

Chinese expert consensus statement on issues related to small specimen sampling of lung cancer

Chinese Thoracic Society, Chinese Alliance against Lung Cancer

INTRODUCTION

Lung cancer is a malignant disease with the highest morbidity and mortality in the world. Radical surgery cannot be used for the 75% of lung cancer patients who have advanced lung cancer at first presentation.^[1] Further treatment of these patients with advanced lung cancer should be based on a minimally invasive diagnostic workup that provides an accurate histopathological diagnosis and identifies the molecular subtype and stage. For nearly 80% of patients with advanced lung cancer, the diagnosis is confirmed by evaluation of a small biopsy specimen.^[2] The treatment of lung cancer has recently entered the era of precision medicine; treatments are based on the combined results from histological subtyping and molecular profiling. Therefore, adequate and high-quality lung cancer specimens are of vital importance for an accurate histological and molecular diagnosis and require multidisciplinary collaboration. In addition, selected patients can be monitored for disease progression and changes in molecular profiles by repeated biopsies or biopsies of multiple sites.

Due to the current extensive use of small specimens from patients with lung cancer and the clinical need for precision lung cancer treatment, Chinese experts in related fields have carried out multiple discussions,

studies, and searches of relevant worldwide publications by lung cancer experts on lung cancer research and treatment. Ultimately, the “Chinese expert consensus statement on issues related to small specimen sampling of lung cancer” (hereinafter referred to as “the consensus”) came into being. The aim of the consensus is to enhance the awareness of the domestic medical personnel who care for patients with pulmonary tumors, with regard to the importance of small biopsy samples. By encouraging the standardization of the operative procedures used for biopsies of lung tissue, which include transbronchial lung biopsy and transthoracic core needle biopsy (CNB), the consensus should lead to marked improvement in the efficiency of the biopsy procedure and the quality of the sample, while reducing the complication rate. The consensus can also promote and popularize medically relevant technology in our country and encourage the attempts to improve minimally invasive diagnostic procedures and precision therapies for lung cancer to the level of international standards. The aims and effects of the consensus should lead to improvement in the diagnostic yield of biopsies for early lung cancers and ameliorate the effects of therapy while improving the outcomes of patients with advanced disease.

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Address for correspondence

Dr. Chong Bai, Department of Respiratory and Critical Care Medicine, Changhai Hospital of Second Military Medical University, 168 Changhai Road, Shanghai 200433, China. E-mail: bai_chong@163.com

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In accordance with the different methods that are used for sampling, this consensus is primarily focused on several important technical aspects of bronchoscopic sampling, including bronchoalveolar lavage (BAL) and bronchoscopic biopsy, as well as endobronchial ultrasound (EBUS)-guided transbronchial needle aspiration (TBNA) and transthoracic CNB. The critical issues common in clinical practice that are presented for each discussed category are dealt with in a question-and-answer format.

BRONCHOALVEOLAR LAVAGE

BAL is a bronchoscopic sampling technique that obtains a sample for diagnostic analysis, which can contain cells, inhaled particulate matter, infectious pathogens, and solutes from the distal airways and alveoli. BAL is easy to perform and is well tolerated by patients. The best location for lavage, correct operative techniques, and appropriate methods for transporting and processing BAL fluid (BALF) should benefit the analysis and elucidation of BAL results.

How to choose the location of bronchoalveolar lavage

Conventional BAL is usually performed in the right middle pulmonary lobe or lingula of the left lung because the bronchoscope can easily be wedged into the two sites, and the yields of fluid and cells recovered from these sites are about 20% higher than the yields from BAL performed in the lower pulmonary lobes.^[3] However, whether a diffuse pulmonary disease or focal pulmonary lesion is suspected, the first recommendation is to choose a BAL location based on the imaging (primarily computed tomography [CT]) findings. In general, the optimal BAL sites are the lobes or segments with groundglasslike shadows that can indicate abnormal alveoli, multiple nodules or spaceoccupying lesions, or regions with significant reticulonodular shadows suggestive of an interstitial lesion. High-resolution CT images obtained within 6 weeks before the BAL procedure are ideal.^[4]

What are the optimum number of times for bronchoalveolar lavage and optimum total volume of bronchoalveolar lavage fluid?

In general, a 20 mL or 60 mL syringe is applied to instill sterile sodium chloride solution (normal saline) at about 37°C (or room temperature). The recommended times of lavage range from 3 to 5 and the optimum total volume of BALF ranges from 100 to 200 mL.^[4] A BALF volume of <100 mL may lead to increased

risk of bronchial exfoliation and abnormal increases in BALF concentrations of bronchial lavage components.

What should the percentage of recovered bronchoalveolar lavage fluid be?

In general, the recovered percentage of BALF ranges from 40% to 70% of the total volume of lavage fluid instilled into the right middle lobe and left lingula, and at least 30% of the volume of lavage fluid instilled into the lower lobes or other lobes.^[3,4] Studies have shown that recovered volumes of BALF of <10% of the total volume of lavage fluid may result in inaccurate cell counts. The results of BALF analysis are unreliable for recovered BALF volumes of <5% of the total volume instilled. In addition, such procedures with poor recovery should be considered unsuccessful and stopped to avoid a large volume of fluid retention in the lung. The amount of recovery used for BALF cell counts should generally reach 10–20 mL and should be at least 5 mL.^[4]

What is the suitable method for obtaining optimal recovery of bronchoalveolar lavage fluid?

The bronchoscope should be wedged snugly into the bronchial opening so that fluid cannot leak around it. Fluid recovery should be immediately performed after each injection of fluid, using a syringe with a plunger or by applying suction directly through the bronchoscope, which is connected to a sterile container. Excessive negative pressure during suction can lead to airway collapse, mucosal injury, and reduced volume of recovered BALF; any bleeding will contaminate the BALF sample. Optimal suction should be visually controlled by the operator: a pressure ranging from 25 to 100 mmHg (1 mmHg = 0.133 kPa) is appropriate.^[3,4]

What method (s) should be used to transport bronchoalveolar lavage fluid?

BALF should be submitted for laboratory testing within 1 h of recovery. The recommendations for transporting BALF are as follows: (1) newly acquired BALF can be immediately used for laboratory testing; (2) if the transport time exceeds 30 min, BALF should be transported at 4°C (placed on ice); (3) if the transport time exceeds 1 h, BALF should be centrifuged at a low speed (250–300 g, 10 min); to maintain cellular integrity, the pellet should be resuspended in cell culture medium (Modified Eagle Medium [MEM] + 25 mmol/L 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid [HEPES] or Roswell park memorial institute [RPMI] 1640 medium + 25 mmol/L HEPES), and the

resuspended pellet should be stored at 4°C and tested within 24 h; and (4) if no centrifuge is available, MEM or RPMI should be added to the recovered BALF, and the mixture should be stored at 4°C and tested within 12 h. BALF should not be frozen or placed on dry ice during transport.^[4]

How to process the bronchoalveolar lavage fluid before testing?

The recommendations for processing BALF are as follows: (1) filter BALF using a piece of cotton gauze or nylon mesh to reduce contamination by bronchial mucosa and epithelial cells, and if necessary, use dithiothreitol to resolve residual amounts of mucus; (2) measure the total volume of BALF; (3) centrifuge BALF at 500 g for 10 min; and (4) store BALF supernatant frozen at -80°C for subsequent analysis.^[3-5]

How to classify and count bronchoalveolar lavage fluid cells?

The recommendations for assessing BALF cells are as follows: (1) stain the BALF cells (WrightGiemsa or MayGrunwaldGiemsa method) and count at least 400 cells; (2) the BALF differential cell count of healthy nonsmoking adults references is established as follows: alveolar macrophages >85%, lymphocytes 10%–15% (CD4⁺/CD8⁺ ratio = 0.9–2.5), neutrophils ≤3%, eosinophils ≤1%, and squamous cell/ciliated columnar epithelial cells ≤5%. Results showing lymphocytes >15%, neutrophils >3%, eosinophils >1%, or mast cells >0.5% suggest possibility of related diseases; and (3) squamous cells in BALF indicate contamination by respiratory secretions, and a large number of bronchial epithelial cells indicates that the BALF specimen is not lavage fluid from a distal air chamber.^[4]

TRANSBRONCHOSCOPIC BIOPSY

How many times of biopsy is adequate for testing?

For visualized endobronchial lesions, 3–4 passes can significantly improve the diagnostic yield (70%–90%). More than four passes, however, will not increase the diagnostic yield.^[6] A previous report showed that sampling through five passes of centrally located focal lesions could optimize the diagnostic sample yield, thereby providing more accurate molecular subtyping and molecular test results.^[7] We suggest that without the capability of rapid onsite assessment (rapid onsite evaluation [ROSE]), at least 3–4 passes should be performed to obtain an amount of target lung cell

suspension that is adequate for histopathological diagnosis and classification. The remaining samples can be reserved for additional molecular diagnostic testing.^[8]

Which is the right tool for performing a biopsy of peripheral lung lesions?

TBNA under Xray fluoroscopy provides better sensitivity for the diagnosis of malignant peripheral lung lesions than forceps biopsy or bronchial brush biopsy. In addition, obtaining specimens by more than one type of biopsy method is better than obtaining a specimen by a single method. Needle aspiration biopsy provides the highest diagnostic yield for malignant lesions, while forceps biopsy is best for benign lesions. Thus, the combination of both methods may be the optimal solution.^[3]

What is the value of existing positioning technology for sampling peripheral lung lesions?

The current positioning technology in the airways for obtaining specimens for the diagnosis of peripheral lung lesions includes radiographic guidance, virtual navigation, electromagnetic navigation, radial EBUS, and ultrafine bronchoscopy. The use of guidance technology can significantly improve the diagnostic yield of biopsy over the traditional transbronchial biopsy of lung lesions. The diagnostic yield of a single guidance device has been reported to be approximately 70%,^[9] and the use of more than one type of guidance modality provides a higher diagnostic yield.^[9-11] Electromagnetic navigation or virtual navigation combined with radial probe EBUS-guided biopsy is currently used in clinical practice more frequently than other modalities.^[12-13] The electromagnetic navigation guide sheath is expensive, and fine-, or ultrafine bronchoscopy can somewhat compensate for the lack of a navigation guide sheath. Fine or ultrafine bronchoscopy together with radial probe EBUS guidance can also be used in clinical practice.^[14-16] The use of ordinary light microscopy together with fluorescence spectroscopy/narrow banding imaging technology can improve the accuracy of locating the lesion for biopsy.^[17,18] If an advanced guidance device is not available, chest CT images should be used for guidance. Transbronchial lung biopsies performed in bronchial subbranches that correspond to radiographic images of bronchial lesions may also improve the diagnostic yield.

Can sampling methods combined together provide a higher diagnostic yield?

Studies have shown that various sampling methods such as bronchial brush biopsy, forceps biopsy

needle aspiration, and lavage combined together provide a higher diagnostic yield than a single method.^[5,19] However, the question remains as to which sampling methods should be used together. The types of methods to be used are based on the following conditions: location of the lesion, available equipment, and the operator's skill level. In general, the combination of two or three methods together is appropriate. The combination of more than three methods is time consuming, and increases the risk of complications.^[5,19]

Does the type and size of the biopsy forceps affect the diagnostic yield of a transbronchial biopsy?

Commonly used biopsy forceps include the following types: movable serrated edge (alligator) biopsy forceps, regular serrated edge (alligator) biopsy forceps, standard biopsy forceps, and oval biopsy forceps with a needle. To the best of our knowledge, studies assessing biopsy forceps for central bronchial and intratracheal lesions have not been performed. Therefore, the choice of biopsy forceps usually depends on the operator's experience and preferences. Some investigators believe that a large biopsy forceps provides a larger tissue specimen. However, no study has shown that large biopsy forceps improve the diagnostic yield.^[3,5]

Are there special operating techniques and specimen handling methods needed for bronchial brush biopsy?

The two types of bronchial cell brushes commonly used, with or without sheaths, show no significant differences in diagnostic efficacy. Currently, cell brushes are single or repeated-use devices. A disposable cell brush is recommended for preventing crosscontamination and infection.^[3] Two processing methods are used for the cytological specimens obtained by brushing. The brush can be applied directly to a glass slide or be placed in saline, which is then shaken vigorously. The saline is then centrifuged, and the cells are collected. In current literature, studies assessing the merits of these two processing methods are not available.

In what order should bronchoalveolar lavage, bronchial brush biopsy, and biopsy be performed on the patient?

A bronchoscopic brush biopsy can only obtain a specimen that reflects the surface of bronchial mucosa, but it cannot be used to sample lesions under the mucosa or within the bronchial wall. A bronchial brush biopsy is performed first to reduce the impact of blood contamination on the cytological assessment. The order

of procedures is controversial for BAL combined with transbronchial biopsy or bronchial brush biopsy. Studies have shown that BAL performed before a biopsy or after brush biopsy did not affect the diagnostic yield for visible lesions in a cavity or lesions that are not visible. Since BAL and bronchial brush biopsy provide similar diagnostic efficacy for visible lesions inside a cavity, either can be combined with transbronchial biopsy. BAL combined with transbronchial biopsy is recommended for nonvisible lesions.^[20] Since the diagnostic yield of BAL is relatively low for lung cancer, to reduce healthcare costs, some investigators have suggested storing and sending BALF for testing only if samples obtained by other methods are negative. However, BAL provides better diagnostic value for diffuse infiltrative lung cancers such as diffuse lung adenocarcinoma and pulmonary lymphangitic carcinomatosis.^[4]

TRANSBRONCHIAL NEEDLE ASPIRATION AND ENDOBRONCHIAL ULTRASOUNDGUIDED TRANSBRONCHIAL NEEDLE ASPIRATION

How many passes should be performed to obtain a satisfactory sample for each target lesion?

To obtain a definitive diagnosis and staging for patients with suspected lung cancer, if ROSE is not available to evaluate the quality of the specimen, at least three EBUS-TBNA passes should be performed per target lymph node or pulmonary nodule, or at least 3–4 conventional TBNA passes should be performed.^[21–23] To obtain sufficient sample for molecular diagnostics, four EBUS-TBNA passes should be performed for per target lesion.^[24] A plateau in yield after 7 times of aspirate per nodal site was reported, so more passes would not improve the diagnostic yield.^[25]

How to choose an appropriate puncture needle or biopsy tool?

A 21G, or 22G puncture needle can be applied to obtain cytology samples; during TBNA or EBUS-TBNA, the differences in diagnostic yield and quality of samples provided by a 21-G, or 22G needle used for TBNA or EBUS-TBNA of lung lesions suspicious for lung cancer were not significant.^[20,26–29] The operator can use either-sized needle, based on the biopsy site and its blood supply. An 18-G or 19G needle is generally used for conventional TBNA because they obtain larger core tissue samples and may improve the diagnostic accuracy.^[30] EBUS-guided forceps biopsy is not recommended for patients with

suspected lung cancer. However, EBUS-guided forceps biopsy can be used for some specific malignancies such as lymphoma or sarcoma.^[21]

Is negative pressure suction required for transbronchial needle aspiration or endobronchial ultrasound-guided transbronchial needle aspiration?

Previous studies have found that samples obtained with or without suction were similar for diagnostic yield, sufficient amount of specimen, and specimen quality; therefore, the choice to use negative pressure suction can be based on the personal preference of the operator.^[21,29,31,32] Theoretically, a larger specimen can be obtained with negative pressure suction. However, if a TBNA sample is contaminated with blood, subsequent samples from the same site should be taken without suction. For lesions with a sonographically vascular signal, needle aspiration without suction or with a low negative pressure is recommended.^[29]

What type of sedation or anesthesia should be used for performing transbronchial needle aspiration or endobronchial ultrasound-guided transbronchial needle aspiration?

There are four levels of sedation: mild sedation, moderate sedation (conscious sedation), deep sedation, and general anesthesia. The optimal anesthesia during TBNA or EBUS-TBNA will enable the operator to acquire optimal samples, increase the patient's comfort, and decrease the risk of procedure-related complications.

General anesthesia *versus* conscious sedation for lung cancer patients undergoing EBUS-TBNA was compared, but no significant difference was observed in sensitivity, specificity, operative time, and tolerance; however, the rate of mild procedure-related complications was higher in the patients receiving conscious sedation.^[31] In addition, there were no differences between deep or conscious sedation. Therefore, we recommend choosing an appropriate method of sedation based on the patient's desire and physical state and the anesthesia capabilities of the local hospital.^[21,29]

Do the samples obtained by transbronchial needle aspiration or endobronchial ultrasound-guided transbronchial needle aspiration need special processing or staining?

TBNA specimens can be processed as cytological smears, cellblocks, or core specimens. In general, a cytological smear can be evaluated for the cytological diagnosis of lung cancer. When necessary, a cell smear

prepared for ROSE can be decolorized and used for further cytological evaluation, immunohistochemical staining, or diagnostic molecular pathology.^[21] Both cell blocks, and core specimens can be used for histological examination and provide similar diagnostic yields for lung cancer. Therefore, either preparation can be used, based on the preference of the pathologist. If possible, some of the biopsy specimens should be reserved in a solution such as formalin, saline, or Hank's salt solution, which can be used for producing cellblock that can be applied for detailed histologic and molecular subtyping by immunohistochemistry and molecular diagnostics.^[33-35]

The common techniques for processing and staining cell slides include liquid-based cytology, Wright-Giemsa staining, Papanicolaou staining, and rapid Romanowsky staining. While all methods can achieve satisfactory results, the choice of stain is based on the preference of the pathologist and cytologist.^[21]

Is rapid onsite evaluation necessary to the procedure?

Currently, most endoscopy centers abroad perform ROSE during the biopsy procedure for patients with suspected lung cancer, but the value of ROSE is controversial.^[21] However, ROSE can aid in evaluating the quality of the specimen and may allow instant diagnosis, which can decrease the number of passes and shorten the procedure. Therefore, TBNA with ROSE is highly recommended for patients with suspected lung cancer or mediastinal/hilar lymphadenopathy^[21,36-41] and is essential for patients desiring genetic testing, for which malignant cells of sufficient quality and quantity are required.^[41,42]

Is the obtained specimens possible for molecular diagnostics? What are the influencing factors?

The vast majority of cytological samples obtained by conventional or EBUS-guided TBNA can be used for molecular diagnostics, which depend on the absolute number of tumor cells in a sample (preferably >100 cells), the proportion of tumor cells, and the quality of tumor cells. The sensitivity of the molecular detection methods is also important.^[21,29,35]

1. When conventional TBNA or EBUS-TBNA is used to obtain an adequate sample for molecular diagnostics, the recommended number of passes of the target lesion is 4.^[24] In current literature, there are no definitive data on the impacts that type of needle, application of biopsy forceps, application of liposuction, type of sedation, time the needle remains in the target lesion, and number of movements, on the yield of the molecular diagnostic procedures for lung cancer.^[21]

2. The types of biopsy samples that can be used for molecular testing include cytological smears, cellblocks, and core specimens. Cellblocks and core tissue specimens are more suitable for gene mutation analysis, as well as anaplastic lymphoma kinase translocation detection. If the cellblocks, core specimens, or tumor cells in the sample are insufficient, cytology slides can be used for testing genetic mutations of epidermal growth factor receptor and other genes.^[21]
3. As previously mentioned, ROSE aids in the assessment of tumor cell load in the samples and is recommended for molecular testing.^[21,29,42]

When should a water balloon be used during endobronchial ultrasound?

A single-use water balloon can be added to the distal end of an EBUS bronchoscope. If the balloon is filled with saline solution, ultrasonic transducers can fit more closely with the airway wall, thereby reducing artifacts and allowing a clearer ultrasound image. However, whether a water balloon improves the diagnostic accuracy of EBUS-TBNA remains unclear. Reports have shown that the water balloon is generally applied for biopsies in the paratracheal regions (right upper paratracheal [2R], left upper paratracheal [2L], right lower paratracheal [4R], and left lower paratracheal [4L] lymph nodes), the right and left hilum (10R and 10L, respectively). However, for the biopsies of station 7 and 11 lymph nodes, the balloon is not necessary.^[29]

TRANSTHORACIC CORE NEEDLE BIOPSY

Transthoracic CNB is performed based on radiography or under the guidance of Bmode ultrasound or CT, with a fine needle to penetrate the lesion and extract cells or small amounts of tissues for histopathological diagnosis. In 1886, Menetrier introduced transthoracic CNB for the diagnosis of lung cancer. In 1976, Haaga carried out transthoracic CNB under CT guidance, which improved the accuracy of the biopsy procedure and resulted in an important technical improvement for the diagnosis of pulmonary disease.^[43] Subsequent clinical studies have further clarified the diagnostic efficiency of lung biopsy and the incidence of complications.

What are the indications for transthoracic core needle biopsy?

The indications include: (1) A solitary nodule or mass that is newly discovered or has increased in size during followup; (2) Multiple lung nodules in a patient with no

previous history of malignant disease or nodules that do not resolve after treatment for malignant disease; (3) Persistent invasive pulmonary lesions after treatment; and (4) Pleural and mediastinal lesions.^[44]

What size nodules can be successfully sampled by transthoracic core needle biopsy?

According to the location of the lesions on the chest image, a smooth needle track can be set, and there are no obvious limitations in the size of nodules; however, when a nodule is smaller than 1 cm, the falsepositive rate will increase obviously. In such a situation, the success of transthoracic CNB depends on the technical skill of the operator, the detection and location of the lesion on radiological imaging, and the sensitivity of histopathological analysis. The procedure should be developed with inputs from the departments responsible for the procedure (Departments of Respiratory Medicine or Oncology), together with the Departments of Radiology and Pathology.^[45]

What are the contraindications for performing transthoracic core needle biopsy?

There are no absolute contraindications for transthoracic CNB. However, the biopsy is not recommended for patients with high risk of complications associated with the biopsy or who cannot tolerate the procedure.

Currently, the contraindications for transthoracic CNB are as follows: (1) coagulation abnormalities; (2) inability to tolerate the examination because of severe cachexia or cardiac or pulmonary insufficiency; (3) severe emphysema, pneumothorax, or pulmonary bullae or cysts in the area targeted for biopsy, which may increase the risk of pneumothorax or inability to tolerate pneumothorax after biopsy; (4) cor pulmonale, pulmonary hypertension, pulmonary vascular disease, severe, uncontrolled hypertension, and all of which may increase the risk of bleeding or worsen the condition; (5) severe cough; (6) history of acute myocardial infarction within 6 weeks of the planned procedure and chronic renal or hepatic insufficiency;^[46] and (7) some medications are contraindicated, including aspirin and clopidogrel, which may increase the risk of bleeding. Oral aspirin has an inhibitory effect on platelets that lasts 4–7 days, and the life span of platelets is 7–10 days. Aspirin should not be taken for at least 1 week before a biopsy is performed, and a biopsy should not be performed for patients who have stopped warfarin until the blood coagulation index is normal.^[47]

The operator must confirm the indications for biopsy, the feasibility of the procedure, and fully assess the pros and cons to minimize the risk of biopsy.

What methods are used for transthoracic biopsy?

To date, two methods are employed for transthoracic biopsy: fineneedle aspiration (FNA) and CNB. The differences between the two methods in diagnostic sensitivity and the incidence of complications have not been found to be significant. The sensitivity and specificity of FNA have ranged from 82% to 99% and 86%–100%, respectively, and the diagnostic accuracy for malignant disease has ranged from 64% to 97%. The diagnostic accuracy for malignant disease and sensitivity and specificity of CNB were 92.9%, 95.3% and 95.7%, respectively.^[48,49]

Since CNB can obtain a larger specimen, apart from routine histopathological diagnosis, it allows molecular diagnosis, which can identify tumor subtypes.^[49] Therefore, CNB is recommended for patients who can tolerate it and have no significant risk factors. FNA is safer for patients with small lesions, lesions adjacent to large blood vessels and the heart, and lesions containing vessels, which may lead to bleeding. However, because of the increased falsenegative rate for lesions <1 cm in diameter, despite the increased risk of pneumothorax, CNB is recommended for histological diagnosis.^[45]

How to choose the biopsy needle for transthoracic core needle biopsy?

The following FNA needles are used: the Chiba needle, Turner needle, and the Madayag, Greene, Franseen, and Westcott needles. The Chiba, Greene, Turner, and Franseen needles sample using a ring tip, while the Westcott needle has an oblique cutting edge.^[50] Previous studies have used a 14-G FNA needle, but currently 16-G and 18-G FNA needles are used. Typically, the larger diameters can obtain more tissue. A CNB usually employs cutting needles or needles in a coaxial system. The biopsy needle in a coaxial system is composed of an outer sleeve and an inner core needle with an oblique cutting groove. The needle is quickly ejected by the puncture gun; the tissue is cut by the cutting groove and the outer sleeve and remains in the groove. The procedure requires a single puncture of the pleural membrane, and the puncture needle can perform repeated biopsies through the outer sleeve. When using a single needle, a needle coaxial system can reduce the number of pleural punctures, is easy to locate, and prevents air from entering the pleural cavity.^[51]

The CNB needles in the current application include the following: Tru-cut puncture needle, Temno needle, and Bard needle. The common sizes are 16, 18, and 20-G^[49] with 18- and 20-G needles most commonly used at lengths of 100 and 160 mm. Studies have confirmed that 20-G needles used for percutaneous biopsy are safe and can provide sufficient tissue for molecular diagnostics.^[50,52] Results of a study suggest that 100- and 160mm needles are effective for puncture depths <5 cm and >5 cm, respectively.^[43]

The type of needle to use is affected by many factors including tumor size, preset needle track, complications, amount of tissue required for histopathological diagnosis, medical condition of the patient, and personal experience of the operator.^[50] For example, a largerdiameter needle has a greater risk of pneumothorax, and if the patient's risk of pneumothorax is too high, an 18-G cutting needle or 16-G aspiration biopsy needle should be considered, and if necessary, a 14-G needle can also be chosen.

How to prevent or manage the complications of percutaneous lung puncture?

The common complications include the following:

1. Pneumothorax with complication rates ranging from 0% to 60%; most can be discovered on CT imaging after the puncture. Factors affecting the risk of pneumothorax include the following: tumor size, distance from the pleura, the presence or absence of emphysema, multiple positions, repeated punctures, and the angle between the puncture needle and pleura.^[53] Treatment of a small pneumothorax (lung collapse <30%) consists of bed rest and selfadministered oxygen. An uncertain proportion of patients with closed pneumothorax can be treated by thoracentesis. Closed thoracic drainage is required for 1.6% to 17% of patients with pneumothorax presenting with severe chest tightness, severe chest pain, lung collapse of >30%, and rapid progression of pneumothorax.^[54]
2. Bleeding is the second most common complication of percutaneous lung puncture and can include pulmonary hemorrhage and thoracic internal hemorrhage. The common presentation includes chest pain and hemoptysis. The amount of bleeding depends mainly on the blood vessels in and around the lesion and the puncture path through the blood vessels.^[55] The distance from the pleural lesions and the nature of the lesion itself (lung consolidation, interstitial lung disease and cavitory lesions) may also be factors that affect bleeding. Damage to intercostal arteries and veins that causes hemothorax

is relatively rare. A small amount of bleeding after the puncture procedure does not require special treatment. However, hemoptysis requires additional treatment including having the patient lie on the affected side, administering oxygen therapy, comforting the patient, and encouraging the patient to cough up blood. The patient should be prescribed bed rest with hemostatic tamponade and receive an artificial airway, if necessary. With massive hemoptysis and poor response to medical treatment, interventional embolization should be considered.^[56] Hemostatic tamponade combined with closed thoracic drainage is recommended. In cases with a marked decrease in hemoglobin level, we recommend blood transfusions to correct anemia.

3. Pleural reaction is common in patients with mental stress, patients who undergo repeated puncture, and patients who are not sufficiently anesthetized. Pleural reaction occurring during the procedure is treated by stopping the operation, placing the patient on supine bed rest, and administering oxygen.^[57]
4. Pain at the puncture site and fever are common adverse reactions to the puncture procedure. Pain may be due to the needle puncture and tissue damage. Fever may be associated with bleeding and blood absorption. The recommended treatment is symptomatic and supportive. If necessary, chest infection should be excluded by chest CT.^[56]
5. Air embolism is relatively rare but has a high mortality rate. The operator should take care to avoid the penetration of pulmonary vessels. When the needle is inserted into the biopsy site, the trocar should be blocked by a stylet immediately. Cough suppressant should be administered to patients with severe cough to avoid pulmonary hypertension, which could result in the introduction of air into blood vessels.^[58,59]
6. Tumor seeding of the needle tract is of great concern and has generated controversy. Studies have shown that the incidence of tumor metastasis to the needle track is 0.01%. In 1980, Smith reported an incidence of 0.005%. A subsequent study reported 2144 cases of percutaneous lung biopsy in patients with no occurrence of needle tract metastasis. The needle should be kept in the trocar when pulled out, to prevent the biopsy specimens falling off along the needle path.
7. Mortality has been rarely reported in studies of percutaneous lung puncture biopsies. A study of 5444 lung biopsies reported a mortality rate of 0.15%. The main causes of death were bleeding after the biopsy (hemoptysis, pulmonary hemorrhage and serious hemothorax), cerebrovascular accident, and air embolism.^[58,60]

What type of imaging guidance should be used for percutaneous lung biopsy?

The methods currently used for imaging guided percutaneous lung biopsy are ultrasound and CT.

1. Ultrasound guidance provides the advantages of real-time monitoring, short operating time, high flexibility, ability to avoid large blood vessels and vital organs, and identification of atelectasis and masses. It can be performed at the bedside and is a means of avoiding exposure to radiation.^[61,62] However, ultrasound is only suitable for positioning lesions near the chest wall, and so, very small lesions may not be correctly located; therefore, ultrasound can only be used for relatively large lesions. Ultrasound depicts lesions and needle position less clearly than CT; during the puncture, the ultrasound probe touches the needle and may potentially lead to contamination of the biopsy site.^[62]
2. Conventional CT guidance provides the following advantages: a wide range of applications; accurate positioning; improved imaging of the needle track, thereby avoiding fissures, bullae, and larger vessels and allowing minimization of the risk of bleeding and pneumothorax; guidance for small lesions, lesions at a distance from the pleura, central lesions, and mediastinal lesions;^[63] and ability to distinguish intact tissue from necrotic tissue in the lesion, which leads to increased diagnostic yield, thereby increasing the success rate.^[59] CT has the following disadvantages: inability of real-time monitoring; inability to guide the needle directly into the lesion, possibly leading to multiple needle punctures and increasing operative time, and high radiation dose.^[64]
3. CT fluoroscopy guidance has all advantages of conventional CT; it can also provide real-time CT guidance. It is faster than conventional CT, thereby reducing the operative time up to 21.7%, with a corresponding reduction in the number of passes and the incidence of complications, and provides higher diagnostic yield for small lesions.^[65] A shortcoming of this modality is that the operators receive an increased radiation dose.

What are the preparations before percutaneous needle lung biopsy?

1. The patient should be completely informed about the purpose and importance of the puncture procedure, the operative process, and possible complications. The physician must obtain a signed informed consent from the patient.
2. The following routine preoperative examinations are needed to assess the patient for contraindications and

- ability to tolerate the biopsy and puncture: routine blood tests, coagulation analysis, electrocardiogram, and pulmonary function testing. Enhanced chest CT is recommended for excluding vascular lesions, clarifying the relationship between the lesion and the blood vessels, and planning the best track for needle puncture.
- Intravenous access should be established and required hemostatic measures and oxygen delivery apparatus should be prepared. If there is a significant risk of pneumothorax, equipment for thoracentesis or chest drainage should be prepared, including puncture items, seal bottles, and syringes.
 - Effective antitussive agent, such as codeine, should be administered to patients with obvious cough at least 30 min to 1 h before the procedure.

What is the appropriate patient positioning for puncture? What type of anesthesia should be used?

The patient's position during puncture is mainly based on the location of the lesion and the relationship of the lesion to the surrounding tissue. The supine and prone positions are most frequently chosen because they are well tolerated by the patient, and the patient can therefore cooperate better with the doctor. The lateral position may be considered to avoid too-deep a puncture, blood vessels, and thick muscle. This position can lead to reduced cooperation by the patient, whose position may change during the puncture, so pillows supporting the patient's back and stabilizing the patient are recommended. If a puncture is performed in the interscapular region of the patient in the prone position, his or her arms should be fully extended to expose the interscapular region.

Percutaneous lung puncture requires the patient's cooperation and respiratory adjustments. Local anesthesia consisting of 5 mL of 2% lidocaine is administered layer by layer to the pleura; the amount of anesthesia varies, based on the patient's response, the effect of anesthesia, and depth of puncture.

How to perform the percutaneous needle lung biopsy?

- The body position of the patient depends on the location of the lesion, and deep breathing and coughing should be avoided during the procedure. Therefore, the patient should be instructed on how to breathe correctly to accommodate the puncture. Natural breathing is recommended because the location of the lesion changes as the depth of breathing or breath holding changes. In addition, most obviously, lesions located in the lower lobe, especially near the diaphragm, are

affected by the patient's respiratory rate. A successful puncture might require careful regulation of the patient's breathing. If necessary, the needle should be advanced gradually.

- Surface marking and CT-guided positioning mostly use homemade markers (10 cm × 10 cm) that include 10–12 metal strips with approximately 1 cm interval. It can be fixed to the skin surface corresponding to the lesion with adhesive tape, according to the planned needle track. The female breast and injured and infected skin should be avoided. CT should be performed to determine whether the metal marker on the surface corresponds with the lesion. The corresponding access plane, point, angle and depth of the needle must be selected under the guidance of a CT scan with a slice thickness of 3 mm. The intersection of the metal marker corresponding to the planned access point and body surface display line of the CT section is marked as the puncture point with a marker pen.^[66]
- When the scanning bed moves, the same height should be maintained. After routine disinfection, sterile towel and local anesthesia are applied, and referring to the angle and depth of puncture confirmed by CT scan, the lesion is punctured directly or gradually according to actual condition. A second CT scan is performed to confirm whether the tip of the needle is located near or inside the lesion. Then, the depth of tissue cutting is set and number of passes is decided. When the puncture needle has been removed, the wound should be disinfected and pressed by sterile gauze.

The number of the passes for percutaneous needle lung biopsy

The amount of tissue sample that can be obtained with cutting needle depends on the length of the cutting groove; once the lesion is punctured with core needle, usually enough tissue can be obtained for a definitive pathological diagnosis. If the lesion is large and the risk of bleeding is not markedly increased, multiple puncture passes can be applied to ensure sufficient sample for further testing.^[67] If the lesion is small or bleeding of the puncture needle tract is obvious, a single pass should be considered, based on the quality of the biopsy tissue. The number of passes depends on the characteristics of the lesion, the difficulty of puncture, and the quality of the specimen.^[64] Some investigators prefer at least two passes.^[43]

The number of passes for FNA is based on the size of the lesion and perilesional blood vessels. If the lesion and surrounding tissue are relatively safe,

multiple passes should be performed to obtain sufficient diagnostic specimens. One to two passes should be recommended for smaller lesions or abundant peripheral blood vessels, to reduce the occurrence of adverse events.

How to manage the patient after the puncture?

1. Immediately after the puncture, CT is recommended to assess the presence of bleeding and pneumothorax. Absolute bed rest for 24 h after the operation is recommended, and hemostatic drugs and oxygen are administered, based on the amount of bleeding and the presence of pneumothorax. Electrocardiographic monitoring is performed, based on clinical signs and symptoms. If the patient has chest pain, the possibility of delayed pneumothorax should be considered. Recommendations include bedside radiography and if necessary, closed thoracic drainage. Usually after 24 h, if radiography shows absorption of the pneumothorax and there are no new serious complications, the patient can be allowed to ambulate.^[64]
2. Recommendations for specimen processing include fixing tissue samples in 10% formalin, while FNA specimens should be put into new ThinPrep liquid (Hologic, Marlborough, MA, USA) for further downstream processing. If ROSE is available during the FNA, the diagnostic yield can be significantly increased. If the specimen cannot be immediately sent to pathology, it should be stored at 4°C in new ThinPrep liquid overnight and sent to pathology as soon as possible to prevent tissue degradation.

In summary, with safe and minimally invasive approaches, a small, but sufficient and quality specimen of lung cancer can be obtained and used for accurate histological and molecular testing, which can guide the patient's treatment. These methods not only follow the trends of medical progress but also place increased demands on the medical staff involved with the care of patients with suspected lung cancer. We hope that our consensus will play an important role in regularizing the procedures of small specimen sampling of lung cancer in China and encouraging medical units to adopt these minimally invasive biopsy techniques.

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Conflicts of interest

There are no conflicts of interest.

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THE EXPERT CONSENSUS PANEL LIST (in alphabetical order by last names)

Chong Bai (Department of Respiratory and Critical Care Medicine, Changhai Hospital of Second Military Medical University); Chunxue Bai (Department of Respiratory, Fudan University Zhongshan Hospital); Lejie Cao (Department of Respiration Disease, Affiliated Provincial Hospital of Anhui Medical University); Liangan Chen (Department of Respiratory Disease, Chinese People's Liberation Army General Hospital); Chenping Hu (Department of Respiratory Disease, Xiangya Hospital of Central South University); Jianan Huang (Department of Respiratory and Critical Care Medicine, First Affiliated Hospital of Suzhou University); Faguang Jin (Department of Respiratory and Critical Care Medicine, Tangdu Hospital of Fourth Military Medical University); Jian Kang (Department of Respiratory Disease, The First Hospital of China Medical University); Mingyao Ke (Department of Respiratory Disease, No. 2 Hospital Xiamen); Qiang Li (Department of Respiratory, Shanghai General Hospital of Shanghai Jiao Tong University); Shiyue Li (Department of Respiratory, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou Institute of Respiratory Disease and State Key Laboratory of Respiratory Diseases); Weimin Li (West China Hospital of Sichuan University); Guisheng Qian (Department of Respiratory Disease, Xinqiao Hospital of The Third Military Medical University); Yong Song (Department of Respiratory and Critical Care Medicine, Nanjing General Hospital of Nanjing Military Area Command); Changhui Wang (Department of Respiratory Medicine, Shanghai 10th People's Hospital of Tongji University); Chen Wang (China-Japan Friendship Hospital); Guangfa Wang (Peking University Department of Respiratory and Critical Care Medicine, First Hospital of Peking University); Mengzhao Wang (Department of Respiratory Disease, Chinese Academy of Medical Science, Peking Union Medical College and Peking Union Medical College Hospital); Guojun Zhang (Department of Respiratory Medicine, The First Affiliated Hospital of Zhengzhou University); Jian Zhang (Department of Respiratory Disease, Xijing Hospital of the Fourth Military Medical University); Jianying Zhou (Department of Respiratory Disease, The First Affiliated Hospital of Zhejiang University); Xiangdong Zhou (Department of Respiratory Medicine, Southwest Hospital of Third Military Medical University).

PRINCIPLE AUTHORS (in alphabetical order by last names)

Chong Bai; Shiyue Li; Yong Song; Jianying Zhou.

SECRETARY PANEL LIST

Ning Wu (Department of Respiratory and Critical Care Medicine, Changhai Hospital of Second Military Medical University); Yanwen Yao (Department of Respiratory and Critical Care Medicine, Nanjing General Hospital of Nanjing Military Area Command); Weizhan Luo (Department of Respiratory, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou Institute of Respiratory Disease and State Key Laboratory of Respiratory Diseases).