Advanced bronchoscopic diagnostic techniques in lung cancer

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Abstract

The increasing incidence of incidental pulmonary nodules necessitates effective biopsy techniques for accurate diagnosis and treatment planning. This paper reviews the widely used advanced bronchoscopic techniques such as radial endobronchial ultrasound-guided transbronchial lung biopsy, electromagnetic navigation bronchoscopy and the cutting-edge robotic-assisted bronchoscopy. In addition, the cryobiopsy technique, which can enhance diagnostic yield by combining with conventional biopsy tools, is described for application to peripheral pulmonary lesions and mediastinal lesions, respectively.

Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide. (1) As a result of The National Lung Screening Trial (NLST), screening using low-dose CT in high-risk groups aged 55-74 with a smoking history of 30 pack years or more reduced the mortality rate from lung cancer by 20%. (2) In addition, the United States Preventive Task Force (USPSTF) recommends annual screening for lung cancer with low-dose computed tomography (LDCT) in adults aged 50 to 80 years who have a 20 pack-year smoking history and currently smoke or have quit within the past 15 years according to the results of the Nelson Trial. (3, 4) Accordingly, incidental pulmonary nodules are increasing. (5, 6)

The NCCN guidelines suggest that biopsy should be considered if an incidentally discovered pulmonary nodule is larger than 8 mm and the patient is a high-risk group for lung cancer. (7) Pathological examination through biopsy can also determine whether a patient has primary lung cancer or metastatic cancer and classify the histologic subtype of lung cancer. In addition, a sufficient amount of tissue is required to predict the therapeutic response to driver mutations or immune checkpoint inhibitors (ICIs). (7)

Transbronchial lung biopsy with radial endobronchial ultrasound (rEBUS-TBLB) and CT-guided transthoracic needle biopsy (CT-TTNB) are two commonly used methods to investigate peripheral lung nodules. According to a meta-analysis of randomized controlled trials, CT-TTNB had a higher diagnostic yield than rEBUS-TBLB (83.45% vs 68.82%, risk difference -0.15, 95% CI, [-0.24, -0.05]) especially for lesion size 1-2 cm (83% vs 50%, risk difference -0.33, 95% CI, [-0.51, -0.14]). However, rEBUS-TBLB was found to have a significantly better safety profile with lower risks of pneumothorax (2.87% vs 21.43%, OR = 0.12, 95% CI [0.05–0.32]) and combined outcomes of hospital admission, hemorrhage, and pneumothorax (8.62% vs 31.81%, OR 0.21, 95% CI, [0.11–0.40]). (8)
Recently, new techniques such as robotic-assisted bronchoscopy have been introduced to complement the diagnostic yield of rEBUS-TBLB. (9) Additionally, studies have been published on improving diagnostic yield using cryobiopsy along with conventional biopsy devices. (10-12) In this review, we will describe both widely used advanced bronchoscopy techniques and newly introduced ones.

1. Radial endobronchial ultrasound-guided transbronchial lung biopsy (rEBUS-TBLB)

rEBUS-TBLB uses a miniature ultrasound probe (radial EBUS probe) emits ultrasound waves that are reflected back by the tissue, creating a 360-degree real-time image of the airway and the surrounding lung tissue. This allows the physician to identify the location of the lesion and guide the biopsy devices to the target lesion for biopsy. The radial EBUS probe is inserted through the working channel of a flexible bronchoscope or catheter (guide sheath). This enables the clinician to determine the lesion's exact location and size. (13, 14)

In a recent systematic review and meta-analysis including fifty-one studies with a total of 7,601 subjects, the pooled sensitivity of rEBUS-TBLB was 0.72 (95% CI, 0.70-0.75), and the area under the sROC curve was 0.96 (95% CI, 0.94-0.97), and the pneumothorax incidence rate was only 0.7% (95% CI, 0.3%-1.1%). (15)

1-1. With Guide sheath (GS) versus Without GS

A guide sheath (GS) is a thin tube that is used in conjunction with a radial EBUS probe during bronchoscopy biopsy. The guide sheath is inserted through the working channel of a flexible bronchoscope and helps to improve diagnostic yield and safety profile by allowing for more accurate placement of the biopsy forceps or needle. In addition, one study found that using a guide sheath as an extended working channel (EWC) helps minimize bleeding risk during TBLB in high-risk patients. The researchers hypothesized that the EWC produces a tamponade effect in the close vicinity of the biopsy site, both reducing bleeding risk and restricting bleeding to a smaller segment. (16)

One multicenter retrospective cohort study compared the diagnostic yield, complication rate and procedure time of rEBUS-TBLB with and without a GS for malignant PPLs. Adding a GS to rEBUS-TBLB did not improve the diagnostic yield for malignant PPLs (79% versus 78%; p=0.649). GS guidance was seemingly associated with a lower number of complications (7.2% versus 5.8% for bleeding; 1.9% versus 0.6% for pneumothorax) but contributed significantly to a longer procedure
However, according to a recent multicenter study randomized trial, the use of a guide sheath during rEBUS-TBLB enhances the diagnostic yield for small peripheral pulmonary lesions (<30 mm in diameter). The study found that the diagnostic yield of histological specimens from the group using a guide sheath was significantly higher than that from the group without a guide sheath (55.3% versus 46.6%; p=0.033).

1-2. rEBUS-GS-TBLB combined with conventional forceps TBLB

rEBUS-GS-TBLB improves the diagnostic yield from peripheral pulmonary lesions (PPLs). However, one disadvantage of using small 1.5 mm forceps through a guide sheath (GS) during rEBUS-GS-TBLB is that the small specimens obtained may impede diagnosis. In contrast, conventional TBLB using larger 1.8-1.9 mm forceps may provide larger specimens that are more suitable for diagnosis and molecular analysis.

Kunimasa Kei et al. evaluated the diagnostic utility of performing additional conventional TBLB with standard forceps after rEBUS-GS-TBLB for the diagnosis of PPLs. The results showed that of the 88 eligible patients, 57 (65%) were successfully diagnosed by rEBUS-GS-TBLB. In the 31 patients not diagnosed by rEBUS-GS-TBLB, 15 (48%) were successfully diagnosed by additional conventional TBLB. The researchers concluded that additional conventional TBLB could be useful in cases where the distance between the rEBUS probe and the lesion is less than 2.55 mm.

Park et al. investigated the diagnostic significance of performing additional conventional TBLB with standard forceps after rEBUS-GS-TBLB. The study retrospectively reviewed data from 55 patients who underwent conventional TBLB after rEBUS-GS-TBLB for the diagnosis of peripheral pulmonary lesions (PPLs). The results showed that rEBUS-GS-TBLB was diagnostic in 30 (54.5%) patients, and subsequent conventional TBLB yielded additional diagnostic information in 8 (14.5%) patients.

1-3. Thin bronchoscope versus ultrathin bronchoscope

An ultrathin bronchoscope (UTB) is a type of bronchoscope that is smaller in diameter than a traditional thin bronchoscope (TB). It has a diameter of 2.8–3.2-mm and a 1.2–1.7-mm working channel. This smaller size allows the UTB to access more peripheral areas of the lung, which can be useful for diagnosing small peripheral pulmonary lesions.
Oki, Masahide et al. showed multimodal bronchoscopy using a UTB was superior to that using a TB in the diagnosis of peripheral pulmonary lesions. They conducted a randomized trial to compare multimodal bronchoscopy using a UTB and a TB with multiple sampling methods for the diagnosis of peripheral pulmonary lesions. The overall diagnostic yield was significantly higher in the UTB group than in the TB group (70.1% vs 58.7%; \( p=0.027 \)) and the procedure duration was significantly shorter in the UTB group (median, 24.8 vs 26.8 min; \( p=0.008 \)). The complication rates were 2.8% and 4.5%, respectively (\( p=0.574 \)).

In real practice, a UTB is frequently used subsequent to an unsuccessful access attempt using rEBUS-guided approach. A multicenter prospective study found that the use of UTB in addition to TB improved the diagnostic yield for peripheral pulmonary lesions. In this study, 87 (87/342, total n = 342) peripheral pulmonary lesions without ‘Within’ orientation on rEBUS image were subsequently accessed using UTB. The diagnostic yield increased from 12.6% (11/87) to 46.0% (40/87) by the addition of UTB. (22)

2. Electromagnetic navigation bronchoscopy (ENB)

Electromagnetic navigation bronchoscopy (ENB) is a medical procedure that utilizes electromagnetic technology to localize and guide endoscopic tools or catheters. The magnetic field and generator create a low-intensity electromagnetic field around the patient’s chest, which allows the location sensor at the tip of the guide catheter to be tracked in real time. The computer software uses the sensor data to display the position of the catheter on the 3D bronchial map, which helps the physician navigate to the target lesion.(23)

In 2004, the Medtronic superDimension/Bronchus system, also known as the inReach™ system (superDimension, Ltd, Israel), was approved by the Food and Drug Administration (FDA). Using electromagnetic guidance for managing peripheral lung lesions, this system is a minimally invasive image-guidance localization and navigation system.

The NAVIGATE study, a large, multicenter cohort study including 1,215 consecutive subjects from 29 sites, showed a diagnostic yield of 73% at 1-year follow-up results. This study diagnostic yield was comparable to other studies, even though it included only 48.5% (60–70% in other studies) of subjects with a positive CT bronchus sign (CTBS), which is known as a significant favorable factor. (24-27) In other studies, when CTBS is negative, the diagnostic yield is only 31-49.6%, but in the NAVIGATE study, it was reported to be 67.1%. (25, 28)
What brought about this difference?

In the NAVIGATE study, three or more biopsy tools were used in 72.7% of cases, and the diagnostic yield was significantly higher compared to when less than three tools were used. (OR 1.44, 95% CI, [1.01–2.04]; p=0.04)(27) Although this was not replicated in the 24-month results, it is possible that the use of new instruments capable of penetrating the normal bronchial barrier between the bronchi and the target lesion improved accessibility in CTBS-negative lesions (Figure 1).(29)

A recent systematic review and meta-analysis of the sensitivity and safety of ENB reported a pooled sensitivity of 77% (95% CI, 72%-82%; I² = 80.6%) and a specificity of 100% (95% CI, 99%-100%; I² = 0%) for malignancy. ENB achieved a sufficient sample for ancillary tests in 90.9% (95% CI, 84.8%-96.9%; I² = 80.7%). The risk of pneumothorax was 2.0% (95% CI, 1.0-3.0; I² 45.2%).(30)

Therefore, to date, ENB has shown comparable results to rEBUS-TBLB in terms of diagnostic performance and safety.(15)

3. Robotic-assisted bronchoscopy (RAB)

Robotic-assisted bronchoscopy is a procedure that uses a robotic arm to guide a flexible tube with a camera and biopsy tools into the lungs. RAB systems were designed to reach the peripheral lung airways, similar to the traditional electromagnetic navigation system, but with better stability and steerability during the biopsy. There are currently two RAB systems available: the Monarch Platform (Auris Health Inc.) and the Ion Endoluminal System (Intuitive Surgical). The two systems are similar in planning the path to the target lesion using a 3D airway map reconstructed from pre-procedure thin section chest CT images, but the navigation principles are totally different.

3-1. Monarch Robotic Platform

The Monarch platform basically uses the principle of ENB to navigate to the target lesion. The Auris Bronchoscope is made up of two parts: an inner scope with a diameter of 4.4 millimeters and an outer sheath with a diameter of 6.0 millimeters. The bronchoscope is equipped with a camera that provides the visual inspection, as well as an integrated light source. Additionally, the bronchoscope has a working channel with an inner diameter of 2.1 mm, which allows for the insertion of biopsy tools and rEBUS probe (Figure 2). The outer sheath can be inserted into the lobar or segmental bronchus, and then peripheral lung lesions are approached using the inner scope.

Chaddha et al. retrospectively reviewed data on consecutive cases in which robot-assisted
bronchoscopy was used to sample lung lesions at four centers in the US (academic and community) from June 15th, 2018 to December 15th, 2018. The study found that navigation was successful in 88.6% of cases and tissue samples were successfully obtained in 98.8% of cases. The diagnostic yield estimates ranged from 69.1 to 77%, depending on whether the cases of biopsy-proven inflammation without any follow-up information were considered non-diagnostic or diagnostic. Pneumothorax and significant bleeding occurred in 3.6% and 2.4% cases, respectively.(31)

The BENEFIT study is the first prospective, multicenter study that evaluated the use of a robotic bronchoscopic system in patients with PPLs ranging from 1 to 5 cm in size. The study aimed to evaluate the success of lesion localization using rEBUS and the incidence of procedure-related adverse events. The results showed that lesion localization was successful in 96.2% of cases, and the rate of adverse events was comparable to that of conventional bronchoscopic procedures. Post-procedural pneumothorax was found in 3.7% (2/54) of cases, with 1.9% (1/54) of cases requiring tube thoracostomy. The diagnostic yield was 74.1% (40/54).

3-2. Ion Endoluminal System

The Ion Endoluminal System navigates to PPLs in a completely different way than other robotic-assisted bronchoscopy platforms. This is called shape-sensing technology that uses sensors to detect and measure the shape or deformation of an object. The Ion Endoluminal System uses this technology to provide real-time location information for the dedicated scope as it navigates through the small and complex airways of the lungs. Unlike the Monarch platform, the Ion Endoluminal System uses a single ultrathin scope with a 3.5 mm outer diameter and a 2.0 mm working channel (Figure 3).

Recently published retrospective studies using the Shape-Sensing Robotic-Assisted Bronchoscopy (ssRAB) have reported remarkable results. Kalchiem-Dekel and colleagues conducted a retrospective analysis of data from consecutive cases at a cancer center in the United States from October 2019 to July 2020. During the procedures, 159 pulmonary lesions were targeted. The median size of the lesions was 18 mm, with 59.1% located in the upper lobe and 66.7% beyond a sixth-generation airway. The success rate of navigation was 98.7%, while the diagnostic yield was 81.7%. The overall complication rate was 3.0%, and the pneumothorax rate was 1.5%.(32)

Styrvoky et al. reported that the diagnostic accuracy reached 91.4% when ssRAB was combined with rEBUS and cone beam computed tomography (CBCT). Two hundred ssRAB procedures were performed to sample 209 nodules in 198 patients. The median size of the lesions was 19 mm, with
47.8% located in the periphery. Pneumothorax was the sole complication, occurring in 1% (2 out of 200) of the procedures, with half of those cases necessitating the insertion of a chest tube.(33)

Yu Lee-Mateus, Alejandra et al. retrospectively analyzed the diagnostic performance of ssRAB and computed tomography-guided transthoracic biopsy (CTTB). The study included a total of 225 participants, with 113 assigned to the ssRAB group and 112 to the CTTB group. The overall diagnostic yield was 87.6% for ssRAB and 88.4% for CTTB. In terms of malignancy, ssRAB demonstrated a sensitivity of 82.1% and a specificity of 100%, while CTTB exhibited a sensitivity of 88.5% and a specificity of 100%. Complication rate was significantly higher for CTTB compared to RAB (17% vs. 4.4%; p=0.002). Four patients in the RAB group and 18 in the CTTB group experienced a pneumothorax that necessitated hospital admission for monitoring or the insertion of a chest tube.(9)

The PRECIsE study is a prospective, multi-center, single-arm, clinical study enrolled subjects ≥ 18 years old with solid or subsolid pulmonary nodules greater than 1 cm but less than 3.5 cm in diameter. The aim of the study was to evaluate the clinical utility and performance of ssRAB.(34) The study reported preliminary data from 69 subjects who were enrolled across six medical centers beginning in March 2019. Mean nodule diameter was 17.0 ± 5.5 mm and the incidence of CT Bronchus sign was 25%. The diagnostic yield was 83% (57/69). The study reported similar diagnostic yield for both smaller and larger nodules. Nodules with a diameter of 1-2 cm showed a diagnostic yield of 82% (40/49), and nodules with a diameter of 2-3 cm showed a diagnostic yield of 85% (17/20). There was no pneumothorax complication requiring chest tube insertion.(35)

4. Transbronchial lung cryobiopsy (TBLC)

The development of cryobiopsy technology was inspired by the Joule–Thomson principle, where rapid freezing occurs with the sudden expansion of certain gases as they move from a high-pressure to a low-pressure environment.(36) TBLC has been widely accepted as a biopsy method for interstitial lung diseases (ILD).(37) This technique utilizes a freezing probe to collect lung tissue samples that are superior in size and quality compared to those obtained through conventional transbronchial lung biopsy.(38) Cryobiopsy can be used in combination with ENB or RAB as well as conventional biopsy modalities to improve diagnostic yield.(39, 40)

Recently, TBLC has been widely used in the diagnosis of peripheral pulmonary lesions (PPLs). In particular, with the development of a 1.1 mm cryoprobe, it has become possible to perform cryobiopsy through a GS following conventional biopsies such as forceps, aspiration needle, and
It has been reported that diagnostic yield increases when cryobiopsy is used in combination with conventional biopsy methods. In the case of ‘Adjacent to’ on rEBUS, relatively higher benefit can be obtained than in the case of ‘Within’. Several retrospective studies have reported that an additional diagnostic yield of 14.5% to 29.9% can be obtained when cryobiopsy is performed following conventional biopsy in the ‘adjacent to’ lesions. In addition, Matsumoto Y, et al. reported that lesions with a negative Bronchus sign had a relatively high additional diagnostic yield compared to lesions with a positive Bronchus sign (15.4% vs. 6.3%; p=0.011).

The reason why a high additional diagnostic yield can be obtained when cryobiopsy is performed in the ‘Adjacent to’ orientation is because normal anatomical structures (e.g. bronchial mucosa) are removed together when obtaining the cryobiopsy specimen. Therefore, the location where the tissue is obtained gradually moves to the center of the lesion as cryobiopsy is performed repeatedly (Figure 4).

In PPLs, cryobiopsy increases the risk of bleeding, but no deaths have been reported, and it is known to be relatively safe to perform even in high-bleeding-risk patients by an experienced operator.

5. Transbronchial mediastinal cryobiopsy

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) plays a crucial role in the staging of lung cancer, particularly in determining the extent of mediastinal lymph node involvement. The diagnostic performance of EBUS-TBNA to identify malignancy in lymph nodes had a sensitivity of 92.3%, a specificity of 100%, and a negative predictive value of 96.3%.

EBUS-TBNA also can be used for pathological diagnosis in central lesions and mediastinal lesions. However, the diagnostic yield of EBUS-TBNA in certain types of mediastinal lesions can be limited due to the inability to obtain sufficient intact tissue samples. In diagnosing mediastinal tuberculosis lymphadenitis, the sensitivity and specificity were 72.4% and 100.0% respectively. For diagnosing sarcoidosis, the sensitivity and specificity were 71.4% and 100.0% respectively.

Transbronchial mediastinal cryobiopsy is a biopsy method that has been introduced in recent years and is currently being performed in several institutions. It is performed by inserting a cryoprobe into the lesion combined with EBUS-TBNA. Typically, a 1.1 mm cryoprobe is used. It can provide larger and better-quality samples than EBUS-TBNA, which might improve the diagnostic yield for
certain conditions, such as uncommon tumors and benign disorders (Figure 5). (45, 46)

Ye Fan et al. carried out an open-label, randomized trial across three medical facilities in Europe and Asia. The study included patients who were 15 years or older and had at least one mediastinal lesion measuring 1 cm or more in the short axis. Participants were randomly assigned (1:1) to the combined use of EBUS-TBNA and transbronchial mediastinal cryobiopsy (combined group, n=136) or EBUS-TBNA alone (control group, n=135). When mediastinal cryobiopsy was added to conventional EBUS-TBNA, the overall diagnostic yield increased from 81% to 93% (p=0.0039). When cryobiopsy was added in benign diseases, the diagnostic yield was significantly higher than the EBUS-TBNA alone group (34% vs. 24%; p=0.0009). However, there was no significant difference in diagnostic yield between the two groups in lung cancer and uncommon tumors. (45) Grade 3 or higher bleeding occurred in two patients (1%) and three patients (2%) in the EBUS-TBNA alone group and combined group, respectively (p=1.00), and pneumothorax occurred in four patients (3%) and two patients (1%), respectively (p=0.67).

Genomic testing for lung cancer and PD-L1 immunohistochemistry assay were applicable in nearly all (37 out of 38, 97%) of the non-small-cell lung cancer samples obtained through the combined method, while they were only feasible in 30 (79%) out of 38 samples from the EBUS-TBNA alone method (RR = 1.23, 95% CI [1.04–1.47]; p=0.033).

Therefore, to date, there is little evidence for the need for mediastinal cryobiopsy in terms of diagnostic yield for lung cancer, but it can be considered when genomic testing and PD-1 immunohistochemistry assay are necessary.

6. EBUS guided intranodal forceps biopsy (EBUS-IFB) & Flexible 19G needle for EBUS-TBNA

A meta-analysis indicates that the addition of forceps to conventional endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) enhances diagnostic accuracy in tissue diagnosis of intrathoracic adenopathy. This study demonstrates a significant increase in diagnostic yield with the combined method, achieving 92% (428 out of 467 cases), compared to a 67% yield (312 out of 467 cases) when utilizing EBUS-TBNA alone. Notably, in specific pathologies such as lymphoma and sarcoidosis, the combined approach substantially elevates diagnostic yield: 86% for lymphoma versus 30% for EBUS-TBNA alone, and 93% for sarcoidosis in contrast to 58% with the solitary EBUS-TBNA method. (47)

Studies using 19-gauge TBNA needles were conducted to overcome the limitations of standard 21-
and 22-gauge EBUS-TBNA needles, which have a small amount of core and a crushed structure. These studies revealed that while the use of a 19-gauge needle did not enhance the diagnostic yield, it facilitated the acquisition of larger tissue samples, proving more beneficial for comprehensive histopathological evaluation and molecular testing without an increase in complications. (48, 49) Although the 19-gauge needle may have potential benefits in situations necessitating assessment of cellular architecture, such as in lymphoma subtyping or in the presence of necrotic tissues, definitive evidence supporting its superiority remains inconclusive to date. Therefore, the choice of needle gauge should be contingent upon individual patient needs and the specific requirements of the diagnostic evaluation.

**Conclusion**

With the development of various advanced bronchoscopic techniques, the minimally invasive non-surgical biopsy methods have become a trend in the diagnosis and staging of lung cancer. These techniques can be used alone or in combination. Cryobiopsy increases diagnostic yield when combined with conventional biopsy tools and can be used together during rEBUS-GS-TBLB, ENB, RAB and EBUS-TBNA procedures.
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References


**Figure 1.** Penetrating biopsy tools used in NAVIGATE study. 

**Figure 2.** (A) MONARCH™ Platform. (B) screen during navigation. 

**Figure 3.** (A) Ion™ Endoluminal System. (B) shape-sensing catheter technology. 
(https://www.intuitive.com/en-us)

**Figure 4.** A case in which a specimen containing adenocarcinoma was obtained through three crybiopsies. (A) The arrow indicates bronchial mucosa, and the dotted arrow indicates cartilage. / 'Adjacent to' on rEBUS. (B) Atypical cells are observed in the dotted oval. / 'Adjacent to' on rEBUS. (C) Adenocarcinoma observed in dotted circle / 'Within' on rEBUS.

**Figure 5.** Size comparison of lymph node between specimens obtained by EBUS-TBNA and cryobiopsy (A) 21G EBUS-TBNA - the diameter of the area containing adenocarcinoma is 270 μm. (B) 1.1 mm cryoprobe – 1,950 μm.
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