

Peer review file

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**Reviewer A**

Comment: The references you have cited seem to be relatively old. Making a conclusion of a history of fossil fuel exposure would involve an extensive study and a direct correlation may be even more difficult to prove. In a large study by Korkmaz et al [1], they have found that SUVmax values for anthracotic lymph nodes after EBUS was found to be 6.31 +/- 4.3, reactive lymph nodes 5.07 +/- 2.53, and malignant lymph nodes 11.02 +/- 7.3. This seems to be slightly lower than your study. The low number of subjects limits the significance of the study, however, the study still has merit.

Reference:

Korkmaz C, Demirbas S, Vatansev H. "The value of endobronchial ultrasound - guided transbronchial needle aspiration, 18-fluorodeoxyglucose positron emission tomography/computed tomography, and ultrasonography imaging techniques in the diagnosis of mediastinal and/or hilar malignant, anthracotic, and other benign lymph nodes." *Medecine* 2021;100:7(e2427).

Reply:

*Thank you for your review of this manuscript and for this reference suggestion. We read with the suggested manuscript great interest and have incorporated its findings into our manuscript. It has been included as citation 7 and then we cite it throughout the manuscript including: Page 4, line 91, page 9, line 186 and 187, page 10, line 218*

**Reviewer B**

Thank you very much for the opportunity to review an interesting manuscript by Ivanick et al describing the clinical and imaging characteristics of 20 patients with thoracic nodal anthracosis. I have one major conceptual issue regarding the context within which the authors have placed their findings. Their emphasis appears to be on the fact that PET/CT has a number of causes of false-positivity which are the reason why FDG-avidity needs to be confirmed cytohistologically, and that they have discovered another novel cause of such false positivity: anthracosis. None of these observations is a big revelation: I don't think we need this study to remind us about the well-known fact that PET lacks specificity for cancer, and it wouldn't be accurate for the authors to contend that anthracosis as a cause of PET false-positivity is novel--there have been both bigger and more detailed series (e.g., PMID: 33607816, PMID: 26422878). I think the way to redeem this manuscript is to discuss the findings in these 20 patients not in the above context but in the context of already existent literature on the subject of anthracosis mimicking malignancy--to compare and contrast these findings with the totality of the available literature, which is not as

scant as the authors seem to imply. They include only the study by Park et al, but there are a number of others, and that should be the focal point of the discussion rather than the well-known problem of staging inaccuracy if PET were used without tissue confirmation. With this in mind, I would also like to offer the following specific comments:

Reply: *Thank you very much for this thoughtful and detailed review of our manuscript. Your review highlights a number of excellent points which we have addressed. We have revised our manuscript to address your general concerns as follows:*

- 1. All mention of “novel” has been removed from our manuscript.*
- 2. We have changed the title of the manuscript to better reflect the role of BAL in cancer evaluation.*
- 3. We have incorporated your excellent journal article citations into our paper by addressing them in the discussion of the manuscript.*

*We have addressed your specific concerns in a point by point response as noted below.*

*In order to address the suggested literature above, we have added the 2 new citations (PMID: 33607816, PMID: 26422878). Please see reply above from Reviewer A for details of inclusion of PMID 26422878). In addition we have included PMID33607816 as citation number 13 . We have included this manuscript into our discussion and have cited it throughout the manuscript including: page 9. Line 186, 187, page 10, line 214 and 218.*

Comment 1: P3 L76: PET/CT is more sensitive for what?

Reply 1: *We have clarified that PET CT is more sensitive for “nodal metastasis as well as distant metastatic disease”. This change is seen on page 4, line 80*

Comment 2: P4L103: Six patients had surgical confirmation of negative nodal status on follow up. This is a vague statement--please clarify.

Reply 2: *WE agree this statement is vague and unnecessary. We have changed page 5, line 106 to read:*

*“Six patients had surgical resection of lymph nodes that were biopsied with EBUS as part of their surgical management for lung cancer.”*

Comment 3: P5L131: Lymph nodes and FDG uptake were measured. Another vague statement--please clarify.

Reply 3: *We agree this is vague and have replaced the statement with the following on page 7, lines 140-141*

*“Lymph node size and SUV measurement were obtained from the index PET/CT scan. Lymph node size was measured by the authors in short axis diameter and SUV was taken from the radiologists quantitation.”*

Comment 4: The first sentence of the results section is redundant with information provided in the Methods section. Suggest removing and then revising the new sentence that would begin that section.

Reply 4: *We agree that the first sentence was redundant. We have removed the first sentence of*

*the results section and edited the second sentence as a lead in sentence for the start of the result section.*

Comment 5: P5L147: I assume non-endothelial is supposed to be non-epithelial?

*Reply 5: Thank you for identifying this. We have revised the text to “non-epithelial” on page 8, line 157*

Comment 6: P5L151: Please expand BAL at its first occurrence.

*Reply 6: We have expanded BAL when it first occurs on page 8, line 156.*

Comment 7: P6L166: As stated above, I object to calling anthracosis a "novel" cause of FDG avidity.

*Reply 7: We have removed all mentions of new or novel from the manuscript and edited the discussion extensively to place our findings in the context of the larger field of literature.*

Comment 8: P8L281-226: That whole discussion is very repetitive with the end of the Results section and in fact reads more like something that belongs in the Results section than in the Discussion section. As mentioned earlier, this is a particular place where the authors perseverate on limitations of PET for staging, which is well-known, tangential to the findings of this study, and obfuscates what should be the focal point of the Discussion--what does this study add to our understanding of thoracic LN anthracosis through the prism of PET/CT and the subsequent EBUS-TBNA that patients like this invariably undergo after their positive PET.

*Reply 8: Thank you for these suggestions, we have edited the discussion to take into account the above suggestions. Specifically, we have discussed our findings of LN SUVmax, LN size LN distribution and the bilateral nature of LNs. We agree that this makes our discussion more beneficial to the field at large. We have also removed portions of the discussion that might seem repetitive.*

Comment 9: P13 Figure 3a,b: Last line should be Figure 3b: rather than Figure 3.

*Reply 9: Thank you for catching this error; we have changed this to figure 3B.*

Comment 10. P15 Table 3: The subheadings under the part of the table called Surgical Confirmation of LN are unclear: What does the heading "Pathology" correspond to? What does "Biopsy Stage Shift" mean? Is biopsy here referring to EBUS or surgical sampling? This all needs greater clarification. Clarify these there.

*Reply 10: We agree that this language is confusing. We have deleted the column listing the “Biopsy Stage Shift” as this is apparent from the first 2 columns. WE have also changed “Pathology” to “LNs surgically resected” to illustrate that some of the LNs that were biopsied by EBUS were later surgically resected.*

## **Reviewer C**

In this study, the authors showed that benign anthracotic lymphadenosis (BAL) might be an important cause in PET false-positive lymph nodes.

I felt there was no novelty in this manuscript.

First, there are quite few samples size case study. Therefore, it is difficult to mention the definitive conclusion about the reason of PET false-positive lymph nodes.

In addition, it is well known that high FDG uptake in bilateral hilar lymph node, SUV<sub>max</sub> >2.5 and others could show PET false-positive (Kaseda et al. Thorac Cancer 2016). And Toba et al. has already showed that anthracosis, anthrasilicosis, calcification and follicular lymphoid hyperplasia were the causes of false-positive accumulation of FDG (J Medical Invest 2010).

*Reply summary: Thank you for your review of our manuscript. We have incorporated your input into our manuscript by citing the additional recent references suggested above (see other 2 reviewers who had similar comments and we have responded with line number). We have also removed discussion of the novelty of this finding, as noted in general responses. The authors would like to point out that while bilateral PET avid hilar LN's are identified in sarcoidosis, we were unable to find a mention of bilateral PET avid LNs in the Kaseda et al article references above. We were also unable to find mention of the bilateral nature of BAL in the larger review articles from (first authors) Yilmaz, Park, Toba or Korkmaz.*

*We have added the citation above by Toba as reference # 20 and mention in the text on page 10 line 200, line 214.*