

## Peer Review File

Article information: <https://dx.doi.org/10.21037/jtd-22-35>

### Reviewer A

**Comment 1:** The primary objective of this study is the proportion of TTNB and surgical biopsy. Unfortunately, because the number of patients is small and the study was conducted at a single institution, the results of this study only show statistics of the institution that conducted the study.

Reply 1: We agree that this is a limitation of our study and it is mentioned in the article on page 15, lines 375-376.

Changes in the text: None.

**Comment 2:** In addition, for biopsy of small peripheral pulmonary nodule, a safer endobronchial approach than TTNB, such as EBUS-GS-TBLB or ENB using radial EBUS, is being used in many cases and on an increasing trend, so the clinical application of this study is limited.

Reply 2: We agree that these techniques are used in many cases and on an increasing trend, but we still believe that TTNB should be used in some cases, especially for lesions <2cm in the peripheral third of the lungs. Furthermore, these techniques are not accessible in all centers. Thus, we still think that our study is relevant.

Changes in the text: We added data on ENB and EBUS on page 5, lines 133-136, and mentioned it in the conclusion as well, page 16, lines 411-412.

### Reviewer B

**Comment 1:** The manuscript investigates the outcome and clinical implications of

surgical versus TTNB in malignancy suspected pulmonary nodules. This study is of great importance for the field of pulmonary oncology and thoracic surgery. The manuscript is well written with proper English and structured according to the authors guidelines. The Title, methods and conclusion are in accordance with the aims of the study. However, it has some limitations regarding results and discussion, therefore it should be considered for publication with minor revision.

Reply 1: Thank you for your comments.

Changes in the text: None

**Comment 2:** Conclusion: it is roughly a copy and paste from the results section. In conclusion, the results should be valued and compared with current stand of knowledge. This section can be improved.

Reply 2: Thank you for the comment. We modified the conclusion in the main text as well as in the abstract.

Changes in the text: see page 3, lines 58-62 and pages 15-16, lines 388-415

**Comment 3:** Since PET- CT uptake is also determined in this study, it would be interesting to have a rough overview of the likely impact of PET CT in confirming pre-operative malignancy. Is there any impact of PET on the decision making for TTNB or surgery?

Reply 3: There was no difference for median SUV between the 2 groups (TTNB vs upfront surgery), as shown in Table 1.

Changes in the text: None.

**Comment 4:** Statistic: Why do you use the Wilcoxon rank-sum test and not the U test?

Reply 4: The Mann–Whitney U test and the Wilcoxon rank-sum test are the same. They are nonparametric, involve summation of ranks and apply to independent samples. They must be distinguished from the Wilcoxon signed-rank test that is applied to matched or dependent samples.

Changes in the text: None

**Comment 5:** Discussion: page 8 line 230: ... no study comparing TTNB with other diagnosis”. Some work showed comparison of TTNB with PET CT (Susam S et al. Clin Respir J. 2020 May;14(5):453-461. doi: 10.1111/crj.13152. Epub 2020 Jan 26. PMID: 31922654.) The authors found: “The high negative predictive value of PET-CT is effective in preventing the unnecessary biopsies and surgical procedures”. If this or others have an impact on the discussion it should be considered to add.

Reply 5: We meant other interventional diagnostic methods, which do not include PET-CT.

Changes to text: None

**Comment 6:** Diss, 244-245: 80 days delay from CT imaging to surgery is very long. Because the OP indication is resulted from a high probability of malignancy, it is incomprehensible why the time is so long.

Reply 6: 80 days is not that long. After the initial CT, patients need to be referred to see a respirologist, and to have other tests performed such as pulmonary function tests and PET scan. Then, they need to be referred to see a surgeon and to wait for surgery. For example, in a recent article, mean time to surgery was 70 days. <https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2780403>

Changes to text: None

**Comment 7 :** I noticed some problems. Please give a statement.

In the surgical group without TTNB 48% were operated by low/ intermediate cancer probability. Interestingly, 86.7% (26/30) had a malignancy. Is the current pretest probability of malignancy reliable? Can you explain? How should be handled operable patients with a low/ intermediate cancer probability? Excluding from surgery?

Reply 7: Thank you for the comment. We added statements in the discussion and conclusion to address these questions.

Changes to text: See discussion, page 14, lines 356-362, and conclusion page 15, lines 390-392 and page 16, lines 406-409.

**Comment 8:** By using TTNB only in 72.4% the biopsy was diagnostic. The patients with non-specific diagnose (12), insufficient or undetermined (2) and suspicious (10) must be classified as non-diagnostic. This should be added in the discussion.

Reply 8: Thank you for the comment. This statement was added in the discussion.

Changes to text: See discussion, page 12, lines 304-305.

**Comment 9:** In the surgery group with prior TTNB there are at least 6% benign diagnoses despite TTNB. In the surgery group without prior TTNB there are 8%. One could conclude that TTNB is unable to decrease significantly the rate of futile surgery resulting from benigne diagnosis.

Reply 9: This study being retrospective, it was not easy to identify the exact factors who made the clinician still go for surgery despite a benign diagnosis with TTNB. Still, TTNB was useful in our cohort as the number of TTNB needed to avoid 1 surgery was 6.7, while the number needed to 'harm' ('futile' surgeries) was 12.5.

Changes to text: None

**Comment 10:** Discussion: 227-229: in Tab. 2 you cite 29 Patients. But in only 5 Patients (5.9%; 5/85) with a specific benign diagnosis the malignancy is safe excluded. The patients with non-specific diagnose (12), insufficient or undetermined (2) and suspicious (10) must be classified as non-diagnostic.

Reply 10: There was a mistake here in the calculation which was corrected. In total, 106 patients who had surgery were diagnosed with malignancy (table 3). An additional 19 patients had TTNB with proven malignancy and were treated with SBRT. An additional 3 patients had TTNB which was suspicious for malignancy and considered as malignancy, and treated with SBRT. Hence, the total of patients with definitive (125) or strongly suspected malignancy (3) is 128 and not 93. This was corrected in the text. We also agree that the yield of TTNB is 72.4% as per comment #8 and this was corrected as well.

Changes to text: corrections made page 2 line 48, page 3 line 59, page 11 line 270, page 12 line 302, page 15 line 382, page 15 line 382, page 15 line 388.

**Comment 11:** Statement in Discussion: 237-238: I can't completely agree. The diagnostic yield with TTNB is 72.4% (63/87) and with surgery 100%. It's also important to get a diagnosis of patients with an unclear SPN. The benign diagnosis is also an important diagnosis to take away the fear. Additional with surgery the nodule will be remove and the patients must not underwent surveillance with serial CT scans. A lot of SPN are resectable with VAT procedure. It would be of interest how many patients out of the 8 patients with benign nodule had a VAT procedure.

Reply 11: We agree with you, that is why the brackets around the term 'harm'. These 8 patients had a VATS procedure. We added statements regarding the low rates of complications with VATS, as well as your point regarding patient anxiety and the fact that surveillance with serial CT scans can be avoided.

Changes to text: See page 13, lines 327-329.