Informed Consent Form

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Study Title: A Multicenter, Prospective Randomized Controlled Trial Evaluating the Efficacy and Safety of Tubeless Anesthesia Versus Conventional Endotracheal Intubation Anesthesia for Thoracoscopic Surgery Combined With Concurrent Microwave Ablation in the Treatment of Multiple High-Risk Ground-Glass Nodules—Patient-Reported Outcomes (PSA-LUNG) as Primary Endpoint

Study Institution: The First Affiliated Hospital of Guangzhou Medical University

Principal Investigators: Jun Liu, Xingyang Xue

Dear Research Participant:

We hereby invite you to participate in a study entitled "a multicenter, prospective, randomized controlled study evaluating the efficacy and safety of tubeless anesthesia versus conventional tracheal intubation anesthesia in video-assisted thoracoscopic surgery combined with simultaneous microwave ablation for the treatment of multiple high-risk ground-glass nodules, with patient-reported outcomes (PSA-LUNG) as the core." This study has been reviewed and approved by the Ethics Committee for Research Project Review of the First Affiliated Hospital of Guangzhou Medical University. Before you decide whether to participate, please read this informed consent form carefully and make a well-considered decision about whether to take part. If you have any questions, please raise them with the study physician or study staff. You may discuss the study with your family and friends, and you will have sufficient time to consider. If you are currently participating in another study, please inform your study physician or study staff. The main contents of this study are described below.

1. Study Background:

With the widespread use of low-dose computed tomography (LDCT), the detection rate of primary lung cancer presenting with ground-glass

nodules (GGNs) has increased, particularly for multiple GGNs. Multiple high-risk ground-glass opacities (GGOs) are a common imaging finding, frequently associated with early-stage lung adenocarcinoma or pre-cancerous lesions, especially multiple primary lung cancer (MPLC). For such patients, surgery is an important treatment modality; however, conventional video-assisted thoracoscopic surgery (VATS) requires general anesthesia with tracheal intubation, which may cause airway injury, postoperative pain, and impairment of pulmonary function. This is particularly concerning for patients with multiple nodules, in whom repeated surgeries are more likely to affect lung function.

Tubeless video-assisted thoracoscopic surgery, which avoids tracheal intubation and adopts spontaneous-breathing anesthetic techniques, is expected to reduce surgical trauma and promote postoperative recovery, and has been demonstrated to be safe and feasible in the treatment of early-stage lung cancer. Meanwhile, microwave ablation (MWA), as a minimally invasive local treatment modality, can effectively manage deep or difficult-to-resect lesions while preserving pulmonary function.

In view of the above, this study proposes combining tubeless video-assisted thoracoscopic surgery with simultaneous MWA for the treatment of multiple high-risk GGNs. Currently, there is insufficient clinical evidence regarding the efficacy and safety of tubeless anesthesia under this combined modality, particularly its impact on patients' postoperative symptoms and quality of life. Accordingly, we plan to conduct this study to compare the effects of tubeless anesthesia versus conventional tracheal intubation anesthesia on the quality of postoperative recovery in this combined surgery. This study is a single-center, randomized controlled trial designed to compare, in the setting of VATS combined with simultaneous MWA for multiple high-risk GGNs, the effects of tubeless anesthesia versus conventional tracheal intubation anesthesia on patients' health-related quality of life at 1 month postoperatively, with the PSA-LUNG scale as the core measure. The results of this study will provide clinical evidence for optimizing perioperative anesthetic strategies in this patient population.

2. Study Objectives:

This study aims to compare, in patients undergoing VATS combined with simultaneous MWA for multiple high-risk ground-glass nodules:

(1) whether tubeless anesthesia leads to better postoperative symptom recovery (as measured by the PSA-LUNG scale); and
(2) whether there are differences in safety between tubeless anesthesia and conventional tracheal intubation anesthesia (e.g., complications, adverse events, and whether intraoperative conversion to intubation is required).

3. Study Subjects:
This study plans to enroll approximately 80 subjects. You may be eligible to participate if you meet the following criteria (subject to the final assessment of the study physician):
1. Age 18–80 years;
2. Either sex;
3. Chest CT shows ≥2 multiple high-risk pulmonary ground-glass nodules; the nodules have persisted for more than 3 months; and the lesions are highly suspected to be malignant after multidisciplinary team (MDT) evaluation. In addition, the nodules must meet the following criteria: (1) on chest CT, the maximum diameter is ≤2 cm and the consolidation-to-tumor ratio (CTR) is ≤0.5; (2) for surgically resected nodules, wedge resection is feasible after discussion within the thoracic surgery team, with an expected margin distance of ≥2 cm or ≥ the maximum diameter of the nodule; and (3) for ablated nodules, wedge resection is not suitable after discussion within the thoracic surgery team (mainly located in the inner two-thirds of the lung);
4. Eastern Cooperative Oncology Group (ECOG) performance status of 0–1; preoperative systemic organ function assessment indicates that the basic requirements for VATS and ablation therapy are met;
5. American Society of Anesthesiologists (ASA) physical status classification I–III;

6. Preoperative PET-CT or other necessary imaging examinations are performed to exclude mediastinal lymph node metastasis and distant organ metastasis;
7. Expected survival ⩾12 months, with the ability to cooperate with the entire study process and follow-up;
8. The subject agrees to sign the written informed consent form and is able to comply with the protocol-specified visits, treatment plan, laboratory examinations, and related procedures.

You may not be eligible to participate if any of the following conditions apply (including but not limited to):
1. Have undergone pulmonary surgery, radiotherapy, or other ablation therapy within the past 3 months;
2. Have contraindications to surgery, ablation, or anesthesia; be unable to tolerate tubeless non-intubated anesthesia (e.g., anticipated difficult airway during surgery, laryngeal stenosis unsuitable for a laryngeal mask, etc.);
3. Plan to receive other treatments during the trial that may affect the study results (e.g., systemic chemotherapy, targeted therapy, etc.);
4. Have a primary malignant tumor in an extrapulmonary organ or other active malignancy;
5. Be unable to comply with the relevant study regulations or to attend follow-up visits; refuse to sign the informed consent form or withdraw consent during the trial;
6. Be a woman who is pregnant or breastfeeding, or who plans to become pregnant during the study;
7. Be considered by the investigators to be unsuitable for the study;
8. Be concurrently participating in other clinical trials.

If you experience serious complications, unexpected serious

adverse events, pregnancy, inability to cooperate with follow-up, or severe intolerance to the relevant medical devices during the study, the investigator may recommend that you withdraw from the study early. You may also withdraw at any time without conditions.

4. Study Procedures:

(1) Screening and Enrollment (approximately 14 days before surgery to the day of surgery)

The study physician will verify whether you meet the inclusion/exclusion criteria;

Collect basic information and medical history (e.g., age, height, body weight, past medical history, etc.);

Perform necessary preoperative examinations (examination results accepted by the investigator that were obtained before signing consent and within 30 days before surgery may be used):

Imaging: chest CT, etc. (PET-CT, etc. if necessary);

Laboratory tests: complete blood count, biochemistry, coagulation function, infection-related tests (e.g., HIV, syphilis antibodies, etc.), tumor markers, etc.;

Pulmonary function assessment;

Pregnancy test (urine or blood) for premenopausal women.

You will complete a PSA-LUNG electronic questionnaire before surgery as the baseline.

(2) Randomization

This is a randomized controlled study with a planned enrollment of 80 subjects. After enrollment, you will be randomly assigned (similar to a “drawing of lots”) to one of the following two groups (1:1):

Experimental group: tubeless anesthesia (Tubeless) VATS + simultaneous

microwave ablation;

Control group: conventional tracheal intubation anesthesia VATS + simultaneous microwave ablation.

Both groups will receive active treatment of “VATS resection of the main lesion + simultaneous MWA of secondary lesions,” and the main difference lies in the anesthetic approach.

(3) Perioperative and In-Hospital Observation

Record whether surgery/ablation is completed successfully (technical success rate);

Record whether conversion to tracheal intubation with mechanical ventilation is required during surgery (which may occur in the tubeless group);

Record postoperative recovery (e.g., time to ambulation, time to discharge, total length of hospital stay, etc.);

Record perioperative complications (graded according to the Clavien-Dindo classification);

Record adverse events/serious adverse events;

Perform assessments related to postoperative pain and quality of life;

Postoperative days 1–7: you are required to complete a PSA-LUNG electronic questionnaire on the day of surgery, on postoperative day 1, and on the day of discharge.

(4) Post-Discharge Follow-up (the first 4 weeks after surgery constitute the main follow-up period)

Weeks 1–4 after discharge: complete a PSA-LUNG electronic questionnaire once per week; follow-up may be conducted online or at the outpatient clinic (according to the study arrangements);

The study physician will follow up on your recovery, readmissions, medication use, and whether you experience any discomfort/adverse events;

Approximately 1 month after surgery: relevant examinations will be repeated according to the study arrangements (at the discretion of the investigator based on the specific circumstances), which may include tumor markers, etc.

Note: The protocol also includes longer-term dynamic monitoring of tumor markers (e.g., at 3, 6, and 12 months after surgery), subject to the arrangements of the study center.

5. Study Samples:

This study may require collection of your blood and/or urine samples for routine preoperative assessment and follow-up testing (e.g., complete blood count, biochemistry, coagulation, infection screening, tumor markers, pregnancy tests, etc.). The frequency and volume of sampling will be based on clinical and research follow-up needs and, in principle, will not exceed the reasonable amount required to complete the assessments.

Any residual samples from this study will be disposed of as medical waste in strict accordance with national laws and regulations and relevant hospital policies.

6. Alternative Treatments: Even if you do not participate in this study, you may still choose conventional diagnostic and treatment options under the advice of your physician, for example:

(1) VATS resection under conventional tracheal intubation or tubeless anesthesia (the extent of resection to be determined based on clinical assessment);

(2) Image-guided microwave ablation/other ablation modalities (suitability requires evaluation by a physician);

(3) Different combinations or staged treatment of surgery and

ablation;

(4) Close follow-up observation (applicable to some patients with low-risk nodules or those not currently suitable for intervention).

The study physician will explain the available options and their advantages and disadvantages based on your specific condition.

7. Potential Risks and Discomforts:

The risks of participating in this study mainly arise from surgery, anesthesia, microwave ablation, and perioperative examinations and follow-up. The study team will monitor and manage these risks in accordance with standard practice.

(1) Anesthesia-Related Risks (including but not limited to)

Conventional intubation anesthesia may cause: sore throat, hoarseness, airway injury, dental or oral mucosal injury, nausea and vomiting, etc.; mechanical ventilation may have a certain effect on pulmonary function.

Tubeless anesthesia may cause: respiratory depression, hypoxemia, hypercapnia, retention of airway secretions, coughing, or poor intraoperative cooperation, etc.; if necessary, emergency conversion to tracheal intubation with mechanical ventilation may be required.

(2) VATS-Related Risks (including but not limited to)

Bleeding, infection, air leak, atelectasis, pneumonia, pleural effusion, arrhythmia, pain, deep vein thrombosis/pulmonary embolism, etc.; in severe cases, reoperation or admission to intensive care may be required.

(3) Microwave Ablation-Related Risks (including but not limited to)

Pneumothorax, bleeding/hemoptysis, chest pain, fever, pleural effusion, infection, injury to adjacent tissues, etc.; in severe cases, closed thoracic drainage, blood transfusion, or further management may

be required.

(4) Examination/Blood-Sampling-Related Discomfort (including but not limited to)

Blood sampling may cause transient pain, subcutaneous bruising, dizziness, etc.; imaging examinations may involve the risk of contrast-related (if used) allergy or renal function impairment (whether contrast is used is determined clinically).

(5) Monitoring of Adverse Events and Serious Adverse Events

Adverse events will be recorded from the time you sign the consent form until the end of study follow-up. Serious adverse events (e.g., life-threatening events, events requiring hospitalization or prolonged hospitalization, disability, or death) will be reported in accordance with the required procedures within the specified time limits and will be followed up until stabilization or recovery.

8. Expected Benefits:

(1) Potential direct benefits: As a subject in this study, you will receive active treatment for multiple high-risk ground-glass nodules and will receive dedicated follow-up provided directly by the study team after surgery. This follow-up is intended to closely monitor your postoperative recovery, and its features and value are as follows:

1. Professionalism: The follow-up is directly managed by core members of the study team (e.g., study physicians and study nurses) who are familiar with this study protocol and your individual condition, ensuring that the follow-up is targeted and professional.

2. Convenience: The study team will proactively coordinate follow-up times with you, usually conducted within the study hospital, providing a more convenient and continuous follow-up arrangement compared with routine outpatient visits.

3. Limited scope: This dedicated follow-up is part of this study protocol; its content, frequency, and duration are clearly defined by the study protocol and are mainly intended to collect the safety and efficacy data required for the study. It cannot replace all routine medical re-examinations and follow-up that you may need based on your own health condition. After the protocol-specified follow-up period ends, your long-term health management will still need to return to routine medical pathways.

(2) Social/indirect benefits: Your participation will help physicians better understand the impact of different anesthetic strategies on symptom recovery and safety in patients under this combined treatment modality, thereby providing evidence for optimizing diagnosis and treatment in the future.

9. Privacy Protection and Data Confidentiality

If you decide to participate in this study, your participation and all personal data collected during the trial will be kept confidential. Information identifying you will not be disclosed to anyone outside the study team unless you give your permission. All study staff and the study sponsor are required to keep your identity confidential. Your records will be stored in a locked filing cabinet and accessible only to study personnel. To ensure that the study is conducted in accordance with regulations, if necessary, members of government regulatory authorities or the ethics review committee may, following the prescribed approval procedures, review your personal data at the study site. When the results of this study are published, none of your personal data will be disclosed.

10. Costs:

The costs of surgery and inpatient diagnosis and treatment related to this study will strictly follow routine diagnostic and treatment standards and fee schedules, and will be borne by you (the subject) or your medical insurance through routine channels. This study does not provide any financial support.

Compensation for health impairment: The sponsor has insured this study with Taiping Property & Casualty Insurance Co., Ltd. (the insurer: Taiping Property & Casualty Insurance Co., Ltd.), with a per-person compensation limit of RMB one hundred thousand yuan (¥100,000). The insurance coverage includes trial-related personal injury caused by participating in this trial (use of the investigational product and the examinations and procedures performed in accordance with the protocol). If the actual loss exceeds the insurance compensation limit or if a portion is not payable by the insurance in accordance with the law, the study institution will still bear the treatment costs and provide corresponding compensation in accordance with Chinese laws and regulations. However, the study institution's compensation applies only to trial-related injury (unexpected or beyond the routinely known complications); routine disease progression, expected adverse reactions, and the subject's own fault are not covered by compensation.

As a research subject, you are required to:

(1) Provide your medical history, medication history, and current health status truthfully;

(2) Complete the questionnaires and follow-up as required by the study, and promptly inform the study physician of any discomfort or abnormality;

(3) Inform the study physician whether you are currently or have recently participated in other clinical studies;

(4) Women of childbearing potential are required to cooperate with pregnancy screening; if pregnancy occurs during the study, you must promptly inform the study team, withdraw from the study, and continue to receive follow-up.

You may choose not to participate in this study, or you may notify the investigator at any time to request withdrawal from the study. Data that have already been collected from you will be included in the study results, and your medical treatment and rights will not be affected in any way.

If you require other treatment, if you do not comply with the study plan, if a study-related injury occurs, or if any other condition for suspension or termination arises, the study physician may suspend or terminate your continued participation in this study.

You may inquire about information and progress related to this study at any time. If you have any questions about this study, if you experience any discomfort or injury during the study, or if you have questions about your rights as a study participant, you may contact the relevant personnel by telephone. Contact person: Xingyang Xue; Telephone: 15876522723. If you have any questions or complaints about the investigators during the study, you may contact the Ethics Committee for Research Project Review of the First Affiliated Hospital of Guangzhou Medical University; Telephone: 020-81566265.

Subject Signature Page

☐ I have read the above introduction to this study, and the study physician has explained the study contents to me in detail. I have no further questions regarding the study that require consultation before signing this informed consent form. On this basis, I voluntarily agree

to participate in the clinical study described herein, and my decision is based on a full understanding of the potential risks and benefits of participating in this study. Furthermore, the investigator has not used deception, inducement, coercion, or other means to force me to agree to participate in the study, and I understand that I may withdraw from the study unconditionally at any stage.

☐ This subject, being unable to act or having limited capacity to act, has this informed consent signed on his/her behalf by a guardian or legal representative.

Signature of Subject:

Date:

Signature of Fair Witness:

Date:

Contact Information of Fair Witness:

Investigator’s Statement:

I confirm that I have explained the details of this study to the patient, in particular the potential risks and benefits of participating in this study.

Signature of Investigator:

Date:

Contact Information of Investigator:

Note: This page is the subject signature page. The study physician will explain the study contents and related information to the subject in detail, and the informed consent will be signed by the subject/guardian/legal representative and the study physician who

provided the explanation. If the subject has any questions about the study contents, the investigator should explain them in detail to the subject in person immediately. After signing, both the investigator and the subject shall each retain one original copy.