depth of these topics, we feel that these topics would be best addressed in a future study.

In my opinion, the discussion of the hybrid scope of EBUS and EUS at the end raises some doubts (unless it is actively developed by a specific manufacturer). Longer scopes have limited applications, such as right adrenal puncture, and may complicate procedures in the transbronchial approach. In addition, it may cause confusion regarding compatibility of

biopsy devices.

Response: Thank you for your comment. We have deleted this sentence as per your suggestion.

Lines 199-203: Please italicize "EGFR" and "EML4-ALK".

Response: We have made changes as per your suggestion. (revised manuscript, page 9, line 214-218)

Line 249: Please spell out "22-G" as "22-gauge".

Response: We have made changes as per your suggestion. (revised manuscript, page 11, line 264)

Reviewer C

This review explains the importance of EUS-B-FNA as a diagnostic technique, covering its application in diagnosing lung cancer, sarcoidosis, and extrathoracic lesions, as well as potential adverse events and the need for proper training. As such, it should be of great interest to readers of this journal.

1. P4L109; Please provide a list of references cited for the technique described as follows: "The CP-EBUS scope is inserted into the esophagus carefully rotating and advancing the scope under visual control to the gastric fundus."

Response: Thank you for your comment. We have added references. (revised manuscript, page 16, reference no.14 and 15)

2. P4L111; The authors recommend making circular movements and performing intermittent suction during scope insertion to localize anatomic landmarks, stating that this helps prevent the esophageal tract from deflating. However, it is unclear whether this approach is appropriate for confirming images by EUS, as the collapse of the esophagus may be necessary for optimal visualization. Without proper clarification, this recommendation seems inconsistent with the goal of EUS examination. Therefore, the authors should either provide additional information on the need for luminal observation, or consider deleting this sentence altogether.

Response: Thank you for your comment. We have deleted this sentence as per your

suggestion.

3. P4L113; The authors note that they sometimes inject low-flow oxygen (1-2L/min) through the working channel using a connected tube during the transesophageal approach to facilitate visualization. However, it is unclear whether this technique has been previously reported for EUS-B-FNA. If this is the case, the authors should provide appropriate references to support their approach. Otherwise, they should consider removing this sentence from the review.

Response: Endoscopic visualization of EUS-B-FNA is limited while maneuvering the scope within the esophagus, because it remains collapsed. However, instilling oxygen through the working channel of the bronchoscope can partially improve visibility. We have added two references to support this approach (revised manuscript, page 16, reference no. 14 and 16). According to Lee et al., this approach of injecting low-flow oxygen is utilized to facilitate visualization. (reference no. 14: PLoS One 2014;9:e91893. See Materials and Methods, EUS-FNA-B/E using a EBUS bronchoscope session)

4. P9L273; Are you sure you're not misspelling 'celiac' as 'coeliac'?

Response: We have rechecked and “coeliac” is the correct spelling. (you can see it reference no.54)

5. Describe whether complications of EUS-B-FNA for left adrenal lesions have been reported.

If not reported, please describe them.

Response: There were no reported complications of EUS-B-FNA for left adrenal lesions. (revised manuscript, page 20, reference nos. 45–52)

6. P10L324; The authors suggest that a hybrid scope combining the capabilities of an EUS scope with the size of an EBUS scope could potentially enhance the diagnostic yield of EUS-B-FNA for intrathoracic and extrathoracic lesions, and make the technique more widely accessible. However, there is limited evidence to support this claim, and it is currently unclear whether such a device is feasible. Therefore, the authors should consider revising this statement or providing additional evidence to support it, or alternatively, they may choose to remove this sentence from the review.

Response: We have deleted this sentence as per your suggestion.

Reviewer D

This is an interesting and comprehensive narrative review aimed at describing the technical issues, the indications, the safety profile and the performance characteristics of EUS-B-FNA. No reviews are available in the literature with a specific focus on this endosonographic technique.

I have only minor comments.

-Introduction/lines 89-92: I suggest adding two references to this conclusive sub-paragraph (Mondoni M, et al 2015 Oct;106(5 Suppl 1):13-9 and Oki M, et al. Chest. 2015 May;147(5):1259-1266)

Response: Thank you for your comment. We have added the two references as per your suggestion. (revised manuscript, page 15-16, reference No.12 and 13)

-Techniques/lines 117-120. All this paragraph should be carefully explained and rephrased. What does “the TBNA portion of the esophagus” mean? The sentence “in some ways EUS-B-FNA.....hollow organ” should be carefully clarified

Response: We are referring to the targeted puncture point of the esophagus. The statement, “In some ways, EUS-B-FNA is more difficult, because the esophagus is a soft, hollow organ,” is further clarified by the following sentence: “There are no anatomical landmarks on the esophageal wall. (revised manuscript, Page 6, lines 131-132.)”

-Technique/lines 126-128. I suggest adding also celiac nodes.

Response: Thank you for your comment. We have added celiac nodes as per your suggestion. (revised manuscript, page 6, line 141)

-Techniques/lines 129-130. Why performing EBUS-TBNA after EUS-B-FNA is not recommended? This issue should be better clarified and a reference is advisable.

Response: As you might be aware, there are no official guidelines for EUS-B-FNA. This procedure is performed with a convex EBUS scope, which is designed for EBUS-TBNA. Several studies have shown that EUS-B-FNA provides a good alternative for accessing mediastinal lesions when EBUS-TBNA is not feasible. Moreover, the convex EBUS scope is suitable for evaluation in the airway. Therefore, in real clinical practice, it is recommended that EUS-B-FNA be performed after EBUS-TBNA.

-Technique: does EUS-B-FNA involve the use of different needles than EBUS-TBNA? This issue should be briefly commented in this technical paragraph.

Response: Yes, EUS-B-FNA involves the use of the same needles, such as the 21 or 22 G dedicated EBUS-TBNA needle, because it is executed with the convex EBUS scope. We have now added the sentence “EUS-B-FNA involves the use of the same dedicated EBUS-TBNA needles” to the technical paragraph. (revised manuscript, page 6, lines 122-123)

-EUS-B-FNA in the diagnosis and staging of lung cancer/lines 146: In the cited study, surgical staging was compared with endosonography as first technique and subsequent surgical staging in case of negative endoscopic sample. I suggest editing as follows: “...was compared to endoscopic staging as first procedures followed by surgical procedures in case of negative endosonography”

Response: We have made changes as per your suggestion. (revised manuscript, page 7, lines 158-159)

-EUS-B-FNA in the diagnosis and staging of lung cancer/lines 152-153. In this paragraph, I suggest emphasizing the findings of the SCORE study, which first demonstrated the importance of a systematic endoscopic nodal staging and the added value of EUS-B-FNA.

Response: We have added the sentence, “Notably, a previous study demonstrated that the systematic use of EBUS followed by EUS-B increased sensitivity for the detection of N2/N3 disease by 9% compared to PET-CT-targeted EBUS alone” (revised manuscript, page 7, lines 168-170).

-Is there any study in the literature evaluating the performance characteristics of EUS-B-FNA in the diagnosis of mediastinal tuberculous lymphadenitis? The Authors should comment on this topic.

Response: To the best of our knowledge, there are no studies to date on the performance characteristics of EUS-B-FNA in the diagnosis of mediastinal tuberculous lymphadenitis.

Reviewer E

The topic is useful, well described and timing. The bibliography is updated and the methods compared objectively.

However, it would be necessary to specify that the diagnostic yield of the EUS-B-FNA and EBUS-FNA, is conditioned by the tissue collection and handling of cytological samples (doi: 10.1007/s00428-022-03399-0.). Therefore, it would be very useful to insert a table containing, for each study reported, the type of cytological method used (smears/cytocentrifugates/cell block).

Response: Thank you for your comment and we agree with your feedback. However, most of the studies we referred to in this review article did not separately report results based on cytological method results including smear and cell block.

Page 5,

line 138: What about Primary Lung Lymphoma? Please, describe FNA in this entity.

Response: Unfortunately, there is very little research on EUS-B-FNA in patients with lymphoma. We found only one case report (Respirol Case Rep. 2022 Aug 15;10(9):e01022.) and one retrospective study that included no results for diagnostic yield on EUS-B-FNA (J Bronchology Interv Pulmonol. 2019 Jul;26(3):199-209). This retrospective study included only 5 EUS-B-FNA cases in 92 subjects. Due to the scarcity of data, we did not include it in this paper.

line 147 Please, describe diagnostic yield in EBUS TBNA on 464 samples from lung lesions and mediastinal lymph nodes with Cell block method (doi: 10.1111/1759-7714.14581)

Response: As per your suggestion, we have added the sentence, “A previous study reported a 95.5% (448/464 samples) diagnostic yield for EBUS-TBNA in NSCLC patients regarding adequacy for the site, and 92.6% (430/464) adequacy for diagnosis (18).” (revised manuscript, page 7, lines 160-162)

Page 7, line 198-201: Confusing sentence. Please, better describe the usefulness of the procedures FNA for acquiring samples in the case of advanced lung cancer for the determination of bioprognostic and predictive factors (Molecular profiling and ALK, ROS and PD-L1 immunohistochemistry) and add the most large study in this field (doi: 10.1111/1759-7714.14581)

Response: We have added the Parente *et al.* study (doi: 10.1111/1759-7714.14581) as a reference. (revised manuscript, page 7, lines 160-162. reference no.18)

Page 7, lines 205-206: Inaccurate sentence. FNA provides cytological samples (not biopsy).

Response: We have corrected this sentence as per your suggestion. (revised manuscript, page 9, lines 223)

Line 208: sampled is more appropriated.

Response: We have made the change as per your suggestion. (revised manuscript, page 9, lines 220)

line 217: Please describe the need of standardizing cytology sampling processing to improve diagnostic yield (doi: 10.1007/s00428-022-03399-0.)

Response: Our study primarily focuses on EUS-B-FNA and does not delve into the specifics of cytologic sample handling and processing methods. Thus, a detailed discussion on this topic may not align with the main focus of our study.

Page 9, line 275: EUS-B, Do you mean EUS-B-FNA?

Response: Yes, it means EUS-B-FNA.

page 9, line 281: sampling is better.

Response: We have made the change as per your suggestion. (revised manuscript, page 12, lines 297)

For more details, please find the file enclosed.

Response: We have made the relevant changes in the text.

Reviewer F

Authors reviewed the previous literatures of EUS-B-FNA including actual techniques in clinical settings. This is a nice review and I think this manuscript provides useful information to the readers. However, I have some comments in this study before acceptance. My comments are as follows.

1. In abstract, please include concrete results (e.g. the range of sensitivity and specificity). In the main text, authors showed two head-to-head studies of EBUS-TBNA and EUS-B-FNA, and EUS-B-FNA seemed to be desirable. Do authors think EUS-B-FNA should be always combined with EBUS-TBNA, or single EUS-B-FNA is enough? Please add these in the

conclusion section in abstract and main text.

Response: Thank you for your comments. The present review indeed compiles information from multiple studies on EUS-B-FNA leading to a wide range of results that makes it challenging to present concrete numbers in the abstract. For an overview of the results, we suggest referring to the tables included.

In cases where EUS-B-FNA cannot adequately access a lesion, EBUS-TBNA is recommended, as the two procedures provide complementary access to the mediastinum. We have added this information to the conclusion section in both the abstract and the main text.

(revised manuscript, page 2, lines 48-49 and page 14, line 340-347)

2. The techniques section is very informative to the readers who are unfamiliar with EUS-B-FNA. Are there any references in this section? Please include the actual echo images during EUS-B-FNA. Also, please include information on the timing of oral intake after EUS-B-FNA and the preventive administration of antibiotics.

Response: We have added appropriate references in the Techniques section for greater clarity (revised manuscript, page 6, lines 124, 127). We have also included the actual echo images from EUS-B-FNA procedures (see Figure 1).

With regard to post-procedural oral intake and the administration of preventive antibiotics for EUS-B-FNA, currently there are no established official guidelines. However, we can refer to the EUS-FNA guidelines, which suggest that oral intake can be started as early as 6 h to 1 day post-procedure. These guidelines do not advocate for prophylactic antibiotic use prior to the procedure. Although these guidelines are not explicitly mentioned in our review, they provide useful context for our discussion.

The European Society of Gastrointestinal Endoscopy does not recommend antibiotic prophylaxis for EUS-guided sampling of solid masses or lymph nodes (low quality evidence, strong recommendation).

3. Please add the conclusion section in the main text.

Response: We have added the Conclusion section to the main text. (revised manuscript, page 14, lines 340-347)

4. Please provide the tables about the diagnosis of thoracic sarcoidosis and extrathoracic lesions.

Response: We have added the tables on the diagnosis of thoracic sarcoidosis (Table 3) and

extrathoracic lesions (Table 4). (revised manuscript, page 24)