CLINICAL GUIDELINE

Chinese multidisciplinary expert consensus: Guidelines on percutaneous transthoracic needle biopsy

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Abstract

Biopsy has been used to diagnose thoracic diseases for more than a century. Percutaneous needle biopsy plays a crucial role in the diagnosis, staging, and treatment planning for tumors in the lungs, thoracic wall, hilum, and mediastinum. With the continuous improvement in imaging techniques, the range of clinical applications for percutaneous needle biopsy is also expanding. It has become important to improve Chinese professionals' and technicians' understanding of percutaneous transthoracic needle biopsy (PTNB) in order to standardize operating procedures and to strengthen perioperative management. However, there is currently no Chinese expert consensus that provides systematic standardization and guidance for PTNB in clinical practice. The Committee of Chinese Society of Interventional Oncology (CSIO) of the Chinese Anti-Cancer Association (CACA) initiated a Chinese multidisciplinary expert consensus on PTNB. The consensus includes image-guided methods, indications, contraindications, multidisciplinary team recommendations, biopsy procedures, daytime/outpatient biopsy, complications, pathological examination, and management of negative results.

Introduction

Biopsy has been used to diagnose thoracic diseases for more than a century. Depending on how specimens are collected, thoracic tumor biopsy can be divided into bronchoscopic transbronchial biopsy, percutaneous needle biopsy, thoracoscopic biopsy, and open chest biopsy. Percutaneous transthoracic needle biopsy (PTNB) is a type of biopsy performed under the guidance of imaging equipment. With the continuous improvement in imaging techniques, the range of clinical applications for percutaneous needle biopsy is also expanding. From its earliest use in pathological diagnosis to the classification of tissue subtypes and genetic diagnosis, the clinical need for percutaneous needle biopsy is increasing. It has become especially important to improve Chinese professionals' and technicians' understanding of PTNB in order to standardize operating procedures and strengthen perioperative management. As early as 2003, the British Thoracic Society (BTS) published guidelines on percutaneous lung needle biopsy.[1] In 2016, the Chinese Thoracic Society and Chinese Alliance Against Lung Cancer published the "Chinese expert consensus statement on issues related to small specimen sampling of lung cancer,"[2] which categorized the key issues in common clinical practice of percutaneous needle biopsy of the lungs and discussed the corresponding solutions. However, there is currently no Chinese expert consensus that provides systematic standardization and guidance for PTNB in clinical practice. Therefore, the Committee of Chinese Society of Interventional Oncology (CSIO) of the Chinese Anti-Cancer Association (CACA) initiated the development of a Chinese expert consensus on PTNB. Built upon updated evidence from the BTS Guidelines, the "Chinese expert consensus statement on issues related to small specimen sampling of lung cancer," and opinions from a panel of multidisciplinary experts, a Chinese expert consensus on PTNB relevant to China's national conditions has been developed. This consensus does not include bronchoscopic transbronchial biopsy, thoracoscopic biopsy, or open chest biopsy. The Committee of CSIO of CACA will update the content of this consensus based on technological advancements, such as changes in diagnostic and tissue sampling methods, as well as the emergence of new evidence.

Literature search

Literature search strategy

English-language electronic databases, including PubMed, Embase, and the Cochrane Library were searched using the following terms: needle, needles, fine-needle, fine needle, biopsy, rebiopsy, lung, chest, pleura, pleural, thoracic, pulmonary, thorax, mediastinum, and mediastinal. Similarly, Chinese-language databases, China National Knowledge Infrastructure (CNKI), VIP (Weipu), and Wanfang, were searched using the terms: lung cancer, thoracic wall tumor, pleura tumor, mediastinum tumor, biopsy, and needle biopsy. References cited in the retrieved articles were included in the supplementary search. The literature search was conducted for articles published from the date when the databases were first established to June 2017 (Fig 1).

Inclusion criteria

The following publication types were included: (i) original articles; (ii) systematic reviews; (iii) meta-analyses; and (iv) consensus or guidelines related to percutaneous needle biopsy of pulmonary nodules or masses, or a comparison of percutaneous needle biopsy and other specimen collection methods, such as bronchoscopy.

Exclusion criteria

The following publication types were excluded: (i) studies in which PTNB was not performed; (ii) articles that were not published in English or Chinese; (iii) studies published in national journals from non-English-speaking countries in which the full text was not available; and (iv) conference posters, conference abstracts, and seminars.

Overview

Percutaneous needle biopsy plays a crucial role in the diagnosis, staging, and treatment planning for tumors in the lungs, thoracic wall, hilum, and mediastinum. Needles used for percutaneous biopsy can be categorized as aspiration or cutting needles according to their sample-collection principles. Aspiration needles allow the collection of high-quality cytological specimens for disease diagnosis, whereas cutting needles are used to collect histological specimens because of their larger needle diameters compared to aspiration needles. Based on the type of biopsy needle, percutaneous needle biopsy can be divided into two main categories: fine needle aspiration (FNA) and core needle biopsy (CNB).
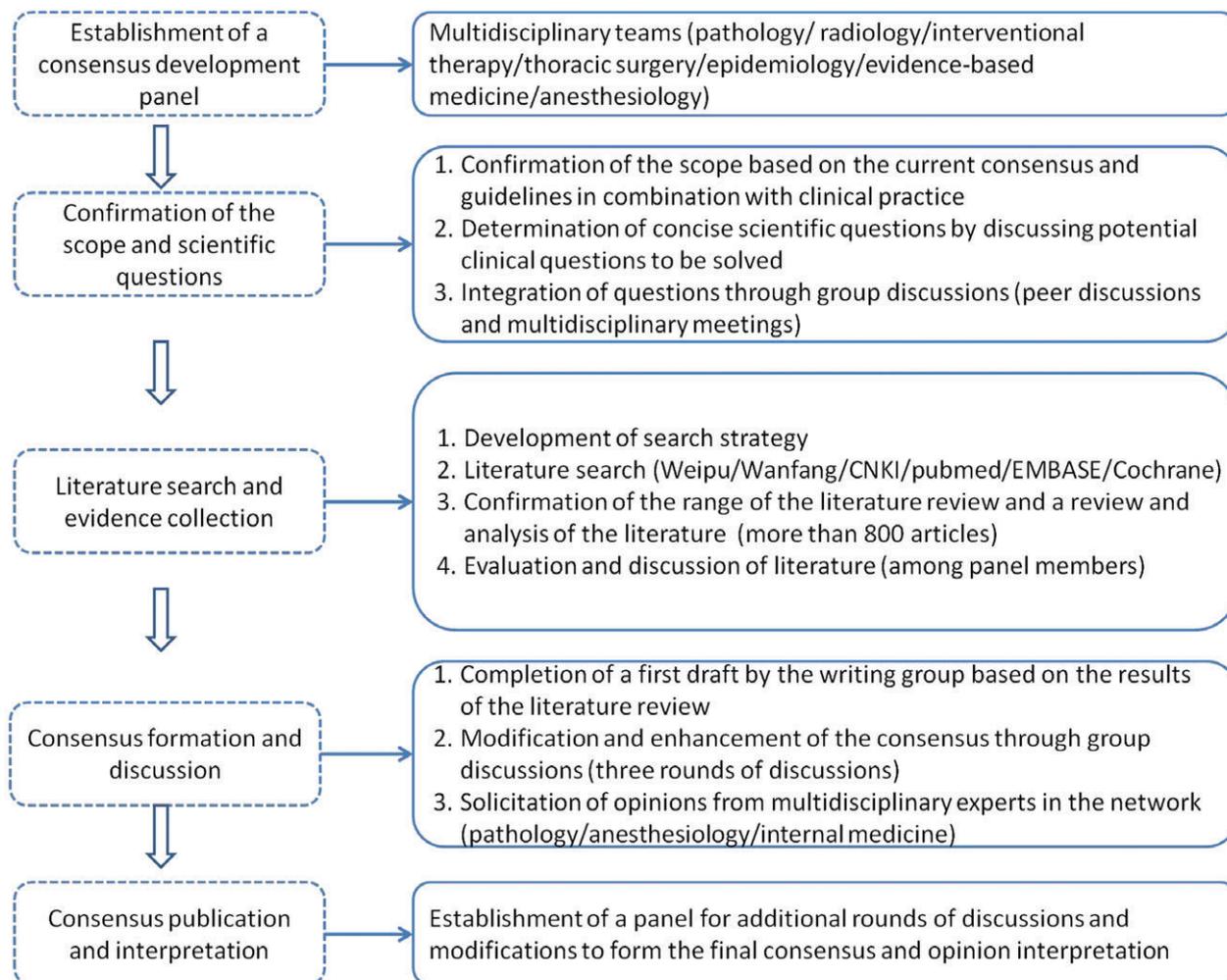
Establishment of a consensus development panel → Multidisciplinary teams (pathology/ radiology/interventional therapy/thoracic surgery/epidemiology/evidence-based medicine/anesthesiology)

Confirmation of the scope and scientific questions →
1. Confirmation of the scope based on the current consensus and guidelines in combination with clinical practice
2. Determination of concise scientific questions by discussing potential clinical questions to be solved
3. Integration of questions through group discussions (peer discussions and multidisciplinary meetings)

Literature search and evidence collection →
1. Development of search strategy
2. Literature search (Weipu/Wanfang/CNKI/pubmed/EMBASE/Cochrane)
3. Confirmation of the range of the literature review and a review and analysis of the literature (more than 800 articles)
4. Evaluation and discussion of literature (among panel members)

Consensus formation and discussion →
1. Completion of a first draft by the writing group based on the results of the literature review
2. Modification and enhancement of the consensus through group discussions (three rounds of discussions)
3. Solicitation of opinions from multidisciplinary experts in the network (pathology/anesthesiology/internal medicine)

Consensus publication and interpretation → Establishment of a panel for additional rounds of discussions and modifications to form the final consensus and opinion interpretation

Figure 1 Consensus development methods and processes.

Methods for imaging guidance

Image-guided methods for PTNB include X-ray fluoroscopy, C-arm cone-beam computed tomography (CT), CT or CT fluoroscopy, ultrasound, and magnetic resonance imaging (MRI). Guidance methods should be selected based on factors such as lesion size, location, visibility, relationship to surrounding important anatomical structures, available imaging equipment, and operator preferences.[3–6]

X-ray fluoroscopy

X-ray fluoroscopy is a traditional guidance method primarily used for needle biopsy of peripheral lung diseases and larger lesions.[7,8] This method cannot display clear vascular anatomy around the lesion and is gradually being replaced by CT guidance.[9]

C-arm cone-beam computed tomography (CT)

C-arm cone-beam CT may also be used for image-guided PTNB.[10] The advantages of this approach include low radiation dose and the capacity to simulate real-time guidance, but the density resolutions of the images are inferior to those of conventional CT.

CT

Computed tomography is widely used because it produces images with high spatial and density resolutions. Chest CT scans can clearly show the lesion size and depth, as well as the relationships between the lesion and the ribs, mediastinum, interlobar fissures, and blood vessels. This information assists the design of safe needle tracks and also allows for the early detection of complications.[6] CT has become the primary choice and most common guidance method

for PTNB. Contrast-enhanced CT can assist the identification of necrotic and solid areas in the tumor and help to determine the blood supply around the lesion. These properties may improve the positive rates of biopsy and reduce the probability of postoperative complications. CT fluoroscopy can provide near real-time imaging, which allows physicians to manipulate the needle based on patient breathing. It also helps needle insertion into moving nodules and the avoidance of rib puncture,[11] which shortens procedure time and reduces complications. This is particularly advantageous for elderly patients[12] or patients with poor cooperativity. However, this method can significantly increase the radiation exposure to the patient and operating physicians.[11,13] The learning curve for CT-guided biopsy is short, but obtaining sufficient tissues with pathologic diagnostic value, especially from small or moving lesions, requires meticulousness, the mastery of relevant techniques, and sufficient practical experience.

Ultrasound

Ultrasound can be used to monitor the insertion process, angle, and depth of the biopsy needle in real time.[14,15] It can accurately locate the needle tip and help to avoid damage to nearby structures. It is usually used for the biopsy of superficial lesions adjacent to the thoracic wall.[16] Contrast-enhanced ultrasound can clearly show tumor blood vessels and necrotic lesions,[17–21] which can partially reduce the false-negative rates of needle biopsy.[11,22]

Magnetic resonance imaging

Compared to other imaging techniques, MRI has a superior resolution for tissues and multiplanar imaging capability. It produces near real-time imaging without radiation. The use of respiratory gating technology to capture images can shorten the scan time. MRI has unique advantages in defining thoracic blood vessels and in guiding biopsies for tumors in the mediastinum, hilum, and thoracic wall. MRI-guided percutaneous needle biopsy of thoracic tumors has been reported in the literature.[23,24] However, MRI-related consumables and equipment need to be compatible with magnets. MRI is also expensive and requires a longer operation duration. MRI-guided needle biopsy can be performed in hospital units with available resources.

Indications

1 Isolated nodules or masses, multiple nodules or masses, and pulmonary consolidation that require characterization;
2 Focal consolidation that cannot be confirmed by bronchoscopy, sputum cytology, or sputum culture;
3 Ground-glass nodules suspicious for malignancy;
4 Malignant lesions that require classification of histology or molecular pathology (rebiopsy);
5 Re-evaluation of local histology or molecular pathology after disease progression or relapse (rebiopsy);
6 Other conditions, such as hilar mass with failed or negative results of bronchoscopic biopsy, undiagnosed mediastinal mass, and mediastinal lymph nodes suspicious for malignancy.

Contraindications

Absolute contraindications
1 Severe cardiopulmonary insufficiency, such as severe pulmonary arterial hypertension;
2 Uncorrectable coagulopathy.
  Relative contraindications
1 Anatomical or functional lung isolation;
2 Prominent infectious lesions on the needle path;
3 Pulmonary bullae, chronic obstructive pulmonary disease, emphysema, or pulmonary fibrosis;
4 Mechanical ventilation (ventilator).

Multidisciplinary team construction

Preoperative multidisciplinary panel discussion is recommended. Percutaneous needle biopsy should be performed by or under the guidance of an experienced surgeon.[25,26] Well-trained doctors and nurses are needed to manage preoperative, intraoperative, and postoperative procedures. The presence of a cytopathologist during surgery can improve diagnostic accuracy. If necessary, anesthetic intervention should be considered to ensure successful completion of the surgery.

Biopsy procedures

Preoperative evaluation and management

Prior to surgery, patient details such as medical history, medication history, and allergy history must be obtained and a physical examination must be performed. Patient cardiopulmonary function and ability to cooperate, such as the ability to hold their breath or stay still, should be assessed. Contrast-enhanced chest CT or contrast-enhanced chest MRI should be conducted prior to surgery to determine the lesion location, shape, size, and relationship to surrounding organs, blood vessels, and nerves to design the needle track. Patients suspected via chest CT examination to have hydatid cysts or vascular malformations should not undergo biopsy.[3] Prior to surgery, it is recommended that all patients undergo complete blood count, coagulation testing,[27] infection screening (such as

hepatitis B virus, hepatitis C virus, syphilis, and human immunodeficiency virus [HIV]), electrocardiogram, blood biochemistry, and blood type testing. In specific populations with a high risk of increasing capillary fragility, the construction of vascular elasticity diagrams is also recommended. For patients with underlying lung diseases, such as chronic obstructive pulmonary disease and emphysema, pulmonary function tests are recommended to assess the oxygenation capacity and functional residual capacity of the patients.

Discontinuation of anticoagulant and antiplatelet drugs and re-examination of complete blood count and coagulation functions prior to surgery are recommended, as follows: (i) warfarin should be replaced with low molecular weight heparin 1 week prior to surgery and low molecular weight heparin should be discontinued 24 hours before surgery; (ii) aspirin and clopidogrel should be discontinued for at least 7 days before surgery[28] and (iii) biopsy can be performed only if the platelet count is > 50 × 109/L and the international normalized ratio (INR) is < 1.5. For biopsies in patients receiving anti-angiogenic drugs, discontinuing the drug according to the in vivo elimination half-life of the drug is recommended. For example, it is recommended that bevacizumab be discontinued 6 weeks prior to surgery.

Formulating a biopsy plan

Patient imaging data must be carefully reviewed prior to surgery. A biopsy plan should be formulated based on lesion size, location, anatomic relationships, image-guiding method, and operator experience. Multidisciplinary expert discussion is recommended for patients with relative contraindications or in special circumstances.

The needle track should be designed on the premise that vital organs and skeletal structures, such as ribs and scapula, are avoided, while concurrently avoiding bullae, great vessels, the trachea, and interlobar fissures. Additionally, the distance between the lesion and needle puncture point in the pleura and the traversal of normal lung tissues should be minimized.

Informed consent

Prior to surgery, patients and their authorized representatives should be informed of the purpose, benefits, and possible risks of the surgery, as well as any available treatment alternatives. Written informed consent must be obtained from the patient or their authorized representative (see Appendix I–III for details).

Preoperative preparations

Preoperative psychological and spiritual counseling are recommended to alleviate patient anxiety and tension. Patients should be trained to breathe calmly and to coordinate their breathing during surgery. Venous access catheters should be implanted prior to surgery and monitored by electrocardiograph.

Anesthesia and sedation

Percutaneous transthoracic needle biopsy requires patients to maintain a certain level of consciousness to cooperate during surgery and monitoring; therefore, local anesthesia is routinely used.[4] Basic anesthesia and sedation may be considered for patients with anxiety or cooperative difficulties during surgery. However, patients must be conscious enough to follow and complete instructions relevant to the surgery.

Steps for biopsy

Selection of needle puncture point
Simulation by CT or other imaging techniques should be performed prior to surgery. The shortest needle track should be selected on the premise that important anatomical structures, such as bones, blood vessels, and the trachea, are avoided.

Local anesthesia
After local skin disinfection, sterile drapes are covered. Local anesthesia should then be performed using a 1–2% lidocaine solution. The dose of anesthesia may be adjusted accordingly based on the patient's response, anesthetic efficacy, and needle depth.

Needle puncture and acquisition of specimens
Using CT-guided needle puncture as an example, multiple needle passes are recommended. Based on positions identified by CT, the biopsy needle should first be inserted into the parietal pleura for local anesthesia, followed by insertion into the lung tissues. The correct positioning should be confirmed by image scans. If the needle advances appropriately along the track, the needle can puncture the lesion directly. The biopsy site should be selected based on lesion characteristics. For larger lesions, central areas with ischemic necrosis should be avoided. For cavitary lesions, biopsy specimens should be obtained from solid tissues.

Coaxial technique
The coaxial technique allows multiple biopsy specimens to be obtained with only one puncture and causes less trauma.[29] In cases of pneumothorax or hemothorax, the

coaxial channels can be used to remove accumulated gas or blood, or to inject drugs, which allows the immediate treatment of complications. The protective effects of the coaxial channels may partially reduce the risk of implantation metastasis along the needle track.

Postoperative monitoring

A complete chest CT scan is recommended immediately after CT-guided biopsy to observe the presence of complications, such as pneumothorax and hemorrhage. Treatment should be initiated if necessary. Patients who do not require treatment can be transferred to the ward or observation room to monitor vital signs, blood oxygen saturation levels, etc. Patients should be reminded to minimize activities that may increase chest pressure, such as coughing and talking. A chest X-ray examination is recommended within 24 hours after surgery. If the patient's conditions have changed, additional chest X-ray or chest CT scanning should be performed in a timely manner.

Daytime/outpatient biopsy

For patients who have been preoperatively evaluated as low-risk for needle biopsy, completion of biopsy at a daytime or outpatient clinic may be considered. If no abnormalities are observed within four hours of the outpatient biopsy, patients may leave the clinic after the chest X-ray has been reviewed. Follow-up must be conducted for at least 24 hours after the biopsy. Patients should be reminded to visit the hospital without delay if they experience any abnormalities, discomfort, or symptoms.[30]

Complications and treatment

The most common complications of PTNB include pneumothorax, hemorrhage, and pleural reaction. Complications such as systemic air embolism, cardiac tamponade, and tumor implantation along the needle track are relatively rare. The mortality rate of PTNB is between 0.02% and 0.15%.[31] The leading causes of death include acute or pulmonary hemorrhage, cardiac arrest, and air embolism.

Pneumothorax

Pneumothorax is a common postoperative complication of PTNB. The incidence rate of pneumothorax reported in the literature ranges from 2.4% to 60% (average 20%), and 5–18% of patients with pneumothorax require thoracic drainage catheters.[25,32–34] Factors attributable to the increased incidence of pneumothorax and/or the increased requirement of drainage catheters include: tall and thin body types, old age, smoking, underlying lung diseases (e.g. emphysema or chronic obstructive pulmonary

disease),[13,35] deeply located lesions, lesions with small diameters,[36–38] a biopsy needle not perpendicular to the pleural section, multiple punctures at the pleura,[39,40] the needle track traverses intrapulmonary fissures or pulmonary bullae,[41] and long operative duration. Pneumothorax generally occurs within an hour after surgery,[42] but some patients may develop delayed pneumothorax (24 hours or later) after surgery.[43] If pneumothorax is not treated properly, subcutaneous emphysema may develop.[44]

Treatment principles: small pneumothorax, asymptomatic, and stable pneumothorax do not require special treatment. If the pneumothorax exceeds 30%, the pneumothorax area continues to increase, or if the patient shows severe clinical symptoms, a chest tube should be inserted for suction or fluid drainage through a closed chest drainage system.

Prevention: Patients should remain quiet and avoid talking or coughing[5] an appropriate needle track should be chosen, and the number of punctures should be reduced. It is not currently known whether the use of exogenously injected biogel, injectable gelatin sponge, or sterile saline to seal the needle track can effectively reduce the development of pneumothorax.[45–48]

Hemorrhage and hemoptysis

Hemorrhage (with or without hemoptysis) is another common complication of PTNB. The incidence rate of hemorrhage reported in the literature is between 5% and 16.9%, and that of hemoptysis is between 1.25% and 7%.[6,25,49,50] Hemorrhage is usually self-limited, but deaths caused by massive intrapulmonary hemorrhage have also been reported.[51] Factors attributable to the increased risk of intrapulmonary hemorrhage include: distance between the lesion and the pleura,[52,53] number of biopsies,[53–55] type of biopsy needle (cutting-needle biopsy),[56] lesions located in the mediastinum or next to the heart or mediastinum,[57] lesions with a rich blood supply (such as metastatic renal cell carcinoma), lesions close to branches originating from dilated bronchial arteries (chronic cavitary disease),[52,57] coagulopathy, and pulmonary hypertension.

Treatment principles

Mild hemoptysis, intraparenchymal hemorrhage, bleeding along the needle track, and small hemothorax can be resolved spontaneously without special treatment.[44,58] For massive hemoptysis, it is recommended to place the patient in a lateral decubitus position ipsilateral to the bleeding site (needle puncture point facing downward) to prevent blood from being inhaled into the contralateral bronchus. The airways should remain clear and intubation may be performed if necessary. Hemostatic drugs,[58,59] blood transfusion[25] and other treatments may also be applied. For

massive hemothorax, draining with a thoracic catheter is recommended.[60] If there is a large amount or continuous bleeding, interventional procedures or surgery should be performed in a timely manner and relevant departments should be informed to organize appropriate treatments.[25]

Pleural reaction

Pleural reaction refers to a series of manifestations that occur during needle puncture at the pleura, including continuous cough, dizziness, chest tightness, paleness, sweating, and even syncope, which may be related to a vasovagal reaction. Possible factors leading to pleural reaction include a thin body type, anxiety, low baseline blood glucose, and multiple punctures at the pleura.

Most patients have mild symptoms that resolve spontaneously without treatment. In severe cases, patients may experience excessive sweating, progressive decline in blood pressure, or even shock or syncope. If these occur, all procedures must be halted immediately. The patients should immediately be administered adrenaline or glucose solution based on their conditions and concurrently treated with oxygen therapy. The patients should be kept warm and their vital signs should be monitored. Precautions should be taken to prevent shock.

Systemic air embolism

Systemic air embolism can be divided into systemic venous air embolism and systemic arterial air embolism. The incidence rate of systemic air embolism is 0.02%–1.80%.[31,49,61,62] While most systemic venous air embolism is asymptomatic, systemic arterial air embolism is the most serious complication of lung biopsy and can lead to serious consequences, such as shock, cardiac arrest, and hemiplegia. Although systemic air embolism is rare, surgeons should be mindful of the condition because of its fatal clinical consequences.

At present, the mechanism of systemic arterial air embolism is believed to be the direct introduction of air into the pulmonary vein through the coaxial cannula[61] or iatrogenic bronchopulmonary or alveolar-pulmonary venous fistulas as a result of injury caused by puncture.[61] The gas enters the pulmonary vein and refluxes into the left side of the heart, which then enters blood vessels, such as the coronary and intracranial arteries, through systemic circulation. The causes of systemic arterial air embolism may include biopsy of cavitary or vascular inflammatory lesions (such as ground glass), coughing, and positive-pressure ventilation. Patients may be asymptomatic if the amount of air entering the chambers on the left side of the heart is relatively small, and cause no significant effect on hemodynamics.[60,63] In coronary air embolism, patients may experience a transient loss of consciousness and their electrocardiography may reflect myocardial ischemia.[60,64,65] In

intracranial air embolism, patients may experience seizures[65] or loss of consciousness.[60,66] CT scans can reveal the gas in the organs or blood vessels with embolism, which may serve as objective evidence for the diagnosis of air embolism.[60,63–66]

Treatment principles: It is crucial to rapidly identify air embolisms and to initiate treatment immediately, which may help to improve the prognosis of some patients. Once air embolism is suspected, the needle should be immediately withdrawn. The patient should be placed in the Trendelenburg position.[64] If there is a relatively large amount of gas in the chambers on the left side of the heart, the patient should be placed in a right lateral decubitus position, which makes the left atrium higher than the left ventricle. This position can prevent the gas from entering the systemic circulation through the base of the left ventricle outflow tract, a situation that may lead to the aforementioned serious complications. Vital signs should be monitored closely at the same time. Oxygen masks and other rescue measures should be proactively administered. If intracranial arterial air embolism occurs and conditions allow, the patient can be transported to a hyperbaric oxygen chamber for treatment.[65]

Prevention: (i) The types of lesions, such as cavitary and vasculitic lesions, for needle biopsy should be carefully selected; (ii) needle biopsy on patients standing erect should be avoided; (iii) needle biopsy under positive-pressure ventilation should be avoided; (iv) the needle core should be inserted in a timely manner without allowing long exposure of the coaxial cannula to the air; (v) iatrogenic injury, such as bleeding during surgery, should be reduced, for example, by avoiding repeated puncture; and (vi) behaviors such as coughing, deep breathing, and talking should be minimized during surgery.

Other uncommon and rare complications

Implantation metastasis along the needle track is extremely rare,[31,67,68] with reported incidence in the literature between 0.012% and 0.061%.[69] The coaxial technique can reduce the risk of its occurrence. Other rare complications include cardiac tamponade,[70] intercostal artery pseudoaneurysm,[71] atrial fibrillation,[72] chest infections,[49,73–75] vasovagal reaction,[44] and pleural metastasis.[76–79]

Pathological examination

Specimen processing

Specimens for cytological examination should be smeared immediately after they are obtained. The samples should be smeared gently and evenly and should be wet-fixed immediately to prevent cell degradation. Wet fixation should be performed with 95% alcohol for at least

15 minutes. Liquid-based smear samples should immediately be placed in digestive or preservative solutions and sent to the laboratory for further processing according to the operating procedures. Both rapid on-site evaluation of cytology (ROSE) and on-site imprint cytology involving cytopathologists can improve diagnostic accuracy.[80–88] Specimens for histopathological examination should be fixed immediately after they are obtained by placing the samples in a 10% neutral buffered formalin fixative. If the freshly obtained tissues are to be used for molecular testing, they should, in principle, only contain tumor components that meet the quality control requirements. The tissues obtained should be quickly frozen in liquid nitrogen storage or stored in an RNA preservation solution.

Before the samples are sent for examination, the pathology test request form should be accurately completed, with detailed descriptions of the patient's basic information, medical history, history of related examinations and treatment, preliminary clinical diagnosis, biopsy location, and the number of punctures.

Staining method
Smears prepared from FNA specimens may be used for Papanicolaou or hematoxylin and eosin staining after fixation. Samples suspicious for lymphoid or hematopoietic malignancies may be considered for air-drying followed by Wright–Giemsa staining. Diff-Quik staining is commonly used on-site to evaluate the sample quality. After a diagnosis is made with liquid-based cytology slides, the current practice is to centrifuge the remaining samples and embed as much sample as possible in paraffin wax to preserve the cells for immunocytochemistry or gene mutation testing. Significant data have confirmed that microsamples of cells can provide similar results in immunocytochemistry or gene mutation testing and histological examination. Histopathological specimens from CNB are routinely paraffin-embedded, sectioned, and stained with hematoxylin and eosin. Immunohistochemical staining or related molecular pathology testing can be conducted if necessary. Specimens used for molecular pathology testing should have passed pathological quality control before commencing the molecular testing process.

Clinical diagnostic value

Accuracy rate
Percutaneous transthoracic needle biopsy shows high diagnostic accuracy for malignant thoracic diseases (peripheral pulmonary lesions, hilar lymph nodes, hilar masses, and mediastinal masses). The diagnostic accuracy of FNA for malignant diseases ranges from 64% to 97%,[26,89,90] but its use in the diagnosis of benign diseases is limited, with accuracy rates between 10% and 50%.[91–95] FNA also shows

a limited capacity for the accurate classification of tumor types. The diagnostic accuracy of CNB for malignant diseases is similar to that of FNA (74–95%),[96–98] but its accuracy for diagnosing benign diseases is higher than FNA.[99] The factors that may affect diagnostic accuracy include lesion size and location, operator experience, choice of guidance, and on-site cytology evaluation.

Follow-up management of negative biopsy
The reasons for a negative biopsy may include poor patient cooperation,[100,101] very small lesions, special tumor types, and difficulties in pathological diagnosis. For patients with negative biopsy results who are highly suspected of malignant disease, rebiopsy is recommended. Patients who have not undergone rebiopsy are recommended to attend regular follow-up imaging tests. If patients show disease progression during follow-up, additional biopsy or surgery is recommended.

Rebiopsy
Rebiopsy, also called second biopsy, refers to a biopsy performed after a patient has a confirmed diagnosis and has received corresponding treatment based on the results of the first biopsy, but because of disease progression, additional tissues of the lesion or blood samples are required. The rebiopsied samples are used to monitor disease progression and interpret drug resistance mechanisms, which may guide the selection of follow-up treatment plans for patients who show disease progression after targeted therapy or those who develop drug resistance. In patients with non-small cell lung cancer diagnosed with *EGFR* mutations in the first biopsy, 33–63% have confirmed *EGFR* T790M mutations in the rebiopsy performed after they have shown disease progression following EGFR-tyrosine kinase inhibitor therapy.[102–105] The timing of rebiopsy after disease progression does not affect the detection rate of T790M mutations.[106] Patients who are temporarily unsuitable to undergo biopsy should be scheduled for a rebiopsy during subsequent treatment. Histological examination of the rebiopsy sample is recommended. The use of CT-guided methods to obtain tissue has a high success rate and is relatively safe (incidences of pneumothorax and hemorrhage are 6% and 7%, respectively).[107]

Disclosure

No authors report any conflict of interest.

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Appendix I: Informed consent form for percutaneous transthoracic needle biopsy (reference only)

Name _____ Sex_____ Age_____ Department _____ Outpatient admission number _____ Inpatient admission number _____.

    Clinical diagnosis: _____Biopsy type: _____.

    Guidance method: _____ Type of anesthesia: _____.

Main purpose:

1.Identify the pathological subtypes to guide treatment planning;

2.Genetic testing to guide the use of targeted therapy;

3.Others: _____.

If the patient refuses to undergo a percutaneous needle biopsy, the alternative courses of treatment include: _____.

Potential risks and possible complications:

1.There are risks associated with all surgical procedures involving anesthesia.

2.All drugs have the potential to cause allergies or adverse effects. Mild symptoms may include nausea and rash. Severe symptoms may include anaphylactic shock and cardiorespiratory arrest and can be life-threatening.

3.The risk of surgery may increase in patients with heart disease, hypertension, diabetes, renal insufficiency, venous thrombosis, and other related conditions. These conditions may be exacerbated during or after surgery. Patients may experience cardiovascular or cerebrovascular events or even death.

4.The potential risks and possible complications of this surgery may include, but are not limited to, the following:

1) Hemorrhage, hematoma, and local infection at the puncture site or surrounding organs and tissues, which may require hemostasis and anti-infective treatment. Severe cases can be life-threatening;

2) Puncture may lead to great vessel injury or tumor rupture, causing hemorrhage and shock, and may require open surgery to stop the bleeding. Severe cases can be life-threatening;

3) Symptoms such as numbness, pain, and motor dysfunction may occur in the organs, tissues, or nerves near the puncture site;

4) Symptoms such as cough, hemoptysis, chest pain, chest tightness, and fever may occur during or after surgery;

5) Complications such as pleural reaction, pneumothorax, hemothorax, hemopneumothorax, and air embolism may occur during or after surgery. Severe cases can be life-threatening;

6) Cardiovascular or cerebrovascular events, vasovagal reaction, atrial fibrillation, cardiac tamponade, intercostal artery pseudoaneurysm, subcutaneous emphysema, stress ulcer, and gastrointestinal bleeding may occur during or after surgery;

7) Damage to the tissues and organs other than the targets, such as normal lung tissue, trachea, thoracic wall, etc.;

8) Potential tumor metastasis along the puncture site, needle track, or traversed organs;

9) If pathological examination after the surgery suggests malignancy, immunohistochemistry may be needed to further confirm the diagnosis;

10) The pathological outcome of the first biopsy may be false-negative and a rebiopsy should be performed if necessary;

11) The surgery may be abandoned if the initially planned procedures require modification or the surgery cannot be performed smoothly due to anatomical deformity of the lesion or other unforeseen circumstances;

12) Some image-guided procedures may have potential risks of radiation exposure;

13) Specific risks (list according to the specific condition of the patient): _____;

14) Other unpredictable medical risks and rare complications.

Statement of patients and their authorized relatives

1. I understand that based on my current disease condition and clinical diagnosis, the above surgery is necessary for the further diagnosis and treatment of my disease;

2. Before indicating my acceptance of the surgical plan, the doctor has explained to me the surgical method, anesthesia method, intraoperative and postoperative complications, and other risks and has answered my questions related to this surgery. I clearly understand all of the contents explained by the doctor. I _____ (agree/disagree) with the above surgical plan for needle biopsy, and I _____ (agree/disagree) to undertake the risks and consequences of needle biopsy;

3. In addition to the above situations, I understand that unpredictable situations may occur during surgery. I hereby authorize the doctor to contact my family immediately in the event of an unexpected situation. If the situation is urgent and

my family cannot be contacted, I should be treated based on my best interests and in accordance with routine medical practice. If the above situation occurs, I believe that the medical staff will exert their maximal efforts to treat me. I have undergone sufficient mental preparation and will actively cooperate with the doctor during the treatment;

4. I authorize the doctor to handle and use the tissues or specimens obtained from the surgery, including for pathological and cytological examination purposes, and for medical waste disposal;

5. Others:_____.

Patient's signature: _____ Date:_____.

If the patient is unable to sign the informed consent form, their authorized relatives should sign here:

Authorized relative's signature: _____ Relationship with patient: _____ Date: _____.

Physician's signature: _____ Surgeon's signature: _____ Date: _____

Appendix II: Types of biopsy needles

Needles used for FNA: The Chiba needle is one of the most commonly used aspiration biopsy needles. Other needles include the Tuner, Madayag, Greene, and Franseen needles.

Needles used for CNB: Cutting needles are usually used for CNB. The most common biopsy needles used for CNB include the Trucut, Temno, Bard, Fullcore, and Rotex needles. The most commonly used specification is 18 G, but 16 G and 20 G are also used.

Appendix III: Estimation of the amount of biopsy material

The lower limit of the amount of biopsy materials is estimated according to the amount of materials acquired by commonly used biopsy needles and the quality of pathological diagnosis.

An example using an 18G biopsy needle for a 1 cm specimen is described below. The amount of specimen acquired with biopsy needles of different specifications or for specimens with different lengths can be estimated using ratios.

Type of biopsy	18 G cutting biopsy needle for a semi-cylindrical cutting	18 G cutting biopsy needle for a full cylindrical cutting
First biopsy	1 cm × 1–2 pieces (approximately 4–5 mm^3/piece)	1 cm × 1 piece (approximately 7–8 mm^3/piece)
Rebiopsy	1 cm × 4–5 pieces (approximately 4–5 mm^3/piece)	1 cm × 2–3 pieces (approximately 7–8 mm^3/piece)