Reviewer's report

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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Reviewer: José Belda

Reviewer's report:

Congratulations on the paper. I would like to ask you some questions and to make some comments.

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/EUS-NA in this group of patients?

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

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…?

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?

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

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

Did you analyze the procedure incidence complication rates of the EBUS/EUS-NA among the operators?

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

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.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

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