RESEARCH PROTOCOL

Project Name (English): The comparative study of Electromagnetic Navigation Bronchoscopic with Ultrathin Cryobiopsy and Forceps Biopsy in the Diagnosis of Peripheral Pulmonary Nodules

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I. REAEARCH BACKGROUND

The Global Cancer Statistics Report shows that lung cancer is currently the second most prevalent cancer globally. According to data released by the National Cancer Center in 2022, China recorded 4.064 million new cases and 2.414 million deaths from malignant tumors in 2016, while lung cancer accounted for 828,000 new cases and 658,000 deaths [1]. The overall cancer incidence in China continues to rise, with lung cancer remaining the leading cause of both incidence and mortality. Lung cancer remains the primary cause of new cases and deaths in China, which may be attributed to the high smoking rate. The "2020 China Smoking Hazards Report" issued by the National Health Commission indicates that between 2007 and 2017, the global smoking rate among people aged 15 and above decreased to 19.2%. In contrast, Chinas smoking rate among people aged 15 and above reached 26.6% in 2018, with 68.1% of non-smokers exposed to secondhand smoke in public places.

With the rapid advancement and widespread adoption of imaging technologies, chest CT has become standard equipment in secondary and even primary healthcare institutions. This has enabled earlier detection of pulmonary nodules, where malignant and benign nodules may exhibit similar imaging characteristics in early stages. Accurate and timely diagnosis is therefore crucial for determining treatment strategies and prognosis, which holds significant importance for clinical management of pulmonary nodules. However, relying solely on clinical and imaging data often fails to achieve definitive diagnoses. In such cases, invasive lung nodule biopsy is recommended to provide sufficient specimens for pathological evaluation and subsequent molecular analysis.

With advancements in respiratory interventional techniques, the overall diagnostic rate of pulmonary nodules guided by bronchoscopy can exceed 70%, while electromagnetic navigation bronchoscopy provides enhanced access to the entire lung [2-5]. Electromagnetic navigation bronchoscopy (ENB) utilizes three-dimensional reconstruction of CT images to create virtual bronchial images. The electromagnetic

positioning sensor at the bronchoscope tip provides three-dimensional spatial coordinates and directional information, allowing real-time visualization of lesion locations on pre-generated navigation maps. By comparing intra-lens images with reconstructed three-dimensional bronchial trees and lesion positions, ENB accurately guides bronchoscopy to target lesions. Current primary biopsy methods for peripheral lung nodules include forceps biopsy (TBFB), needle aspiration biopsy (TBNA), and cryobiopsy (TBCB). Among these, forceps biopsy remains the predominant ENB-guided approach. Meta analyses indicate a positive detection rate of 69.4-75.6% for ENB-guided biopsies [4], though this remains slightly lower than diagnostic accuracy in surgical specimens. Additionally, the growing demand for molecular diagnostics has driven increased need for larger sample sizes. A new method for sampling peripheral lung nodules, Electromagnetic Navigation Bronchoscopic Guided Cryobiopsy (ENB-TBCB) is poised for clinical implementation, combining the advantages of cryobiopsy and ENB technology. Compared to conventional TBFB, this innovative method enables larger tissue sampling while demonstrating lower complication rates (bleeding and pneumothorax) and enhanced safety with 1.1mm cryobiopsy probes, compared to standard 2.4mm and 1.9mm probes [6-9]. Studies have shown that 1.1mm probes provide sufficient tissue samples for lung cancer biopsy, meeting requirements for DNA/RNA sequencing [10]. These factors confirm the technical feasibility of ENB-TBCB, which can be safely performed by physicians proficient in ENB techniques. However, before its routine clinical adoption, extensive controlled trials are needed to evaluate diagnostic accuracy and safety compared to traditional TBFB, as well as to determine whether TBFB combined with ultra-thin cryosurgical probes can outperform conventional bronchoscopic biopsy. This would provide crucial guidance for optimizing diagnostic strategies in peripheral pulmonary nodule management.

Therefore, this project aims to validate the feasibility, effectiveness, and safety of electromagnetic navigation bronchoscopy-guided cryobiopsy in diagnosing peripheral lung nodules through a national multicenter randomized controlled trial. By establishing traditional TBFB as the control group and ultrathin cryoprobe biopsy as

the experimental group, the study seeks to provide an efficient and minimally invasive diagnostic method for peripheral pulmonary nodule detection.

II. RESEARCH OBJECTIVES

A national multicenter randomized controlled study was conducted to verify the safety and effectiveness of electromagnetic navigation bronchoscopy ultrathin cryobiopsy compared with biopsy forceps biopsy in the diagnosis of peripheral lung nodules.

III. RESEARCH PROGRAMME AND TECHNICAL ROUTINE

3.1 Research design

This study employed a prospective, multicenter, randomized controlled trial design to continuously enroll patients with idiopathic peripheral lung nodules, suspected malignant pulmonary nodules, or indeterminate nodule characteristics. Participants were randomly assigned (1:1) into two groups: the experimental group received ultrathin cryoprobe biopsy and the control group underwent biopsy forceps biopsy. The study compared pathological confirmation rates, incidence of procedure-related complications, and specimen size quality metrics.

3.2 Research subjects

3.2.1 Study population

The study population was hospitalized patients who received treatment in Beijing Chaoyang Hospital (central unit) and participated in the research unit from August 2025 to July 2027, and had chest CT nodules in the peripheral lung, suspected malignant pulmonary nodules or unknown nature of nodules, and planned to perform electromagnetic navigation bronchoscopy lesion biopsy.

3.2.2 Inclusion criteria

Participants in this study must meet all of the following criteria:

① Age 18 or above, male or female;

② Chest CT found lung nodule, suspected malignant nodule or unknown nature needs biopsy to confirm;

③ Chest CT indicates that the nodule to be biopsied is located in the bronchus below the segment, with the maximum diameter of the nodule ≥ 8mm and ≤ 30mm, which is not accessible in the conventional bronchoscopy view;

④ If chest CT shows multiple nodules in the lung, one of the lung nodules is selected as the target lesion;

⑤ Voluntarily accept electromagnetic navigation bronchoscopy and meet the preoperative requirements of bronchoscopy;

⑥ Good compliance, able to cooperate with the study observation, fully informed about the purpose and method of the study, accept the potential risks of the two biopsy methods, agree to participate in the study, and sign the informed consent form.

3.2.3 Exclusion criteria

Eligibility for exclusion from this study will be determined by meeting any of the following criteria:

① Contraindications for bronchoscopy include: active massive hemoptysis; recent myocardial infarction or unstable angina attack; severe cardiopulmonary dysfunction; severe hypertension and arrhythmia; uncorrectable bleeding tendency or severe coagulation disorders (e.g., platelet count <60×10^9/L), uremia; severe pulmonary hypertension; severe superior vena cava obstruction syndrome; intracranial hypertension; acute cerebrovascular events; aortic dissection or aneurysm; multiple pulmonary bullae; extreme systemic failure; breastfeeding or pregnant women, or female patients undergoing pregnancy planning.

② The site of planned biopsy has high risk of bleeding such as bronchial artery penetration or suspected lung metastasis of renal cancer;

③ The body contains electromagnetic source implantation equipment;

④ There are contraindications for anesthesia; allergic to anesthetics; or have a history of severe allergies, hereditary allergies;

⑤ Those who participated in other studies within 3 months and did not quit or end will affect the observation of this study;

⑥ Unwilling to participate in this study and unwilling to accept the follow-up plan;

⑦ Other circumstances that the researcher considers unsuitable for participation in this study.

3.2.3 Midterm withdrawal criteria

Patients who meet the inclusion criteria but do not complete the study for some reason, including subjects who withdraw of their own accord and those who decide to withdraw.

① Subjects are entitled to withdraw from the trial at any time without reason and to be given appropriate follow-up or recommended as appropriate treatment.

② Withdrawal from the trial at the investigators discretion: if any of the following occurs, after clinical relevance has been assessed,

If the investigator determines that the subject is unable to continue the clinical trial, the subject may withdraw from the trial in advance:

A medical condition occurs and the investigator determines that continued participation may endanger the safety of the subject;

Other managerial reasons.

3.3 Research steps and research endpoints

3.3.1 Intervention steps

① Collect patients with peripheral lung nodules that meet the discharge criteria continuously, and enroll them in the study after signing the informed consent.

② Collect preoperative chest CT and other laboratory test data of patients.

③ According to the pre-prepared random envelope, subjects were randomly assigned to the ultrathin cryoprobe biopsy group and biopsy forceps biopsy group (1:1).

④ Thin-layer CT (1mm) was used for 3D reconstruction before surgery to plan the path of bronchoscopy with electromagnetic navigation.

⑤ Improve routine preoperative preparation, and combine intravenous anesthesia with high-frequency mechanical ventilation or tracheal intubation mechanical ventilation during surgery.

a) Ultrathin Cryoprobe Biopsy Group (TBCB): After completing routine bronchoscopy, the probe is navigated to the nodule site using electromagnetic guidance. The biopsy site is confirmed through radial ultrasound and/or cone-beam CT imaging. A 1.1mm cryoprobe is inserted via the electromagnetic navigation catheter, with each freeze lasting 4-10 seconds. This procedure is repeated 2-3 times to obtain at least two tissue samples, each measuring no less than 5mm in diameter.

b) Forceps Biopsy Group (TBFB): After completing routine bronchoscopy, the team navigates to the nodule site using electromagnetic navigation guidance. The biopsy site is confirmed through radial ultrasound and/or cone-beam CT imaging. A 1.8mm biopsy forceps is inserted via the electromagnetic navigation catheter to obtain at least five tissue samples through precise clamping.

c) During the procedure, radial ultrasound and/or cone-beam CT can be used for localization verification. The biopsy specimens obtained from both groups are fixed in formalin and sent for pathological examination. The pathological diagnosis is confirmed when two pathologists independently evaluate the results. If their assessments differ, a third experts evaluation is conducted, with final determination made through consultation among all three specialists.

⑥ Data Collection: Clinical data should include medical history, physical signs,

laboratory tests, pulmonary function evaluations, and imaging studies. Documentation should cover procedure duration, specimen quantity, surgical complications such as hemorrhage, pneumothorax, or infections (including those occurring within 7 postoperative days), severity assessment of complications like bleeding or pneumothorax, and pathological findings.

⑦ Follow-up: Short-term follow-up involves collecting data at 4 weeks post-surgery to evaluate the occurrence of delayed complications such as bleeding, pneumothorax, or infections. Long-term follow-up extends to 12 months post-operation for patients with unclear histopathological diagnoses, assessing their final diagnosis through imaging monitoring of pulmonary nodule absorption or stability, along with other invasive diagnostic evaluations.

3.3.2 Study endpoints

1） Subject outcome measures:

Indicator 1, clear histopathological diagnosis, such as malignant lesions, benign lesions with clear pathogen (granuloma, tuberculosis, etc.).

Indicator 2, Clinical follow-up for 12 months to obtain a clear diagnosis. Diagnostic examinations or treatment plans related to pulmonary lesions should be collected during the follow-up period, such as biopsy or invasive surgery, imaging, and microbial evaluation.

Indicator 3, such as histological diagnosis of nonspecific benign lesions or non-diagnostic pathology, with imaging follow-up for 12 months, the lesion is absorbed or unchanged.

2） Main destinations:

① The pathological diagnosis rates of ultrathin cryoprobe biopsy and forceps biopsy were calculated separately.

Pathological specimens carry diagnostic significance. When demonstrating definitive malignant outcomes or specific benign findings, they can elucidate pathological characteristics and guide subsequent treatment. Non-specific benign lesions (acute/chronic inflammation) and non-diagnostic abnormalities (atypical cells, normal lung parenchyma, interstitial changes, insufficient effective tissue) are generally considered non-pathologically significant. For patients with non-specific benign or non-diagnostic pathology identified in this study, definitive diagnosis is confirmed through 12-month clinical/imaging follow-up (or until additional surgery or confirmation of regression without cancer treatment). This approach ensures accurate identification of true negative or false-negative outcomes.

Pathological diagnosis rate: (number of pathological malignant diagnosis cases + number of pathological specific benign diagnosis cases)/total number of cases

② The sensitivity, specificity, positive predictive value and negative predictive value of the two groups of different biopsy methods for diagnosing benign and malignant pulmonary peripheral nodules were calculated based on the final diagnostic results.

Sensitivity: Number of cases diagnosed as malignant/number of all cases diagnosed as malignant after 12 months of follow-up

Specificity: Number of benign cases diagnosed/number of all benign cases followed up to 12 months

Positive predictive value: number of true malignancies/number of malignant cases diagnosed by biopsy

Negative predictive value: number of true benign cases/number of benign cases diagnosed by biopsy

2) Secondary endpoints:

Navigation success rate: the biopsy tool successfully reached the target lesion, which

was confirmed and identified by navigation software and imaging.

Biopsy operation time: from the start of application of two biopsy tools to the final removal of biopsy tools.

Time per biopsy: time of operation/number of attempts to biopsy.

Successful acquisition of core tissue: Acquisition of samples for pathological examination.

Size and quality of tissue samples: measure the size (length * width) of each tissue with a ruler, number, and pathological experts assess whether the sample size is adequate (including effective histiocytes and molecular diagnosis).

Related complications: pneumothorax, hemorrhage, respiratory failure, infection, and severe complications requiring tracheal intubation and mechanical ventilation transfer to intensive care unit.

3.4 Adverse events/comorbidities observation

3.4.1 Recording and reporting of adverse events

During treatment, clinical adverse events may occur in participants. When such events (including major adverse events) are identified, they must be documented in detail on the Case Report Form (CRF), including the time of occurrence, clinical manifestations, management procedures, duration, progression, and relationship to the intervention. Patients with abnormal laboratory test results should be followed up until their test results return to normal levels, reach baseline intervention values, or are confirmed unrelated to the intervention. In cases of severe adverse events, a Serious Adverse Event Form (SAE Form) must be completed and reported to the sponsor, ethics committee, CFDA, regulatory authorities, and health administration departments within 24 hours.

3.4.2 Severity assessment of adverse events/comorbidities

Level 1: Mild; asymptomatic or mild; only clinically or diagnostically observed; no

treatment required.

Level 2: Moderate; requires small, local or non-invasive treatment; limited instrumental daily living activities for their age.

Level 3: severe or medically significant but not immediately life-threatening; resulting in hospitalization or prolonged hospital stay; disability; and impaired self-perceived daily living activities.

Level 4: Life-threatening: requires urgent treatment.

Level 5: Death associated with adverse events.

Instrumental daily activities refer to cooking, buying clothes, using the telephone, managing money and so on.

Self-sustaining daily activities refer to bathing, dressing and undressing, eating, washing, taking medicine, etc., without being bedridden.

3.4.3 Occurrence and management of adverse events/comorbidities

Potential intraoperative and postoperative complications of pulmonary cryobiopsy and bronchoscopy include hemorrhage, pneumothorax, coughing, air embolism, pleural effusion, and pulmonary inflammation. Bronchoscopy procedures may involve risks such as anesthesia-related drug allergies, bleeding, infections, temporomandibular joint dislocation, radiation exposure during fluoroscopy, pneumothorax, cardiovascular accidents, laryngospasm, laryngeal edema asphyxia, respiratory arrest, cardiac arrest, and even death. The study-related examination of cryobiopsy may increase associated risks including hemorrhage, pneumothorax, and fluoroscopy-related radiation exposure. For potential intraoperative and postoperative complications, close monitoring and follow-up will be conducted regardless of their relevance to the study. Appropriate interventions will be promptly implemented based on investigator evaluations and clinical guidelines. Recommended management strategies for major potential complications are as follows:

① Pneumothorax: Intraoperative or delayed pneumothorax may occur. Small pneumothorax may not be treated, and medium to large pneumothorax can be thoracentesis or closed drainage device placed in the chest cavity. If tension pneumothorax occurs, biopsy should be stopped immediately.

② Hemorrhage: Minor intraoperative bleeding can be managed with suction therapy. Moderate bleeding may require hemostatic agents or balloon occlusion. Immediate cessation of biopsy procedures is necessary for massive hemorrhage, with patients being transferred to the intensive care unit for further treatment. Interventional embolization or thoracotomy may be performed when required. Postoperative hemoptysis typically follows a self-limiting course.

③ Lung infection: chest X-ray or chest CT scan (recommended) for confirmation, and adjust antibiotics according to sputum, blood or pus culture results; if chest X-ray or chest CT scan indicates lung/cavity abscess, catheter drainage should be placed.

④ Pleural effusion: Generally, observation or conservative treatment can be done. If moderate to large pleural effusion occurs, puncture aspiration or closed thoracic drainage should be performed.

⑤ Others: appropriate treatment measures should be taken in time according to the researchers evaluation and clinical routine diagnosis and treatment norms.

3.5 Sample size calculation

To compare differences between the groups, based on meta-analyses [4] of electromagnetic navigation bronchoscopy (Prasanth Balasubramanian, 2024) and a preliminary exploratory study [11] of ultrathin cryoprobe biopsy for peripheral lung nodules (Soo Han Kim, 2023), we set the diagnostic rates for ENB cryobiopsy and forceps biopsy at 90% and 72.7% respectively. Using a 90% confidence level, α=0.05, and a 10% dropout rate, we performed sample size calculations using PASS 21.0 software. The results indicated that each group required 114 participants, totaling 228 subjects. We ultimately planned to enroll 228 participants.

Tests for Two Proportions

Numeric Results for Testing Two Proportions using the Z-Test with Unpooled Variance

Hypotheses: H0: P1 - P2 = 0 vs. H1: P1 - P2 ≠ 0

Target Power	Actual Power*	N1	N2	N	P1	P2	Diff D1	Alpha
0.9	0.90202	102	102	204	0.9	0.727	0.173	0.05

* Power was computed using the normal approximation method.

Summary Statements

Group sample sizes of 102 in group 1 and 102 in group 2 achieve 90.202% power to detect a difference between the group proportions of 0.173. The proportion in group 1 (the treatment group) is assumed to be 0.727 under the null hypothesis and 0.9 under the alternative hypothesis. The proportion in group 2 (the control group) is 0.727. The test statistic used is the two-sided Z-Test with unpooled variance. The significance level of the test is 0.05.

Dropout-Inflated Sample Size

	Sample Size			Dropout-Inflated Enrollment Sample Size			Expected Number of Dropouts		
Dropout Rate	N1	N2	N	N1'	N2'	N'	D1	D2	D
10%	102	102	204	114	114	228	12	12	24

3.6 Data collection and analysis

3.6.1 Data collection

① Baseline data: demographic information, medical history, symptoms and signs, physical examination, hematological examination, imaging characteristics, etc.;

② Operation related information: operation time, sample number, etc.;

③ Pathological data: pathological results, tissue sample quality, molecular detection results, etc.;

④ Safety evaluation data: type of complications, treatment methods, length of hospitalization, etc.;

⑤ Postoperative follow-up: For those who failed to obtain clear evidence of malignancy in the pathology, the nature of the nodule was determined by imaging or whether a repeat biopsy was performed after 12 months of follow-up.

Research process table

	Preoperative	During surgery	Postoperative		Follow.up		
Visitation	1	2[f]	3[f]	4	5	6	7
Number of days enrolled	D-30~D-1	D0	D1-7	Postoperative 1 month	Postoperative 3 months	Postoperative 6 months	Postoperative 1 2 months
Visit window (number of days)	/	/	/	±7	±15	±15	±15
Sign the informed consent form	×						
Inclusion and exclusion criteria	×						
Demographic information collection	×						
history-taking	×						
Collection of combined medication	×	×	×	×			
vital sign	×	×	×	×			
chest CT	×				×	×	×
pulmonary function test	×						
laboratory examination	×						
Electromagnetic navigation bronchoscopy		×					
Radial ultrasound /CBCT		×					

biopsy		×					
Chest X-ray			×				
pathological examination			×				
Clinical diagnostic results							×
Collection of adverse events		×	×	×			

Note: Patients with histopathological examination of malignancy do not require follow-up.

3.6.2 Statistical analysis

Statistical analysis was performed using SPSS 22.0 software (IBM, Armonk, NY, USA). Demographic and radiological data were presented with mean ± standard deviation for continuous variables and frequency/percentage for categorical variables. Intergroup comparisons of continuous variables employed t-tests, while categorical variables were analyzed using chi-square tests (or Fishers exact test). The McNemar test was used to evaluate differences in diagnostic rates between two methods. A p-value <0.05 was considered statistically significant.

3.7 Quality control measures

① Strictly implement the bronchoscopy operation procedures, and the intraoperative operation is completed by the same operator. The operator has more than 50 experience in electromagnetic navigation bronchoscopy examination to avoid operational differences.

② The pulling force of intraoperative cryobiopsy and the clamping force should be standardized, and the pulling speed of cryobiopsy and the closing speed of clamping should be consistent.

③ The pathological diagnosis results are identified by two pathologists back to back, and the results are consistent, that is, the diagnosis is confirmed; if the results are inconsistent, a third pathologist is identified, and finally determined by the three experts after consultation.

④ Intraoperative image localization verification. Radial ultrasound and/or cone beam CT were used to confirm the biopsy position before the two biopsy methods.

⑤ Participants in the study must undergo unified training, with unified recording methods and judgment criteria. Researchers should truthfully, detailedly and carefully record all contents of the case report form according to the requirements of the case report form, so as to ensure that the content of the subjects case report form is complete, true and reliable.

IV. STUDY RELEVANT ETHICS

4.1 Ethics Committee review

This study was conducted in compliance with the "Regulations on the Supervision and Administration of Medical Devices (2014)", "Good Clinical Practice for Medical Devices (2016)", "Helsinki Declaration", and other relevant laws, regulations, and trial protocols. Prior to the commencement of the trial, the principal investigator must submit the trial protocol, informed consent forms, and all related documents to the ethics committee for approval before proceeding with clinical trials. The sponsor is required to promptly report any serious adverse events occurring during the study, including participant risks and other issues. Any modifications to the trial protocol must first obtain prior approval from the ethics committee and be formally filed with them.

4.2 Informed consent

All participants must complete both oral and written disclosures of the clinical trial details and sign an informed consent form before being enrolled in the study. The signed consent forms are made in duplicate: one copy is retained by the investigator in the designated clinical trial management records, while the other is kept by the participant.

V. CRRPTOSECURITY

The findings from this research project may be published in medical journals. However, we will maintain patient information confidentiality as required by law. Patient personal data will not be disclosed unless legally mandated. When necessary, government regulatory authorities and hospital ethics committees may access patient records in accordance with established protocols.

VI. DATE MANAGEMENT AND SECURITY

6.1 Data input and verification

The patient screening number combines the S+ center code (a two-digit Arabic numeral, e.g., 01) with a three-digit Arabic numeral, such as S01001. The enrollment number uses a three-digit Arabic numeral, for example: 001. Each research center collects the patients CRF form and inputs it into the Electronic Data Capture (EDC) system. A computerized verification system is then used to double-check the entered data, ensuring its completeness and accuracy.

6.2 Data management

The main researchers will manage the data and save them in paper and electronic form. Except for the members of the research group, the data will not be exposed to anyone outside the research group.

VII. EXPECTED SCHEDULE AND COMPLETION DATE OF THE RESEARCH PROJECT

Expected progress: to clarify the diagnostic efficacy and safety of ultrafine frozen probes for peripheral lung nodules under navigated bronchoscopy.

Completion date: July 2028

August 2025-July 2027: Conduct case screening and study intervention.

August 2027 to July 2028: Conduct data processing, statistical analysis and summary of all technical data, write a paper, and submit the final report.

REFERENCE

1. Zheng, R., et al., Cancer incidence and mortality in China, 2016. J Natl Cancer Cent, 2022. **2(1): p. 1-9.**
2. Zhang, W., et al., Meta-analysis of the diagnostic yield and safety of electromagnetic navigation bronchoscopy for lung nodules. J Thorac Dis, 2015. **7(5): p. 799-809.**
3. Mehta, A.C., et al., The Evolutional History of Electromagnetic Navigation Bronchoscopy: State of the Art. Chest, 2018. **154(4): p. 935-947.**
4. Balasubramanian, P., et al., Diagnostic yield and safety of diagnostic techniques for pulmonary lesions: systematic review, meta-analysis and network meta-analysis. Eur Respir Rev, 2024. **33 (173).**
5. Tang, Y., et al., Transbronchial lung cryobiopsy for peripheral pulmonary lesions. A

narrative review. Pulmonology, 2024. **30(5): p. 475-484.**

6. Bondue, B., et al., Trans-bronchial lung cryobiopsy in patients at high-risk of complications. BMC Pulm Med, 2021. **21(1): p. 135.**
7. Matsumoto, Y., et al., Diagnostic Outcomes and Safety of Cryobiopsy Added to Conventional Sampling Methods. Chest, 2021. **160(5): p. 1890-1901.**
8. Nakai, T., et al., Safety profile and risk factors for bleeding in transbronchial cryobiopsy using a two-scope technique for peripheral pulmonary lesions. BMC Pulm Med, 2022. **22(1): p. 20.**
9. Nakai, T., et al., Diagnostic Utility and Safety of Non-Intubated Cryobiopsy Technique Using a Novel Ultrathin Cryoprobe in Addition to Conventional Biopsy Techniques for Peripheral Pulmonary Lesions. Respiration, 2023. **102(7): p. 503-514.**
10. Kim, M.H., et al., Next-generation sequencing using tissue specimen collected with a 1.1 mm-diameter cryoprobe in patients with lung cancer. Respirology, 2024. **29(4): p. 333-339.**
11. Kim, S.H., et al., Clinical outcomes of transbronchial cryobiopsy using a 1.1-mm diameter cryoprobe for peripheral lung lesions - A prospective pilot study. Respir Med, 2023. **217: p. 107338.**