Informed Consent Form

Clinical Utility of Needle-Based Confocal Laser Endomicroscopy for Peripheral Pulmonary Lesions

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Dear participant,

You are invited to take part in a clinical study entitled “Clinical Utility of Needle-Based Confocal Laser Endomicroscopy for Peripheral Pulmonary Lesions” Before deciding whether to participate, please read the following information carefully. It is intended to help you understand the study, why it is being conducted, what procedures and time commitment are involved, and the possible benefits, risks, and inconveniences of participation.

1.Study background

Peripheral pulmonary lesions (PPLs) are focal abnormalities detected on chest imaging that cannot be directly visualized by conventional bronchoscopy. With the widespread use of low-dose computed tomography for lung cancer screening, pulmonary nodules are being detected more frequently, and most are located peripherally. Early and accurate diagnosis of these lesions has clear clinical importance and may reduce lung cancer-specific mortality by approximately 20%.

Current diagnostic methods for PPLs mainly include transbronchial biopsy and CT-guided percutaneous lung biopsy. Conventional bronchoscopy has a relatively low diagnostic yield for PPLs. CT-guided biopsy has a higher diagnostic yield but is more invasive and carries a greater risk of complications such as pneumothorax. Radial probe endobronchial ultrasound (r-EBUS) can help localize the lesion, but it cannot confirm the instrument position continuously during biopsy, so off-target sampling may occur. Navigation bronchoscopy can guide biopsy instruments to the target lesion, but its localization may be affected by respiratory movement and the equipment is costly. A minimally invasive, precise, and safe method for evaluating PPLs is still needed.

Needle-based confocal laser endomicroscopy (nCLE) is a newer optical biopsy technology. A miniature probe can be introduced into the lung through the bronchoscope to obtain real-time, in vivo microscopic images at cellular-level magnification. These images may help physicians assess the nature of a lesion immediately before biopsy and identify a more appropriate sampling site. Previous studies suggest that nCLE can assist in the diagnosis and targeted biopsy of pulmonary lesions.

2.Study purpose

This study aims to evaluate the diagnostic performance and clinical utility of nCLE combined with r-EBUS for PPLs during bronchoscopy, with navigation used as needed. Using histopathology as the principal reference standard, the study will evaluate the feasibility, accuracy, and safety of nCLE for distinguishing malignant from benign PPLs.

3. Study Procedures

Patients with PPLs who require bronchoscopic biopsy to determine the nature of the lesion will be screened. All participants must have a routine clinical indication for bronchoscopy and biopsy. The study procedures will follow authoritative domestic and international guidance, including the Chinese Technical Specifications for Diagnostic Bronchoscopy (2021 Edition)

and the British Thoracic Society Guideline for Diagnostic Flexible Bronchoscopy in Adults. Patients who agree to undergo bronchoscopic biopsy and participate in the study will sign this informed consent form, and relevant clinical data will be collected for analysis.

Patients who agree to undergo bronchoscopic biopsy and participate in this study will sign an informed consent form. Patient information will be collected for study analysis.

(1). Study type: This is a multicenter, prospective, observational clinical study.

(2). Study period and follow-up period: October 2026 to October 2027.

(3). Planned enrollment: A total of 100 participants will be enrolled, based on previous studies and sample-size calculations. The First Affiliated Hospital of Ningbo University is expected to enroll 34 participants.

Inclusion criteria

(1) Age 18 years or older.

(2) A PPL identified on chest CT.

(3) Bronchoscopic biopsy considered clinically necessary by the treating physician to establish a pathologic diagnosis.

(4) Willingness to undergo r-EBUS and nCLE examinations.

(5) Voluntary participation with written informed consent.

Exclusion criteria

(1) A contraindication to bronchoscopy, including severe cardiopulmonary disease, coagulation disorder, failure to discontinue anticoagulant therapy or anticoagulant medication for at least 5 days before the procedure, poor tolerance of anesthesia, psychiatric illness, or severe neurosis.

(2) Pregnancy or breastfeeding.

(3) Known allergy to fluorescein sodium.

(4) Coagulation disorder.

(5) A known allergic disorder, history of asthma, hepatic failure, renal failure, or another contraindication to fluorescein sodium injection.

(6) Continued use of a systemic beta-blocker on the day of the procedure, or inability to discontinue the beta-blocker safely as assessed by the investigator and anesthesiologist.

(7) Inability to cooperate with the study for any reason, or any other condition that the investigator considers unsuitable for enrollment.

Criteria for study discontinuation

(1) You may stop participating at any time without prejudice. If you withdraw, the reason will be recorded in the electronic case report form when you agree to provide it.

(2) The sponsor or a regulatory authority may terminate the study.

4. What Do You Need to Do If You Participate

Please provide accurate information about your medical history and current health. Tell the investigator promptly about any discomfort during the study so that appropriate medical assessment, treatment, or advice can be provided. Do not take any restricted medication or food if instructed not to do so. Tell the investigator whether you have recently participated in another study or are currently participating in one, whether you are pregnant or breastfeeding, and about any other matter that may affect this study.

Before enrollment, a physician will ask about and record your medical history and perform a physical examination. You will undergo a complete blood count, liver and renal function tests, serum electrolyte testing, coagulation testing, arterial blood gas analysis, hepatitis B serology, syphilis and HIV antibody testing, electrocardiography, chest CT, and other clinically necessary tests to determine whether you can participate. If you meet the eligibility criteria, you may choose freely whether to participate and sign this form. If you do not wish to participate, your doctors will continue to provide appropriate clinical care according to your wishes.

The purpose, risks, and possible complications of the examination will be explained to you. The general procedure will also be described to reduce anxiety and help maintain stable blood pressure, heart rate, and other vital signs. You will be asked not to eat or drink for 4 hours before the procedure. Intravenous access will be established, and intravenous fluids may be given if clinically necessary until the procedure is completed.

If you choose to participate, tissue specimens from the target lesion will be collected for pathologic examination. Your examination and treatment will follow the Chinese Technical Specifications for Diagnostic Bronchoscopy (2021 Edition), the British Thoracic Society Guideline for Diagnostic Flexible Bronchoscopy in Adults, and routine clinical practice at the participating hospital.

5. Possible Benefits of Participation

This is an observational study. nCLE may provide additional information about the target lesion and may help identify an appropriate biopsy site, but direct benefit to you cannot be guaranteed. Your routine clinical care will not be withheld or reduced because of the study, and your doctors will continue to examine and treat you according to your individual condition and accepted clinical practice. Information obtained from this study may help future patients with the same or similar conditions and contribute to medical knowledge.

6. Possible Adverse Reactions Risks and Protective Measures

6.1 Common Risks During and After Bronchoscopy

(1) Bronchospasm or an asthma attack.

(2) Airway mucosal injury and bleeding.

(3) Cardiac arrhythmia.

(4) Chills or fever after the procedure.

(5) Pneumothorax or bleeding.

(6) Allergic reaction to anesthetic agents or fluorescein sodium.

(7) Failure to establish the diagnosis, including a biopsy pathology result that does not agree with the clinical impression.

6.2 Risk Mitigation

(1) Routine preprocedural examinations will be completed and contraindications carefully excluded.

(2) The procedure will be performed gently and in accordance with technical standards.

(3) If an adverse reaction or complication occurs, the study physician will provide appropriate management according to the circumstances.

6.3 Adverse Events Complications and Management

Bleeding will be managed according to severity. Minimal bleeding may require no treatment. Mild bleeding may be treated with local hemostatic medication, such as irrigation with 1 mg epinephrine diluted in 10 mL normal saline. Moderate bleeding may require balloon occlusion for hemostasis. Severe bleeding may require surgical or interventional treatment.

Your personal information will not be disclosed to individuals or companies outside the study team and will not be used for unrelated research.

6.4 Risks Related to Fluorescein Sodium

Drug-related risks, discomfort, and protective measures: Not applicable to an investigational drug because this study does not test a study drug.

Other study-related risks and protective measures: nCLE imaging requires intravenous fluorescein sodium, which may cause an immediate, type I hypersensitivity reaction. A hypersensitivity test will therefore be performed before the imaging dose is given. Approximately 60% of fluorescein sodium binds to serum proteins after entering the body. It does not bind tightly to tissues or participate in human metabolism. Most is excreted by the kidneys in urine, and a smaller proportion is excreted through the biliary tract. It is generally considered to have low toxicity and to be a relatively safe contrast agent. Adverse reactions may nevertheless occur after injection, although life-threatening reactions are rare.

(1) Nausea and vomiting: These reactions may begin approximately 30 seconds after injection and last 1-3 minutes. Predisposing factors may include rapid injection, low solution temperature, fatigue, frailty, fasting or overeating, anxiety, and young male sex. They are usually transient and require no treatment. You will be reassured and asked to relax; deep breathing may help nausea, and a receptacle and tissues will be provided if vomiting occurs.

(2) Urticaria: Urticaria may begin 3-10 minutes after injection and may persist for several hours. Predisposing factors include an allergic constitution and female sex. Management may include observation and oral fluids to promote excretion of the contrast agent; monitoring of breath

sounds, respiratory rate, pulse, and blood pressure when necessary; oral antihistamines if symptoms worsen; intravenous corticosteroids and calcium preparations if further antiallergic treatment is required; and topical corticosteroid ointment for affected skin.

(3) Extravasation: Extravasation may occur at the time of injection and cause severe pain at the injection site; superficial phlebitis may develop 1-2 days later. Predisposing factors include displacement after venipuncture, poor venous access, and rapid injection. If most of the contrast agent has entered the vein and only a small amount has extravasated, the examination may proceed. If most has extravasated, another intravenous site may be used. Local cold or ice compresses may be applied during the first 48 hours, followed by warm compresses after 48 hours to promote resolution.

(4) Vasovagal syncope: This may present with fainting, bradycardia, hypotension, sweating, or chills and must be distinguished from anaphylactic shock. Predisposing factors include anxiety, panic, fatigue, fasting, and hypoglycemia. Management may include placing you supine, monitoring vital signs, and administering intravenous atropine 0.5-1 mg if heart rate and blood pressure do not recover.

(5) Anaphylactic shock: This may present with impaired consciousness, a sudden fall in blood pressure, bronchospasm, urticaria, itching, or tachycardia. Predisposing factors include a previous severe urticarial reaction during fluorescein angiography and an allergic constitution. The emergency response plan includes the following: initiate emergency resuscitation; place the patient in the shock position; provide oxygen and establish intravenous access; immediately administer 0.5 mg of 0.1% epinephrine subcutaneously or intramuscularly and observe for 15-20 minutes, with repeat administration if blood pressure does not recover; administer dexamethasone 5-10 mg intravenously and promethazine 50 mg intramuscularly; provide rapid intravenous fluid replacement; for an asthma attack or dyspnea, administer aminophylline 0.25 g (5 mg/kg) in 500 mL of 5% glucose solution by intravenous infusion; perform endotracheal intubation or tracheotomy if airway obstruction cannot be relieved; and promptly transfer the patient for emergency or specialist medical care.

Potential effects and risks to an embryo, fetus, or breastfed infant: Not applicable because pregnant and breastfeeding individuals are excluded from participation.

8. Costs

The nCLE examination will be provided free of charge by the study team. Before bronchoscopy, fluorescein sodium must be administered intravenously. The listed cost is RMB 87.32 and is payable by the participant, subject to applicable medical insurance reimbursement. For bronchoscopic biopsy, local or general anesthesia may be selected as clinically appropriate. The listed cost of general anesthesia is RMB 810 for endotracheal general anesthesia, with an additional material charge of RMB 72 for a laryngeal mask airway or endotracheal tube. No anesthesia fee is charged for local anesthesia.

There is no study-related participation payment or other compensation.

9. Compensation for Research-Related Injury

If you experience any discomfort or unexpected situation during the study, regardless of whether it is related to the study, you should promptly inform the study doctor. The doctor will assess the situation and provide medical management. If your injury is confirmed to have been caused by the study, the sponsor will bear reasonable treatment costs and provide corresponding economic compensation or reimbursement in accordance with the relevant laws of the People's Republic of China.

10. Alternative Treatment and Its Main Benefits and Risks

This is a prospective, multicenter, observational diagnostic study. If you do not wish to participate, your clinical care will not be affected. An available alternative is to proceed directly to biopsy after the lesion has been localized, without using nCLE for additional confirmation or imaging.

11. Confidentiality of Your Personal Information

Your medical records, including study records, case report forms, and laboratory reports, will be retained at the hospital where you receive care. Test results will be recorded in your medical record. Subject to confidentiality requirements and applicable laws and regulations, investigators, monitors, auditors, ethics committees, and drug regulatory authorities may be permitted to review your medical records. Public reports of the study will not disclose your identity. Every reasonable effort will be made to protect the privacy of your medical information to the extent permitted by law.

Study data and personal information will be used only for this study. They will not be supplied externally or used for product development, data sharing, or secondary research.

Individual study results will not be routinely returned directly to participants. Study results may be published in medical journals, but your identity will not be disclosed and all directly identifying information will remain confidential.

12. Voluntary Participation and Withdrawal

Whether you participate is entirely your choice. You may refuse to participate or withdraw at any time. Your decision will not affect your relationship with your doctors, the medical care you receive, or any other rights or benefits.

To protect your best interests, the treating physician, investigator, or ethics committee may discontinue your participation at any stage of the study.

If new information becomes available after you join the study that may affect your decision to participate, you will be informed promptly. You may then reconsider whether to continue or withdraw.

13. Who to Contact If You Have Questions

If you experience a research-related injury or have any questions about the study, please contact the study physician, Chen Zhongbo, at 13777125910. This study has been reviewed and approved by the Medical Ethics Committee of the First Affiliated Hospital of Ningbo University. For questions about research ethics or your rights as a participant, please contact the Ethics Committee Office at 0574-87085233.

14. What Should You Do Now?

The decision to participate is yours, together with your legally authorized representative when applicable. Before deciding, please ask your physician any questions you may have. Thank you for reading this information. If you decide to participate, please tell your physician, who will arrange the study procedures. Please keep a copy of this document.

15. Consent Statement and Signatures

I confirm that I have read and understood this informed consent form. I have had the opportunity to ask questions, and all of my questions have been answered. I understand that participation is voluntary and that choosing not to participate or withdrawing at any time will not affect or harm my rights or medical care. I voluntarily agree to participate in this study, including the study-related procedures, and I agree that my medical data may be used for this study and its resulting publications.

Participant Signature: _____
Telephone:_____

Date and Time: _____

Legally Authorized Representative If Required

Representative Signature: _____

Relationship to Participant: _____

Telephone: _____

Date and Time: _____

Impartial Witness Statement If Required

If the participant or legally authorized representative is unable to read: I confirm that the information in this informed consent form has been accurately presented and explained to the participant and/or legally authorized representative, that the participant and/or representative understood the information, and that consent to participate was given freely.

Impartial Witness Signature: _____

Telephone: _____

Date and Time: _____

Investigator Statement

I confirm that I have explained the study in detail to the participant, including the participant's rights and the possible benefits and risks.

Investigator Signature: _____

Date and Time: _____

Telephone: _____