Author’s response to reviews

Title: Are there differences among operators in false-negative rates of endosonography with needle aspiration for mediastinal nodal staging of non-small cell lung cancer?

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Author’s response to reviews:

José Belda (Reviewer 1): Congratulations on the paper. I would like to ask you some questions and to make some comments.

C1. According to the ACCP and ESTS/ERS guidelines, additional surgical mediastinal staging (by means of a mediastinoscopy or any other surgical staging method) should be performed if the result of EBUS/EUS-NA is negative but the suspicion of mediastinal lymph node metastasis persists (mainly because of the sensitivity of EBUS/EUS-NA is not high enough to completely rule out nodal metastasis). Nevertheless, all the patients cN2-3 on PET-CT with a negative EBUS/EUS-NA were submitted to surgical resection. Could you briefly comment your lung cancer staging and treatment protocol? Is this decision based on the sensitivity (and negative predictive value) of your EBUS/EU-NA in this group of patients?

R1. Thank you for your thoughtful comments. In our hospital, of course, the patients with highly suspicion of false negative EBUS/EUS-NA results on N2/3 are confirmed by surgical staging such as VATS, mediastinoscopic biopsy, or Chamberlain procedure. Actually, of total 705 patients, 697 patients underwent definitive lung resection with MLND (mediastinal LN
dissection) and 8 patients underwent VATS MLND to confirm the mediastinal metastasis after negative results of EBUS/EUS-NA. We modified the sentences in the Methods and Results section and Figure legend.

C2. How do you define "suspected" clinical N3, N2, and N1 LN on PET-CT?

R2. We apologized for lack of clarity of the terms. We defined positive LN in imaging study as short-axis of LNs > 1 cm in CT or maximum standardized uptake value of LNs > 2.5 in PET. We added this sentences in the Methods section.

C3. Did you analyze pathologic LN characteristics (patients with tumors pN2 or pN3) associated with a EBUS/EUS-NA false negative results? What was the reason? Could be the size of the LN metastasis (micrometastases), tumor necrosis…?

R3. We already analyzed the characteristics of patients (Table 1) and LNs (Table 2) of EBUS/EUS-NA false negative group and discussed in the second paragraph of the Discussion section. As your comments, it is likely to have false negative in LNs with tumor necrosis or micrometastasis in the previous reports (Reference #17), unfortunately, this was not able to analysis in this study because we could not get the detailed pathologic information, retrospectively.

C4. Regardless of inaccessible locations or areas difficult to access, 15.7% (ranging from 8.3% to 21.4% depending of the operator) of the patients had positive results to N2 or N3 from MLND (false negative on EBUS/EUS-NA). Do you think is this an acceptable rate of false negative pN2-3 in this group of patients? The working group to develop the revised ESTS guidelines for preoperative mediastinal lymph node staging for non-small-cell lung cancer considers a maximum rate of unforeseen pN2 disease of 10% as acceptable (De Leyn, EJCTS 2014). Which is in your opinion the maximum acceptable rate of pN2-3 results? What would be the best way to decrease false negative rates to N2/3 on EBUS/EUS-NA?

R4. We totally agree with your opinion that it is ideal to minimize false negative rate below 10%. However, according to the meta-analysis of 15 articles (Korevaar et al., Added value of combined endobronchial and oesophageal endosonography for mediastinal nodal staging in lung cancer: a systematic review and meta-analysis. Lancet Respir Med 2016;4:960-968), false negative rates of EBUS/EUS-NA in several articles were reported to 4–32% (Table 1, false negative rate = 1 – sensitivity). In Table 2 of this meta-analysis article, overall false negative rate was 17% (95% CI, 13-23%). Especially, it is well known that the accuracy (sensitivity, NPV, FN) of EBUS/EUS-NA is depended on the prevalence of N2/3. Korevaar et al. reported the
sensitivity was 0.80 (0.71-0.86) in the studies with prevalence N2/3 ≤ 34% and 0.86 (0.81-0.90) in those > 34%. In another meta-analysis study of 13 studies for radiologically normal mediastinum (El-Osta et al., Endobronchial ultrasound for nodal staging of patients with non-small-cell lung cancer with radiologically normal mediastinum. Ann Am Thorac Soc 2018;15:864-874), pooled prevalence of N2/3 was 12.8% (10.4-15.7%) and pooled sensitivity was 49.5% (36.4-62.6%) (Figure 2). In addition, in figure 15 of 2013 ACCP guideline, the relationship between the prevalence and false negative is reversed.

Therefore, it is difficult to present the maximum acceptable rate of unforeseen N2/3 because the false negative rate varies depending on how wide the indication of the EBUS/EUS-NA is.

C5. What staging procedure do you recommend in patients with inaccessible cN2-3 LNs (high clinical suspicion of mediastinal LN involvement).

R5. We have confirmed with surgical staging such as VATS or Chamberlain procedure in case with inaccessible highly suspicion of mediastinal LN involvement.

C6. What is the reason for the observed differences among operators in the frequency of EUS combination, number of the evaluated lesions and the number of the punctures per node?

R6. In previous reports on the learning curve of the EBUS/EUS, there was a difference in the procedure details according to the operators. We think it is just a difference of operators’ tendency.

C7. What would be the reason because of larger size of LNs had a trend for higher false negative rates?

R7. There are many reports that LNs with false negative EBUS/EUS-NA results were larger than LNs with true negative. Sanz-Santos J et al. (Reference #9) reported enlarged LNs on CT scan had an OR as 7.77 (2.19-27.51) for false negative N2 (Table 4), Talevian Yazdi M et al. (Reference #10) reported nodal enlargement on CT had an OR as 3.2 (1.3-7.8) for EBUS, 2.5 (1.4-4.8) for EUS, and 4.9 (1.4-17.6) for EBUS/EUS, respectively.

These results should be interpreted with caution. Mediastinal LNs with false negative are larger than those with true negative, not larger than those with true positive. We think that this is the result of a micrometastasis or tumor necrosis inside a large benign reactive LNs and these lesions are difficult to detect by needle technique such as EBUS/EUS-NA.
C8. Did you analyze the procedure incidence complication rates of the EBUS/EUS-NA among the operators?

R8. Thank you for interesting comments. Unfortunately, we cannot evaluate the complication rate because of limitations of retrospective study. We added this information as limitation of this study in the Discussion section.

C9. Did you analyze the correlation between the FN results and the extensiveness of endobronchial ultrasound sampling?

R9. We already analyzed the number of evaluated lesions (separately to mediastinal and hilar LNs and lung parenchymal lesion) in Table 1. There was no correlation between numbers of evaluated lesions and false negative results.

C10. In my opinion, the lack of information about the exact false negative rates of EBUS/EUS-NA among patients who were not able to undergo surgical resection (with MLND) or missed follow-up is not necessarily a limitation of the study. The study has been focused in the surgically treated patients and, in this group of patients, the false negative rate of preoperative invasive minimally invasive staging procedures is a crucial factor for determining the best treatment option.

R10. Thank you for your suggestion. We deleted the sentences as your comments.

Rosa María López-Lisbona, M.D. (Reviewer 2):

C1. In this retrospective study the authors evaluate the influence of operator-related factors in the false negative rate of EBUS/EUS-NA for the staging of NSCLC in 705 patients. They analyze the procedures of 6 different operators with the same training, but with different grades of experience and compare the false negative rate of individual operators and if there are changes according to accumulation of experience. They adjust the data for patient's characteristics and procedure-related factors. Finally, they conclude there are no differences between operators in false negative rates, but if the operators have completed a training curve.
This study is of interest since the importance in the training of the operators to improve and guarantee the good results in EBUS technique is well known. To know the influence of different operator-related factors in these results should be helpful for clinical practice.

I have a number of concerns regarding the design of this study

R1. Thank you for giving us important comments to be a better paper. We hope that these changes we have made meet your approval.

C2. By using the term "endosonography with needle aspiration" as "EBUS/EUS-NA", it is confused if all authors performed EBUS and/or EUS and/or EUS-B (with endobronchial scope) and this is not clear in the methods. But in the results (table 1), only in 69 patients the EUS was performed.

I would like to suggest that the procedure should be more standardized (if only a few operators performed EUS, include only EBUS) and analyze if the operator's experience is related to the realization of EUS and if that modifies the results.

R2. We apologized for lack of clarity of the Methods section. All operators in present study were able to perform the EUS-B, but, according to the preference of each operator, the rates (1.25-18.2%) of performing EUS-B were different (e-Table 1). We have performed EBUS-TBNA as a base tool of mediastinal staging, and EUS-NA could be added for the specific lymph node stations which are accessible with EUS. That is the reason why EUS have been performed in only 10% of entire subjects. We added this information in the Methods section.

C3. The authors do not specify the time from EBUS/EUS-NA mediastinal staging to the surgical intervention.

R3. The reviewer makes a very important point. There were no statistical differences of time interval between EBUS/EUS-NA and surgical intervention among the operators. We added this information in the Tables.

C4. It appears to be a study based in the operator's characteristics, but the authors don't describe the criteria followed by the different operators during the staging procedure (complete, systematic…) and neither if there were any changes in time related to the lack of experience at the beginning…

R4. Each operator performed an independent procedure after having accumulated 200 cases of observation and practice under supervising. And, all operators sequentially approached the LNs
N3 --> N2 --> N1 station, systematically and completely. We modified the sentences in the Methods section. We analyzed the associations between the degrees of accumulated experience of each operator and false negative rates in Figure 4.

C5. Also the level of experience of each operator is not clearly determined (e-figure-1).

R5. We added more detailed information for clarifying the level of experience in the Figure legend of e-Figure 1. Also this information added in the Methods section.

C6. There are some unclear points in the lymph node classification:

The definition of inaccessible LN is not correct according to the guidelines (Vilmann et al. EurRespir J 2015): "EUS with real-time guided fine needle aspiration using the EBUS scope (EUS-B-FNA) can reach the following locations that are relevant to lung cancer diagnosis and staging: lung tumors close to the esophagus; mediastinal lymph nodes in stations 2L, 4L (high and lower left paratracheal nodes); station 7 (subcarinal node); stations 8 and 9 (nodes located in the lower mediastinum); and structures below the diaphragm, i.e., retroperitoneal lymph nodes close to the aorta and the celiac trunk, and tumors in the left liver lobe and the left adrenal gland". If you used the term EBUS/EUS-NA, the operators should be able to reach the 8 and 9 stations.

R6. Thank you for your thoughtful comments. As your comments, station #8 and #9 cannot be accessible by EBUS, however, they can be accessible by EUS. Actually, we have performed EBUS/EUS-NA to #8 and #9 in some patients having suspicious metastasis in these LNs (Table2). We modified the definition of inaccessible LNs to #3A, #5, and #6, and the overall results associated with them.

C7. In relation to the unattempted accessible LN, the operator's criteria for not examined them should be further explain.

R7. Based on previous research (Reference #16), we usually performed EBUS/EUS-NA on LNs of more than 5 mm in size on EBUS/EUS. As shown in Table 2, there were 10 unattempted accessible LNs with false negative (#7 [n = 5], #4R [n = 4], and #2R [n = 1]). All of them were less than 5 mm in short-axis on the CT image (these lesions cannot be retrospectively measured on ultrasound because the operator did not capture ultrasound image on these lesions). We added the information in the Results section.
C8. I have some comments about the results:

There is a big amount of data reported in the results (text and different tables) that is not even mentioned in the methods.

R8. Thank you for your kind suggestion that more explanations of the study design is required in the Methods section. We added this information in the Methods section.

C9. A description of the characteristics of each operator in the results is missed.

R9. We added the information of each operator in the Methods section. And, we already described the characteristics of each operator in the Results section (line 209-215 and 228-234 in unmarked version).

C10. The authors have a big number of patients with a lot of data to analyze, but the design of the study should be focused to really answer the initial question. I truly encourage reviewing and reorganizing the data to the authors.

R10. Thank you for your sincere comments. To find the answer to the initial question “whether there is a change in the false negative results of EBUS/EUS-NA to N2/3 LNs depending on operator and/or accumulated experience”, we investigated all the baseline characteristics about patients and LNs. There were some LNs which were located on the inaccessible site or were missed by operators. Therefore, we analyzed the initial question according to each situation. As your comments, there are a lot of data in results but it was inevitable to analyze the main object adjusting various factors and situations. However, through this seemingly complicated process, we think we can reach a firmer conclusion.