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Abstract

Transbronchial Lung biopsy (TBBx) also known as “Bronchoscopic Lung Biopsy” is one of the most important sampling procedures performed during flexible bronchoscopy. In majority of cases, TBBx is performed under conscious sedation in an outpatient setting. TBBx is performed for obtaining tissue specimen from peripheral lung masses and focal or diffuse lung infiltrates. The technique is useful in patients with suspected lung cancer, fungal and mycobacterial lung infections, unexplained infiltrates in immunocompromised hosts and in patients with suspected pulmonary sarcoidosis, lymphangitic carcinomatosis, and in selected cases of pulmonary Langerhan’s cell histiocytosis, lymphangioleiomyomatosis, and cryptogenic organizing pneumonia. TBBx also plays important role in assessment of rejection and infectious complications following lung transplantation. TBBx is not useful for histological diagnosis of idiopathic pulmonary fibrosis or for distinguishing histological subtypes of idiopathic interstitial pneumonia. The diagnostic yield is also suboptimal in lung nodules smaller than 2 cm in diameter. Several recent techniques such as radial probe endobronchial ultrasound with guide sheath, electromagnetic navigation bronchoscopy, and virtual bronchoscopy navigation have been devised to improve the diagnostic yield of TBBx for solitary lung nodule. Hemoptysis and pneumothorax are the two leading complications of TBBx, occurring in less than 2 % of cases. Every bronchoscopists must be able to perform TBBx.

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Introduction

Transbronchial Lung Biopsy (TBBx) also known as Bronchoscopic Lung Biopsy (BLBx) is one of the most important applications of flexible bronchoscopy. A diagnostic TBBx may obviate the need for an open lung biopsy. Even though the procedure is generally safe, serious and sometimes life-threatening complications may occur during TBBx. Therefore, decision to proceed with TBBx should be taken only after a careful risk–benefit analysis. In this chapter, we discuss the technique, clinical applications, limitations, and complications of transbronchial biopsy.

Technique

Performing TBBx is an essential skill for every bronchoscopist. Apart from mastering the technique, all bronchoscopists must have a thorough understanding of indications, clinical uses, and the limitations of the procedure. Also, one must be ready to manage its immediate complications, such as bleeding and pneumothorax. Several studies have established the safety of TBBx in an outpatient setting under moderate sedation [1, 2].

Patient Evaluation

A detailed history, physical examination, and chest roentgenograms (Chest X-Ray and Computed Tomography of Chest) are essential before TBBx. The purpose, risks, and the limitations of TBBx should be thoroughly discussed with the patient before the procedure. The patients must understand that underlying diagnosis cannot be confirmed in all instances with this technique. Routine complete blood counts, coagulation profile, blood chemistry, arterial

blood gas analysis, pulmonary function tests, and electrocardiogram are not required prior to the procedure. The decision to perform these tests should be based on individual clinical evaluation. For instance, evaluation of clotting mechanism is indicated for patients with bleeding diathesis, those receiving anticoagulation therapy and for those who are at a high risk of bleeding due to liver disease or renal insufficiency.

General contraindications to TBBx are listed in Table 2.1. Patients with low platelet count should receive platelet transfusion immediately before the procedure to increase platelet count to at least 50,000/mm³. We have also encountered excessive bleeding in presence of platelet count more than 1 million/mm³. Correction of clotting mechanism may need administration of vitamin K and fresh frozen plasma. There is no need to stop aspirin [3], but a very high incidence of bleeding after TBBx has been reported in patients receiving clopidogrel [4], which must be held for at least 5–7 days prior to TBBx. A practical approach to identification and correction of coagulopathy prior to TBBx is summarized in Table 2.2.

Because of the higher risk of bleeding in uremic patients after transbronchial biopsy, serum creatinine should be measured when renal insufficiency is suspected. According to a survey,

Table 2.1 Contraindications for transbronchial biopsy

• Refractory hypoxemia
• Uncorrected coagulopathy (see Table 2.2)
• Uncontrolled cardiac arrhythmia
• Active myocardial ischemia
• Severe pulmonary hypertension
• Uncontrolled bronchospasm
• Uncooperative patient
• Inability to control cough
• Lack of adequate facilities for patient resuscitation
• Abnormal platelet counts (<50 K or >1 million)

Table 2.2 General guidelines for detection and correction of coagulopathy before transbronchial biopsy

History and physical examination

- Known bleeding or clotting disorder
- Prior history of epistaxis, petechial hemorrhage, GI bleed, hematuria, menorrhagia
- Excessive bleeding during prior surgeries
- Transfusion of blood products
- Renal insufficiency
- Liver disease
- Hematological malignancy
- Immunocompromised state
- Medications: aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), clopidogrel (Plavix), ticlopidine (Ticlid), prasugrel (Effient), dabigatran (Pradaxa), rivaroxaban (Xarelto) Coumadin, unfractionated heparin, low-molecular-weight heparin

Laboratory tests (based on clinical assessment)

- Platelet counts
- Prothrombin time (PT-INR)
- Activated partial thromboplastin time (aPTT)
- Renal functions
- Liver function tests

Specific recommendations^a

- Proceed with TBBx only when: PT-INR < 1.5, aPTT < 50 s, platelet counts > 50 K
- No need to stop aspirin or NSAIDs
- Stop clopidogrel, ticlopidine, and prasugrel for 5–7 days
- Hold Coumadin for 3 days; check PT-INR before the procedure
- Hold unfractionated heparin for 6 h and check aPTT before the procedure
- Hold low-molecular-weight heparin for at least 12 h
- Hold dabigatran and rivaroxaban for 2 days (hold for a longer period in presence of renal insufficiency)
- Transfuse platelets if counts are < 50 K and check counts immediately prior to TBBx
- Reconsider decision to perform TBBx in patients with uremia. For BUN > 30 mg/dl and creatinine > 3.0 mg/dl, administer DDAVP: 0.3 µg/kg IV in 50 ml of saline and administer over 30 min; start infusion 60 min prior to procedure, or 3 µg/kg intranasal spray 30 min prior to TBBx

^a Consult prescribing physician (e.g., cardiologist) before holding anti-platelet agents or anticoagulants. Consider bridge therapy in selected patients using standard clinical guidelines. Discuss the risk of holding anticoagulation with the patient

about one-half of bronchoscopists consider uremia a contraindication to transbronchial biopsies [5]. Specifically, BUN level of >30 mg/dl and creatinine level of >3.0 mg/dl (both together) are

thought to increase the risk of bleeding after TBBx due to associated platelet dysfunction. For example, in a study reported in 1977, significant bleeding was encountered in 45 % of immunocompromised uremic patients undergoing bronchoscopic lung biopsy [6]. Somewhat more reassuring are results from a small retrospective study in which only 1 of 25 patients (4 %) with end stage renal disease had major and 1 (4 %) had minor bleeding after transbronchial biopsies [7]. Similarly, no association was found between the risk of bleeding and elevated serum creatinine in 45 immunocompromised patient who underwent transbronchial biopsies for evaluation of lung infiltrates [8]. The risk of bleeding in uremic patients may be reduced by intravenous infusion of 0.3 µg/kg desamino-8-D-arginine (DDAVP) over 30 min, starting 1 h before the TBBx. The same medication can also be administered in form of a nasal spray at a dose of 3 µg/kg about 30 min prior to the procedure (Table 2.2).

A vast majority of bronchoscopists consider pulmonary hypertension an absolute or relative contraindication to TBBx [5]. However, there is little evidence of excessive risk of bleeding after TBBx in these patients. For example, in a prospective, blinded study, the presence of pulmonary hypertension on echocardiography did not increase the risk of bleeding after TBBx [9]. However, patients with clinically evident pulmonary hypertension or cor-pulmonale were excluded from the study. Similarly, in a retrospective study, there was no significant increase in bleeding complications with TBBx in 24 patients with variable severity of pulmonary hypertension, as compared to 32 control subjects [10]. Since there were only a handful of patients with severe pulmonary hypertension in this study, the authors concluded that TBBx is safe in patients with mild to moderate pulmonary hypertension.

Radiologic Investigations

Chest radiograph is essential in all patients prior to transbronchial biopsies. Routine chest Computed Tomography (CT) scan is also useful

in patients with localized lung infiltrates and in patients suspected to have lung cancer. In these cases, CT shows the location of lung infiltrate or mass and its relation with the bronchopulmonary segment, which is a useful information to have during TBBx [11]. One study reported higher diagnostic yield from TBBx when the site of biopsy was chosen on the basis of chest CT scan in human immunodeficiency virus (HIV)-infected patients with localized lung infiltrates [12].

Biopsy Forceps

More alveolar tissue is obtained when the TBBx is performed with a large as compared to the small biopsy forceps [13]. The difference in the size of the biopsy specimen does not always translate into higher overall diagnostic yield or complications [14]. One problem with large biopsy forceps is difficulty in opening its cusps in the small peripheral airways, thus reducing the likelihood of obtaining desired alveolar specimen of lung parenchyma [15]. Alligator forceps tend to provide larger lung tissue specimen than cup forceps of comparable size. Cusps of the alligator forceps tear the tissue while that of the cup forceps cut the tissue; latter limiting the volume of the biopsy specimen. Our preference is to use alligator biopsy forceps for TBBx in most cases.

Fluoroscopic Guidance

Some investigators have performed TBBx without fluoroscopic guidance [16]. However, we recommend performing the biopsy under fluoroscopic guidance. The use of fluoroscopy during TBBx clearly improves the diagnostic yield of TBBx for focal lung infiltrates and lung masses [17]. The diagnostic yield of TBBx is similar with or without fluoroscopic guidance for diffuse lung infiltrates. Nevertheless, even in diffuse lung disease, fluoroscopy helps the bronchoscopist to select different areas for biopsy and allows the operator to obtain biopsy from the periphery of lung near the pleural surface. Moreover, fluoroscopy reduces the risk of pneumothorax

during TBBx. The main drawback of using fluoroscopy for TBBx is its availability in resource-limited settings and radiation exposure to the patient and the staff [18]. There is no evidence that radiation exposure during diagnostic bronchoscopy has any long-term ill-effects on the patients or the bronchoscopy staff. The fluoroscopy time can be reduced with proper training and instructions [19]. Future health risks can be minimized with sound radiation hygiene practices [20]. Nevertheless, TBBx can be successfully performed without fluoroscopic guidance. This is a common practice when the procedure is performed on intensive care unit patients with diffuse parenchymal disease.

Biopsy Technique

The technical aspects of TBBx have been reviewed elsewhere [21, 22]. A thorough airway examination should precede the TBBx because bleeding after lung biopsy may preclude adequate airway examination. Adequate control of cough with topical application of lidocaine and systemic administration of opiates is essential for optimal biopsy procedure and to reduce the risk of pneumothorax.

The choice of biopsy site depends on radiological and fluoroscopic findings. Under no circumstance should TBBx be attempted from both lungs during the same bronchoscopic procedure on the same date due to delayed risk of bilateral pneumothorax. Selection of the site for the TBBx is simple while dealing with focal disease. However, in cases of diffuse, five lobe disease selection of the site for the TBBx requires some consideration. In the latter event, we prefer to perform the biopsy from the dependent parts of the lungs; right and left lower lobes. In an event of bleeding, the blood is at least contained in this area before spilling into the other lobes. Also we prefer left over the right lower lobe as the longer length of the left main bronchus allow more volume for blood to accumulate before it spills into the contralateral side. This also allows more time to recognize and react to the complication. On the contrary we try to avoid performing the biopsy

from the right upper lobe segments. Bleeding from this particular site soils both lungs and limits the reactionary time.

Once the biopsy site is chosen, the distal end of the bronchoscope is wedged into the specific segmental bronchus. Subsequent procedure is performed under fluoroscopic guidance when available. The assistant is asked to introduce and advance the forceps through the biopsy port into the working channel. Mild resistance is usually felt when the biopsy forceps reaches the distal end of flexible bronchoscope, especially during TBBx from the upper lobes and from the superior segment of lower lobes. This is because the distal bending section needs to be flexed at a sharp angle to reach these segments. In this situation, one should not apply excessive force to push the biopsy forceps out of the scope as it can damage the inner channel of the instrument. Instead, the operator should reduce the degree of flexion of the bending section by easing off from angulation control lever and gently advance the biopsy forceps through the distal end. Although this simple maneuver is usually successful, it can compromise the wedged position of bronchoscope. If this maneuver is unsuccessful, the best course is to pull the bronchoscope back into the lobar or main stem bronchus, and push the biopsy forceps a few centimeters beyond the distal end of the bronchoscope and push the biopsy forceps into the desired sub-segmental bronchus. The bronchoscope can then be advanced onto the wedged position using the biopsy forceps as a guide wire. This maneuver allows the biopsy forceps to be introduced into the difficult-to-reach bronchopulmonary segments while minimizing the risk of damage to the bronchoscope.

To obtain the specimen from a diffuse lung infiltrate under fluoroscopic guidance, the biopsy forceps is advanced into the lung parenchyma towards the pleura till resistance is met. The forceps is then pulled proximally by approximately 1.5–2 cm and the patient is instructed to take a deep breath and hold breath at maximum inspiration. This maneuver dilates the peripheral airway allowing cusps of the forceps open wide. While patient is holding breath, the assistant is instructed to open the biopsy forceps. The patient is then

asked to breathe out and during expiration, the biopsy is gently advanced into the area of interest under fluoroscopic guidance, making sure that the forceps tip does not cross the pleural margins. While patient is breathing, resistance to advancing biopsy forceps is met. This is due to the fact that the open cusps are anchored at the bifurcation of the respiratory or the terminal bronchioles. At this stage the assistant is asked to close the biopsy cusps and the forceps is gently retracted. Usually a “tug” is felt when the lung tissue is sheared off. This sensation, however, does not guarantee that a good biopsy specimen has been retrieved. One should carefully look for actual movement of the lung infiltrate on fluoroscopy screen as the biopsy forceps is pulled back. In our experience, this movement of the infiltrate during TBBx strongly predicts the successful sampling of the diseased lung parenchyma. Lung tissue is obtained by actually tearing off the respiratory/terminal bronchioles. There is no need to make forceful and jerky movements while withdrawing the biopsy forceps.

To obtain the biopsy from a focal lesion, such as a lung cancer, the forceps is advanced till the margin of the mass is reached (Fig. 2.1). At this time, resistance is felt and it is not possible to push the forceps any further. At this time, “C” arm of the fluoroscopy unit is rotated to look at the movement of biopsy forceps and the lung mass relative to each other on the fluoroscopy screen. If the forceps is seen to move away from the lung mass with this maneuver, the forceps need to be repositioned. The forceps is in good position for biopsy if lung mass and the forceps move together as fluoroscopy is rotated. After confirming the proximity of biopsy forceps and lung mass, the biopsy forceps is pulled back 0.5–1 cm and the assistant is asked to open the forceps cusps. The cusps of open biopsy forceps are pushed firmly into the mass and the contact between the forceps and the mass is verified on fluoroscopic screen. The forceps is closed and is gently retracted. Respiratory maneuvers are usually unnecessary for the biopsy of lung masses. Again, as the biopsy forceps is retracted, the movement of lung mass on fluoroscopy predicts the successful sampling from the lung mass.

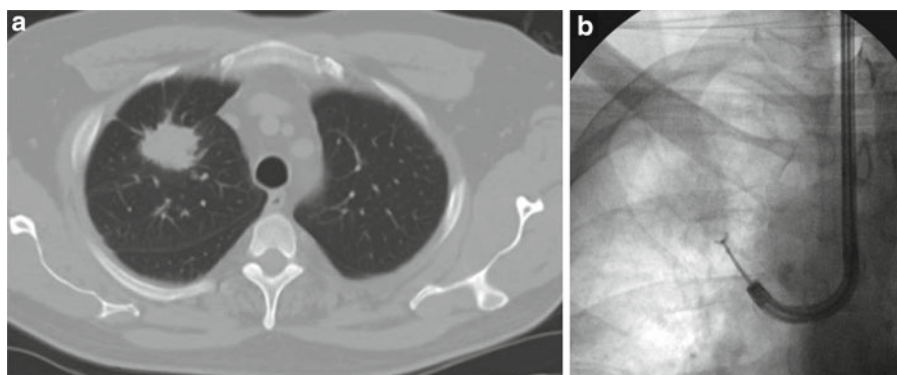


Fig. 2.1 (a) Chest CT showing right upper lobe lung nodule. (b) Biopsy forceps is advanced to the lesion under fluoroscopic guidance to obtain biopsy

Further biopsies should be obtained from the area of interest while maintaining the wedged position as much as possible. The purpose of wedging the bronchoscope is to create a tight seal around the distal part of the bronchoscope to tamponade the bleeding source and to prevent blood from spilling into more proximal airways. It is prudent to keep the bronchoscope wedged for at least 4 min (normal bleeding time) after all biopsies are taken from a lung segment. No suction should be performed at this time.

Number of Biopsy Specimens

There is limited information on the optimal number of transbronchial biopsies. In general, four to six biopsy specimens are adequate in majority of patients with diffuse lung disease [24]. In one study, 53 % of diagnoses were provided with the first specimen, and 33 % of diagnoses were provided with the second specimen [25]. In patients with stage II and III sarcoidosis 4–6 TBBx specimens provide optimal diagnostic yield [26]. However, for stage I sarcoidosis up to ten biopsy specimens may be needed for maximum diagnostic yield [27]. For localized peripheral lung mass and lung infection, a minimum of 6 and if feasible, up to 10 biopsy specimens should be obtained [28]. In a large study, the diagnostic yield from localized lesions increased from 23 % with 1–3 specimens to 73 % with 6–10 specimens [24].

Post-biopsy Fluoroscopy

A fluoroscopic examination should be performed at the conclusion of the procedure to rule out pneumothorax. The patient should be observed in the recovery room for at least 1½ h. A routine chest radiograph has a low diagnostic yield for pneumothorax after uncomplicated TBBx procedure in clinically stable patients [23], but is indicated for chest discomfort, dyspnea, excessive hemoptysis, or unexplained hypoxemia after the transbronchial biopsies.

Specimen Handling

The lung biopsy specimens are collected by opening the cusps and gently shaking the forceps in sterile saline. A toothpick may be used to retrieve the specimen from the biopsy forceps. Due to infection control concerns, using a needle to remove biopsy specimens should be avoided. After all biopsies are obtained, the specimens can be transferred to a container with 10 % formalin for routine pathological examination. Undue delay in immersion of biopsy specimens in the fixative solution should be avoided as much as possible. When infectious disease is likely, one or more tissue specimen may be submitted to the microbiology laboratory in sterile Ringer's lactate. Biopsy specimens for special studies such as electron microscopy, immunostaining

and flowcytometry should be collected and transported in consultation with the receiving pathology laboratory.

Quality of Biopsy Specimen

The quality and adequacy of transbronchial biopsies are difficult to assess during the procedure. The usual size of tissue fragment from TBBx varies from 1 to 3 mm. Due to their small size, TBBx are inherently limited for assessment of disease processes such as interstitial pulmonary fibrosis in which pathological diagnosis requires identification of typical architectural changes in the lung parenchyma.

Sometimes, the biopsy material contains predominantly bronchial mucosa with very little or no alveolar tissue. This happens when TBBx is obtained from proximal area of the lung. Of course, biopsies with little or no alveolar tissues are not expected to provide meaningful information about the pathological process involving lung parenchyma. It is proposed that lung biopsy specimens with alveolar tissue are more likely to float when placed in 10 % formalin and show representative pathological changes than biopsy specimen with no alveolar tissue. For example, in one study, the TBBx specimens with alveolar tissue were more likely to float on 10 % formalin than specimens without alveolar tissue, and in patients with sarcoidosis, specimens containing non-caseating granuloma were more likely to float than specimens without non-caseating granuloma [29]. However, the practical value of float sign remains unproven because another study that had more heterogeneous patient population could not reproduce these results [25]. Besides more proximal biopsy may cause more bleeding while too distal biopsy increases the risk for pneumothorax.

Most pathologists accept a kidney biopsy specimen containing 5 or more glomeruli as an adequate specimen. No such consensus exists for TBBx. One group has proposed that TBBx specimen containing 20 or more alveoli should be considered adequate as it is more likely to detect a pulmonary infection than a specimen with fewer

alveoli [30]. However, this concept has not been validated for other diagnoses such as pulmonary malignancies and most experts continue to believe that diagnostic yield from TBBx is more closely related to the number of the specimens obtained rather than actual number of alveoli in each biopsy specimen.

Clinical Applications of TBB

Lung biopsy is required for appropriate diagnosis and management of a variety of pulmonary diseases. Samples of lung tissue for diagnostic purpose may be obtained through the TBBx, CT-guided fine needle aspiration (CT-FNA), and video-assisted thoracoscopic or surgical lung biopsy. With few exceptions, surgical lung biopsy is the gold standard for obtaining lung tissue for patients with interstitial lung diseases but it is invasive, costly, requires general anesthesia and hospital admission. The application of CT-FNA is largely limited to peripheral pulmonary nodules or masses. The specimen from CT-FNA is generally insufficient for tissue diagnosis of benign disease processes. Pneumothorax develops in up to a quarter and chest tube is required in about 10 % of patients after CT-FNA [31]. In contrast, TBBx has wider clinical applications, the complication rate is low and the procedure can safely be performed in an outpatient bronchoscopy suite under conscious sedation. Serial lung biopsies are also best obtained with the transbronchial approach.

Several large case series have addressed the diagnostic yield of TBBx in heterogeneous groups of patients with a variety of underlying disease processes [24, 32–36]. Even though TBBx provided adequate lung specimen in 70–90 % of cases, a specific diagnosis could not be rendered in a significant proportion of the patients. The overall diagnostic yield for specific diagnosis varies widely, depending on the size, location and extent of lung infiltrates, and the nature of underlying lung disease. The results of TBBx also depend on the experience and technical skills of the bronchoscopist. Caution is warranted in interpreting the literature on diagnostic

Table 2.3 Pulmonary diseases in which transbronchial biopsies are useful

<i>Malignancy</i>
• Lung cancer
• Metastasis
<i>Infections</i>
• Tuberculosis
• Non-tubercular mycobacterial infections
• Fungal infection
• Pneumocystis pneumonia
• Viral infections such as CMV pneumonitis
<i>Acute lung transplant rejection</i>
<i>Undiagnosed infiltrates in mechanically ventilated patients</i>
<i>Diffuse lung diseases</i>
• Sarcoidosis
• Lymphangitic carcinomatosis
• Pulmonary alveolar proteinosis
• Pulmonary Langerhan's histiocytosis
• Alveolar microlithiasis
• Amyloidosis
• Lymphangioleiomyomatosis
• Bronchiolitis obliterans with organizing pneumonia

yield of TBBx because most authors have included nonspecific fibrosis or organizing pneumonia in the diagnostic yield and only a few have applied more stringent criteria for pathologic interpretation of TBBx specimens. Nonspecific findings on TBBx are often unhelpful and can lead to erroneous clinical decisions. Pulmonary disorders in which a confident diagnosis is possible with TBBx are listed in Table 2.3. In case of diffuse lung diseases, TBBx is more likely to establish the diagnosis of diseases such as sarcoidosis and lymphangitic carcinomatosis than in pulmonary vasculitis and diffuse lung diseases such as idiopathic pulmonary fibrosis for which low-magnification architectural overview is essential for diagnosis. In pulmonary Langerhans' cell histiocytosis (PLCH), and lymphangioleiomyomatosis (LAM), the TBBx are reliable but have a low diagnostic yield due to sampling error. Therefore, the presence of typical histological findings in these conditions is sufficient for diagnosis, but their absence does not exclude the diagnosis. The diagnostic role of TBBx in selected conditions is discussed below.

Lung Cancer

Flexible bronchoscopy is the most widely used technique for diagnosis of peripheral lung cancer. Usually, a combination of sampling procedures such as bronchial washing, brush, TBBx and peripheral TBNA are performed in these patients to maximize the diagnostic yield. According to an evidence-based review, FB provided diagnostic specimen in 36–88 %, with an average of 78 % in 16 studies of patients with peripheral lung cancers [37]. TBBx is the most useful sampling method for the diagnosis of peripheral lung cancer. The average diagnostic yield from TBBx is 57 % with a range of 17–77 % in patients with peripheral lung cancers. When performed in conjunction with bronchial washing and brushing, TBBx provides exclusive diagnosis in up to 19 % of the patients [38]. TBBx provides exclusive diagnosis in 7 % of patients if peripheral-transbronchial needle aspiration (P-TBNA) is also performed in addition to other sampling methods.

Although CT-guided fine needle aspiration (CT-FNA) is the diagnostic procedure of choice, flexible bronchoscopy with TBBx will provide diagnosis in 30–40 % of patients with superior sulcus tumor [39, 40]. Bronchoscopy with TBBx has a high diagnostic yield in patients with lymphangitic carcinomatosis [41, 42]. There is a limited data on usefulness of TBBx in metastatic pulmonary tumors but in one study the biopsy provided diagnostic tissue in only 2 of 12 (17 %) of such patients [43].

The diagnostic yield of TBBx for lung cancer increases with the number of biopsy specimens. In one study, the diagnostic yield was 21 % when 1–3 TBBx specimens were obtained and 78 % when 6–10 specimens were obtained [24]. In another study, the diagnostic yield increased from 45 % with the first specimen to 70 % with multiple TBBx specimens [28]. Based on these studies, 6–10 TBBx should be obtained in these patients for an optimal diagnostic yield.

The size of the lesion is the single most factors affecting the sensitivity of bronchoscopy for diagnosis of peripheral lung cancers. Pooled data from ten studies shows a diagnostic yield of 34 %

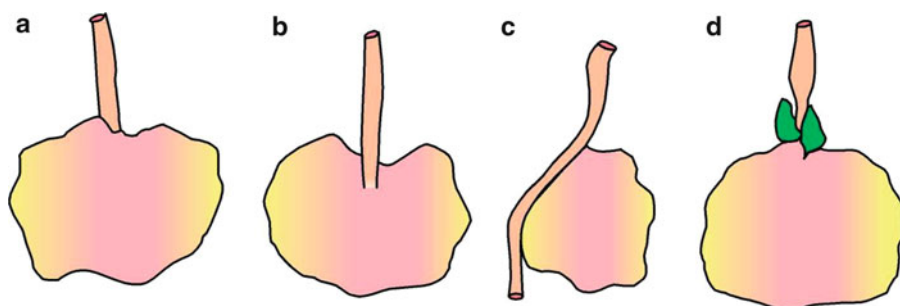


Fig. 2.2 Tumor–bronchus relationship: (a) Type I: bronchus is patent up to the tumor, (b) Type II: the bronchus is contained within the tumor mass, (c) Type III: the bronchus is compressed, narrowed and displaced by the tumor

mass, but the bronchial mucosa is intact (d) Type IV in which the proximal bronchus is narrowed by the submucosal and peribronchial spread of the tumor, fibrosis, or enlarged lymph nodes

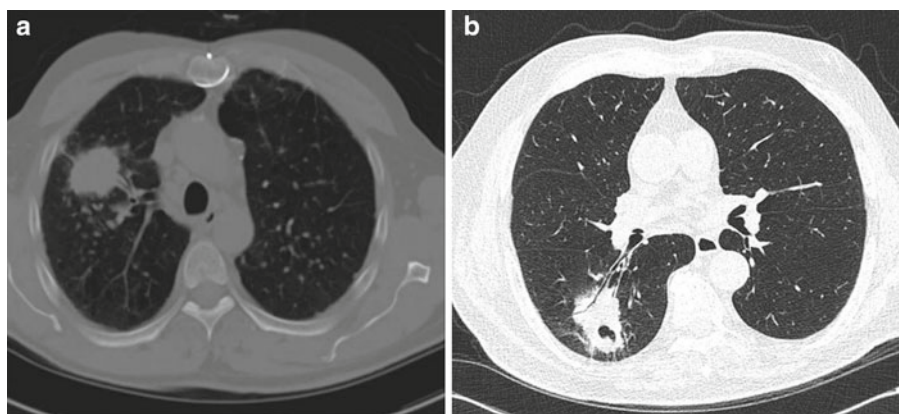


Fig. 2.3 Chest CT showing (a) Type I tumor–bronchus relationship, (b) Type II tumor–bronchus relationship

for lesions <2 cm and 63 % for lesions ≥ 2 cm in diameter [37]. Due to a very low yield was reported for lesions ≤ 2 cm in diameter located in outer one-third of the lung, some authors suggest an alternative approach such as CT-FNA for obtaining tissue diagnosis [44].

Tumor–bronchus relationship also affects the diagnostic yield of TBBx in peripheral lung cancers. Tsuboi and associates examined surgically resected specimens in 47 patients and identified four types of tumor–bronchus relationship: type I, in which the bronchus is patent up to the tumor, type II, in which, the bronchus is contained within the tumor mass, type III, in which the bronchus is compressed, narrowed and displaced by the tumor mass, but the bronchial mucosa is intact, and type IV in which the proximal bronchus is

narrowed by the submucosal and peribronchial spread of the tumor, fibrosis, or enlarged lymph nodes [45] (Fig. 2.2). The authors also noted that more than 60 % of tumors that were <3 cm in diameter had only one bronchus involved, whereas three or more bronchi could be identified approaching 60 % of tumors that were >3 cm in diameter [45]. High-resolution chest computed tomography demonstrates different types of tumor–bronchus relationship with a high degree of accuracy [46] (Fig 2.3).

Bronchus sign on CT refers to the finding of a bronchus leading directly to or contained within the peripheral lung mass [47]. The diagnostic yield of bronchoscopy for peripheral lesions is 0–44 % when the bronchus sign is absent, as compared with 60–82 % when it is

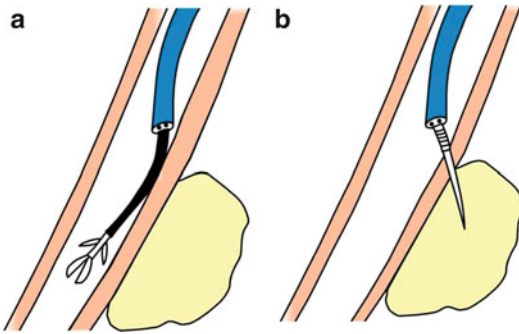


Fig. 2.4 (a) Biopsy forceps is displaced away from the lesion with type III tumor-bronchus relationship. (b) Transbronchial needle is seen to pierce the bronchial wall and obtain sample from the tumor

present [46–50]. Peripheral-TBNA procedure has a higher success rate in obtaining tissue diagnosis from peripheral masses with type III or IV tumor-bronchus relationship than with conventional sampling procedure including TBBx [51]. In one study, P-TBNA provided diagnostic tissue from 20 of 26 (77 %) lesions, whereas TBBx provided diagnosis in 5 of 26 (19 %) of lesions with type III or IV tumor-bronchus relationship [48]. The higher success of P-TBNA in lesions with type III or IV tumor-bronchus relationship may be related to the ability of TBNA needle to pierce the displaced bronchial wall or traverse the narrowed and stenotic segment of the bronchus to reach the core of the tumor, which may not possible with standard TBBx forceps (Fig 2.4).

Lung Infections

Non-resolving Pneumonia

Flexible bronchoscopy is frequently performed for further evaluation of non-resolving pneumonia [52]. TBBx provides useful information in these cases. For example, in one study, TBBx provided diagnosis in 57 % of patients with community-acquired pneumonia who failed antimicrobial therapy [53]. TBBx specimens can demonstrate mycobacterial or fungal infection, and may provide tissue diagnosis of other conditions that can mimic pneumonia such as

bronchioloalveolar cancer (Adenocarcinoma in situ), cryptogenic organizing pneumonia, and hypersensitivity pneumonitis. In cavitary lesions, obtaining biopsies from the wall of the cavity increases the chances of detecting underlying lung pathology (Fig 2.5).

Tuberculosis

Flexible bronchoscopy is frequently performed for patients with smear negative pulmonary tuberculosis. In most cases, a combination of bronchial washing, bronchoalveolar lavage and TBBx is performed to maximize the diagnostic yield. TBBx provides rapid diagnosis in 17–60 % of cases with confirmed active tuberculosis [54–57] and is the exclusive source of diagnostic specimen in 10–20 % of these patients [58–60]. TBBx also provides rapid diagnosis in miliary tuberculosis. Furthermore, in a significant proportion of patients, TBBx uncovers other disease processes such as lung cancer and fungal infection that can mimic tuberculosis. Therefore, it is appropriate to perform TBBx whenever flexible bronchoscopy is performed in patients suspected to have sputum negative tuberculosis.

Non-tubercular Mycobacteria

The diagnosis of non-tubercular mycobacterial infection is difficult to establish because the NTM are shed intermittently in the sputum. Further, the presence of NTM in the sputum often raises the possibility of contamination or colonization rather than true infection [61].

Flexible bronchoscopy with TBBx is frequently needed to confirm the diagnosis in these cases. According to the current American Thoracic Society/Infectious Disease Society guidelines, in the presence of appropriate clinical setting, the diagnosis of NTM requires one of the following microbiological criteria: (1) positive culture results from at least two separate sputum samples, or (2) positive culture results from at least one bronchial wash or lavage, or (3) transbronchial biopsies showing granulomatous inflammation, stainable acid-fast bacilli and positive NTM cultures or mycobacterial histological features and one or more sputum or bronchial wash culture positive for NTM [62].

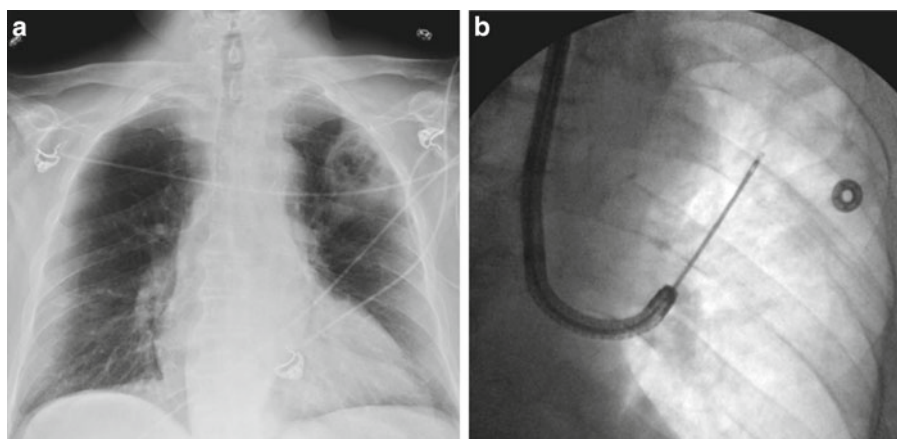


Fig. 2.5 (a) Chest radiograph showing a left upper lobe cavitary lesion in an immunocompromised patient. (b) Transbronchial biopsy is obtained from the wall of cavitary lesion

Accordingly, TBBx should be performed whenever bronchoscopy is needed in patients suspected to have NTM infection.

Fungal Infections

Bronchial washing and bronchoalveolar lavage are the most valuable bronchoscopic procedures for the diagnosis of pulmonary fungal infections [63–66]. A modest improvement in diagnostic yield is achieved with addition of TBBx in these patients [67–69]. We routinely perform TBBx whenever FB is required for patients with suspected fungal infection of the lung.

Infections in Immunocompromised Hosts (Non-HIV)

Immunocompromised hosts are subject to a wide spectrum of serious and life-threatening opportunistic pulmonary infections. FB with BAL provides diagnostic information in up to two-third of these patients with minimum procedure-related complications. While the diagnostic value of BAL is well established, the role of TBBx in altering management and improving outcome in these patients is a matter of some controversy. TBBx provides diagnostic information in 15–68 % of immunosuppressed patients with pulmonary infiltrates [8, 70–80]. Unfortunately, potential for

serious procedure-related complications with TBBx limits its utility in these patients.

In a prospective study, Stover and associates performed bronchoscopy in 97 immunocompromised patients with lung infiltrates [70]. Bronchoalveolar lavage was diagnostic in 61 of 92 (66 %) diseases, whereas TBBx were diagnostic in 36 of 57 (63 %) diseases, for a combined yield of 83 %. We performed bronchoscopy in 104 immunocompromised patients with lung infiltrates [8]. TBBx was performed in 45 of these patients. The overall diagnostic yield of bronchoscopy was 56 %. TBBx provided specific diagnosis in 38 % of patients. The combined yield of BAL and TBBx (70 %) was better than diagnostic yield from BAL (38 %) alone. In this study, TBBx was exclusively diagnostic in 13 % of procedures and was more likely to detect non-infectious causes of lung infiltrates in the immunocompromised hosts than BAL. The procedure-related complications were encountered in 31 % of patients who underwent TBBx, but there were no procedure-related deaths. In a large retrospective study, Cazzadori and associated reviewed their experience with TBBx in 142 immunocompromised patients with lung infiltrates [72]. Overall, the diagnostic yields of TBBx and BAL were 68 % and 36 %, respectively. The only complications were pneumothorax in 3 patients and bleeding in 1 patient.

Notwithstanding, the limitations of TBBx in these patients must be noted. First, not all studies have found TBBx to be useful in immunocompromised with lung infiltrates. For example, in a retrospective study, White and associates reviewed the results of bronchoscopy in 52 bone marrow transplant (BMT) patients with lung infiltrates. A total of 68 bronchoscopies were performed [81]. TBBx was performed in addition to BAL in 42 procedures. Only 1 additional diagnosis was made with TBBx in this study. Complications were encountered in 15 % of patients. In another study, TBBx was performed in 71 patients with hemopoietic stem cell transplantation [82]. The pathologic findings were nonspecific in 82 % of patients. Specific diagnoses were obtained in less than 10 % of patients undergoing the procedure. Complications were encountered in 8 % of patients. These data cast some doubt on the value of routine TBBx in BMT patients with lung infiltrates.

Second, most immunocompromised patients who require bronchoscopy are critically ill and have associated comorbid conditions that place them at a high risk for procedure-related complications [8]. In many instances, TBBx cannot be performed in these patients due to safety considerations. Studies have consistently shown higher complications rate with TBBx, than with bronchoalveolar lavage in these patients. It can be clearly seen that in some reports TBBx is not pursued in a vast majority of immunocompromised patients due to safety concerns [83–85].

Furthermore, nonspecific inflammatory and fibrosis are commonly reported on TBBx in immunocompromised patients with lung infiltrates. Clinicians need to interpret these nonspecific findings with caution. Some authors find nonspecific findings on TBBx to have a high negative predictive value for a treatable process. For example, in one study, specific diagnoses were obtained in 16 of 35 (48 %) patients undergoing TBBx [86]. The majority of remaining patient who had nonspecific histological findings either showed clinical and radiographic improvement, or had an untreatable disease. The authors reported 84 % sensitivity and 100 % specificity of TBBx for a treatable opportunistic infection

in these patients. Nevertheless, others have experienced different results and have concluded that nonspecific findings on TBBx do not assure absence of a treatable lung infection or a correctable noninfectious disease process in immunocompromised patients with lung infiltrates [87]. Therefore, a thorough clinical review is essential if TBBx shows nonspecific findings in immunocompromised patients with pulmonary infiltrates. Surgical lung biopsy is often considered in this situation. The diagnostic yield of surgical lung biopsy is reported to vary from 46 to 85 % in immunocompromised patients with lung infiltrates [88–96]. Surgical lung biopsies in these patients have shown both noninfectious diseases such as malignancy, lymphoma, drug toxicity and cryptogenic organizing pneumonia, and infectious diseases such as pneumocystis carinii pneumonia, legionella pneumonia, CMV pneumonia, invasive aspergillosis, gram-negative pneumonia, nocardiosis, and pulmonary toxoplasmosis. Many of these disease entities are expected to resolve with institution of appropriate therapy. Therefore, surgical lung biopsy should be considered when TBBx is non-diagnostic and the patient fails to improve with empirical treatment [97].

Infections in HIV-Infected Patients

Pulmonary complications are very common in patients infected with human immunodeficiency virus (HIV). Flexible bronchoscopy has played a critical role in the diagnosis and appropriate management of pulmonary complications of HIV infection [98]. In recent times, with advances in antiretroviral therapy, there is a clear decrease in the incidence of pulmonary complications and need for diagnostic bronchoscopy. Nonetheless, in resource poor areas, pulmonary complications continue to pose a serious threat to patients with HIV infection. A large retrospective study early in AIDS epidemic reported that 91 % of all pulmonary infections could be diagnosed by a combination of BAL and TBBx [99]. Subsequent studies have reported 65–96 % diagnostic yields when both BAL and TBBx are

performed [100–104]. Stover and associates performed BAL and TBBx in 72 patients with acquired immunodeficiency syndrome [100]. Overall, the bronchoscopy provided diagnosis in 65 % of patients. The diagnostic yield of FB was 94 % for *Pneumocystis pneumonia* (PCP), 67 % for *Cytomegalovirus pneumonia*, and 62 % for *Mycobacterium avium-intercellulare* infection. The main value of TBBx over and above BAL in this series was for the diagnosis of PCP. Broaddus and associates reported results of FB with BAL and TBB in 171 patients with acquired immunodeficiency syndrome [102]. The overall diagnostic yield of bronchoscopy was 96 %. BAL and TBBx had diagnostic yields of 86 % and 87 % respectively. BAL had a diagnostic yield of 89 % and TBB had a diagnostic yield of 93 % in patients with PCP. TBBx was the sole mean of diagnosis in 11 % of these patients. Pneumothorax developed after 9 % of procedures and chest tube was needed in 6 % of patients. Because BAL had high yield and TBBx was associated with complications, the authors concluded that TBBx could be avoided in patients at high risk of complications after bronchoscopy. Somewhat different results have been reported in a study from Rwanda in which FB with BAL and TBBx were performed in 111 HIV patients with lung infiltrates of unclear etiology [103]. In this study, BAL provided diagnosis in 26 % of patients, whereas TBBx provided diagnosis in 82 % of patients. Final diagnoses were nonspecific interstitial pneumonitis (NSIP) in 38 %, tuberculosis in 23 %, cryptococcosis in 13 %, Kaposi sarcoma in 9 % and PCP in 5 % of study patients. Diagnosis remains unclear in 16 % of patients. TBBx and BAL were the only source of diagnosis in 74 % and 18 % respectively. Complications were encountered in 13 % of patients, including hemorrhage in 5 % and pneumothorax in 8 % of patients. The low yield of BAL in this series was clearly due to low incidence of PCP in the study patients.

TBBx has provided diagnostic material in as many as 58 % of patients with AIDS-related non-Hodgkin's lymphoma [105]. In contrast, TBBx has limited in pulmonary Kaposi's sarcoma and surgical lung biopsy is frequently needed for

diagnosis [100, 106, 107]. In some reports, a diagnosis of NSIP has been made on the basis of TBBx in HIV infected patients with lung infiltrates [108, 109]. NSIP is diagnosed on the basis of histologic evidence of diffuse alveolar damage in association with chronic inflammation in the interalveolar septa in the absence of microbial pathogens on BAL stains, or cultures and on histopathological examination. Many of these patients show clinical and radiological improvement with empirical treatment.

Some investigators have questioned the value of routine TBBx in HIV infected patients with lung infiltrates [110]. This conclusion is largely based on studies in which the majority of patients had *pneumocystis carinii* pneumonia. On the contrary, when the role of FB in HIV-infected patients with a wider spectrum of pulmonary complications is analyzed, TBBx clearly improves the overall diagnostic yield. Even in PCP, some authors have found a significant improvement in diagnostic yield of FB when TBBx is performed with BAL as a routine. For example, in a recent study, BAL had a diagnostic yield of 74 %, whereas TBBx and BAL had a yield of 95 % in patients with PCP infection [111]. TBBx also seems to increase the diagnostic yield of FB for the patients receiving aerosolized pentamidine prophylaxis as the diagnostic yield of BAL is significantly lower in these patients [112]. We recommend both TBBx and BAL during FB for HIV infected patients with pulmonary infiltrates whenever feasible.

The usefulness of surgical lung biopsy in face of a non-diagnostic BAL and TBBx in HIV-infected patient is a debatable issue. Surgical biopsy is usually considered in these patients whenever the cause of lung infiltrate remains unclear and when the patient fails to respond to the treatment directed towards the diagnosis established with flexible bronchoscopy. In one study, the management was altered in only 1 of 66 patients who underwent surgical lung biopsy for these indications [113]. More favorable results are reported in other studies in which management was changed in a substantial proportion of carefully selected patients subjected to surgical lung biopsy [114, 115]. In one series, of

42 surgical lung biopsies, useful diagnosis was obtained in all 4 patients who had no preceding bronchoscopy, 13 of 18 patients who had non-diagnostic TBBx and BAL, 8 of 11 patients who had non-diagnostic BAL, but only 1 of 9 patients who had deterioration despite appropriate treatment for diagnosis established by bronchoscopy [116]. Based on these results, the authors did not support surgical lung biopsy on patients whose condition continued to worsen despite receiving appropriate therapy. We strongly recommend involvement of an expert in the field of HIV medicine before a decision is made to request surgical lung biopsy in these patients.

Lung Transplantation

TBBx plays a crucial role in the long-term management of lung transplant patients. A detailed discussion on the role of TBBx in lung transplant recipients is beyond the scope of this chapter and readers are referred to recent reviews for details [117, 118]. We briefly highlight a few important points.

In many centers, routine TBBx are performed for surveillance in asymptomatic lung transplant recipients, but their role for this purpose is controversial. Several studies have found surveillance bronchoscopy with TBBx to be a high-yield procedure. In an early study, 90 surveillance transbronchial biopsies were performed in 43 lung transplant recipients. Specific histological features of rejection or infection were found in 57 % of procedures [119]. In another study, 836 TBBx procedures were performed in 230 lung transplant recipients over a 5-year period [120]. Histological features of acute rejection, lymphocytic bronchiolitis, or infection were detected with 19 % of procedures. The yield of surveillance TBBx between 4 and 12 months post lung transplant was 6.1 % for acute graft rejection. In another study, clinical utility of 353 surveillance bronchoscopy procedures was studied in 124 lung transplant recipients [121]. High incidence of clinically important acute rejection was reported up to 1 year after the lung transplantation in these patients.

In contrast, others have found no benefits of surveillance bronchoscopy and TBBx in lung transplant recipients [122–124]. For example, in one study the outcome of 24 lung transplant recipients undergoing surveillance bronchoscopy was compared with 23 patients who underwent bronchoscopy for specific clinical indications [125]. A total of 240 TBBx were performed in 47 study patients. No acute rejection episode needing therapeutic intervention was detected with true surveillance bronchoscopy. No significant differences in respiratory infection, acute rejection, bronchiolitis obliterans syndrome (BOS) or survival were found in two groups.

More favorable results have been reported with FB and TBBx in assessment of clinically suspected acute rejection or pulmonary infection in lung transplant recipients. In fact, TBBx is the diagnostic procedure of choice for suspected acute allograft rejection [126]. TBBx has a sensitivity and specificity of 94 % and 90 % respectively for this indication [127]. Most transplant centers obtain at least 6–10 satisfactory transbronchial biopsies in these patients [128].

The clinical reasons for performing bronchoscopy with TBBx are >10 % decline in forced expiratory volume in 1 s (FEV1), >20 % decline in forced expiratory flow between 25 and 75 % of vital capacity, radiographic infiltrates, clinical suspicion for infection and symptoms referable to respiratory tract. FB with TBBx has high diagnostic yield in these patients. The diagnostic yield of FB with TBBx is close to 70 % when the procedure is performed for clinical indications [119, 129]. Apart from detecting acute rejection, FB with BAL and TBBx is the premier investigation for lung transplant patients for the diagnosis and surveillance of respiratory infections. For example, in one study, infection was diagnosed by bronchoscopy samples in 51 % of clinically indicated FB and 12 % of surveillance bronchoscopies [130]. It must be noted that the majority of infections in this study were diagnosed with analysis of BAL sample.

TBBx is also performed for follow-up of patient after treatment of acute rejection. Several studies have shown persistence of ongoing rejection despite appropriate initial treatment in a

significant proportion of patients [119, 129, 131]. In one study, persistence of acute rejection was detected in as many as 26 % of patients on follow-up TBBx [132]. Bronchoscopy with BAL and TBBx is also reported to have a diagnostic yield of 74 % in lung transplant patients with solitary or multiple lung nodules [133].

Flexible bronchoscopy with TBBx is also performed for suspected chronic allograft rejection but TBBx has low sensitivity for detecting obliterative bronchiolitis, the characteristic histologic findings in chronic rejection [134, 135]. The main value of FB in these cases is exclusion of airway complications, lung infections and acute graft rejection. Another value of TBBx is in predicting the future risk of bronchiolitis obliterans syndrome (BOS). Acute rejection is an established risk factor for BOS [136]. Recent studies seem to indicate that presence of minimal acute rejection (grade A₁) on multiple transbronchial biopsies is also associated with higher future risk of developing BOS [137]. A recent study has also established lymphocytic bronchiolitis on TBBx as a risk factor for BOS and mortality independent of acute rejection in lung transplant recipients [138]. Lymphocytic bronchiolitis on TBBx has also been linked to the occurrence and severity of acute cellular rejection in lung transplant recipients [139].

TBB in Mechanically Ventilated Patients

Flexible bronchoscopy with BAL is commonly performed in mechanically ventilated patients with diffuse pulmonary infiltrates. The procedure is safe and provides useful diagnostic information in a significant proportion of these patients. TBBx is seldom performed in mechanically ventilated patients due to safety concerns. For example, in a prospective study TBBx was performed in only 7 of 147 bronchoscopy procedures in mechanically ventilated patients [140]. Few data are available on precise clinical usefulness of TBBx in mechanically ventilated patients. Papin and associates performed TBBx in 15 patients requiring mechanical ventilation

[141]. Transbronchial lung biopsies provided diagnosis in 5 of 15 (33 %) of patients and altered management in seven patients. Three patients had self limiting bleeding and 1 patient developed delayed pneumothorax. Pincus and associates performed TBBx in 13 mechanically ventilated patients [142]. TBBx established specific diagnoses in 6 of 13 (46 %) of patients. The procedure was thought to have therapeutic implications in all 13 patients. Two patients developed pneumothorax after the procedure. Bulpa and associates performed FB with BAL and TBB in 38 mechanically ventilated patients [143]. All of the study subjects had unexplained pulmonary infiltrates. Diagnosis was established with TBB in 74 % of cases and management was altered in 63 % of patients. The procedure was complicated by pneumothorax in 9 (23 %) patients and self-limiting bleeding in 4 (11 %) of patients. In the largest series till date, O'Brien and associates reported the results of TBBx in 71 mechanically ventilated patients [144]. Specific histological diagnoses were made in 35 % of cases and the management was changed in 41 % of patients. Findings on TBBx also led to an important management change in 26 % of lung transplant recipients. The results of TBBx were similar to those found on surgical lung biopsy or autopsy in 11 of 13 study patients. Pneumothorax developed in 14 % of patients.

Traditionally, surgical lung biopsies are performed in critically ill patients with undiagnosed lung infiltrates. Surgical lung biopsy provides diagnostic information in 45–65 % of these patients [145, 146]. The results lead to an important management change in up to 70 % of patients. However, surgical lung biopsy is more invasive than TBBx with a complication rate of at least 20 %. In one study, surgical lung biopsy carried a mortality rate of 8.4 % in mechanically ventilated patients. TBBx may be safer but several important issues need further clarification. Should TBBx be performed as a routine or should it be done if the initial FB with BAL is non-diagnostic? Do the results of TBBx alter patient outcome? Only well designed prospective studies can answer some of these questions.

Diffuse Lung Diseases

Sarcoidosis

Bronchoscopy with TBBx is very useful for patients with suspected sarcoidosis. In some reports, TBBx have provided diagnosis in 90–95 % of patients with sarcoidosis [26, 147]. The diagnostic yield of TBBx in sarcoidosis depends on the radiological stage varying from 50 to 65 % in stage I, 63 to 82 % for stage II, and 80 to 85 % for stage III disease [148–150]. Ten biopsy specimens in stage I disease [27] and four to six TBBx in stage II and III sarcoidosis [26] are required to achieve optimal diagnostic yield from flexible bronchoscopy. Bronchial mucosa is frequently involved in sarcoidosis and endobronchial biopsies increase the diagnostic yield by as much as 20 % over and above the diagnostic yield of TBBx [148, 151]. Addition of TBNA [148, 150, 152] or EBUS-TBNA [153] to TBBx also increases the diagnostic yield of bronchoscopy for sarcoidosis.

Pulmonary Langerhans' Cell Histiocytosis

Although clinical features and HRCT findings may strongly suggest the diagnosis, histological confirmation is often needed in patients with suspected PLCH. Surgical lung biopsy remains the gold-standard of diagnosis. However, distinctive histological features allow the diagnosis to be established with TBBx in some cases. The diagnostic yield of TBB for PLCH is reported to vary from 10 to 40 % [154, 155]. Low yield of TBBx is due sampling error secondary to patchy distribution of lung pathology in PLCH. Thus, absence of typical histological features on TBBx should not be considered conclusive and surgical biopsy should be performed for further evaluation. The presence of Langerhans' cells staining for CD1a and S100 protein on immunocytochemistry of TBBx specimen further supports the diagnosis. False positive immunocytochemistry results can be observed in smokers. Therefore, stains for these markers should only be performed in the biopsy specimens with histological findings consistent with PLCH [156]. Increased number (>5 %) of Langerhans' cells staining with antibodies to CD1a in bronchoalveolar lavage also support the bronchoscopic diagnosis of PLCH [157].

Lymphangioleiomyomatosis

Surgical lung biopsy is usually performed for a definitive diagnosis of LAM [158]. Transbronchial biopsies may be sufficient for diagnosis in some cases of LAM but caution is needed because LAM cells in the lung parenchyma on TBBx can be misinterpreted as fibrosis. Immunohistochemical studies show positive staining of LAM cells for HMB-45 monoclonal antibodies. Positive staining for estrogen receptors and HMB-45 in the TBBx specimen strongly supports the diagnosis of LAM [159, 160].

Cryptogenic Organizing Pneumonia

The pathologic hallmarks of cryptogenic organizing pneumonia (COP) are proliferation of granulation tissue in the terminal and respiratory bronchioles and alveolar ducts along with extension of organization into alveoli and chronic inflammatory changes in the surrounding interstitial space [161]. Large specimen of lung tissue obtained by thorascopic or surgical lung biopsy is needed to confirm the diagnosis and to exclude other conditions that mimic COP [162]. In some instances, TBBx is found to be adequate for diagnosis [163–165]. Poletti and associates performed TBBx in 32 patients with suspected COP [165]. The sensitivity, specificity, positive predictive value and negative predictive values of TBBx were 64 %, 86 %, 94 % and 40 % respectively. Although the ideal approach remains open to debate, some leading experts in this area recommend TBBx before subjecting the patients to more invasive approach [166]. However, surgical lung biopsy must be performed if the diagnosis remains uncertain after TBBx and when there is inadequate response to oral corticosteroids.

Hypersensitivity Pneumonitis

Hypersensitivity pneumonitis (HP) is fundamentally a clinical diagnosis and routine histological confirmation is unnecessary. Lung biopsy is occasionally indicated when diagnosis is uncertain despite a thorough clinical evaluation. The histologic triad of cellular bronchiolitis, diffuse interstitial infiltrates of chronic inflammatory cells and loosely formed scattered noncaseating granuloma is the usual finding in subacute HP.

These findings are best demonstrated on surgical lung biopsy [167]. However, TBBx is reported to provide adequate specimen in some cases of acute [168] and subacute HP [169]. Chronic HP is less likely to be diagnosed with TBBx [156].

Others

Transbronchial biopsy is the diagnostic procedure of choice for suspected lymphangitic carcinomatosis [41, 42, 170]. In patients with pulmonary alveolar proteinosis, TBBx may demonstrate typical PAS-positive alveolar infiltrates [171]. Similarly, TBBx is a useful initial step for the diagnosis of diffuse pulmonary amyloidosis [172]. TBBx may provide diagnostic material in patients with suspected lipoid pneumonia and pulmonary alveolar microlithiasis [173].

Limitations of Transbronchial Lung Biopsy

Low Yield in Diffuse Lung Diseases

In a large number of diffuse lung diseases, nonspecific findings on TBBx do not allow a confident pathological diagnosis [174]. A common example is idiopathic pulmonary fibrosis (IPF) where the pathological diagnosis is mainly based on low-power architecture of the biopsy specimen that cannot be established with TBBx. In one study, transbronchial lung biopsies from 22 patients with idiopathic pulmonary fibrosis were retrospectively examined to determine if a diagnosis of UIP could be established [175]. All except one of the study patients had already undergone surgical lung biopsy that showed usual interstitial pneumonia (UIP). After examining several TBBx specimens from individual patients, the investigators reported that diagnosis of UIP was possible on TBBx in 7 of 22 (30 %) of patients. However, this study was seriously flawed because the interpreting pathologists were not blinded to the findings of surgical lung biopsy. In an earlier study, Wall and associates performed surgical lung biopsies in 33 patients who had diffuse infiltrative disease with nonspecific or

non-diagnostic transbronchial biopsies [176]. Surgical lung biopsy provided specific diagnosis in 92 % of patients. The findings on surgical biopsy specimen had little relationship to the TBBx results. For example, 9 of 21 patients reported to have normal lung or nonspecific findings on TBBx had idiopathic interstitial pneumonia on surgical lung biopsy. Out of 9 patients thought to have idiopathic interstitial pneumonia on TBBx the diagnosis was confirmed in only 2 patients on surgical lung biopsy. Furthermore, TBBx missed diagnosis of pulmonary Langerhans cell histiocytosis and sarcoidosis in 9 patients. In another study, the majority of patient with nonspecific chronic interstitial inflammation and fibrosis on TBBx had the disease process stabilized or regressed contrary to the natural history expected on the basis of the TBBx findings [177]. Taken together, TBBx cannot be used to diagnose UIP or differentiate it from other histological subtypes of idiopathic interstitial pneumonia such as NSIP [178]. Current evidence based guidelines do not recommend TBBx in patients with idiopathic interstitial pneumonia [179].

Transbronchial biopsy has occasionally provided the diagnostic material in Goodpasture's syndrome, Wegener's granulomatosis (WG), and Churg-Strauss syndrome (CSS) [180, 181]. However, in majority of patients, these diagnoses cannot be confirmed with TBBx. For example, in one study, even though adequate alveolar could be obtained in 17 of 19 patients, the histological diagnosis could be confirmed with TBBx in only 2 of 19 patients with WG [182]. Nonspecific findings were reported in majority of patients. Accordingly, surgical lung biopsy is usually recommended for the diagnosis of pulmonary vasculitis. Similarly, diffuse lung infiltrates due to occupational lung disease such as silicosis and asbestosis, collagen vascular diseases, and pulmonary drug toxicity also require surgical lung biopsy whenever the tissue diagnosis is deemed necessary.

Small biopsy size and the tissue artifacts in the TBBx specimen [183] create considerable diagnostic problems for the interpreting pathologists. In order to obtain larger tissue samples, some investigators have recently used flexible

cryoprobe to obtain TBBx. In one study, 41 patients with diffuse lung disease underwent standard TBBx, followed by cryobiopsies from the same pulmonary segment [184]. All patients undergoing the procedure in this study had an endotracheal tube placed prior to bronchoscopy. The investigators used 2.4 mm flexible cryoprobe to obtain the biopsy. The cryoprobe was introduced via the working channel of flexible bronchoscope and was advanced to the area of interest under fluoroscopic guidance to a distance of 10 mm from thoracic wall. The probe was cooled for about 4 s and was retracted along with the frozen lung tissue. The median area of tissue specimen on the histologic slide was 15.22 mm² for the cryobiopsies compared to 5.82 mm² for standard transbronchial biopsies. The investigators found no artifacts in the cryobiopsy specimens. A confident diagnosis of NSIP could be made in ten patients with cryobiopsies. However, confirmatory surgical lung biopsies were not performed in any of the patient in this study. There was no significant bleeding after cryobiopsies. Similar results have been reported by another group of investigators in 15 patients with diffuse lung disease [185]. These studies have provided useful preliminary data on safety and feasibility of obtaining larger tissue specimens free of crush artifacts with the flexible cryoprobes. Prospective studies are now warranted to investigate the diagnostic accuracy of cryobiopsies in diffuse lung diseases using surgical lung biopsies as the reference criteria.

Low Yield in Solitary Lung Nodule

Establishing a tissue diagnosis of solitary lung nodule is one of the most difficult challenges in pulmonary medicine. Traditional flexible bronchoscopy with TBBx has a low diagnostic yield in these patients. For the lung nodules <2 cm, the data from ten studies shows the average diagnostic yield of FB to vary from 11 to 76 % with an average of 34 % [37]. On multivariate analysis, the independent predictors of obtaining diagnostic tissue sample from lung nodules with flexible bronchoscopy in a recent study were malignant

etiology (odds ratio [OR] 4.8), diameter >2 cm (OR 3.6), and a positive bronchus sign (OR 2.4), again reinforcing the importance of size and bronchus sign as important determinants of diagnostic yield of conventional bronchoscopy in these patients [186]. Benign etiology of SPN is seldom established with transbronchial biopsies. Malignant etiology of SPN cannot be ruled out on the basis of negative bronchoscopy and transbronchial biopsies. The low yield of TBBx in SPN is mainly due to (1) inability to visualize the lesion on fluoroscopy, [187] and (2) inability to maneuver the biopsy forceps to its target in the absence of a favorable tumor-bronchus relationship.

Several attempts have been made in recent years to offset some of the limitations of traditional bronchoscopic methods to obtain biopsy specimen from SPN. The advanced techniques have been designed specifically to address the difficulties encountered in obtaining biopsy specimen from a small lung nodule. For example, CT-fluoroscopy and radial probe EBUS have been used to improve the likelihood of visualizing the lesion before obtaining the biopsy specimen. Virtual bronchoscopy navigation and electromagnetic navigation bronchoscopy (ENB) have been used to help the bronchoscopist to select the most appropriate path to reach the target for biopsy. Improved maneuverability is made possible with the use of ultrathin bronchoscope that can be advanced to seventh to ninth generation bronchi under direct operator control, steerable probe used with electromagnetic navigation, and double-hinged curette used with radial probe EBUS. In many instances, combinations of aforementioned techniques have been used to maximize the chances of obtaining diagnostic tissue from peripheral lesions smaller than 2–3 cm in diameter.

Several studies have looked into the feasibility of using CT-fluoroscopic guidance to obtain biopsy specimens from peripheral lung nodules. The main advantage is ability to localize the forceps in axial plane and visually confirm the contact between the forceps and the lesion [188]. In one study, a correct diagnosis could be established in 8 of 12 (67 %) of peripheral lesions with an average diameter of 2.2 cm with TBBx

under CT-fluoroscopy guidance [189]. In another study, for the lesions <15 mm diameter, diagnosis could be established in 22 of 45 (49 %) patients with TBBx under CT-fluoroscopy guidance compared to only 3 of 26 (12 %) under conventional fluoroscopy guidance [190]. In contrast, in a recent randomized study, no difference was found in the diagnostic sensitivity of TBBx performed under CT versus conventional fluoroscopic guidance [191]. Overall, only 33 % of lesions ≤ 3 cm in size could be diagnosed with TBBx under CT or conventional fluoroscopic guidance in this study.

There are several problems with the use of CT-fluoroscopy with conventional bronchoscopy. The ability to visualize the lesion does not guarantee that the operator will be able to advance the biopsy instrument to the target. Also, performing bronchoscopy in CT room poses major scheduling and logistic difficulties. Bronchoscopy is often an awkward experience both for the patient and the operator, and the CT room may be ill-equipped to manage a serious bronchoscopy-related complication. Perhaps the most important drawback is the risk associated with excessive radiation exposure to the patients and the operators. According to current estimates, the radiation exposure to the patients with CT-fluoroscopy is 2–5 times that of conventional fluoroscopy [189, 191]. With the emergence of radiation neutral alternatives such as radial probe endobronchial ultrasound with guide sheath (EBUS-GS) and virtual bronchoscopy navigation (VBN), excessive use of diagnostic radiation with CT-fluoroscopy for this purpose is a direct contradiction to the principle of justification, and optimization- the guiding principles of radiation use in clinical practice [192].

Several studies have recently established usefulness of EBUS-GS to localize small lung nodules prior to biopsy (Chap. 4). In one study, diagnostic tissue could be obtained from 116 of 150 (77 %) of peripheral lesions using EBUS-GS technique [193]. Although the diagnostic yield for lesions >3 cm in size (92 %) was significantly higher than that for lesions ≤ 3 cm in size (74 %), the investigators could establish diagnosis in 59 of 81 (73 %) of lesions ≤ 2 cm in size. Further, the

investigators could obtain diagnosis in 40 of 54 (74 %) lesions ≤ 2 cm in size that could not be located on fluoroscopy. In a prospective randomized study, the diagnostic yield of EBUS-GS directed TBBx was compared with that of standard fluoroscopically guided TBBx in 221 patients [194]. For patients with lung cancer, the diagnostic sensitivity in EBUS group (79 %) was significantly higher than that in standard TBBx group (55 %). On sub-group analysis, the diagnostic sensitivity was similar with either technique for lesions >3 cm. However, the diagnostic sensitivity was higher with EBUS-GS technique for lesions <3 cm in diameter (75 % vs. 31 %) as well as for lesions <2 cm in diameter (71 % vs. 23 %) than with the standard TBB technique.

A major advantage of EBUS-GS is in biopsy of those lesions that are not visible on conventional fluoroscopy. For example, in a prospective study, the investigators could obtain tissue diagnosis in 38 of 54 (70 %) of lesions with an average diameter of 2.2 cm that were not visible on fluoroscopy [187]. A additional advantage of this technique is better ability to navigate the biopsy instruments to the target lesions using the double-hinged curette introduced through the guide sheath [193]. It is typically used in those cases in which the lesion cannot be located with the EBUS.

Some limitations of this technique must also be noted. First, a high diagnostic yield for solitary lung nodules <2 cm has not been reproduced in every study. For example, in one study, TBBx using EBUS-GS technique was performed in 100 consecutive patients with lung nodules <2 cm in diameter [195]. The investigators could locate the lesions in 67 (67 %) patients with EBUS and obtain diagnostic tissue in 46 (46 %) of patients. Similarly, in another study, the diagnostic yield of TBBx with EBUS-GS technique for peripheral lesions >2 cm in diameter was 76 % but the diagnostic yield for lesions ≤ 2 cm in diameter was only 30 % [196]. Moreover, a recent randomized trial that enrolled 246 patients failed to show any difference in the detection rate of cancer between the EBUS-GS group (36 %) and the conventional bronchoscopy group (44 %) [197]. In fact, for lesions <3 cm in diameter, the diagnostic yield

was higher with conventional TBBx under fluoroscopic guidance than with EBUS-GS directed biopsies in this study. Some of the variation in reported results with this technique may be related to experience and training of the operators performing the procedure.

Electromagnetic navigation bronchoscopy (ENB) is an image-guided localization system that allows real time navigation of the biopsy instruments to small peripheral lesions during flexible bronchoscopy (Chap. 6). Several studies have reported encouraging initial results in obtaining biopsy from small peripheral lesions with this technique. In a prospective study, investigators from The Cleveland Clinic Foundation have reported a diagnostic yield of 74 % in 54 peripheral lesions with an average diameter of 2.28 cm [198]. The diagnosis was established in 23 of 31 (74 %) of lesions ≤ 2 cm in diameter in this study. The overall diagnostic yield has ranged from 63 % to 84 % for lesions of all sizes and from 50 to 76 % for lesions ≤ 2 cm in diameter in several other studies [199–203]. The diagnostic yield of ENB is significantly higher for lesions with a CT bronchus sign than for those without a discernible CT-bronchus sign [202]. The technique appears to have a steep learning curve [203]. One disadvantage of the technique is that there is no real time confirmation that the biopsy is actually obtained from the lesion. The other disadvantages are high initial cost of the equipment and high cost of the disposable accessories used during the procedure.

Virtual bronchoscopy navigation is emerging as an important method to facilitate accurate navigation of bronchoscope and biopsy instruments to small peripheral lesions (Chap. 7). In this technique, virtual images of endobronchial tree are reconstructed from the CT data to simulate actual bronchoscopy. The display of most appropriate endobronchial route to the target lesion on virtual bronchoscopy images helps the operator to navigate the bronchoscope to the correct airways leading to the target lesion. Apart from navigational capabilities, the current VBN systems allow the images to be rotated and to go forward and backwards to emulate the actual bronchoscopy images. In most case series, the

investigators have combined VBN with ultrathin bronchoscope in order to come as close to the lesion as possible. In some studies, biopsies have been performed under CT-fluoroscopy [204] and in others, under standard fluoroscopy guidance [205]. The overall diagnostic yield of TBBx using VBN with ultrathin bronchoscope have varied from 63 to 82 % and the diagnostic yield for peripheral lesions ≤ 2 cm in diameter has varied from 62 to 82 % in different studies [206–209]. The application of this technique during bronchoscopy does not need additional radiation exposure or costly accessories. However, the best results are achieved with the use of ultrathin bronchoscope which is not universally available. Further, the majority of data on application of VBN comes from investigators who are highly familiar with this technique.

To further improve the diagnostic yield of bronchoscopy for small peripheral lung nodules, several recent studies have combined ENB or VBN to navigate the bronchoscope and the accessory instruments bringing them close to the target and radial probe EBUS to confirm that the target is reached before obtaining the biopsy specimen. Very encouraging results have been reported with this multi-modality approach. Eberhardt and associates studied the usefulness of combining ENB and EBUS-GS in a prospective randomized study [210]. Biopsies were performed using EBUS-GS alone in 39 patients, ENB alone in 39 patients and combination of EBUS-GS and ENB in 40 patients. The diagnostic yield of EBUS-GS + ENB guided procedures (88 %) was significantly greater than the diagnostic yield of EBUS-GS guided procedures (69 %) or ENB-guided procedures (52 %). In another study, Asano and associates studied the usefulness of combining VBN, ultrathin bronchoscope (BF-type P260F, external diameter 4.0 mm, working channel 2.0 mm, Olympus Corporation), and EBUS-GS to obtain specimens from 32 peripheral lesions [211]. Diagnostic specimens could be obtained in 27 of 32 (84 %) of all lesions and 22 of 24 (79 %) of lesions ≤ 3 cm in diameter. The preliminary results from this study were confirmed in a recent randomized trial in which the 199 patients with peripheral lesions ≤ 3 cm in

diameter were randomized to undergo biopsy with assistance of VBN+EBUS-GS ($n=102$) or EBUS-GS alone ($n=97$) [212]. The diagnostic yield in VBN+EBUS-GS group (80 %) was significantly higher than that in EBUS-GS group (67 %). The diagnostic yield with the combined approach was 76 % and that with EBUS-GS alone was 59 % for lesions <2 cm in diameter. There can be no doubt that application of multiple advanced techniques is increasing the ability to obtain biopsy specimen from lesions that cannot be diagnosed with conventional TBBx under fluoroscopic guidance. Unfortunately, many of these techniques are expensive and vigorous cost-effectiveness studies are needed before they can be incorporated in routine clinical practice.

CT-guided fine needle aspiration (CT-FNA) remains in common use for diagnosis of peripheral lung nodules. It has a diagnostic sensitivity of 90 % (range 65–94 %) but is associated with pneumothorax in 15–43 % (median 27 %) needing chest tube in 4–18 % (median 5 %) [213]. The diagnostic sensitivity of CT-FNA depends on the size of the lesion. For the lesions <2.0 mm in diameter, the diagnostic sensitivity of CT-FNA has varied from 74 to 77 % with 22–28 % risk of pneumothorax after the procedure [214, 215]. In these patients, advanced bronchoscopic techniques discussed above offer a safer alternative with a lower risk of pneumothorax and a similar or higher diagnostic yield compared to CT-FNA.

Complications of Transbronchial Biopsies

TBBx is generally safe, although severe and life-threatening procedure-related complications are occasionally encountered. According to a recent nationwide survey from Japan, the complication rate after forceps biopsy for a peripheral pulmonary lesion was 1.79 % [216]. In comparison, a review of 173 procedures from a university hospital has reported a complication rate of 6.8 % after TBBx [217]. Two most common complications of TBBx are bleeding and pneumothorax.

The reported incidence of bleeding after transbronchial biopsy has varied from 0 to 26 %

in different series. Serious bleeding occurs in 1–2 % of patients undergoing transbronchial biopsies [1, 218]. The risk of bleeding is significantly higher in immunocompromised patients and in patients with underlying renal insufficiency [6, 8, 81]. Reports of deaths due to uncontrolled bleeding after TBBx are exceedingly uncommon, but it is plausible that it is under-reported. In the Japanese survey mentioned above, 0.85 % of 57,199 patients experienced significant bleeding after TBBx, but there were no deaths [216].

A major bleeding complication after transbronchial biopsy is unnerving, but the bleeding can be controlled in the majority of cases in the bronchoscopy room without adverse patient outcome [219]. The main danger of bleeding after transbronchial biopsy is aspiration of blood into non-bleeding segments rather than risk of exsanguination. Therefore, the top priority is to prevent the flooding of airways with large amounts of blood. As soon as significant bleeding is detected, tilt the bronchoscopy table so that bleeding side is dependent. The most effective way to control bleeding is to maintain the bronchoscope in wedged position into the bleeding segment till a blood clot is formed. Sometimes, the wedged position is compromised while pulling back the biopsy forceps. In these cases, the bronchoscopist should make every effort to immediately place the bronchoscope back into the bronchus. Fluoroscopic guidance may be needed in some cases as presence of blood may obscure the endoscopic view. After maintaining bronchoscope in wedged position for about 5 min, the bronchoscope is gently withdrawn. Bronchoscopist should be ready to re-wedge the bronchoscope if sudden gush of blood is seen. Cold saline lavage and topical application of dilute epinephrine are usually unsuccessful in controlling bleeding after the TBBx due to diluting effect of blood and distal bleeding site. If significant bleeding continues despite local measures and if the bronchoscope has slipped out of the bleeding segment, it is best to secure the airway with endotracheal tube and consider either balloon tamponade or selective intubation of contralateral lung. The facilities for rigid bronchoscopy must be held in readiness to

manage a bleeding episode that cannot be controlled with the flexible bronchoscope. Management of hemoptysis is further discussed in Chap. 14.

Pneumothorax is reported in 1–6 % of patients after transbronchial biopsies [1, 24, 220]. Failure to control coughing during transbronchial biopsies greatly increases the risk of pneumothorax. Patients receiving positive pressure ventilation are also more likely to develop pneumothorax after transbronchial biopsies. Risk may also be higher in presence of bullous emphysema and in patients with pneumocystis pneumonia [102]. Appropriate fluoroscopic guidance during transbronchial biopsies reduces the risk of pneumothorax. Fluoroscopic examination detects pneumothorax immediately after the biopsies but in some case, slowly developing delayed pneumothorax can manifest several hours after completion of procedure [1]. Tension pneumothorax is very uncommon after transbronchial biopsies. Nonetheless, mild to moderate pneumothorax may cause disproportionate symptoms due to underlying pulmonary limitation in some patients undergoing flexible bronchoscopy. If no symptoms develop for 4 h after completion of procedure, a clinically significant pneumothorax is unlikely. Chest roentgenogram should be performed after ½ to 1 h after completion of biopsies when the pneumothorax is clinically suspected despite normal findings on immediate post-bronchoscopy fluoroscopy. Severity of symptoms and the extent on chest roentgenogram dictate the management of pneumothorax after bronchoscopy. Supplemental oxygen and observation in the hospital is sufficient in most cases. Moderately symptomatic patients with significant pneumothorax may be managed with Heimlich's valve placed in the bronchoscopy suite. These patients can be discharged with Heimlich's valve after 4–6 h of observation if repeat chest roentgenogram shows no further increase in pneumothorax. Patients who develop severe symptoms or tension pneumothorax, and those who fail to show resolution of pneumothorax with Heimlich's valve require chest tube placement. Chest tube should also be placed without further delay when pneumothorax develops in patients on mechanical ventilation.

Conclusions

Transbronchial biopsy is an essential skill for every bronchoscopist. Transbronchial biopsy is usually performed in outpatient setting under conscious sedation. A successful TBB may obviate need for surgical lung biopsy, which is more invasive and needs general anesthesia. The most common indication of TBBx is to obtain biopsy specimen from peripheral lung masses. The diagnostic yield of TBBx for peripheral lung cancer depends on the size of the tumor and the presence or absence of bronchus sign. TBBx is also useful in evaluation of patients with suspected tuberculosis, fungal infection, unexplained lung infiltrates in immunocompromised hosts and in post-lung transplant patients, both for surveillance as well as evaluation of rejection or opportunistic infections. Among noninfectious diseases, TBBx is most useful in diagnosis of sarcoidosis, lymphangitic carcinomatosis, and in some cases of PLCH and LAM. Transbronchial biopsy is not useful for histological diagnosis of idiopathic pulmonary fibrosis or for distinguishing histological subtypes of idiopathic interstitial pneumonia. The diagnostic yield is also suboptimal in lung nodules smaller than 2–3 cm in diameter. Several recent techniques such as radial probe endobronchial ultrasound with guide sheath, electromagnetic navigation bronchoscopy and virtual bronchoscopy navigation have been used to improve the diagnostic yield of TBBx for solitary lung nodule. Hemoptysis and pneumothorax are the two leading complications of TBBx, occurring in less than 2 % of cases. We believe that all bronchoscopists must develop proficiency in performing TBBx and managing complications that can arise after the procedure.

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