Reviewer’s report

Title: Diagnostic yield and risk/benefit analysis of trans-bronchial lung cryobiopsy in diffuse parenchymal lung diseases: a large cohort of 699 patients

Version: 1 Date: 01 Dec 2018

Reviewer: Michele Mondoni

Reviewer's report:

This is an observational retrospective study that evaluates a very large cohort of patients with interstitial lung diseases requiring an etiological diagnosis, that underwent transbronchial cryobiopsy.

On the basis of their findings (both diagnostic yield and complications), Authors aim to suggest some sampling strategies related to this technique in the diagnostic work-up of diffuse parenchymal lung diseases.

The following comment should be carefully evaluated:

MAJOR COMMENTS

1. Table 6 caption, page 23. Why did Authors discard biopsies taken from the middle lobe and the lingula (that belongs to the left upper lobe)?

The biopsies obtained from these segments should be necessarily included in the analysis (and compared for both diagnostic yield and complications). Furthermore, this statement should be inserted and explained in the Methods section.

MINOR COMMENTS

1. Abstract

- Methods (page 1, lines 31,32): I suggest deleting the following sentence from this section "We report the largest series of patients with suspected diffuse parenchymal lung disease undergoing cryobiopsy; 699 patients were included". This is related to the Results of the study.

In this section I would insert the epidemiological design of the study (i.e. This is an observational, retrospective cohort study) and the aim (i.e. The aim of the study is to suggest
some sampling strategies related to transbronchial cryobiopsy in the diagnostic work-up of patients with diffuse parenchymal lung diseases)

- Results: I would insert the number of the patients enrolled (i.e. 699 patients with suspected diffuse parenchymal lung disease were recruited)

1. Text

   - Methods:

   - page 3, line 58: As previously stated, the number of the recruited patients should be deleted from this section.

   - page 3, lines 67, 68: Authors stated "samples taken from one site or multiple sites depending on the radiological pattern and distribution of disease". I think that this aspect should be discussed more in depth: which were the radiological patterns requiring samples from one site Vs. multiple sites?

   - Results:

   - page 4, line 100: I would delete "could".

   - page 5, line 107-120: In my opinion, abbreviations should be defined at the first mention in the text (i.e. usual interstitial pneumonia, UIP)

   - page 6, lines 127, 128 and Table 6, page 22: In 166 patients, biopsies were taken from two sites in the same lobe. Authors should clarify if these samples were always obtained from different segments in the same lobe or also from different sites in the same segment. This is a crucial aspect to study the diagnostic yield of this sampling method: in a previous study Authors demonstrated a better yield related to samples obtained from different segments in the same lobe (Ravaglia et al. Respiration 2017).

   - page 6, line 137 and 144-145: Authors demonstrated that 2.4 mm probe shows the same diagnostic yield of 1.9 mm probe but with a significantly increased rate of pneumothorax. Furthermore, in some patients (excessive resistance during retrieval due to bronchomalacia and/or sampling in the upper lobes particularly difficult - see page 5, lines 102, 103 and more difficult placement in the lung periphery - see page 11, lines 259-260) it may be difficult to employ.

   Why should 2.4 mm probe be used despite these disadvantages (not related to a better yield)?
Discussion

This sentence is not supported by the findings of the study. As stated before it is not clear whether samples within the same lobe were obtained from different segments or from different sites within the same segment.

Conclusions

see the previous comment (i.e. page 8, lines 193-194)

on the basis of the findings of the study, the sampling recommendations may be summarized as follows: 1. It is advisable to obtain two samples from two different sites in order to enhance the diagnostic yield (e.g. from different lobes in case of inter-lobar radiographic heterogeneity). Taking samples from different segments in the same lobe may rise the diagnostic yield; however, this was demonstrated in a previous investigation and may not be inferred from the results of this study; 2. It is advisable to use only 1.9 mm probe (2.4 mm probe shows a higher rate of pneumothorax and more technical problems without increasing the diagnostic yield). 3. Sampling from lower lobes may be associated to a higher rate of complications (both bleeding and pneumothorax) than in upper lobes. 4. The risk of pneumothorax also increases in case of impaired lung function (FVC <50% and DLCO < 35%) and sampling two sites.

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

No

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

No

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

No
Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

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