Complication and cost analysis of transbronchial lung cryobiopsy and awake video-assisted thoracic surgery in diagnosis of interstitial lung disease

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Abstract. *Aim and introduction:* Diagnosing of interstitial lung disease (ILD) is difficult and expensive. The standard diagnostical approaches to ILD are bronchoalveolar lavage, transbronchial lung biopsy, transbronchial lung cryobiopsy (TBLC) and surgical lung biopsy (SLB). SLB is gold standard for the confident diagnosis of ILD but because of the poor performance of the patients it's use is limited. We conducted a retrospective study to point out that TBLC plays an important role in diagnosis of ILD and has fewer complications and lower cost than awake video-assisted thoracic surgery (AVATS). *Material and methods:* 132 patients who underwent TBLC and AVATS with a pre-diagnosis of ILD in our hospital between 2015 and 2020 were evaluated retrospectively. Diagnosis rates, complications and costs were recorded. *Results:* There were no non-diagnostic materials in 44 patients in AVATS arm. Prolonged air leak was observed in 11(25.0%) of the patients, and six of them (13.6%) were discharged with Heimlich Valve (HV). Median length of stay in the hospital was 8 days, while average patient cost was $515.9 (415.2-2662.9) in the AVATS arm. Non-diagnostic material was obtained from 10 (11.3%) of 88 patients in TBLC arm. Six (6.8%) of them had pneumothorax, only one of them required a chest tube. No patient was discharged with HV (p=0.001). Median cost for each patient with a median hospital stay of 2.0 (1.0-21.0) (p<0.001) days was $171.9 (80.8-1493.3) (p<0.001). *Discussion:* Although TBLC is behind AVATS in terms of diagnostic accuracy, it may be an alternative diagnostic tool in the diagnosis of interstitial lung disease due to its acceptable safety profile and cost-effectiveness.

Key words: Interstitial lung disease, transbronchial lung cryobiopsy, awake video-assisted thoracic surgery, complication, cost.

Introduction

Diagnosis of interstitial lung disease (ILD) requires a complex approach. Standard diagnostical

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approaches to ILD are bronchoalveolar lavage, transbronchial lung biopsy, transbronchial lung cryobiopsy (TBLC) and surgical lung biopsy (SLB). Current international guidelines recommend SLB for the confident diagnosis of ILD, which cannot be diagnosed by noninvasive methods (1). However, diagnostic SLB cannot be performed in more than 50% of the patients, because of the older age, multiple comorbidities, severe respiratory failure and high risk of mortality (2). TBLC can be applied to this selected group of patients because it is a procedure with fewer complications, shorter hospital stay, lower costs, and more easily ap-

plicable in daily practice compared to SLB. However, there is a lack of standardization in the application of the process, and diagnostic yield is lower than SLB (3).

Cryosurgical techniques were first used in 1968 for palliative treatment of obstructive endobronchial tumors, and their use in this area still continues (4). In 2009, Babiac et al. used TBLC in 41 patients for the diagnosis of ILD, the diagnosis rate was around 70-80% and it was better than SLB in the safety profile (5). After this study, TBLC has been used for the diagnosis of ILD by the centers specialized in this field (6).

The quality of the sample taken with TBLC and the diagnosis rate is much higher than transbronchial lung biopsy (TBLB) because it provides larger biopsy material, does not have crush artifacts, and contains more alveolar tissue (7-9). Although 96% of the samples taken with TBLC contains adequate specimens, it only avoids surgical biopsy by 80% (5). Despite the fact that TBLC prevents diagnostic surgery mostly, the Latin American Thoracic Society (ALAT) does not recommend TBLC for every patient due to complications, nondiagnostic specimens in 20% of the patients and lack of standardization of the procedure (1). TBLC procedure performed without chest wall incision, has less morbidity compared to video-assisted thoracic surgery (VATS), and is superior in terms of health resource utilization and workforce loss due to the shorter hospital stay (10). The main complications of TBLC are bleeding and pneumothorax (7,3).

Awake thoracic surgery performed under epidural anesthesia was first applied by Buckingham in 1950 (11). The use of awake video-assisted thoracic surgery (AVATS), which has been increasingly used in the last 20 years, has lower anesthesia risk, lower morbidity and shorter postoperative hospital stay compared to intubated thoracoscopy (12,13). However, since the surgical experience in AVATS is still insufficient compared to thoracoscopy, procedural complications and diagnostic accuracy should be considered (14).

Compared to intubated thoracoscopy, AVATS is a more physiological method, better ventilation/perfusion (V/Q) compliance, stable alveolar pressure, reducing the perioperative surgical stress response by reducing postoperative stress hormones and pro-inflammatory mediators, and reducing immunosuppression and neuroendocrine stress. There are also very important disadvantages such as being mobile during the procedure, inability to prevent cough, mediastinal shift and paradoxical breathing, diaphragm displacement and hypercapnia (13).

The main complications of VATS are acute exacerbation of the disease and prolonged air leak (PAL). Even if differential diagnosis is made in ILD by VATS accurately, these are vital complications (15).

The aim of this study was to point out TBLC plays an important role in diagnosis of ILD than AVATS in terms of acceptable safety profile and cost-effectiveness.

Material and methods

A retrospective study was conducted in the department of pulmonology, Dr Suat Seren Chest Disease and Training Hospital between 2015 and 2020. The 132 patients presenting with radiological and clinical features of ILD and required tissue biopsy with either TBLC or AVATS for differential diagnosis were evaluated. The patients were discussed in the multidisciplinary team meeting. Patients with lower clinical performance, more comorbidities, and higher mortality risk in the perioperative evaluation were referred for cryobiopsy, while others were referred to AVATS. All of the patients were over 18 years old. Exclusion criterias were coagulopathy (platelet count $< 70,000 \times 10^9$/L; prothrombin time international normalized ratio > 1.5), FEV_1 less than 1 L , severe heart disease, severe pulmonary hypertension (pulmonary systolic arterial pressure > 40mmHg estimated by echocardiography), and severe hypoxemia ($PaO_2 \leq 55$ mm Hg in room air). Risks and complications were explained to each patient before the procedures and informed consent was obtained from all the patients. All patients were hospitalized before the procedures as a standard in terms of possible complications. Before the procedures, the most affected target area was selected by high-resolution computed tomography (HRCT). While TBLC was performed by interventional pulmonologists, AVATS was performed by thoracic surgeons in the operating room.

In the TBLC procedure, the patients were intubated with a rigid bronchoscope (Dutau-Novatech, BroncialTube size 12, black, 10.7 mm working chan-

nel, 35 cm length) by providing deep sedation with midazolam, fentanyl and propofol. Flexible bronchoscope (Olympus CV 170 with 2.8 mm diameter working channel) was passed through the rigid bronchoscope. Afterwards, the balloon catheter (Broncho Dilator Balloon Catheter) was inserted through the rigid bronchoscope to the entrance of the selected bronchus. Cryoprobe (Erbolryo CA, ERBE, 2.4 mm diameter, 900 mm length) was pushed forward through the flexible bronchoscope and sent to the segment which was most affected detected by HRCT. Under fluoroscopy, the cryoprobe was pushed forward to 10-20 mm near the chest wall. Nitrous oxide (N2O) was used for cooling process. After freezing occurred with cooling that lasted for 3 to 6 seconds, flexible bronchoscope was retracted with cryoprobe. The balloon was inflated as soon as the flexible bronchoscope was removed to control possible bleeding. The sample was put into the saline solution, formalin solution was used for fixation. The procedure was repeated 2 to 5 times by checking the bleeding. At least two biopsies from at least two different segments and at least two biopsies were taken from each patient. Patients were kept in the intensive care unit for 2 hours after the procedure. After 4 hours, chest radiographs were taken for pneumothorax control. Thoracal epidural anesthesia with morphine and fentanyl was applied to the non-entubated patients, after 20 minutes the effect of local anesthesia was controlled and a video thoracoscope (Olympus, OE262H) was placed at the appropriate place with a single incision at the 6th intercostal space on the mid-axillary line. At least two biopsies were taken from the targeted area, with a diameter greater than 1 cm. The incision was closed by placing a chest tube. The chest tube was usually terminated one day later.The need for drainage more than 5 days was evaluated as PAL.

Endobronchial bleeding was classified using British Thoracic Society system: mild bleeding (continued suctioning of blood from the airways, and bleeding stops spontaneously); moderate bleeding (intubation of the biopsied segment with the bronchoscope into the wedge position, use of adrenaline or cold saline to stop bleeding); and severe bleeding (placement of bronchus blocker or catheter, applying fibrin sealant, resuscitation, blood transfusion, admission to critical care unit or death).

Statistical analysis

Analyses were performed with SPSS software v 25.5 (IBM, NY, USA). Shapiro-Wilk normality tests was used to determine whether the parameters were normally distributed. Mann Whitney U test and Student t test were used for comparison of continuous parameters, and Chi-square and Fisher's exact test were used for comparison of categorical parameters. Results were given as median (min-max), mean±sd, number and percentage (%). P value <0.05 was considered statistically significant.

Results

Records of 88 patients who underwent TBLC and 44 patients who underwent AVATS in our hospital between 2015 and 2020 were retrospectively evaluated. These patients were investigated for suspected ILD, but could not be diagnosed with history, physical examination, laboratory tests and thorax HRCT.

The mean age of 88 patients who underwent TBLC was 58.1 ± 9.6, 41 patients (46.6%) were female and 96.6% of them were symptomatic, while the average age of patients who underwent AVATS was 56.3 ± 12.6, 24 patients (54.5%) were female and all patients had symptoms. Multilobar sampling was performed to only one (1.1%) patient with TBLC and 28 (63.6%) patients with AVATS (p <0.001). The demographic and clinical characteristics of the patients are shown in Table-1.

21 (23.9%) patients were diagnosed usual interstitial pneumonia (UIP), 14 (15.9%) patients were chronic nonspecific inflammation, 10 (11.4%) patients were organised pneumonia (OP), 9 (10.2%) patients were hypersensitivity pneumonia (HSP), and 6 (6.8%) patients with nonspecific interstitial pneumonia (NSIP) with TBLC. 28 (63.6%) patients were diagnosed with UIP, 6 (13.6%) patients as HSP, and 3 (6.8%) patients with OP with AVATS. While 11.3% of non-diagnostic biopsy material was obtained with TBLC, all patients were diagnosed with AVATS.

With TBLC, mild bleeding was observed in 26 (61.9%) patients, moderate bleeding in 15 (35.7%) patients, severe bleeding in 1 (2.4%) patient and no bleed-

Table 1. Demographic datas and clinical characteristics of patients

	TBLC n=88	VATS n=44
Age(mean±sd)	58.1±9.6	56.3±12.6
Female	41 (46.6%)	24 (54.5%)
Male	47 (53.4%)	20 (45.5%)
Smoking status n (%)		
Smoker	21 (23.9%)	8 (18.2%)
Ex-smoker	25 (28.4%)	11 (25.0%)
Never smoker	42 (47.7%)	25 (56.8%)
Additional illness		
COPD	18 (20.4%)	0 (0.0%)
HT	61 (69.3%)	8 (18.1%)
CHF	29(32.9%)	5 (11.3%)
DM	19 (%21.5)	3 (6.8%)
Symptom n (%)	85 (96.6%)	44 (100.9%)
Cough	52 (59.1%)	31 (40.9%)
Dyspnea	68 (77.3%)	38 (86.4%)
Sputum	11 (12.5%)	7 (15.9%)
Number of areas biopsied n (%)		
One area	87 (98.8%)	16 (35.4%)
Multiple areas	1 (1.1%)	28 (63.6%)
Diagnosis n (%)		
Chronic nonspecific inflamation	14 (15.9%)	0 (0.0%)
Non-diagnostic	10 (11.3%)	0 (0.0%)
UIP	21 (23.9%)	28 (63.6%)
HSP	9 (10.2%)	6 (13.6%)
OP	10 (11.4%)	3 (6.8%)
Lung cancer	4 (4.5%)	0 (0.0%)
NSIP	6 (6.8%)	2 (4.5%)
Follicular Bronchiolitis	1 (1.1%)	1 (2.3%)
Unclassified ILD	2 (2.3%)	0 (0.0%)
Alveolar proteinosis	1 (1.1%)	2 (4.5%)
Sarkoidoz	1 (1.1%)	0 (0.0%)
Eosinophilic pneumonia	4 (4.5%)	1 (2.3%)
Metastatic lung carcinoma	2 (2.3%)	0 (0.0%)
Pneumoconiosis	1 (1.1%)	1 (2.3%)
Granulomatosis infection	1 (1.1%)	0 (0.0%)
DAH	1 (1.1%)	0 (0.0%)
Chest tube requirement n (%)	1 (1.1%)	44 (100.0%)
Duration of chest tube (days) (median) min-max	0.0 (0-6)	4.0 (2-28)

COPD: Chronic obstructive pulmonary disease, HT: Hypertension, CHF: Congestive heart failure, DM: Diabetes mellitus, UIP: Usual interstitial pneumonia, OP: Organizing pneumonia, NSIP: Nonspecific interstitial pneumonia, ILD: Interstitial lung disease, DAH: Diffuse alveolar hemorrhage.

ing occurred in 46 (52.3%) patients. We used bleeding classification of British Thoracic Society System.

A total of 6 (6.8%) pneumothorax was detected in TBLC group. Only one (1.1%) of these patients required a chest tube. The chest tube requirement in this patient ended on the 6th day of hospitalization and was recorded as PAL (1.1%). PAL was detected in 11 (25.0%) patients in AVATS group (p <0.001), 6 (13.6%) of them were discharged with heimlich valve (HV) (p = 0.001). Duration of the HV in the AVATS subgroup was 9.1±7.0 days.

Death was not observed in both procedures. Acute exacerbation occurred in one of 44 patients who underwent the AVATS procedure, no patient was exacerbated in TBLC procedure. While the mean hospitalization period of patients who underwent TBLC was 2.0 (1.0-21.0) days, and 8 (3.0-46.0) days in AVATS group (p <0.001). Average cost in TBLC arm was $171.9 (80.8-1493.3) and $515.9 (415.2-2662.9) was in the AVATS arm (p <0.001). (Table 2).

Discussion

ILD is a group of diseases that includes more than 200 different disorders and requires a multidisciplinary approach to diagnose (16). UIP is the most common of these disorders and the average life expectancy is up to 3 years due to its rapid progression and loss of time for diagnosis, and also distinguishing UIP from other types of ILD is important for treatment strategies, too. Therefore, since time is important in such patients, we need to reach the diagnosis as soon as possible (4).

Recently UIP guidelines do not recommend tissue biopsy for diagnosis if clinical and laboratory findings suggest UIP and also UIP-specific findings are observed in Thorax HRCT (15). In the absence of these, SLB is still the gold standard in diagnosis of ILD. Nevertheless, less invasive methods such as bronchoalveolar lavage and TBLB are recommended for diagnosis before the surgical procedure.

However, the diagnosis rates of these procedures are low because the biopsy material taken with TBLB is very small and contains crush artifacts (3). TBLC is increasingly being used in the diagnosis of ILD for the last 10 years.

Table 2. Complications and costanalysis

	TBLC n=88	VATS n=44	p value
Complications n (%)	48 (54.5%)	NA	NA
Hemorrhage n (%)			
Mild	26 (61.9%)	NA NA NA NA	
Moderate	15 (35.7%)	NA	
Massive	1 (2.4%)	NA	NA
None	46 (52.3%)	NA	
Pneumothorax	6 (6.8%)	NA	NA
PAL	1 (1,1%)	11 (25.0%)	<0.001
HV	0 (0.0%)	6 (13.6%)	0.001
Duration of hospitalisation (days) (median) (min-max)	2.0 (1.0-21.0)	8 (3.0-46.0)	<0.001
Cost (Dolar) (median) (min-max)	171.9 (80.8-1493.3)	515.9 (415.2-2662.9)	<0.001

PAL: Prolonged air leak, HV: Heimlich valve, NA: Not available

The material taken in TBLC is significantly larger compared to TBLB, and the sample taken during biopsy is protected from crush artifact since it is not passed through the bronchoscope (16, 17). Performing the procedure with fluoroscopy also enables sampling from peripheral alveolar tissue as much as possible.

In our study, we compared TBLC procedure with AVATS, which has fewer complications than classical thoracotomy and intubated VATS, and was also cost effective due to the shorter hospital stay.

A total of 132 patients including 88 patients who underwent TBLC and 44 patients with AVATS were examined. TBLC performed who were at high risk for surgery due to high number of comorbidities and lower clinical performance.

21 (23.9%) of the patients were diagnosed UIP with TBLC, 28 patients (63.6%) were UIP in AVATS group. In the study of Sugino and et al, all 143 patients who underwent VATS the diagnosis was UIP in majority (45%) like our study (15). Non-diagnostic material was obtained in 10 (11.3%) of 88 patients in TBLC arm, while there was no non-diagnostic material in AVATS arm. Romagnoli et al.'s study, non-diagnostic material was obtained with TBLC group in 4 of 21 patients, and all patients were diagnosed with SLB (2). Multilobar sampling in only one of the patients in the TBLC arm may also be a reason for the present diagnostic difference. The point we want to emphasize that our diagnostic value is higher or equal, but we recommend considering TBLC to the selected

patients before SLB, because of the complications and cost.

Although TBLC is applied under operating room conditions, it is not a surgical procedure, and the patient does not need any incision. However, with AVATS, there is a need for single small incision. Although this has not been recorded in our patients, the incision can cause mobilization defects and pain that may last for months, as we have observed in studies conducted with VATS and also in our AVATS patients.

Bleeding complication was detected in 42 (47.7%) patients with TBLC, and most of them were mild bleeding that required no intervention. In this study 61.9% patients had mild, 35.7% patients had moderate bleeding, 2.4% patients had severe bleeding. In Hetzel et al's study, mild bleeding was reported in 61.8% of the patients, and severe bleeding was in 18.2% patients. In the study of Pajares et al. 30.8% of them had mild bleeding and 56.4% of them had moderate bleeding (17, 18).

As AVATS is a surgical procedure, bleeding was not considered as an important complication and surgeons did not record bleeding as a complication. However, it is obvious that there will be more bleeding in AVATS than TBLC, because it is a surgical procedure, this was our limitation in this study.

In TBLC arm 6 (6.8%) out of 88 patients experienced pneumothorax and only one of them (1.1%) required a chest tube. The chest tube could only be terminated on the 6th day of hospitalization, and it was evaluated as PAL. The chest tube was removed before

the patient was discharged. In the review written by Ravaglia et al. 60 (20.2%) of 297 patients who underwent TBLC had pneumothorax, and 46 (15.5%) of them required a chest tube (19). As the experience of the TBLC procedure increases, the complications will be decreasing. However, for this, the process should be done by experienced centers with standardized protocol (20).

In AVATS procedure, pneumothorax is a normal procedure and occurs in every patient and does not considered as a complication. While the procedure is terminated, a chest tube is applied to each patient. It is expected that the chest tube will be terminated one day later under normal conditions. However, sometimes the chest tube had to stay longer due to PAL, and sometimes patients had to be sent home with HV. This is a factor that both reduces the patient's comfort and delays the patient's return to work. PAL was observed in 11 (25.0%) of 44 patients who underwent AVATS, and 6 (13.6%) of them were sent home with HV. In the review of Ravaglia et al. PAL was reported as 3.3% in the VATS arm, although this rate was significantly lower than our AVATS arm, but 3 times higher than the TBLC arm (19). In our study,

pneumothorax was significantly less common in TBLC arm, and this was advantageous for patients because PAL may cause unpleasant conditions such as empyema, atelectasis, pneumonia, and pleurodesis, mechanical ventilation and reoperation due to decreased mobilization and pain due to chest tube (21-23) and it also increases the cost.

The length of the hospital stay is important because of the cost, use of health resources and the burden of the labor loss of the patients on the national economy. In our study, the median length of stay in the hospital was 2.0 (1.0-21.0) days in the TBLC arm, while it was 8 (3.0-46.0) days in the AVATS arm. Ravaglia et al. reported the length of stay similar to us as 2.6 (0–17) days in TBLC group and 6.1 (3–48) days in VATS group (19). In another review by Iftikhar et al., the length of stay was 2.6 days in TBLC and 6.1 days in VATS group (16). In this study median hospital days were four times more in AVATS group, which increased hospital costs.

In terms of cost, the median patient cost in our study was $171.9 (80.8-1493.3) in the TBLC arm,

while it was $515.9 (415.2-2662.9) in AVATS arm. In Gonzalez et al's study, the cost per patient was determined as € 304.69 in TBLC and €1,257.78 in VATS group for patients who were not hospitalised (24). In our study, TBLC procedure was found to be 3 times more cost-effective than AVATS. Moreover, this cost was only hospital expenses, and the cost arising from the loss of workforce of the patients due to the length of hospital stay and complications mentioned above cannot be calculated but should not be ignored, as well. In our country hospital fees are low as a government state policy.

Hagmeyer et al. emphasized in their review that cryobiopsy reduced the need for SLB by 78% and these results were confirmed with SLB at a rate of 90% (25).

The limitations of our study, the datas would be much stronger if TBLC and AVATS were performed on the same patients and in addition, although multisegmenter biopsy was performed in the TBLC arm, multilobar biopsies would be more diagnostical. Incomplete or inaccessible records, as well as surgeons' bleeding records, were a handicap for this study. In the upcoming days, we can plan a prospective study in which both procedures are applied to the same patient group, the materials blindly evaluated by pathologists, with a multidisciplinary approach that includes chest diseases, thoracic surgery, pathology and radiology specialists. Our study still seems to be satisfactory when evaluated in terms of the number of patients.

In conclusion SLB is still gold standard technique in diagnosis of ILD, however nowadays TBLC plays an important role in diagnosis of ILD and prevents SLB because of its higher diagnostic value compared to other non-surgical methods, and lower complications and lower cost compared to AVATS. As experiences with TBLC procecedure increases, it's place in the ILD diagnosis algorithm will be more clear.

Conflicts of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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