Study Protocol

(Version No.: V3.0 Version Date: July 26, 2026)

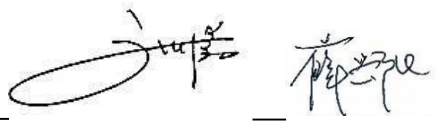
Project Title: A Multicenter, Prospective, Randomized Controlled Study: Evaluating the Efficacy and Safety of Tubeless Anesthesia versus Conventional Endotracheal Intubation Anesthesia in Video-Assisted Thoracoscopic Surgery Combined with Simultaneous Microwave Ablation for the Treatment of Multiple High-Risk Ground-Glass Nodules — With Patient-Reported Outcomes (PSA-LUNG) as the Core Measure

Sponsoring Institution:	The First Affiliated Hospital of Guangzhou Medical University
Responsible Department:	Department of Thoracic Surgery
Principal Investigator:	Liu Jun, Xue Xingyang

Investigator's Statement and Protocol Signature Page

As the principal investigator of this study, I will follow the Measures for Ethical Review of Biomedical Research Involving Human Subjects (2016) issued by the Ministry of Health, the Measures for Ethical Review of Life Sciences and Medical Research Involving Human Subjects (2023), and the ethical principles of the WMA Declaration of Helsinki (2013), use the protocol approved by the Ethics Committee, and conduct the study in accordance with the requirements of this protocol, so as to ensure the scientific validity of the study and protect the health and rights of participants.

Name: Liu Jun, Xue Xingyang

签 名: 

Date: 2026.7.26

Protocol Synopsis

Protocol Title	A Multicenter, Prospective, Randomized Controlled Study Evaluating the Efficacy and Safety of Tubeless Anesthesia versus Conventional Endotracheal Intubation Anesthesia in Video-Assisted Thoracoscopic Surgery Combined with Simultaneous Microwave Ablation for Multiple High-Risk Ground-Glass Nodules - with Patient-Reported Outcomes (PSA-LUNG) as the Core
Version No./Version Date	Version No.: V3.0 Version Date: July 26, 2026
Sponsoring Institution	The First Affiliated Hospital of Guangzhou Medical University
Principal Investigator	Liu Jun, Xue Xingyang
Study Type	Interventional clinical study
Objective	To evaluate whether, among patients receiving the same active treatment of VATS combined with MWA, the use of tubeless anesthesia can provide clinically meaningful, superior postoperative symptom recovery (measured by the PSA-LUNG) and greater safety.
Sample Size	80 participants
Study Population	Patients with multiple high-risk ground-glass nodules (GGNs)
Study Design	Randomized controlled study

Inclusion Criteria	1. Age 18-80 years; 2. Any sex; 3. Chest CT shows >=2 multiple high-risk pulmonary ground-glass nodules; the nodules persist for more than 3 months and are highly suspected to be malignant after MDT assessment. The nodules must meet the following criteria: 1. On chest CT, the maximum diameter is <=2 cm and the CTR is <=0.5; 2. Surgical nodules: wedge resection is feasible after discussion within the Department of Thoracic Surgery, with an expected resection margin of >=2 cm or >= the maximum nodule diameter; 3. Ablation nodules: wedge resection is not suitable after discussion within the Department of Thoracic Surgery (mainly located in the inner two-thirds of the lung);

	4. ECOG performance status 0-1; preoperative assessment of systemic organ function shows that the patient meets the basic requirements for VATS and ablation treatment; 5. ASA physical status classification I-III; 6. Preoperative PET-CT or other necessary imaging examinations to rule out mediastinal lymph node metastasis and distant organ metastasis; 7. Expected survival >=12 months and able to complete the entire study process and follow-up; 8. The participant agrees to sign written informed consent and is able to comply with the visits, treatment plan, laboratory tests, and related procedures specified in the protocol.

Exclusion Criteria	1. Has undergone lung surgery, radiotherapy, or other ablation treatment recently (within 3 months); 2. Has contraindications to surgery, ablation, or anesthesia; patients who cannot tolerate tubeless non-intubated anesthesia (e.g., anticipated difficult airway, pharyngeal/laryngeal stenosis unsuitable for a laryngeal mask); 3. Plans to receive other treatments during the trial that may affect study results (e.g., systemic chemotherapy, targeted therapy); 4. Has a primary malignant tumor in extrapulmonary organs or other active malignancy; 5. Unable to comply with the study regulations or unable to attend follow-up; the patient refuses to sign informed consent; 6. Women who are pregnant or breastfeeding, or who plan to become pregnant during the study; 7. Patients deemed by the investigator to be unsuitable for the study; 8. Concurrently participating in another clinical trial.
End-of-Study Criteria	All planned participants have completed the treatment and follow-up specified in the protocol. All data collection has been completed and verified to be correct. Data analysis has been completed, and both primary and secondary endpoints have been analyzed.

Withdrawal Criteria	Withdrawal decided by the investigator: If any of the follo wing occurs, after the clinical relevance is assessed and the investigator determines that t he participant cannot continue in this clinical trial, the participant may withdraw early: 1. Serious complications that affect efficacy evaluation;

	2. A suspected and unexpected serious adverse event that af fects efficacy evalu- ation; 3. Discontinuation of contraception; 4. Pregnancy; 5. Concurrent uncontrolled other malignancy; 6. Refusal to participate or inability to cooperate with follow-up; 7. Severe intolerance to the investigational medical device; 8. Other administrative reasons; 9. Withdrawal by the participant: the participant has the right to withdraw from the trial at any time without giving any reason.
Treatment Plan	This is a randomized controlled study. According to the randomization results, participants are divided into two groups: the experimental group and the control group. The experimental group receives tubeless (non-intubated) VATS combined with simultaneous microwave ablation; the control group receives conventional intubated anesthesia VATS combined with simultaneous microwave ablation.

Primary Efficacy End point	1. PSA-LUNG scale score: assessed preoperatively (one electronic questionnaire completed as baseline), in the early postoperative period (one electronic questionnaire completed on the day of surgery, on the first postoperative day, and on the day of discharge), and during the postoperative recovery period (one electronic questionnaire completed weekly within 4 weeks after surgery), the assessment is per- formed. It spans the patient's entire perioperative period.

Secondary Efficacy E ndpoints	1. Technical success rate: the proportion of procedures in which the combined surgical and simultaneous ablation procedure is completed successfully without major technical failure (e.g., failure of ablation needle placement, failure to resect the target lesion surgically, or intraoperative conversion to intubated mechanical ventilation in the experimental group). 2. Postoperative recovery: including time to ambulation after surgery and total length of hospital stay. 3. Perioperative complication rate (Clavien-Dindo classification): the proportion of treatment-related complications during the perioperative period.

Exploratory Endpoints	Tumor marker levels: dynamic changes (absolute values or percentage changes) in CEA, CYFRA 21-1, NSE, SCC, and Pro-GRP levels preoperatively and postoperatively (1 month);
Safety Endpoints	Incidence of adverse events and serious adverse events th roughout the study: the incidence of adverse events (AEs and SAEs) related to percutaneous microwave ablation w ithin 30 days and to the surgical procedure, evaluated acc ording to the National Cancer Institute Common Termino logy Criteria for Adverse Events (NCI-CTCAE) v5.0.
Study Timeline	2026.03 Complete the study protocol; 2026.04-2026.05 Obtain ethics approval; 2026.06-2027.06 Complete enrollment of the required sample size; 2027.07-2027.08 Complete trial-related data collection and follow-up; 2027.09-2027.12 Complete trial-related data collection an d manuscript writing and submission.

Statistical Analysis Methods	1. Baseline characteristics (e.g., age, sex, number of GGOs, FEV1 , etc.) are presented as mean +/- standard deviation (continuous variables, normal distribution) or median (interquartile range) (non-normal distribution); categorical variables are presented as frequencies and percentages. Between-group comparisons use the t-test (normally distributed continuous variables), the Mann-Whitney U test (non-normally distributed con- tinuous variables), or the chi-square test (categorical variables); 2. PSA-LUNG scores are analyzed using ANCOVA: the PSA-LUNG score at 1 month postoperatively is the dependent variable, group is the independent variable, and the base- line PSA-LUNG score is adjusted as a covariate. 3. The perioperative complication rate is evaluated according to the Clavien-Dindo classification (>= grade II); 4. Changes in pulmonary function are analyzed using the paired t-test or the Wilcoxon signed-rank test; 5. Tumor marker levels are analyzed using the Wilcoxon signed-rank test and the Mann-Whitney U test;
Publication of Study Results	Academic papers

I. Research Background and Rationale

Research Background

With the widespread application of low-dose computed tomography (low-dose CT, LDCT), the detection rate of primary lung cancer characterized by pulmonary ground-glass nodules (GGNs) is increasing, especially multiple GGNs. Multiple high-risk ground-glass opacities (GGOs) of the lung are a common imaging manifestation and are often associated with early lung adenocarcinoma or precancerous lesions, particularly multiple primary lung adenocarcinoma (multiple primary lung cancer, MPLC). MPLC refers to the simultaneous or sequential occurrence of two or more primary malignant tumors in the lungs of the same patient. According to the time interval between the occurrence of different lesions, histological features, and other characteristics, multiple primary lung cancer can be further divided into synchronous multiple primary lung cancer and metachronous multiple primary lung cancer. According to incomplete statistics, approximately 20%–30% of patients with GGNs have multiple GGNs simultaneously1.

According to existing relevant clinical guidelines2, 3, for multiple GGOs, especially nodules with a diameter ≤3 cm and high-risk features
active intervention is needed to reduce the risk of progression to invasive lung cancer. In particular, for patients with MPLC, in addition to surgical resection, ablation is also an effective treatment option. However, because of the strong heterogeneity of the biological behavior of multiple GGOs, a single treatment modality such as surgical resection or ablation alone may find it difficult to balance efficacy and patient trauma.

The main traditional treatment for multiple GGOs is video-assisted thoracoscopic surgery (VATS), especially uniportal VATS, which is widely used in the treatment of early lung cancer because of its minimally invasive nature. For patients with multiple GGOs, multiple or multi-site operations may cause significant impairment of pulmonary function and increase the risk of postoperative complications, such as respiratory insufficiency or infection. At the same time, because endotracheal intubation is often used during conventional VATS, large amounts of anesthetic drugs and muscle relaxants are required, and mechanical ventilation is relied upon. This not only increases airway injury, postoperative sore throat, hoarseness, and other discomfort, but also interferes with pulmonary function and increases the risk of postoperative complications; especially in high-risk patients, the side effects of intubated anesthesia are more significant4.

Tubeless anesthesia thoracoscopic surgery is a modified thoracoscopic surgical technique that significantly reduces postoperative pain, shortens hospital stay, and lowers the risk of complications by avoiding the use of intraoperative endotracheal intubation. Compared with conventional VATS, tubeless anesthesia surgery shows lower invasiveness and faster postoperative recovery in the treatment of early lung cancer and GGOs. Studies have confirmed the safety and feasibility of tubeless surgery in the treatment of early lung cancer and GGOs5. At the same time, the tubeless anesthesia used in this procedure employs intravenous anesthesia, precise

local anesthesia, and visualized nerve block techniques, which can ensure the anesthetic effect in the surgical field while enabling the patient to maintain spontaneous breathing during surgery, thereby avoiding the potential risks of conventional endotracheal intubation and mechanical ventilation[6, 7, 8]. Non-intubated anesthesia has already achieved success in minimally invasive thoracic surgery and has been widely applied. Most existing studies have focused on conventional thoracic surgical procedures such as lobectomy and sublobar resection[9, 10, 11].

As a minimally invasive treatment modality, lung ablation has the advantages of being minimally invasive, allowing rapid recovery, and being highly repeatable. It is now also widely used in the treatment of patients with MPLC, and plays an important role especially in the management of unresectable lesions or in patients in whom preservation of pulmonary function is prioritized[12, 13]. Lung ablation is a technique that precisely destroys target tissue through thermal energy (such as radiofrequency ablation and microwave ablation), freezing (cryoablation), or other energy forms (such as laser ablation), aiming to achieve local tumor control. Current studies indicate that for the selection of different ablation techniques,

[14] radiofrequency, microwave, or cryoablation are all feasible for pulmonary nodules with a diameter <3 cm. Microwave ablation (MWA), as one of the local treatment modalities, mainly raises the temperature through microwave power radiation and maintains it for a period of time, causing coagulation, degeneration, and permanent death of tissue, thereby achieving in situ inactivation of cancerous tissue. Compared with other ablation modalities, its core advantages are mainly reflected in energy delivery efficiency, treatment speed, and adaptability to special lesions. Existing clinical trials have also demonstrated that MWA has a high technical success rate and safety for the treatment of multiple pulmonary nodules, with a relatively small impact on pulmonary function[15, 16, 17, 18].

At present, there is still no consensus on the optimal treatment strategy for patients with MPLC. In clinical practice, individualized decisions are mostly made based on the patient's overall condition and disease progression, and the relevant treatment pathways remain highly controversial. To improve the current treatment of MPLC, some researchers have proposed a shift from the past "surgery-only treatment" to "multimodal combined therapy," in which thermal ablation combined with surgical resection is a feasible and effective approach. Preliminary explorations of combined VATS and microwave ablation have already been reported in clinical trials. Studies have shown that image-guided MWA combined with thoracoscopic resection has potential advantages in the treatment of multiple pulmonary GGO nodules, significantly reducing surgical trauma and showing good short-term outcomes[19]. Relevant clinical trials have also shown that MWA is safe and feasible for residual nodules in patients undergoing VATS for multiple pulmonary nodules, and the postoperative complication rate is often low and mostly mild[20].

Based on the above background, we believe that studying the safety of tubeless anesthesia thoracoscopic surgery combined with simultaneous MWA for the treatment

of multiple high-risk GGOs has important clinical significance and scientific value: tubeless VATS significantly reduces postoperative pain, shortens hospital stay, and lowers the risk of complications by avoiding endotracheal intubation, and is particularly suitable for patients with multiple GGOs who have poor pulmonary function or advanced age. Microwave ablation, as a minimally invasive local treatment modality, has also been shown to have significant advantages in the treatment of deep or surgically difficult GGOs and in preserving patients' pulmonary function.

At present, research on the efficacy and safety of tubeless anesthesia in VATS combined with simultaneous MWA for the treatment of multiple high-risk GGNs is still insufficient. In particular, studies using patient-reported outcomes (PROs) as the core measure are lacking. Although traditional generic PRO scales (such as EORTC QLQ-C30 and SF-36) can provide an overview of overall quality of life, in the highly specific clinical scenario after lung resection their drawbacks—such as lengthy items, lack of disease relevance, and inability to capture the dynamic changes of key perioperative symptoms—are increasingly exposed, seriously limiting the timeliness and individualization of symptom management21. Studies using the Perioperative Symptom Assessment for Patients Undergoing Lung Surgery (PSA-Lung) scale as the core measure can provide more valuable evidence for clinical practice22. The PSA-Lung scale can comprehensively assess postoperative symptoms and functional status from the patient's perspective, helping to more objectively reflect the impact of anesthesia methods on patients' recovery quality23. Therefore, this study aims to compare the efficacy, safety, and impact on PSA-Lung outcomes of tubeless anesthesia versus conventional endotracheal intubation anesthesia in such surgery.

Therefore, this study aims to conduct a multicenter, randomized controlled trial to compare the effect of tubeless anesthesia versus conventional endotracheal intubation anesthesia on health-related quality of life, with the PSA-LUNG scale as the core measure, at 1 month postoperatively in patients undergoing VATS combined with simultaneous MWA for multiple high-risk GGNs. The results of this study will provide clinical evidence for the optimization of perioperative anesthesia strategies in this patient population.

II. Study Objectives

To compare whether, under the premise of receiving the same active treatment of "VATS+MWA," tubeless anesthesia can bring clinically meaningful better postoperative symptom recovery (measured by PSA-LUNG) and higher safety to patients.

III. Study Protocol and Plan 3.1 Protocol Design 3.1.1.1 Inclusion and Exclusion Criteria

Inclusion Criteria:

1. Age 18–80 years;
2. Any sex;
3. Chest CT showing ≥2 multiple high-risk pulmonary ground-glass nodules; the

nodules persisting for more than 3 months; and a high suspicion of malignancy after MDT evaluation. The nodules must meet the following requirements: 1. chest CT showing a maximum diameter ≤2 cm and CTR ≤0.5; 2. surgical nodules: feasible for wedge resection after discussion within the Department of Thoracic Surgery, with an expected resection margin distance ≥2 cm or ≥ the maximum diameter of the nodule;
3. ablation nodules: unsuitable for wedge resection after discussion within the Department of Thoracic Surgery (mainly located in the inner two-thirds of the lung);
4. ECOG performance status score 0–1; preoperative assessment of systemic organ function showing that the participant meets the basic requirements for thoracoscopic surgery and ablation;
5. ASA anesthesia classification I–III;
6. Preoperative PET-CT or other necessary imaging examinations to exclude mediasti nal lymph node metastasis and distant organ metastasis;
7. Life expectancy ≥12 months and able to cooperate with the completion of the entire stu dy process and follow-up;
8. The participant agrees to sign the written informed consent form and is able to com ply with the visits, treatment plan, laboratory tests, and related procedures specified in the protocol.

Exclusion Criteria:
1. Has undergone lung surgery, radiotherapy, or other ablation treatment recently (within 3 months);
2. Has contraindications to surgery, ablation, or anesthesia; unable to tolerate tubeless non-intubated anesthesia (e.g., anticipated intraoperative airway difficulty, laryngeal s tenosis unsuitable for a laryngeal mask, etc.);
3. Plans to receive other treatments during the trial that may affect the study results (e. g., systemic chemotherapy, targeted therapy, etc.);
4. Has a primary malignant tumor in an extrapulmonary organ or active other malignancy;
5. Unable to comply with study-related regulations or unable to undergo follow-up; refusal to s ign the informed consent form;
6. Women who are pregnant or breastfeeding, or who plan to become pregnant during the stud y;
7. Patients considered unsuitable for the study by the investigator;

3.1.1.3 Withdrawal Criteria

Withdrawal from the trial decided by the investigator: If any of the following occurs an d, after assessment of its clinical relevance, the investigator determines that the particip ant cannot continue in this clinical trial, the participant may be withdrawn from the tria l early:
1. Serious complications that affect efficacy evaluation;
2. Suspected unexpected serious adverse events that affect efficacy evaluation;
3. Discontinuation of contraception;
4. Pregnancy;
5. Uncontrolled concomitant other malignancy;

6. Refusal to participate or inability to cooperate with follow-up;
7. Severe intolerance to the trial medical devices;
8. Other administrative reasons;
9. Withdrawal from the trial by the participant: the participant has the right to withdraw from t he trial at any time without giving a reason;

3.1.2 Group

Allocation 3.1.2.1
Group Allocation
Design
This is a randomized controlled study using the random number table method or a computer-generated random sequence (a commonly used method in clinical RCTs). Patients will be assi gned sequentially to two groups according to a preset random sequence (random numbers gen erated by statistical software) in the order of enrollment, so as to ensure the randomness of all ocation. The patients will be divided into two groups: an experimental group and a control gr oup. The experimental group will receive tubeless anesthesia thoracoscopic surgery combined with simultaneous microwave ablation, and the control group will receive conventional intub ated thoracoscopic surgery combined with simultaneous microwave ablation.

3.1.2.2 Sample Size Calculation
This is a two-arm, randomized controlled trial designed to compare the effect of tubeless anes thesia versus conventional endotracheal intubation anesthesia on early postoperative sympto m recovery (with the PSA-LUNG scale as the core measure) in patients undergoing video-ass isted thoracoscopic surgery combined with simultaneous microwave ablation for multiple hig h-risk ground-glass nodules. The sample size calculation is based on the following premises: Primary endpoint: total PSA-LUNG score (0–10) at postoperative month 1; Type of test: com parison of means between two independent samples (two-sided test); Statistical parameters: α = 0.05 (two-sided), β = 0.20 (power 80%); dropout rate of 10%; 1:1 allocation to the two gro ups. Based on published similar studies (PMID: 36290881, PMID: 38896873, PMID: 406928 67, PMID: 38574304, PMID: 41061814), the mean distribution of symptoms at 4 weeks after uniportal VATS reported by Yang et al. showed that the two PRO items with the highest scor es were cough (2.27) and shortness of breath (2.58). In addition, the early postoperative pain and cough scores of non-intubated anesthesia after thoracoscopic lung resection were signific antly lower than those of the intubated anesthesia group, and the cough score in the tubeless g roup reported by Wang et al. was significantly lower (1.10±1.19 vs. 2.08±1.61, P<0.001). Co mbining the characteristics of the PSA-LUNG scale and clinical practice, the following assu mptions are set: mean PSA-LUNG cough score at postoperative day 1 in the control group (in tubated anesthesia): 2.0; mean PSA-LUNG score at postoperative day 1 in the experimental g roup (tubeless anesthesia): 1.0; the between-group mean difference is 1.0, and the standard de viation (SD, based on experience from similar PRO studies): 1.5. The standardized effect size (Cohen's d) is approximately 0.67 (moderate effect).

$$\text{n per group} = (Z_{1-\alpha/2} + Z_{1-\beta})^2 \times 2\sigma^2 / \delta^2 =$$

$Z_{1-\alpha/2} = 1.96$ ($\alpha = 0.05$, two-sided), $Z_{1-\beta} = 0.842$ ($\beta = 0.2$), $\sigma = 1.5$, $\delta = 1.0$; n per group =

$$\frac{(Z_{1-\alpha/2} + Z_{1-\beta})2 \times 2 \times \sigma 2}{\delta^2}$$

35.28, rounded up to 36 per group.

Considering a 10% dropout rate: actual enrollment per group = 36 ÷ (1 − 10%) ≈ 40; therefor e, the total sample size is 80 participants (40 per group).

3.1.3 Target Lesion Screening:
Chest CT showing ⩾2 multiple high-risk pulmonary ground-glass nodules; the nodules persi sting for more than 3 months; and a high suspicion of malignancy after MDT evaluation. The nodules must meet the following requirements: 1. chest CT showing a maximum diameter ⩽ 2 cm and CTR ⩽0.5; 2. surgical nodules: feasible for wedge resection after discussion within the Department of Thoracic Surgery, with an expected resection margin distance ⩾2 cm or ⩾ the maximum diameter of the nodule; 3. ablation nodules: unsuitable for wedge resection a fter discussion within the Department of Thoracic Surgery (mainly located in the inner two-th irds of the lung);

3.1.4 Outcome Measures and Follow-up Plan

3.1.4.1 Primary Study Endpoint

(1) PSA-LUNG scale score. Assessments will be performed preoperatively (one electronic qu estionnaire completed as baseline), in the early postoperative period (on the day of surgery, o n postoperative day 1, and on the day of discharge, with one electronic questionnaire complet ed at each time point), and during the postoperative recovery period (once weekly within 4 w eeks after surgery, with one electronic questionnaire completed each week). This assessment spans the entire perioperative period.

3.1.4.2 Secondary Study Endpoints

(1) Technical success rate: the proportion of procedures in which surgery combined with sim ultaneous ablation is completed successfully without serious technical failure (e.g., failure of ablation needle positioning, failure to resect the target lesion, intraoperative conversion to int ubated mechanical ventilation in the experimental group). (2) Postoperative recovery: includi ng time to ambulation after surgery and total length of hospital stay.
(3) Perioperative complication rate (Clavien-Dindo classification): the proportion of treatmen t-related complications during the perioperative period.

3.1.4.3 Safety Evaluation Endpoints

Incidence of adverse events throughout the study and incidence of procedure-rela ted adverse events: the incidence of adverse events related to surgical and ablation pro cedures within 30 days after ablation (AE & SAE), assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v 5.0.

3.1.4.4 Exploratory Study Endpoints

Tumor marker levels: dynamic changes (absolute values or percentage changes) i n CEA, CYFRA 21-1, NSE, SCC, and Pro-GRP levels preoperatively and postoperati vely (at 1 month);

3.1.4.5 Follow-up Plan

Schedule of Study Procedures							
	Baseline	**Tubeless VATS Combined with Simultaneous Microwave Ablation**	**Follow-up**				
Visit	**Screening**	**Day 0**	**Days 1-7**	**Postoperative Week 1**	**Week 2 after discharge**	**Week 3 after discharge**	**Week 4 after discharge**
Visit Setting	**Outpatient**	**Inpatient**	**Inpatient**	**Online (telehealth)/Outpatient**	**Online (telehealth)/Outpatient**	**Online (telehealth)/Outpatient**	**Online (telehealth)/Outpatient**
Visit Window	14 days before surgery	Within 2 weeks after screening	+/-6 h	+/-3 d	+/-3 d	+/-3 d	+/-3 d
Visit No.	V0	V1	V2	V3	V4	V5	V6
Eligibility check	√						
Informed consent	√						
Demographics	√						
Medical history	√						
Vital signs	√						
Imaging	√						√
Laboratory tests	√						√
Pregnancy test	√						
ASA classification	√						
Pulmonary function test	√						√
Operative time		√					
Technical success rate			√				

PSA-LUNG score	√	√	√	√	√	√	√

Readmission					√		√
Discharge time			√				√
Total hospitalization cost					√		
Concomitant medications	√	√	√	√	√		√
Adverse events (AEs/SAEs)		√	√	√	√		√
Postoperative pain assessment		√	√	√	√		√
Postoperative quality of life assessment		√	√	√	√		√

Note:

1. Demographics: including sex, age (date of birth), weight, height, BMI, and ethnicity;

2. Medical history: present illness (including diagnosis) and past medical history;

3. Vital signs include body temperature, heart rate, respiratory rate, systolic blood pressure, and diastolic blood pressure; the vital signs on the day of surgery are the first vital signs recorded after the participant returns to the ward following recovery from general anesthesia;

4. The investigator will select appropriate imaging examinations according to the participant's specific situation, including chest X-ray, CT, MRI, ultrasound, radionuclide imaging, PET, and other methods; imaging examinations during the screening/baseline period may accept results obtained before signing informed consent and within 30 days before surgery that are deemed acceptable by the investigator;

5. Laboratory tests during the baseline period include: complete blood count (including white blood cell count (WBC), neutrophil count (NEUT), lymphocyte count (LYMPH), red blood cell count (RBC), hemoglobin (Hb), platelet count (PLT), neutrophil percentage (NEUT%), and lymphocyte percentage (LY%)); blood biochemistry (including albumin (ALB), total protein (TP), alanine aminotransferase (ALT), aspartate aminotransferase
(AST), total bilirubin (TBIL), serum creatinine (CREA), blood urea nitrogen (BUN)/urea (Urea), blood glucose (GLU), serum calcium (Ca), serum potassium (K), serum sodium (Na), and serum chloride (Cl)); coagulation function (including prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen (FIB), thrombin time (TT), and tumor markers); all participants undergo two infection-related tests at baseline (human immunodeficiency virus antibody and Treponema pallidum antibody); laboratory tests may accept results obtained before signing informed consent and within 30 days before surgery that are deemed acceptable by the investigator (if more than one result is available, the result closest to the time of surgery
shall be used).

6. During the follow-up period, the investigator will select appropriate laboratory tests according to the participant's specific situation: for example, tumor marker levels: dynamic changes (absolute values or percentage changes) in CEA, CYFRA 21-1, NSE, SCC, and Pro-GRP levels postoperatively (at 1, 3, 6, and 12 months)

7. Pregnancy test: blood or urine pregnancy testing for premenopausal women;

8. Concomitant medications to be recorded: during the screening/baseline period, record medications for the present illness in the previous 1 month, anticoagulant/antiplatelet medications within 7 days before surgery, medications for preventing surgical complications (e.g., antibiotics), and any drug abuse (e.g., cocaine)
Intraoperative normal saline need not be recorded; if antitumor drugs are used concurrently, or if drugs that may affect the success of surgery are used, they should be recorded; during the follow-up period, record medications for the present illness and concomitant medications for AEs and SAEs; routine intraoperative medications are not recorded;

9. Symptoms or diseases present at the time of participant screening should be regarded as baseline and not reported as adverse events; if some stress reactions during the surgical treatment period are caused by surgery, such as pain, fever (<=38.5C), abnormal complete blood count, etc., if

Stress reactions within the surgical treatment period judged by the investigator as attributable to surgery need not be recorded as AEs; however, if the participant's postoperative condition deteriorates and medical measures are taken for intervention (e.g., drug treatment), the event should be recorded as an adverse event.

Schedule of Study Procedures

	Baseline	Intubated Anesthesia VATS Combined with Simultaneous Microwave Ablation	Follow-up				
Visit	**Screening**	**Day 0**	**Days 1-7**	**Postoperative Week 1**	**Week 2 after discharge**	**Week 3 after discharge**	**Week 4 after discharge**
Visit Setting	**Outpatient**	**Inpatient**	**Inpatient**	**Online (telehealth)/Outpatient**	**Online (telehealth)/Outpatient**	**Online (telehealth)/Outpatient**	**Online (telehealth)/Outpatient**
Visit Window	14 days before surgery	Within 2 weeks after screening	+/-6 h	+/-3 d	+/-3 d	+/-3 d	+/-3 d
Visit No.	V0	V1	V2	V3	V4	V5	V6
Eligibility check	√						
Informed consent	√						
Demographics	√						
Medical history	√						
Vital signs	√						
Imaging	√						√
Laboratory tests	√						√
Pregnancy test	√						
ASA classification	√						
Pulmonary function test	√						√

Operative time		√					
Technical success rate			√				
PSA-LUNG score	√	√	√	√	√	√	√
Readmission					√		√
Discharge time			√				√
Total hospitalization cost					√		
Concomitant medications	√	√	√	√	√		√
Adverse events (AEs/SAEs)		√	√	√	√		√
Postoperative pain assessment		√	√	√	√		√
Postoperative quality of life assessment		√	√	√	√		√

Note:

3. Demographics: including sex, age (date of birth), weight, height, BMI, and ethnicity;

4. Medical history: present illness (including diagnosis) and past medical history;

5. Vital signs include body temperature, heart rate, respiratory rate, systolic blood pressure, and diastolic blood pressure; the vital signs on the day of surgery are the first vital signs recorded after the participant returns to the ward following recovery from general anesthesia;

6. The investigator will select appropriate imaging examinations according to the participant's specific situation, including chest X-ray, CT, MRI, ultrasound, radionuclide imaging, PET, and other methods; imaging examinations during the screening/baseline period may accept results obtained before signing informed consent and within 30 days before surgery that are deemed acceptable by the investigator;

7. Laboratory tests during the baseline period include: complete blood count (including white blood cell count (WBC), neutrophil count (NEUT), lymphocyte count (LYMPH), red blood cell count (RBC), hemoglobin (Hb), platelet count (PLT), neutrophil percentage (NEUT%), and lymphocyte percentage (LY%)); blood biochemistry (including albumin (ALB), total protein (TP), alanine aminotransferase (ALT), aspartate aminotransferase
(AST), total bilirubin (TBIL), serum creatinine (CREA), blood urea nitrogen (BUN)/urea (Urea), blood glucose (GLU), serum calcium (Ca), serum potassium (K), serum sodium (Na), and serum chloride (Cl)); coagulation function (including prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen (FIB), thrombin time (TT), and tumor markers); all participants undergo two infection-related tests at baseline (human immunodeficiency virus antibody and Treponema pallidum antibody); laboratory tests may accept results obtained before signing informed consent and within 30 days before surgery that are deemed acceptable by the investigator (if more than one result is available, the result closest to the time of surgery
shall be used).

8. 6. During the follow-up period, the investigator will select appropriate laboratory tests according to the participant's specific situation: for example, tumor marker levels: dynamic changes (absolute values or percentage changes) in CEA, CYFRA 21-1, NSE, SCC, and Pro-GRP levels postoperatively (at 1, 3, 6, and 12 months)

9. Pregnancy test: blood or urine pregnancy testing for premenopausal women;

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3.1.5 Data Management and Data Processing

3.1.5.1 Data Recording Procedures

Data will be collected and entered through a pre-designed electronic data capture (EDC) system. All investigators will receive training on the EDC system to ensure accurate data entry. Double data entry will be performed by two independent data managers to avoid entry errors.

3.1.5.2 Statistical Analysis

Statistical analysis will be performed according to a pre-defined statistical analysis plan. The analysis will be conducted by qualified biostatisticians using statistical software. Randomization will be performed to assess the effect of the study intervention.

Principles for the analysis of cases converted to intubated mechanical ventilation during surgery:

1. Intention-to-treat (ITT) principle: all patients randomly assigned to the experimental group (tubeless anesthesia), regardless of whether they are converted to intubated mechanical ventilation during surgery, will be included in the primary endpoint analysis according to their original randomization. The conversion to intubation itself will not be used as a reason for exclusion or for changing the group assignment.

2. Primary endpoint PSA-LUNG score: converted patients will still complete the PSA-LUNG follow-up as members of the experimental group after surgery, and their scores will be summarized in the experimental group.

3. Definition of technical success rate: for cases converted to intubated mechanical ventilation for any reason during surgery, the technical procedure will be counted as "failure to maintain tubeless anesthesia until the end of surgery," and the case will be marked as "failure" in the technical success rate indicator. However, the patient will remain in the experimental group for ITT analysis.

4. Sensitivity analysis: to verify the robustness of the conclusions, the following analyses will be performed simultaneously: As-Treated Analysis: converted cases will be classified into the "actually received intubated anesthesia" subgroup in the postoperative analysis; Per-Protocol (PP) Analysis: only experimental group patients who were not converted to intubation during surgery and who completed all follow-up will be included. If the ITT and PP conclusions are consistent, the credibility of the main conclusion will be enhanced; if they are inconsistent, the potential impact of conversion to intubation on the results will be explained in the discussion.

5. Handling of missing data: if converted patients are unable to complete the PSA-LUNG assessment at a certain time point after surgery for reasons such as transfer to the ICU, that time point will be recorded as missing and handled using a mixed-effects model for repeated measures (MMRM) or multiple imputation (MI).

3.1 总体流程图

3.1.5.3 Quality Control

Quality control measures will run throughout the entire study, from data collection to analysis. Regular internal quality reviews will be conducted to ensure data accuracy and procedural compliance. Any data corrections will be documented in accordance with standard operating procedures (SOPs), and the original records will be preserved.

3.1.5.4 Data and Safety Monitoring Plan

Investigators will conduct medical monitoring through an internal intelligent medical monitoring system. Participant information collected through the EDC system can be imported into the medical monitoring system, and continuous medical monitoring activities will be carried out by the MM, including reviewing relevant medical data at the individual patient level based on individual and aggregate data (including external data), reviewing individual patient data meeting certain criteria, and enabling query-based communication and exchange among investigators/CRAs. The scope of medical data monitoring mainly includes:

① Eligibility review;

② Medical data monitoring;

③ Review and consistency check of SAEs.

3.1.5.5 Monitoring/Auditing

Independent monitors (clinical research monitors) will visit the study centers regularly to ensure adherence to the protocol, implementation of SOPs, and verification of study data. The monitoring process will include review of source documents, assessment of the consent process, and verification of data quality. Independent audits initiated by the sponsor, regulatory authorities, or Ethics Committee will be accepted to ensure the compliance of the study and the integrity of the data.

3.2 Implementation Plan

3.2.1 Project Schedule

Time Point	**Phase**
2026.01-2026.03	**Preparation phase** **Ethics approval and regulatory filing** **Training of investigators and relevant staff** **Development and testing of study tools and the data management system; preparation for participant recruitment**
2026.04-2027.04	**Recruitment and implementation phase** **Participant recruitment and screening** **Implementation of allocation and interventions; data collection and entry** **Monitoring and interim data analysis**

2027.05-2027.06	**End of data collection** **Last follow-up of the last participant** **Data cleaning and database lock; preparation for the final analysis**
2027.07-2027.09	**Data analysis and report writing** **Data analysis** **Drafting the report** **Internal and external dissemination of study results**

IV. Risks and Benefits

4.1 Safety Evaluation

4.1.1 Timing of Laryngeal Mask Removal

The patient is awake and can open the eyes when called (Ramsay score ≤2); when breathing air through the laryngeal mask: SpO_2 >95% maintained for 5–10 minutes (or PaO_2 >85 mmHg, $PaCO_2$ <50 mmHg);

Tidal volume >6–8 mL/kg; stable hemodynamic parameters. 4.1.2 Conversion to Another Anesthesia Mode Indications for conversion: Hypoxemia: SpO_2 <85% or hypercapnia with $PaCO_2$ ≥80 mmHg without improvement despite attempts at synchronized intermittent mandatory ventilation, and meeting any of the following criteria:

1) Hemodynamic instability: heart rate >100 beats/min, or a change in systolic blood pressure >30% from baseline, accompanied by blood gas analysis suggesting a metabolic cause, or requiring inotropic support;

2) Arrhythmias not caused by surgical stimulation (e.g., frequent atrial or ventricular premature beats ≥6 beats/min); 3) pH <7.15 on two arterial blood gas analyses (at least 15 minutes apart); 4) excessive bulging of the surgical field causing operative difficulty that does not improve after drug treatment and lasts >5 minutes; 5) significantly increased tracheal secretions or the appearance of bloody secretions leading to aggravation of dyspnea and airway obstruction. Irreversible decrease in tidal volume >30% during spontaneous breathing, or peak pressure >20 cmH_2O during mechanical ventilation; 6) persistent cough (>2 times/min) despite anesthesia of the visceral pleural surface and blockade of the vagus nerve.

3.1 总体流程图

4.1.3 Strategy for Conversion to Endotracheal Intubation:

Patient safety absolutely takes priority over study integrity. At any time during surgery, if the attending anesthesiologist determines that the patient cannot safely maintain spontaneous breathing, regardless of whether the quantitative conversion criteria below are met, the anesthesiologist has the right to immediately perform endotracheal intubation and mechanical ventilation without requesting the investigator or waiting for confirmation from the randomization system. This decision is not restricted by the study protocol and is not regarded as a protocol deviation.

4.1.3.1 Three-Tier Stepped Monitoring and Conversion Criteria
Grade I (warning phase): SpO_2 90–92% and/or $PaCO_2$ 55–65 mmHg. Management: increase oxygen flow, adjust position, deepen sedation, and provide mask-assisted ventilation. Record in the anesthesia record.
Grade II (intervention phase): SpO_2 85–89% and/or $PaCO_2$ 65–80 mmHg and/or pH 7.20–7.25. Management: immediately insert a laryngeal mask or provide nasal high-flow oxygen therapy, manually assist breathing, and call the second-line anesthesiologist. If the condition returns to below Grade I within 30 minutes, it is not regarded as conversion to intubation; if it continues to deteriorate, proceed to Grade III.
Grade III (mandatory conversion phase): SpO_2 <85% and/or $PaCO_2$ ≥80 mmHg and/or pH <7.15 and/or apnea or severe hemodynamic disturbance. Management: immediate endotracheal intubation and mechanical ventilation, and initiation of the emergency rescue process.
4.1.3.2 Requirements for Recording Conversion
Within 5 minutes after completion of the conversion, the anesthesiologist must notify the investigator verbally and record in the anesthesia record: the time point of conversion, the blood gas parameters immediately before conversion (SpO_2, $PaCO_2$, pH), the reason for conversion, and the duration of Grade II warning. This event will be reported separately as a safety endpoint (AE/SAE).
4.1.3.3 Specific Intubation Strategy: Preoperatively, before positioning the patient on the operating table, an additional sheet must be placed beneath the patient's back so that, in an emergency, the patient can be rapidly turned from the lateral to the supine position. This will create better conditions for emergency intubation. Before turning the patient to the supine position, the surgeon can close the small VATS incisions with a thick silk suture within seconds.
Before the start of surgery, the scrub nurse should prepare several large sterile surgical drapes for standby use. These drapes are preferably transparent and can be used to quickly cover the opened thoracic cavity to keep the wound sterile.
1) Single-lumen endotracheal tube + bronchial blocker (preferred);
Double-lumen endobronchial tube (if lung isolation is required because of airway bleeding, a double-lumen endotracheal tube is recommended).
2) Endotracheal intubation in the lateral decubitus position:
Position the head and neck parallel to the body's midline, or tilt the operating table 30 degrees toward the supine position; support the head with a small square pillow to make the anterior-inferior area of the mouth and nose more accessible;
Use of a video laryngoscope is recommended;
Apply tube shaping;
Close cooperation of two medical staff trained in uniportal thoracoscopic surgery is required.

4.1.4 Adverse Event (AE) Definition: An AE refers to any unfavorable medical event that occurs in a participant or clinical trial subject after receiving a drug or treatment regimen
and does not necessarily have a causal relationship with the treatment.
An AE may be any unpleasant sign (including abnormal laboratory test results),

symptom, or disease that has a temporal relationship with the use of a medical product, regardless of whether it is considered related to the medical product. According to regulatory requirements, events occurring before and after treatment are also considered AEs. Therefore, safety monitoring of AE
or SAE reporting should begin when the participant enters the trial (signs the informed consent form) and continue until the end-of-study visit.
AE Grading:

AEs are graded 0–5 according to the NCI Common Terminology Criteria for Acute and Subacute Toxicity (NCI-CTCAE 5.0). For AEs not listed in the NCI toxicity grading criteria, the following criteria may be used for judgment:
Grade I: Mild; asymptomatic or with mild clinical symptoms; only clinical or laboratory abnormalities; no treatment required; no effect on normal daily activities;
Grade II: Moderate; requires minimal, local, or non-invasive treatment; affects normal daily activities (cooking, shopping, making phone calls, counting money, etc.);
Grade III: Severe or medically significant symptoms but not immediately life-threatening; causes hospitalization or prolongation of hospitalization; causes disability; inability to work or perform normal daily activities (bathing, dressing, undressing, eating, using the toilet, taking medication, etc.), but not bedridden;
Grade IV: Life-threatening; requires emergency treatment;
Grade V: Death due to an adverse event.

AE Recording

The name, severity, time of onset, duration, management measures, and outcome of each AE occurring during the trial should be recorded in detail and truthfully filled in the case report form (CRF). Abnormal laboratory test data should be recorded on the CRF, and the test should be repeated at least once a week, with follow-up until return to normal or the end of the study. Adverse events occurring within 30 days after the last administration should be reported and recorded.

4.1.5 Serious Adverse Events (SAE)

1) A serious adverse event (SAE) refers to a medical event occurring during a clinical trial that requires hospitalization or prolongs hospitalization, causes disability, affects work ability, is life-threatening or fatal, or causes congenital malformation, including the following unexpected medical events: events leading to death; life-threatening events (defined as the participant being at risk of death at the time of the event); events requiring hospitalization or prolongation of hospitalization; events that may cause permanent or severe disability/dysfunction; carcinogenesis or teratogenesis; drug overdose. In particular, for tubeless anesthesia, potential risks include respiratory depression, hypoxemia, and hypercapnia. 2) Drug exposure during pregnancy/lactation. In principle, pregnancy and lactation are part of the inclusion/exclusion criteria. If pregnancy occurs during the study, the patient should withdraw from the study immediately and notify the investigator immediately, and the patient should be followed up throughout the entire pregnancy and postpartum period. Even if both mother and child are completely normal without any adverse events, the outcome should be recorded. Even if pregnancy is not an SAE, it should be reported using the SAE report form. 3) Disease progression (including symptoms and signs of progression) should not be reported as a serious adverse event; however, death due to

disease progression within the trial or safety reporting period should be reported as a serious adverse event. Hospitalization due to symptoms and signs of disease progression should not be reported as a serious adverse event. Within the trial or safety reporting period, if the final outcome of cancer is death, the event leading to death must be reported as a serious adverse event. 4) Receiving other antitumor therapy: if the participant begins other antitumor therapy, the reporting period for non-fatal adverse events ends at the start of the new antitumor therapy. If death occurs within the serious adverse event reporting period after the end of study treatment, it must be reported regardless of whether the patient received other treatment. 5) Hospitalization: adverse events leading to hospitalization or prolongation of hospitalization during a clinical study should be regarded as serious adverse events. Any first-time admission to a medical institution (even if shorter than 24 hours) meets this criterion. Hospitalization does not include the following: admission to rehabilitation facilities, nursing homes, routine emergency room visits, same-day surgery (e.g., outpatient/same-day/ambulatory surgery), hospitalization unrelated to worsening of an adverse event, or prolongation of hospitalization that is not itself a serious adverse event, for example: admission for a pre-existing disease without new adverse events and without worsening of the pre-existing disease (e.g., for examination of laboratory abnormalities that have persisted since before the trial); hospitalization for adminis trative reasons (e.g., routine annual physical examination); hospitalization specifie d by the protocol during a clinical trial (e.g., procedures performed according to th e protocol); elective hospitalization unrelated to worsening of an adverse event (e. g., elective cosmetic surgery); pre-planned treatment or surgery should be recorde d in the entire trial protocol and/or the participant's baseline data; admission solely for the use of blood products. Diagnostic or therapeutic invasive procedures (e.g., surgery) and non-invasive procedures should not be reported as adverse events. Ho wever, if the disease condition leading to such a procedure meets the definition of an adverse event, it should be reported; for example, acute appendicitis occurring during the adverse event reporting period should be reported as an adverse event, a nd the appendectomy performed for it should be recorded as the treatment for that adverse event.

6) Drug overdose: drug overdose refers to the participant taking additional study medication within 24 hours (the specific time adjusted according to the specific protocol), with the dose exceeding that specified in the investigator's order. All cases of study drug overdose should be reported as serious adverse events regardless of whether they are related to adverse events/serious adverse events.

SAE Reporting Procedures

Reporting of serious adverse events should begin from the participant's signing of the informed consent form and continue until 30 calendar days (including day 30) after the last use of the study drug. During the trial, if a serious adverse event occurs, it must be reported to the clinical monitor and the principal investigator within 24 hours, and the Serious Adverse Event (SAE) Report Form for New Drug Clinical Research must be completed, signed, and dated, and immediately reported by fax to the sponsor, the leading unit, the Ethics Committee of the study unit, the National Medical Products Administration (NMPA, formerly CFDA), and the food and drug administration of the province or city where the investigator is located.

During the continued drug supply period after the end of the study, if a serious adverse event occurs, it must be reported to the sponsor within 24 hours. All information on serious adverse events should be recorded in the serious adverse event form. Serious

adverse events occurring during the continued drug supply period and up to 30 days after the last administration must be reported. Serious adverse events occurring more than 30 days after the last administration generally need not be reported unless they are suspected to be related to the study drug.

Serious adverse events should be recorded in detail with respect to symptoms, severity, time of onset, time of management, measures taken, follow-up time and method, and outcome. If the investigator considers that a serious adverse event is unrelated to the study drug but potentially related to the study conditions (e.g., discontinuation of the original treatment or complications during the trial), this relationship should be described in detail in the narrative section of the serious adverse event page of the case report form. If the intensity of an ongoing serious adverse event or its relationship to the study drug changes, the serious adverse event follow-up report should be sent to the sponsor immediately. All serious adverse events should be followed up until recovery or stabilization.

4.2 Participant Benefits

The treatment strategies for multiple high-risk ground-glass nodules are curre ntly controversial. Local thermal ablation provides good survival benefits for grou nd-glass nodules and can better preserve patients' pulmonary function. At the same time, according to previous research data, minimally invasive thoracoscopic surge ry under non-intubated anesthesia can provide better benefits through relevant diag nosis and treatment. However, participation in this study may also fail to provide b enefits because of individual differences. In addition, patients can receive high-qu ality care and attention from the medical team preoperatively and postoperatively, and can still receive regular disease follow-up from the team after the completion of this study. Combining the two approaches or performing multiple local interven tional treatments may directly benefit patients or enhance the antitumor effect. In a ddition, physicians will provide professional guidance on disease diagnosis, diseas e tracking and observation, and treatment.

V. Dissemination of Study Results

The publication of the results of this clinical study will strictly follow the Declaration of Helsinki, ensuring that the study data are authentic and reliable, the methods are scientifically rigorous, and there is no data fabrication, falsification, or selective reporting. This study upholds scientific, objective, and fair principles; negative, inconclusive, or positive results will all be made public through appropriate channels, so as to eliminate publication bias and contribute authentic and comprehensive information to the medical field.

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