INFORMED CONSENT

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

Lead research unit: Beijing Chaoyang Hospital affiliated to Capital Medical University

Department: Department of Respiratory and Critical Care Medicine

Version number: 1.2

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Informed Consent

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The informed consent form shall be divided into two parts, which shall include:

Part 1: Informed Consent Form Disclosure Page

I. Introduction to the Trial/Study

This study, titled 'The comparative study of Electromagnetic Navigation Bronchoscopic with Ultra-thin Cryobiopsy and Forceps Biopsy in the Diagnosis of Peripheral Pulmonary Nodules,' was supported by Beijing Chaoyang Hospital affiliated with Capital Medical University, with Dr. Li Wan as the principal investigator.

This study is an experimental study that has been reviewed and approved by the Medical Ethics Committee of Beijing Chaoyang Hospital. Please read this informed consent form carefully and make a prudent decision regarding your participation in this study. Participation in this study is entirely your own choice. As a participant, you must provide written consent prior to joining the clinical study. When your study physician or researcher discusses the informed consent form with you, you may ask them to explain any parts that you do not understand.

This study is a multicenter trial with competitive enrollment, where all participating centers simultaneously enrolled subjects until the total number of participants reached 228. The study unit planned to enroll 150 subjects.

This study will last for 3 years, with follow-up of postoperative complications (including pneumothorax, hemorrhage, pleural effusion, pain, fever, etc.) and diagnostic information for 12 months. Detailed medical records will be collected to better understand your condition. Your treatment plan will be determined by your physician, and no additional investigational drugs will be administered.

2、Purpose of the Trial/Study

1. Research Objective: To conduct a nationwide multicenter randomized controlled trial to evaluate the safety and efficacy of electromagnetic navigation bronchoscopic ultrathin cryoprobe biopsy in the diagnosis of peripheral pulmonary nodules.

2. Research Steps

If you agree to participate in this study, please sign this informed consent form.

① A total of 228 patients with pulmonary peripheral nodules of unknown etiology were

consecutively enrolled in this study. Those with suspected malignant nodules or indeterminate nature were included after signing the informed consent form.

② Review preoperative chest CT and other laboratory test data.

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

④ Preoperative thin-layer CT (1mm) three-dimensional reconstruction was used for preoperative electromagnetic navigation bronchoscopy path planning.

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

a) Ultrathin cryoprobe biopsy group (TBCB): Complete routine bronchoscopy, reach the nodule site under electromagnetic navigation guidance, and confirm the biopsy location through radial ultrasound and/or CBCT. Insert a 1.1mm cryoprobe along the electromagnetic navigation catheter, with a freezing time of 4-10 seconds per session, and perform 2-3 sessions to obtain at least two samples with a diameter of no less than 5 mm.

b) Forceps biopsy group (TBFB): Complete routine bronchoscopy, reach the nodule site under electromagnetic navigation guidance, and confirm the biopsy location through radial ultrasound and/or CBCT. Insert 1.8mm biopsy forceps along the electromagnetic navigation catheter to obtain $\geqslant 5$ tissue samples.

c) During the procedure, radial ultrasound and/or CBCT can be utilized for localization verification. Biopsy specimens obtained from both groups were fixed in formalin and sent for pathological examination. The pathological diagnosis was assessed by two pathologists in a back-to-back manner, with a unanimous result confirming the diagnosis. In case of discordance, a third pathologist was involved in the evaluation, and the final diagnosis was determined through consultation among the three experts.

⑥ Data collection: Clinical data include medical history, physical signs, laboratory tests, pulmonary function tests, and imaging examinations; recording the duration of procedures and the number of specimens; surgical-related complications such as hemorrhage, pneumothorax, and

infection (including within 7 days postoperatively); severity assessment of complications such as hemorrhage and pneumothorax; and pathological results.

⑦ Follow-up: Short-term follow-up refers to postoperative follow-up data at 4 weeks, evaluating the presence of delayed complications such as hemorrhage, pneumothorax, or infection. Long-term follow-up involves patients with non-specific histopathological diagnoses, monitored until 12 months postoperatively. The final diagnosis is assessed based on imaging findings (e.g., absorption or no change of pulmonary nodules) and results of other invasive examinations.

⑧ Organize the data and conduct statistical analysis.

3. Subject Selection

(1) Inclusion criteria:

Participants enrolled in this trial must meet all the following criteria:

① Age ⩾18 years, gender unrestricted;

② Chest CT revealed pulmonary nodules, with suspected malignant nodules or indeterminate nature requiring biopsy for definitive diagnosis;

③ Chest CT indicated that the proposed biopsy nodule was located in the segmental and lower bronchi, with a maximum diameter of ⩾8mm and ⩽30 mm, and was inaccessible within the conventional bronchoscopy field of view;

④ If chest CT reveals multiple pulmonary nodules, select one of them as the target lesion;

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

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

(2) Exclusion Criteria

Subjects meeting any of the following criteria shall not be enrolled in this trial:

① Contraindications for bronchoscopy include: active massive hemoptysis; recent myocardial infarction or unstable angina pectoris; 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 event; aortic dissection or aortic aneurysm; multiple pulmonary bullae; extreme systemic failure; lactating or pregnant women, or women planning pregnancy.

② The proposed biopsy site has high bleeding risk due to bronchial artery invasion or suspected renal cell carcinoma pulmonary metastasis;

③Implantable devices containing electromagnetic sources;

④ Presence of contraindications to anesthesia; hypersensitivity to anesthetic agents; or a history of multiple severe allergic reactions or hereditary allergic predisposition;

⑤ Participation in other studies within three months without withdrawal or completion, which may affect the observation in this study;

⑥ Disagreement to participate in this study or unwillingness to accept the follow-up plan;

⑦ Other circumstances where the investigator deems the participant unsuitable for participation in this study.

4. Grouping and Intervention

According to the pre-prepared random envelope, the subjects were randomly divided into two groups: the ultrafine cryoprobe biopsy group and the biopsy forceps biopsy group (1:1), totaling 228 cases.

5. Exit Criteria

You may opt to withdraw from the study at any time without forfeiting any benefits you are entitled to. However, if you decide to withdraw during the study, we encourage you to consult with your study physician first. If you experience a serious adverse event, or if your study physician determines that continuing participation is not in your best interest, they will decide to allow your withdrawal. The sponsor or regulatory authority may also terminate the study during the study period. However, your withdrawal will not affect your standard medical care or benefits.

If you withdraw from the study for any reason, you may be asked about your participation in the study.

6. Information and biological specimens collected during the study

In this study, your relevant training and surgical procedure information will be collected and stored in the clinical trial project management system. All information will be anonymously and properly preserved to ensure that your data will not be disclosed. The biological samples collected in this study will be stored and disposed of in accordance with hospital procedures. The analysis of biological samples will be limited to the purposes specified in this informed consent form and will not be used for any other purposes.

III. Risks and Benefits

1. What are the risks of participating in this study?

The potential risks associated with participation in this study are as follows. You should discuss these risks with your study physician or, if you prefer, with your regular physician.

Bronchoscopic lung biopsy and cryobiopsy are invasive medical procedures that carry certain medical risks, with potential intraoperative or postoperative complications. For specific details, refer to the informed consent form for bronchoscopy, which primarily includes: (1) Anaphylaxis to anesthetics; (2) Cardiovascular and cerebrovascular accidents: such as severe arrhythmias, cardiac arrest; (3) Massive hemorrhage; (4) Hypoxemia; (5) Bronchospasm and asphyxia; (6) Mediastinal emphysema, pneumothorax, subcutaneous emphysema; (7) Fever, pulmonary infection, pleural infection, empyema; (8) Post-recovery pulmonary edema; (9) Other unpredictable complications. For specific details, refer to the informed consent form for cryobiopsy, which primarily includes: (1) Pneumothorax; (2) Hemorrhage; (3) Pleural effusion; (4) Respiratory failure, etc.

This study is a prospective investigation conducted based on your electromagnetic navigation bronchoscopy. Therefore, your participation in the study will not affect any diagnostic or therapeutic decisions made by your physician. The procedure you undergo is a routine medical intervention, and participation in this study does not entail any additional risks beyond standard medical care.

If you experience any discomfort, new changes in your condition, or any unexpected situation during the study, regardless of whether it is related to the study, you should promptly notify your physician. He/she will make an assessment and provide appropriate medical intervention.

During the study period, you will need to attend hospital follow-ups on schedule and undergo certain examinations, which may occupy some of your time and may also cause inconvenience or discomfort.

2. What are the benefits of participating in the study?

Direct Benefits: If you agree to participate in this study, our physicians will provide you with standardized diagnosis, treatment, and therapeutic recommendations under your current medical conditions, potentially granting you direct medical benefits. Additionally, your physician will conduct close follow-up, enabling both you and your physician to gain a deeper understanding of your condition. With the assistance of your physician, you will be better equipped to manage your disease.

Potential benefits: We will continue to monitor changes in your condition, which may help slow the progression of your disease. The research findings may be of significant importance for the selection of diagnostic methods for more patients with unexplained pulmonary peripheral nodules in the future and for advancing the development of such technologies. We hope that the information obtained from your participation in this study will benefit you or patients with similar conditions in the future.

IV. Voluntary and Privacy Principles

1. Voluntary Principle: Your participation is entirely voluntary. If you voluntarily participate and are successfully enrolled, we expect you to adhere to completing this trial/study. You may decide to discontinue participation or withdraw from the trial/study at any time without any reason. Upon withdrawal, we will conduct a health assessment for you. If abnormalities are detected, follow-up will continue until you return to normal or reach a stable phase. If you withdraw from the trial/study, we guarantee that your future treatment and care will not be affected in any way.

2. Privacy Principle: Your right to privacy will be protected. Your personal information will be kept confidential, but it may be subject to supervision by relevant authorities (such as ethics committees and food and drug regulatory agencies). Results and data from clinical trials may be publicly disclosed, but the privacy-related content of your personal information will not be disclosed externally.

V. Management and Compensation for Test/Study-Related Damages

If you experience trial/study-related harm during this trial/study, you will receive prompt medical care.

VI. Contact Information of the Investigating Physician

During your participation in this clinical trial/research, if you have any questions or emergency situations, please contact your research physician at 13439802812.

VII. Ethical Issues

1. Inform the subject: The research physician will provide you with detailed explanations to ensure your full understanding of the above content, allowing you sufficient time to consider and make a decision regarding participation in the trial/research.

2. During the trial/research period, if any information that may affect the subject's continued participation in the trial/research is obtained, the subject or their guardian will be promptly notified, and a newly signed informed consent form will be obtained from you if necessary.

3. This trial/research protocol has been approved by the Medical Ethics Committee of Beijing Chaoyang Hospital. If any violation of the trial/research protocol occurs during the trial/research process, or if your rights and interests are affected, you may file a complaint with the hospital's Medical Ethics Committee.

4. Contact Information of the Medical Ethics Office at Beijing Chaoyang Hospital: No.8 Gongti South Road, Beijing Chaoyang Hospital; Postal Code 100020; Telephone: 010-85231484 (Please call during working hours from 8:00 AM to 11:30 AM and from 1:00 PM to 5:00 PM); Email: cyylunli2019@163.com; Fax: 010-85231484.

Prior to your (or your guardian's) decision to participate in this clinical trial/research, please carefully read this informed consent form. The study physician will assist you in addressing any questions regarding the investigational product and this trial/research. If you voluntarily participate, please sign and date the last page of the informed consent form after reviewing this material.

Part II Informed Consent Signing

1. I have carefully read the informed consent form for this trial/research project, including the section on informed consent for participants. The research physician has provided me with a detailed explanation and addressed my relevant questions. I fully understand the purpose, process, as well as my rights and risks associated with participating in this trial/research. I voluntarily agree to participate in this trial/research and consent to cooperate with the research physician in treatment and follow-up as outlined in the informed consent form, striving to complete this trial/research.

Subject signature:

(Print) (Hand) Date (Print) (Hand) Date (Print) (Hand) Date__

or a signed statement from a fair witness:

(Print) (Hand) Date (Print) (Hand) Date (Print) (Hand) Date

_____

or guardian's signature (if required):

(Printed) Direct relationship with the subject: (Printed) Direct relationship with the subject:

Handwriting) Date Handwriting) Date

2. I or my research team have fully explained and clarified to the subject the purpose, procedural steps, potential risks, and possible benefits of participating in this trial/study, and have satisfactorily addressed all relevant questions raised by the subject.

Researcher or physician designated by the researcher to sign the informed consent form:

(Print) (Hand) Date (Print) (Hand) Date (Print) (Hand) Date

Both the subjects and the investigators must sign two identical informed consent forms, with each party retaining one copy.