Usefulness of Surgical Lung Biopsies after Cryobiopsies when Pathological Results Are Inconclusive or show a Pattern Suggestive of a Nonspecific Interstitial Pneumonia

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Abstract

BACKGROUND The equivalence of transbronchial lung cryobiopsies (TBLCs) and surgical lung biopsy (SLB) in the diagnosis of diffuse parenchymal lung diseases (DPLDs) is still debated. The aim of this study was to evaluate the benefit of SLBs performed in selected patients after TBLCs.

METHOD We conducted a multicentric Belgian prospective trial in which SLBs were performed after TBLCs when the pathological diagnosis was uncertain or if a nonspecific interstitial pneumonia (NSIP) pattern was observed hypothesizing that SLB could provide additional information and that a co-existent UIP pattern could be missed.

RESULTS 81 patients with TBLCs performed for a DPLD were included in the study between April 2015 and December 2019. A specific histological diagnosis was obtained in 52 patients (64%) whereas no pathological diagnosis following TBLCs was obtained in 13 patients (16%) and a pattern suggestive of a NSIP observed in 16 patients (20%). 14 of these 29 patients had SLBs after TBLCs. SLBs showed a UIP pattern in 11 (79%), a pattern suggestive of a hypersensitivity pneumonitis in two and a NSIP pattern in one patient. Among the 16 patients with pathological NSIP following TBLCs, six benefited from SLBs showing a UIP in five and confirming a NSIP in only one patient. A retrospective pathological analysis of patients having both procedures showed lower diagnostic confidence and agreement among pathologists for TBLCs compared to SLBs. Major determinants underlying the added value of SLBs were, as expected, the bigger size and the subpleural localization of the biopsies.

CONCLUSIONS TBLCs are useful in the setting of DPLDs with a good diagnostic yield. However, our study suggests that SLB provides critical additional information in case TBLCs are inconclusive or show a pattern suggestive of a NSIP, questioning the accuracy of TBLC to identify adequately this histological pattern.

Introduction

Diffuse parenchymal lung diseases (DPLDs) are a heterogeneous group of diseases with a variable amount of fibrosis and inflammation. For prognostic and therapeutic purposes, a precise diagnosis is required. The whole diagnostic process should be performed and discussed within an experienced team during a multidisciplinary discussion (MDD) [1, 2]. When the diagnosis based on clinical, radiological and biological data is inconclusive, a lung biopsy is recommended [1]. Surgical lung biopsies (SLBs) are currently considered as the gold standard for this purpose as stated in IPF guidelines [1].

However, SLB is an invasive procedure, requesting systematic pleural drainage and burdened with an estimate postoperative mortality rate of 2% that ranges to 3,6% [3–7]. Therefore, trans-bronchial lung cryobiopsy (TBLC) is increasingly recognized as an alternative technique for the diagnosis of DPLDs [6, 8–11]. TBLC appears to be safer than SLB, and its contribution to the diagnosis obtained via multidisciplinary discussion is comparable to that of SLB, although the histological diagnostic yield is higher with SLB (approximately 80% for TBLC vs 95% for SLB) [11].

Interestingly, whereas increasingly data support the use of TBLC for the diagnosis of DPLDs, only three studies compared the result of TBLC and SLB performed in a same patient. In these studies, limited data are available concerning nondiagnostics TBLCs or showing a pattern suggestive of a NSIP. In these situations, SLB could provide important additional information. Indeed, idiopathic NSIP that is nowadays considered as a specific entity [2], is defined histologically by variable proportions of interstitial inflammation and fibrosis with a uniform appearance [12]. However, the assessment of this pathological uniformity is based on the analysis of SLBs that are bigger than TBLCs and performed in different lobes.

In consequence, we hypothesized that the accuracy of NSIP diagnosis obtained on smaller biopsies such as cryobiopsies could be lower than on SLB [9]. NSIP pattern could be mistakenly recognized as other important features could be observed in SLB samples. Particularly, the spatial heterogeneity, important for the diagnosis of UIP patterns, could be missed on TBLCs [13]. This misinterpretation is particularly important as it can have prognostic and therapeutic consequences.

Therefore, in our study, we evaluated the added value of SLB performed after TBLC when the latter showed nondiagnostic or unspecific pathological results without confident diagnosis following another multidisciplinary discussion. Preliminary results from this approach were published in 2017, but concerned a very limited number of patients [9]. With the present extension of our study, we provide more evidence supporting the benefit to perform SLBs in these selected cases. Moreover, a blinded retrospective analysis of paired TBLCs and SLBs was conducted by three experienced pathologists in ILDs to highlight the different characteristics in between both sampling techniques.

Material And Methods

Study design

A multicentric prospective observational study was performed between April 2015 and December 2019 in three Belgian academic hospitals. The study was approved by the ethical committees of the non-leading hospitals and by the leading ethical committee of the Erasme hospital (ref P2015/192). Patients were included if a lung biopsy was required for the diagnosis of a DPLD after a multidisciplinary discussion within an experienced team. The composition of the multidisciplinary teams includes at least one chest physician, one pathologist, one thoracic radiologist, one specialist in internal medicine or rheumatologist. TBLCs were performed first and patients informed of the possibility to have a surgical biopsy following the endoscopic procedure in case of unclear pathological diagnosis or a histopathologic pattern suggestive of NSIP. SLBs were obtained by video-assisted thoracoscopic surgery (VATS) and performed in at least two different lobes as recommended in the guidelines for patients with suspected idiopathic pulmonary fibrosis (IPF) [1]. Of note, the multidisciplinary team decided indication of SLB after TBLC and discussed all biopsy results (TBLCs and SLBs). A SLB was not performed in patients with a histological NSIP pattern following TBLCs if there was a relatively high probability that the pathological NSIP pattern could be explained by a related condition (such as a hypersensitivity pneumonitis) by the multidisciplinary team according to the analysis of all the available data. This includes the HRCT pattern,

cellularity of the bronchoalveolar lavage, specific IgG, autoantibodies, drugs, environmental and occupational exposures.

Study population

Written informed consent for participation in the study was obtained from each patient. Patients had to be at least 18 years old and had to have a pulmonary systolic arterial pressure estimated by echocardiography of less than 40 mmHg. Exclusion criteria included the presence of a coagulopathy (platelet count < 100000/mm^3, prothrombin time international normalized ratio - INR > 1.5, activated partial thromboplastin time - APTT > 35), hypoxemia (PaO_2 < 55 mmHg on room air) or hypercapnia ($PaCO_2$ > 45 mmHg), and severe underlying cardiac disease. Collagen vascular disease-associated interstitial lung disease (CVD-ILD) and drug-induced interstitial lung disease (D-ILD) were not formally excluded but efforts were done to avoid lung biopsies in these patients as the diagnosis can be achieved by other means.

Bronchoscopy and cryobiopsy

Procedures were performed as described previously [9]. Briefly, all procedures were performed under general anesthesia. We attempted to obtain four biopsies from two different segments of the most affected lobe. For each biopsy, the cryoprobe (1,9 or 2,4 mm, Erbe, Germany) was pushed under fluoroscopic guidance to the distal parenchyma and the probe was withdrawn of one-two cm from the thoracic wall. To control potential severe bleedings, a Fogarty balloon was systematically placed in the lobar bronchus close to the sampled segment, and inflated immediately after biopsy. The bleeding was scored 0 if no bleeding, 1 (mild bleeding) if bleeding stopped with aspiration only and/or insufflation of the Fogarty balloon less than 5 minutes, 2 (moderate bleeding) if cold saline was used to control the bleeding and/or the Fogarty balloon need to be inflated more than 5 minutes, and 3 (severe bleeding) if any of the following treatment was required: embolization, selective bronchial intubation, transfusion, admission in an intensive care unit (ICU), or resulting in death or prolonged hospitalization.

Biopsy Specimens

Biopsy specimens were fixed in 10% formalin and embedded in paraffin. Hematoxylin and eosin as well as Masson's Trichrome, Giemsa, staining were performed as well as immunostaining against pancytokeratins.

Pathological review

A retrospective histological analysis was also performed for patients having both biopsies (TBLCs and SLBs). Three experienced pathologists in DPLDs (MR, FD, and DH) reviewed all biopsies. Biopsies were de-identified (each sample receiving a code number). For each specimen and pathologist, we recorded the most probable histological diagnosis and its level of confidence (high, low or very low). Histopathological patterns were recognized following the 2018 guideline-refined categories of definite or probable usual interstitial pneumonia, indeterminate for usual interstitial pneumonia, or alternative diagnosis [1]. For some biopsies, no pathological diagnosis could be identified. For them, the diagnostic confidence was

categorized as "not applicable". Histological patterns of probable or indeterminate for UIP were categorized as UIP with a low level of confidence.

Then, each pathologist compared the TBLCs and corresponding SLBs of each patient to evaluate if the SLB provided additional information and to identify the underlying reasons (including the size and the localization of the biopsies). We also determined and compared the agreement between pathologists for TBLCs and SLBs diagnoses and the corresponding level of confidence.

Statistical analysis

According to the results of the D'Agostino & Pearson test used to assess the normality of the sample values, simple comparisons between two groups were tested by unpaired Student t tests or Mann-Whitney tests. Proportions were compared using the Chi^2 test. Statistical analyses were performed using GraphPad Prism 6 (GraphPad Software, La Jolla, California, USA). For all tests, a P-value of less than 0.05 was considered statistically significant.

Results

TBLCs are useful for the diagnosis of DPLDs

81 patients with TBLCs performed for the diagnosis of a DPLD were included between April 2015 and December 2019. Their main clinical characteristics are summarized in the table 1. Four TBLCs were performed in the most affected lobe with a mean size of 21 mm^2 (ranging from 9 to 44 mm^2) (Table 1). The quality of TBLC tissue samples was good to excellent. A specific pathological pattern was observed following TBLCs in 64% of the cases (84% including NSIP patterns). Complications following TBLCs were mainly hemorrhage (mild or moderate in a majority of the cases, severe in 5% of the cases) and pneumothoraxes (21%, a half of them requesting chest drainage) (Table 2).

From these 81 patients, an undetermined or NSIP pattern was observed in 13 and 16 patients respectively (Table 2). Comparison of patient's characteristics between patients with nondiagnostic TBLCs and the others showed no differences in term of HRCT pattern distribution but a significant difference in the size of the cryobiopsies. Indeed, the total surface area per patients of nondiagnostic specimens was smaller than those given a specific diagnosis (65 ± 24 vs 82 ± 27 mm^2, mean ± SD; $p < 0,01$) (Table 1). We further determined that using a cut-off of a total surface area of 110 mm^2, the risk to have nondiagnostic biopsies was lower than 5%.

SLB provides critical additional information in case TBLCs are inconclusive or show a pattern suggestive of a NSIP

Among the 29 patients without specific diagnosis following TBLCs, 7 did not consent to have a SLB (further classified as unclassifiable ILD), and 8 received a provisional diagnosis following a novel MDD (5 chronic HP, 2 IPAF, 1 idiopathic NSIP). A SLB was performed for the other 14 patients (six with a suspected NSIP pattern and eight without pathological diagnosis following TBLCs) (Fig. 1). As expected,

SLB provides ten-fold bigger sample than TBLC (76 ± 27 mm^2 for TBLCs vs 676 ± 307 mm^2 for SLB, mean ± SD) and subpleural area was always present for pathological examination (Fig. 2). In 11 out of the 14 patients, a UIP pattern was observed in the SLB (79%) whereas a NSIP pattern was only confirmed in 1 of the 6 patients with a suspected NSIP on TBLC (17%). Finally, a HP pattern was observed in two other patients without pathological diagnosis following TBLC. Following another MDD discussion taking into account SLB data, the final diagnosis changed in 93% of those patients (83% of those with a NSIP pattern on TBLC). In other words, our data showed that if a SLB is performed in a patient with a NSIP pattern on TBLC, another diagnosis will be observed in 83% of the cases changing significantly the final diagnosis and eventually the subsequent treatment.

Inter-observer agreement and diagnostic confidence are higher for SLBs than TBLCs

Three ILDs experienced pathologists further retrospectively and blindly reviewed all biopsies from the 14 patients who benefited from both procedures. Each pathologist was asked to propose a most probable diagnosis, even with a low confidence level. Major determinants underlying differences between TBLCs and SLBs were depicted. This analysis demonstrated a higher diagnostic concordance among pathologists for SLB (86%) compared to TBLCs (43%) (Fig. 3). Moreover, the level of confidence of the histological diagnoses was much higher for SLBs than for TBLCs (high diagnostic confidence in 88% of SLB contrasting with low and very low level of confidence in 97% of TBLCs) (Fig. 3). The benefit to perform SLB after TBLC in this selected population was not only to improve the diagnostic confidence as it changed the final diagnosis in 60% of the cases in the retrospective pathological analysis (table 3). Accordingly, the overall agreement between paired TBLC and SLB for specific histopathological pattern was 40%. The major determinants underlying this benefit reported by the three pathologists were the size of the biopsies in 90%, a better representation of the subpleural area in 50% and the localization of the biopsies in different lobes in 23%.

Concerning the identification of a NSIP pattern on TBLC, there was only an agreement among the three pathologists for two patients. Of note, a pattern suggestive of a NSIP on TBLC was systematically proposed without high diagnostic confidence (Table 4). Surprisingly, SLB performed in these two patients only confirmed a NSIP pattern for one pathologist whereas a NSIP was proposed on SLB by another pathologist for which the corresponding TBLC was not suggestive of NSIP (Table 4).

Discussion

Increasing data support the use of TBLCs for the diagnosis of DPLDs with diagnostic yield ranging between 72 and 87% [11]. From the 81 patients included in the study, we obtained similar results as published data in term of diagnostic yield (84% when including NSIP diagnoses and 64% when excluding NSIP). The rate of pneumothorax (21%) was relatively high compare to other reports but mostly explained by a high prevalence of fibrotic DPLDs (46%) known to be associated with higher risk of pneumothorax [10]. Bleeding was mild to moderate in a majority of the cases. There was no TBLC related death.

Altogether, our data support that TBLC are safe and globally useful for the diagnosis of DPLD used within MDD.

Beside the growing evidence supporting the use of TBLCs for the diagnosis of DPLDs, only three studies directly compared TBLC and SLB performed in a same patient [14–16]. Romagnoli and colleagues included 21 patients and found a poor agreement for TBLC and SLB histological diagnoses [16]. This result contrasts with data from the recent and bigger COLDICE study including 65 patients showing a histopathological agreement between TBLC and SLB of 71%. Moreover, for TBLC with a high to definite confidence at MDD, 95% of TBLC diagnoses were concordant with SLB diagnoses [15]. In those studies, SLB are performed in all patients whatever the level of confidence obtained after TBLC (5% of non diagnostics TBLCs in the COLDICE study). Moreover, these studies do not specifically address the accuracy of histological NSIP diagnosis from TBLCs compared to SLB results (NSIP was present on TBLC pathological analysis in 2 patients in the COLDICE study and in 3 patients in the Romagnoli study) [15]. In the present study, even if we acknowledge that the number of patients remains low, we specifically assessed the benefit to perform SLB after TBLCs (following MDD) in case of unspecific results including NSIP patterns on TBLC. We prospectively found that SLB provides additional information in 93% of the cases. Our results contrast therefore with those from the COLDICE study in which SLB provides additional information in 23% of the patients with low confidence or unclassifiable TBLCs diagnoses. Interestingly, NSIP pattern was only confirmed in 1 of the 6 patients with a suspected NSIP pattern on TBLC (17%) highlighting that a NSIP diagnosis should be questioned if based on TBLCs data only. Whereas studies showed TBLC affect diagnostic confidence to a similar degree as SLB, within the context of MDD [17], our data showed that SLB results do not only increase the diagnostic confidence but also completely change the final diagnosis in a majority of the cases in this selected population of patients with unspecific TBLCs.

Finally, we also conducted a retrospective and blinded analysis of pathological samples by three pathologists in order to better determine the differences between these two types of biopsies. This analysis does not reflect clinical routine but was interesting as it because highlighted a higher inter-observer agreement among pathologists with higher confidence levels for SLBs diagnoses compared to TBLCs diagnoses. Moreover, the overall agreement between paired TBLC and SLB for specific histopathological pattern was 40%, contrasting to the agreement observed in the COLDICE study of 69·2% [15]. Concerning NSIP, diagnostic confidence was systematically low on TBLCs samples and confirmed on SLB in a minority of cases. Determinants underlying additional information from SLBs were analyzed. The bigger size of surgical biopsies was reported in a majority of the cases (90%) followed by differences in the localization of the biopsy (subpleural vs bronchiolocentric). Interestingly, the benefit to have samples from different lobes was only noted by the pathologists in only 23% of the cases.

Important limitations have to be addressed regarding the study. The number of patients having both procedures is small. Multidisciplinary discussions were not performed blindly and by a unique multidisciplinary team (each of the three participating centers having its own team). Moreover, SLBs were not performed in all patients with TBLCs showing either a NSIP pattern or inconclusive results,

representing another possible limitation. This was explained by a proportion of patients who denied having SLBs after TBLCs (24%) and by patients for which the MDD concluded to a diagnosis with an acceptable level of confidence (this possibility was prespecified in the protocol). Finally, nondiagnostic TBLCs were significantly smaller than those providing a specific diagnosis and we do not evaluate the benefit to perform new TBLCs rather than SLBs in those patients.

Conclusions

Our study supports the role of TBLCs for the multidisciplinary diagnosis of DPLDs when a lung biopsy is required in a majority of the cases. However, even if additional studies are required according to the small number included in the study, our results highlight the benefit of SLB in nondiagnostic TBLCs or when a suspected NSIP pattern is observed. Our data support the concept of the sequential approach (TBLC first, then SLB in selected situations). We believe that this sequential approach will provide the lowest morbidity and mortality with the highest diagnostic accuracy.

Abbreviations

APTT: activated partial thromboplastin time

BMI: body mass index

CVD-ILD: collagen vascular disease-associated interstitial lung disease

D-ILD: drug-induced interstitial lung disease

DLCO: diffusion capacity for carbon monoxide

DPLD: diffuse parenchymal lung disease

FVC: forced vital capacity

HP: hypersensitivity pneumonitis

HRCT: high resolution computed tomography

ICU: intensive care unit

INR: prothrombin time international normalized ratio

IPF: idiopathic pulmonary fibrosis

MDD: multidisciplinary discussion

NSIP: nonspecific interstitial pneumonia

SLB: surgical lung biopsy

TBLC: transbronchial lung cryobiopsy

UIP: usual interstitial pneumonia

VATS: video-assisted thoracoscopic surgery

Declarations

Ethics approval and consent to participate

The study was approved by the ethical committees of the non-leading hospitals and by the leading ethical committee of the Erasme hospital (ref P2015/192).

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

BB received a grant from Roche and Boehringer Ingelheim to support this study. Other authors disclose no conflict of interest in relation to this manuscript.

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Authors' contributions

BB, DL, TP, AF, VH, PA realized the TBLCs. MR, DH and FD performed the histological examination of the lung biopsies. BB, DL, MR analyzed and interpreted the patient data. BB was a major contributor in writing the manuscript. All authors read, corrected and approved the final manuscript.

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Not applicable

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Tables

Due to technical limitations, tables are only available as a download in the supplemental files section.

Figures

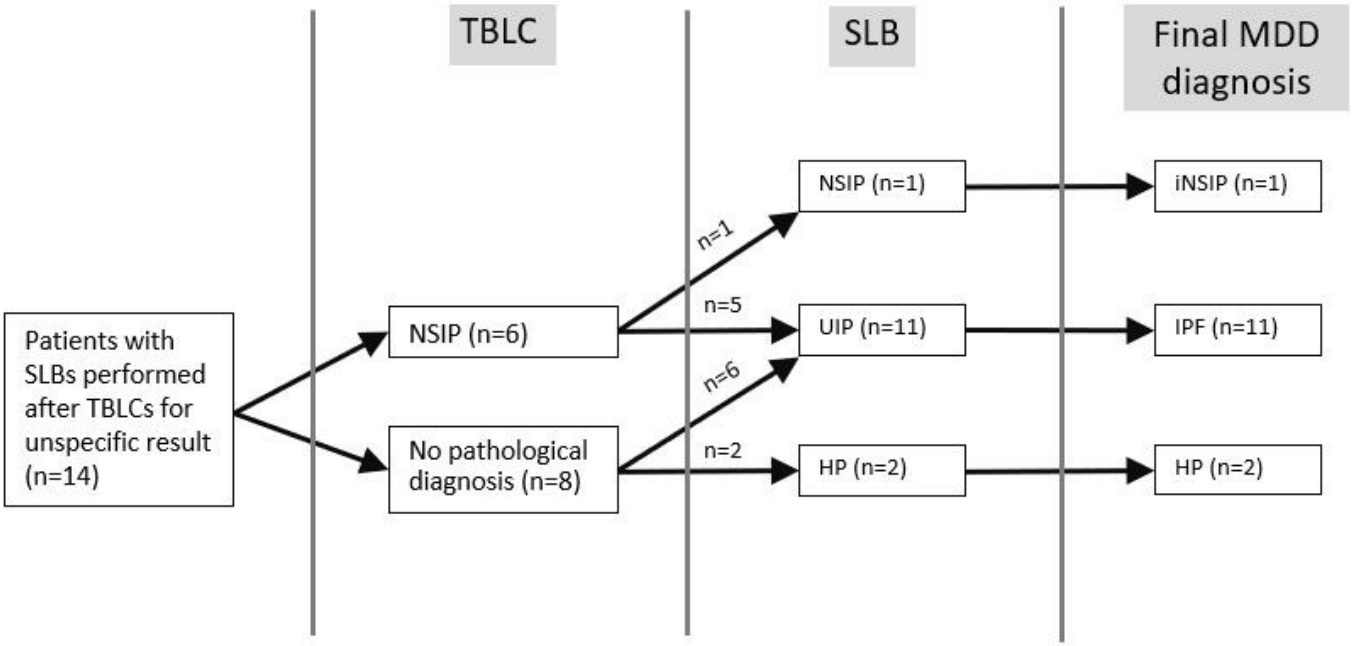

Figure 1

Pathological and final MDD diagnoses obtained in the 14 patients having both TBLCs and SLBs.

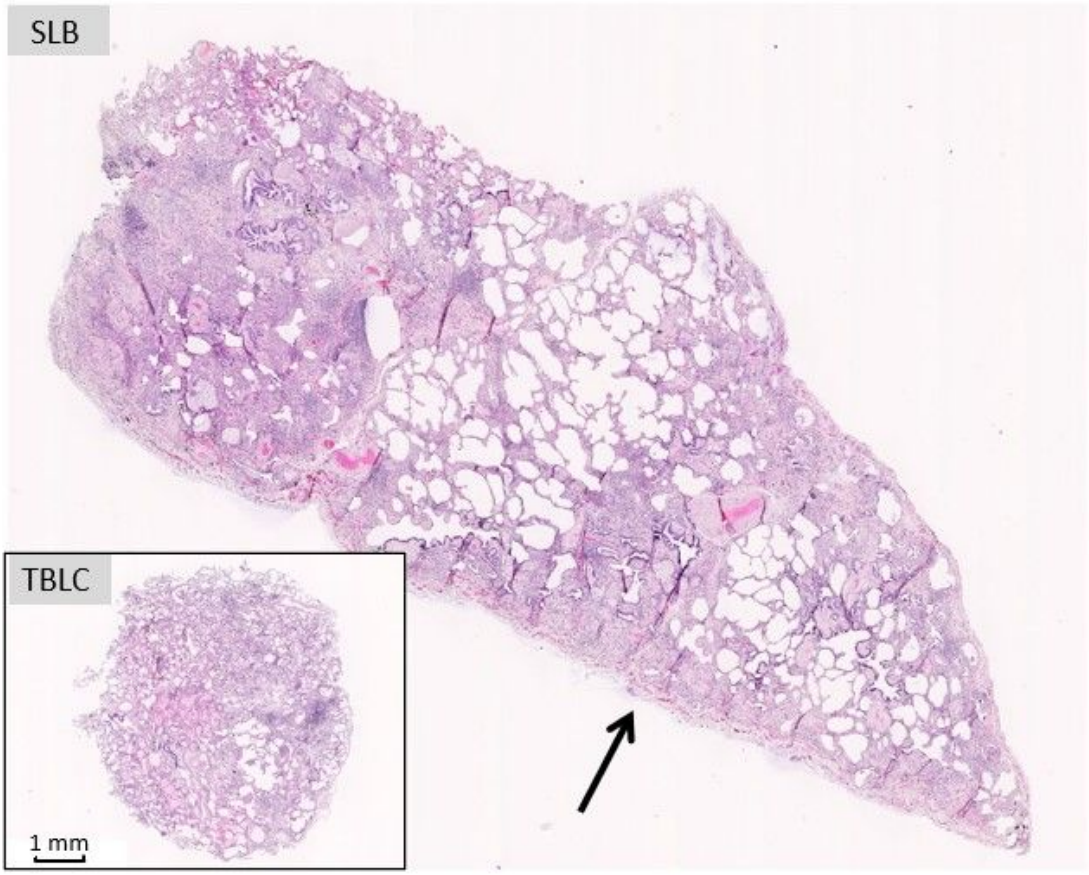

Figure 2

Illustration of the significantly bigger size of SLB compared to TBLC. Hematoxylin and eosin staining. The pleura extensively present in the SLB (marked by the black arrow).

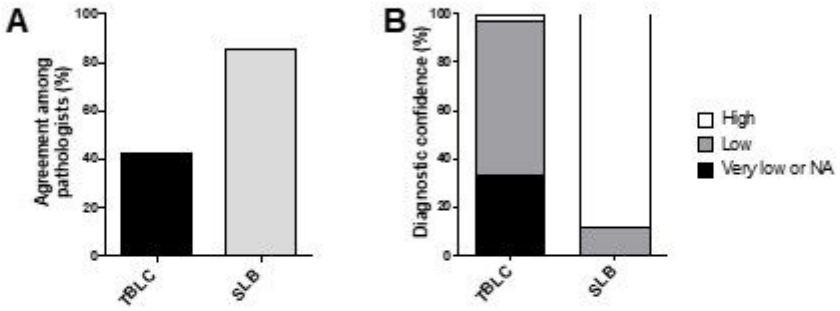

Figure 3

Comparison between TBLC and SLB regarding the percentage of agreement among pathologists for the most likely diagnosis (A), and the corresponding level of confidence (B).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table4NSIPTBLCvsSLB.xlsx
- Table2complicationsanddiagnosticyield.xlsx
- Table1.xlsx
- Table3Histopathologicalreview.xlsx