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Review

The Role of Surveillance Bronchoscopy Following a Lung Transplantation

Shehab Mohamed [1, *], Davide Tosi [1], Sara Pieropan [1], Andrea Cara [1], Giovanni Caffarena [1], Giorgio Alberto Croci [2], Lorenzo Rosso [1]

1. Thoracic Surgery and Lung Transplant Unit Fondazione IRCCS Ca' Granda-Ospedale Maggiore Policlinico, Milan, Italy; E-Mails: shehabmohamedmd@gmail.com; davide.tosi@policlinico.mi.it; sarapieropan90@gmail.com; andrea.cara@unimi.it; giovanni.caffarena@gmail.com; lorenzo.rosso@unimi.it
2. Division of Pathology, Fondazione IRCCS Ca' Granda-Ospedale Maggiore Policlinico, Milan, Italy; E-Mail: giorgio.croci@unimi.it

* **Correspondence:** Shehab Mohamed; E-Mail: shehabmohamedmd@gmail.com

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Abstract

Pulmonary transplantation (LuTx) is established as a treatment option for patients with end-stage lung diseases, such as chronic obstructive pulmonary disease, cystic fibrosis, interstitial lung disease, and pulmonary arterial hypertension. Acute rejection and infection are implicated as potential risk factors in developing complications such as bronchiolitis obliterans syndrome (BOS) and chronic rejection, leading to high morbidity and mortality rates after the LuTx. Thus, surveillance procedures after transplantation are crucial to prevent further complications. Clinical monitoring is done through pulmonary function tests and procedural methods such as surveillance bronchoscopy and transbronchial biopsy of lung allografts, which are the most commonly used diagnostic tests. In this review, we aim to analyze the role of bronchoscopy as a surveillance procedure in determining the presence of infection or rejection as well as the management of airway complications after LuTx. We have also discussed the risk and benefit ratio of standard transbronchial biopsy (TBB) and transbronchial cryobiopsy (TCB) as routine performance after LuTx.

Keywords
Surveillance; bronchoscopy; lung transplantation; rejection; infection

1. Introduction

Pulmonary transplantation (LuTx) is established as a treatment option for patients with end-stage lung diseases, such as chronic obstructive pulmonary disease, cystic fibrosis, interstitial lung disease, and pulmonary arterial hypertension.

The most recent data from the International Society for Heart and Lung Transplantation (ISHLT) revealed the median survival is 6.7 years for adults who have undergone primary LuTx [1].

The main causes of death after adult LuTx are acute graft failure and non-CMV infection during the first year and chronic rejection in subsequent years [1].

To prevent the occurrence of such complications, clinical monitoring is done through pulmonary function tests and procedural methods such as surveillance bronchoscopy, bronchoalveolar lavage, and transbronchial biopsy of lung allografts, which are the most common diagnostic tests.

All lung transplant centers do not use these surveillance procedures as a scheduled or clinically indicated method because, even though the procedure can identify acute rejection in the early stages, allowing early treatment to improve long-term survival, their role in asymptomatic patients is still controversial. Further, this endoscopic technique allows direct visualization of the airways to determine early complications such as anastomotic dehiscence, ischemia, or stricture.

In this review, we aim to analyze the role of bronchoscopy as a surveillance procedure used in determining the presence of infection or rejection and also managing airway complications after LuTx.

We have also discussed the risk and benefit ratio of standard transbronchial biopsy (TBB) and transbronchial cryobiopsy (TCB) as a routine procedure after LuTx.

2. Bronchoscopy after Lung Transplantation

Diagnosis of rejection and infection in asymptomatic patients with lung transplantation could improve the long term survival. Bronchoscopy is a valuable diagnostic tool used as a surveillance procedure. This method uses bronchoalveolar lavage (BAL) to collect the tissue samples for detecting the presence of infection or rejection while assessing airway complications through direct visualization.

2.1 Infection

The incidence of developing overall lung allograft infections after LuTx is higher than the other organ transplants. Lung allograft is more susceptible to infections due to immunosuppression, exposure to the environment through inhaled microorganisms, and ischemic complications.

Several organisms, specifically fungi, are associated with the development of airway complications at the anastomotic site, such as hemorrhage, bronchomalacia, and bronchial stenosis [2].

Viral, bacterial, and fungal infections are known risk factors associated with the development of BOS [3-8].

Community-acquired respiratory viruses account for about 30% of all acute respiratory presentations after the LuTx and are also a dominant cause for new respiratory symptoms. Picornavirus, particularly rhinovirus, is the most frequent causative agent for the development of BOS and is recovered in both the upper and lower respiratory specimens, followed by coronavirus and influenza [9].

Among bacterial infections, *Pseudomonas aeruginosa* is the most common cause for the development of BOS within the first two years of lung transplantation [10].

Similarly, fungal infections are also implicated as a potential risk factor for the development of BOS with high morbidity and mortality rates. The most life-threatening issue is related to invasive aspergillosis [11]. An increased risk of BOS is associated with the colonization of the lung allograft with small conidia *Aspergillus* species and not the larger ones [8].

One of the latest prospective studies that performed BAL described the most common microbiological findings during the first year of LuTx, where *Candida albicans, Pseudomonas aeruginosa*, and coagulase-negative *Staphylococcus* were the most frequent pathogens [12].

Patients with airway infections could be asymptomatic or may present nonspecific symptoms such as cough, secretions, and fever. These clinical indications need to be diagnosed and treated to avoid sequelae.

Infections in asymptomatic patients can be diagnosed using bronchoalveolar lavage (BAL), including microbiological cultures and PCR performed during the surveillance bronchoscopy to guide antibiotic therapy. Contrastingly, for symptomatic patients, computed tomography (CT) scan and bronchoscopy are suggested.

Bronchoscopy is essential not only for BAL or direct visualization of the bronchial anastomosis but also for operative endoscopy procedures, such as debridement of devitalized tissue, dilation of bronchial stenosis, stent placement, laser, cryotherapy, or biopsies.

2.2 Rejection

After LuTx, both vasculature and airways of the allograft could be affected by an acute, antibody-mediated, and/or chronic rejection. Acute rejection is characterized by a mononuclear cell infiltration around small vessels and capillaries and/or small airways, which establishes a condition called lymphocytic bronchiolitis. Acute rejection and lymphocytic bronchiolitis are risk factors linked to the development of BOS and chronic airway rejection.

The guidelines of the International Society for Heart and Lung Transplantation (ISHLT) describe pathological grading of acute and chronic cellular rejection. The former is based on the presence of perivascular and interstitial mononuclear infiltrates with chronic rejection, while the latter is based on the presence of fibrous scarring that involves the bronchioles and is sometimes associated with the fibrointimal changes affecting the arteries and veins [13].

Although acute cellular rejection is histologically well defined, there are no standardized diagnostic criteria for antibody-mediated rejection (AMR).

AMR can lead to a range of clinical severity and features, from being asymptomatic with circulatory donor-specific antibody (DSA) through the spectrum to a chronic graft failure.

To create a uniform definition and consensus document for the diagnosis of AMR, the ISHLT multi-disciplinary society convened a working group in 2016 [14].

This document has identified the following criteria to define an acute pulmonary AMR: allograft dysfunction, DSA positivity, histopathology consistent with AMR, C4d tissue staining, and exclusion of other reasons that cause allograft dysfunction. The degree of confidence in diagnosing AMR is based on the number of criteria present. Clinical AMR is associated with measurable allograft dysfunction, which can be asymptomatic. It may also be sub-clinical, with normal allograft function. Both clinical and sub-clinical AMR were further categorized into three mutually exclusive possibilities (definite, probable, and possible) based on the number of mentioned criteria. “Definite AMR” is identified when all four criteria are met, “Probable AMR” is identified when three criteria are met, or other possible causes have not been excluded, and “Possible AMR” has at least two criteria missing.

Multiple pathological findings of AMR were described in the lung allografts, including capillary inflammation, endothelialitis, and acute lung injury [15-17]. The standard transbronchial biopsy(TBBs) is also essential for the detection and diagnosis of AMR.

Chronic lung allograft dysfunction (CLAD) after the LuTx is described as a clinical manifestation with a range of pathological processes in the airway and parenchyma that lead to a significant and persistent deterioration in the functioning of the lung and occurs for more than three months. This chronic condition is considered a major cause of morbidity and mortality after the LuTx.

CLAD may be presented as a predominantly obstructive ventilatory pattern, a restrictive pattern, or a mixed obstructive and restrictive pattern. The most common manifestations of CLAD are bronchiolitis obliterans syndrome (BOS) and restrictive allograft syndrome, defined by a decrease in the value of FEV1 (amount of air forced from the lungs in 1 s), where FEV1> 20% [18].

Body plethysmography is recommended to measure Total Lung Capacity (TLC) in the patients at three and six months after the transplant and annually thereafter, and also if FEV1 changes to > 10% from the previous values [18].

Bronchoscopy with transbronchial biopsy (TBB) and bronchoalveolar lavage (BAL) play a major role in the detection of treatable causes of acute rejection and CLAD, such as acute cellular rejection. However, some controversy is involved in using it as a surveillance procedure in asymptomatic patients.

Histological samples obtained during the surveillance bronchoscopy may detect an area of bronchiolitis obliterans, which is uncommon, as the process is patchy and sampling is limited to a specific site.

2.3 Primary Disease Recurrence

The recurrence of a primary disease has been reported after lung transplantation, and one such primary disease is sarcoidosis, which is the most common, followed by lymphangioleiomyomatosis (LAM), Langerhans cell histiocytosis (LCH), diffuse granulomatous, diffuse panbronchiolitis, and pulmonary alveolar proteinosis.

The clinically indicated cases are usually diagnosed by high-resolution CT of the lungs, followed by the TBB.

Surveillance TBBs can detect the recurrences as incidental findings.

Recurrence of sarcoidosis after LuTx are described in the literature [19, 20].

Several authors have reported that ACR may be more frequent and severe among patients with sarcoid recurrence due to a common immunopathological mechanism [20].

On the other hand, Banga et al. did not observe an increased frequency or severity of ACR with sarcoidosis recurrence and instead found a protective effect. The frequency of ACR episodes among the patients without recurrence of sarcoidosis was similar to those of the ACR rates among patients with different indications on surveillance FB among patients with different indications.

The typical non-necrotizing granulomas seen on TBB specimens in the absence of any other etiology for granulomatous inflammation were pathologically diagnosed.

LAM is a rare disease with even rarer recurrence post-lung transplantation, with only a few studies reporting about it [21, 22].

A histopathological examination of the transbronchial biopsy that reveals spindle-shaped LAM cells with no evidence of infection and acute or chronic rejection is suggestive of LAM recurrence.

Clinically indicated TBB after the LuTx is a valid method to detect the recurrence of primary disease during the surveillance. The TBBs are crucial when the primary disease is still asymptomatic.

3. Surveillance Versus Clinically Indicated Bronchoscopy

Unfortunately, nowadays, there is no consensus on either performing surveillance bronchoscopy or its frequency in patients with LuTx. This controversy is derived from the possible complications related to the endoscopic procedure. For this reason, there are some variabilities in monitoring practices after the LuTx between different centers.

There is a general agreement on clinical monitoring after the LuTx with spirometry, which is widely used as a non-invasive, cheap, and reproducible method. A drop in the FEV1, greater than 10% from baseline, is used to trigger investigations to find any treatable cause [23]. Reduction in the lung function tests, radiological changes, dyspnea, cough, or other similar symptoms are some conditions that require clinically indicated bronchoscopy with BAL and TBB.

In contrast, surveillance bronchoscopy with TBB is performed as a part of a routine protocol in asymptomatic patients after the LuTx.

The protocols of TBB as a scheduled procedure are applied at different frequencies in different centers.

Some centers perform TBB/BAL as a surveillance procedure at 3-6-9-12 weeks after the LuTx. After the first three months, only clinically indicated bronchoscopy is performed. If the first 3 and 6-week surveillance bronchoscopies are found to be normal with negative rejection results, the 9-week bronchoscopy could be omitted [24, 25].

However, not all the evidence supports the need for routine surveillance bronchoscopy in LuTx cases. In 2002, Valentine et al., through an observational single-institution study, concluded that clinically indicated TBB/BAL without routine surveillance sampling of the lung allograft does not decrease the survival of the patient with lung transplantation. The same authors in 2008 estimated that over 50% of the centers in the United States performed surveillance bronchoscopies, and despite their small study group, the procedure represented a risk to the lung transplant recipient due to no obvious advantage [26, 27].

On the other hand, McWilliams et al. in the same year demonstrated for the first time that bronchoscopy with TBB was a safe procedure in patients with LuTx till the first year. This study

analyzed 353 TBBs from 124 patients and confirmed a high diagnostic yield for clinically silent acute rejection and infection [28].

In 2014, similar results were reported in a retrospective study by Inoue et al., conducted on 206 TBBs from 28 patients who underwent cadaveric lung transplantation. This study reported 49% positive results for surveillance, which showed rejection, infection, or colonization, and 47% for clinically indicated procedures [29].

More recently, Takizawa et al. assessed 1252 bronchoscopies in 247 patients in a single-center retrospective analysis of LuTx recipients who survived the first year. In this study, surveillance bronchoscopy was sufficient to modify the management, mainly in the 2 and 6-week surveillance bronchoscopies, post-LuTx. Also, they concluded that this effect seems to dilute after the second month, making its applicability questionable [30] (Table 1).

Table 1

	Scheduled TBB	Clinically indicated TBB
Tosi et al	223	28
Valentine et al	156	84
McWilliams et al	232	121
Inoue et al	189	17
Takizawa et al	1252	0

In our center, the surveillance procedures are performed to monitor lung allografts at 3, 6, and 12 months after the transplant. These scheduled procedures consist of flexible bronchoscopy performed with local anesthesia and intravenous sedation along with bronchoalveolar lavage (BAL) and transbronchial biopsies (TBBs). Samples are usually taken from the 2/3 segments of the right lower lobe (RLL) with a minimum and maximum of 6 and 8 biopsies, respectively, with a single-use 1.8 mm transbronchial biopsy forceps. We preferred RLL because it is possible to place a balloon-based endobronchial blocker in the bronchus intermedius in case of severe and uncontrollable bleeding, allowing ventilation to not only the left lung but also to the right upper lobe. In the case of bilateral lung transplantation, we performed biopsies only in one lung due to the risk of bilateral pneumothorax.

Our experience confirmed the importance of surveillance protocol performed using TBBs or CrioTBBs in patients with LuTx. Of patients involved in the protocol, 8% were diagnosed with AR without any clinical signs, and upon receiving specific medical treatments, the rejection grades were downgraded at the next check-up [25].

There is still no scientific evidence that demonstrates the need to perform surveillance transbronchial biopsies for the diagnosis of acute rejection in a lung transplanted patient due to the lack of randomized trials.

4. TBB versus TCB

Transbronchial biopsy (TBB) using forceps is considered the gold standard for the diagnosis of acute rejection after the LuTx. However, tissue samples obtained using this technique could be inadequate to assign a pathological grade according to the revision of the 1996 working formulation

for the standardization of nomenclature in the diagnosis of lung rejection [13]. In a large percentage of cases, diagnostic inadequacy is due to the crushing artifacts, atelectasis, and hemorrhage within the alveoli [31].

Transbronchial cryobiospsy (TCB) allows us to obtain larger samples with fewer artifacts compared to TBBs. This technique is largely used for the diagnosis of interstitial lung disease. Despite obtaining larger biopsies with preserved histology, which is free of artifacts and a higher number of alveoli and small airways, only a few studies have reported the use of TCB in lung allografts [31].

Several studies have compared the two methods in terms of diagnostic adequacy and complications. In 2013, Fruchter et al. assessed the safety and quality of TCB compared to TBB in 80 cases with 40 patients in each group. The mean diameter of the TCB specimens was 10 mm compared to 2 mm of the TBB specimens. The increased specimen diameter resulted in providing adequate tissue in 100% of the cases, whereas in TBB specimens, three nondiagnostic cases were found. No major complications occurred in the TCB group, whereas a single pneumothorax (2.5%) case was observed after TBB. 15% of bleeding events occurred in the TCB group compared to 2.5% events in the TBB group [32].

In the same year, Yarmus et al. presented the safety profile and biopsy results from 21 procedures, out of which ten were performed using a rigid bronchoscope whereas 11 were performed with a flexible one. Similar to the previous study, the mean specimen size in the TCB specimen was significantly larger and higher in terms of the percentage of sampled tissue containing open alveoli compared to the TBB; these results were also confirmed by other studies later [31]. TBB samples had significant amounts of crushing artifacts, whereas TCB samples demonstrated no evidence of any artifact, including freezing artifact. Only a single case of pneumothorax was described, which also recovered without treatment, and in almost all the cases, there was bleeding that was not severe enough to require surgical intervention or other invasive treatments [33].

Since 2015, similar complication rates were described in different studies [34-36]. The incidence of mild bleeding in TCB groups ranged between 7.5% and 22.5%, except for Gershmann et al., who reported the incidence as 2.5%.

The incidence of pneumothorax in TCB groups ranged between 4.5% and 12.5%, except for Loor et al. who did not report any case. On the other hand, mild bleeding was observed in the TBB groups, ranging between 2% and 14.6%, while pneumothorax was observed up to 4% (see Table 2-3 for detailed results).

Table 2 Procedures.

	TCB	TBB
Fruchter et al.	40	40
Yarmus et al.	21	21
Roden et al.	27	27
Montero et al.	40	41
Gershman et al.	201	201

Loor et al.	321	0
Mohamed et al.; Tosi et al.	75	223

Table 3 Complications.

	Moderate bleeding (%)		Pneumothorax (%)	
	TCB	TBB	TCB	TBB
Fruchter et al.	15	2, 5	0	2, 5
Yarmus et al.	4, 8	0	4, 8	4, 8
Roden et al.	0	3, 7	0	3, 7
Montero et al.	22, 5	14, 6	12, 5	0
Gershman et al.	2, 5	2	4, 5	4
Loor et al.	7, 5	0	7, 7	0
Mohamed et al.; Tosi et al.	8	1, 3	1, 3	3, 1

Another complication that followed TBBs in patients with LuTx, described in the literature, is the development of new and transient pulmonary nodules (PNs) at the site of biopsies. Mehta et al. hypothesized that these nodules are related to local hematoma and impaired lymphatic drainage. In this retrospective study, PNs were detected in 13% of the procedures within 50 days and needed up to 86 days to resolve spontaneously [37]. These new PNs could be radiologically interpreted as malignancies, opportunistic infection, or post-transplant lymphoproliferative disorder. Based on these results, we suggest that all physicians need to be aware of this iatrogenic etiology to avoid unnecessary workup and radiation exposure. In these cases, close observation is a reasonable management approach.

Recently, we have reported 75 cases of cryobiopsies in 54 lung allograft recipients for surveillance purposes, where only up to 2 samples were retrieved using cryoprobe. Diagnostic rates and complications were described and compared to the TBB data from our previous study. The diagnostic rate of acute rejection using TCB was 100% compared to conventional TBB, where the rate was 83%. Complications described in these two studies were comparable to the previous studies. Moderate bleeding of 6% in the TCB group and 3% in the TBB group were described. Also, only one patient (1%) developed pneumothorax in the TCB group, while 7% developed it in the TBB group [38, 25].

5. Conclusions

Bronchoscopy is a valuable diagnostic tool that is used as a surveillance and clinically indicated procedure. Diagnosis of rejection and infection in asymptomatic patients with lung transplantation could improve the long term survival and avoid sequelae. This method uses bronchoalveolar lavage, which performs tissue sampling to detect the presence of infection or rejection while assessing airway complications by direct visualization.

In conclusion, we recommend surveillance bronchoscopy protocol with BAL and TBB to be performed in all the centers at 3, 6, and 12 months after the transplant. These procedures can allow us to collect specimens from lung allografts with an acceptable risk/benefit ratio and also treat asymptomatic patients with specific medical treatment to reduce the risk of chronic rejection.

Author Contributions

Conception of the work: Shehab Mohamed, Davide Tosi, Lorenzo Rosso; Manuscript writing and editing: All authors; Acquisition, analysis, interpretation of data: Shehab Mohamed, Davide Tosi, Lorenzo Rosso

Competing Interests

The authors have declared that no competing interests exist.

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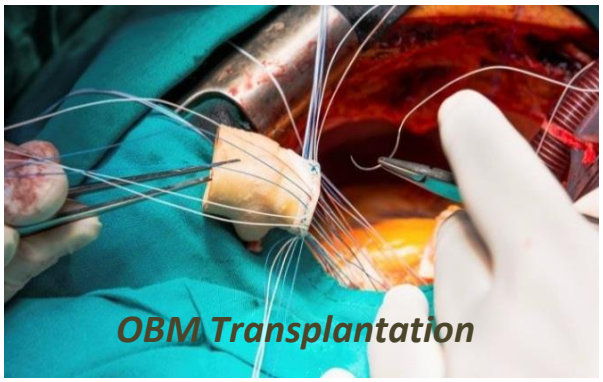

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