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: 06 Dec 2018

Reviewer: Alfons Torrego

Reviewer's report:

The manuscript is a retrospective description of the 6 years experience of a single centre performing transbronchial lung cryobiopsies (TBLC) for undiagnosed diffuse pulmonary fibrotic diseases.

The major novelty is that the study includes the largest series of cases described with this procedure, 699 subjects, which allows confirming previous results as well as to obtain interesting data for the future of this procedure. Results are well described and provide solid evidence to assist in the standardization of this technique, such as the use of haemostatic balloon to control the bleeding risk.

Although the article lacks from direct comparison with surgical lung biopsy, the study demonstrates that TBLC is a good option and alternative to get diagnostic lung samples through a less invasive procedure.

The authors have to be congratulated for the magnitude and importance of this work.

I have some questions and comments to be answered and included somehow in the manuscript:

1- Diagnostic yield is very high in this series compared with some previous data and other groups (almost 88% pathological diagnosis; 90% multidisciplinary diagnosis). This is an excellent result in favour of cryobiopsy for this team although should be mentioned that might be overestimating the "real world" potential of TB cryobiopsy. The great accumulated experience of this group and the presence of world-renowned clinicians and 3 pathologists among the authors probably contributes to this outstanding result. However, this procedure requires a learning curve and most multidisciplinary committees do not have such degree of maximum expertise, which might easily lead to poorer results, certain reported controversy, risk-benefit concerns and clinical frustration.

This point is relevant considering that current international IPF guidelines do not recommend TBLC unless the centre is already expert in the procedure, which clearly is a confusing message for clinicians.
How to define cryobiopsy expertise when the procedure is not fully standardized is not an easy point. Expected results curve and training programs are now important to expand the knowledge and use of this technique, overcome the current vicious circle situation, clarify real expectations as well as the role of TBLC in clinical practice.

2- Almost half of cases were reviewed by 3 different expert pathologists. This is not standard in clinical practice. Agreement-discrepancy % and correlation among the 3 pathological diagnoses should be provided.

3- The authors showed no diagnostic yield differences among 1.9 and 2.4 mm probe, when freezing time was adapted to each probe. In addition, 1.9 probe was associated to lower pneumothorax rate and easier use in some specific situations (upper lobes, bronchomalacia). Considering 2.4 probe has been mostly used for TBLC, do the authors have any conclusion or recommendation in favour of the 1.9 probe? This might change clinical practice in most centres already performing cryobiopsies.

4- The manuscript does not clarify the specific radiological criteria used to select candidates for TBLC. This is significant considering that final diagnosis was UIP in 35% of cases and relatively low for other entities such as HP, OP or sarcoidosis, typically suitable for biopsy. The risk-benefit balance message is crucial for the future of this procedure and the authors should provide more extended information related to the pre-test clinical and radiological diagnosis when cryobiopsy was indicated.

5- In addition, 15 cryobiopsied patients had FVC <50% and 22 patients DLCO < 35%. This is a very high risk group of patients for any invasive procedure. A table with specific data regarding this subgroup should be provided (characteristics, pre-test diagnosis, procedure details, tolerance, specific complications and final result). The last sentence conclusion establishes that, compared with surgical biopsy, TLCB can be indicated in "patients with more compromised baseline lung function or even in patients with a typical radiological UIP pattern". This is a very positive message for cryobiopsy but needs some reconsideration. Safety in the most severe group of patients would require further demonstration. The possible role and risk-benefit of TBLC in the management of patients with typical UIP pattern requires from specific studies since in this group of patients to obtain a biopsy is not mandatory to make a therapeutic decision.

6- Pneumothorax occurred in 1 out of 5 cases. Little other important comorbidities are also described, including 2 deaths due to IPF exacerbation. Again, balance between risk and potential benefit needs to be as clear as possible. Apart from the described associated factors, did the authors observed any relationship between those complications and pre-test radiological pattern?
7- Can the authors provide information about the TBLC therapeutic impact? Specially how the biopsy result affected the multidisciplinary treatment decision in cases with pre-test radiology showing typical UIP pattern?

8- Four patients underwent a second cryobiopsy procedure after previous intend was undiagnostic. Is there any recommendation or comment to support this decision instead to indicate a surgical biopsy after the first cryobiopsy failure?

9- Results (table 5) show that more than 2 biopsies were not related to a better diagnostic yield but increased pneumothorax risk. That was probably an unexpected result considering the average number of biopsies reported by the authors (3.3 x subject). Will the authors change their clinical practice according to these results? Do the authors recommend performing only two cryobiopsies routinely from now on?

10- Table 6 shows that sampling two different lobes was not related to better diagnostic results but increased complications rate. This is contradictory to some previous data. Do the authors have an explanation for such result? Can the authors provide any recommendation to decide one or two lobes strategy, perhaps according to radiological pattern?

11- Table 3: the number of diagnostic and non-diagnostic is total 702 (but study is perform in 699 subjects)

Minor correction:

- Correct parenthesis mistake in table 6 ..... Lower lobes *)

**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
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.

Not relevant to this manuscript

Quality of written English
Please indicate the quality of language in the manuscript:

Acceptable

Declaration of competing interests
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

I declare that I have no competing interests

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal