Annex 3.

Ruijin Hospital of Shanghai Jiaotong University School of Medicine Programme of Scientific Research Projects Involving Human Subjects

(Applicable to prospective studies)

Study Name: Surgical strategies after neoadjuvant or induction chemoimmunotherapy in operable non-small cell lung cancer

Programme No.: NA

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Ruijin Hospital of Shanghai Jiao Tong University School of Medicine

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1. Research Summary

1.1 Abstracts

Study title： Surgical strategies after neoadjuvant or induction chemoimmunotherapy in operable small cell lung cancer

Research Brief: Lung cancer is one ofthe most common malignant tumors worldwide and has the highest mortality rate among malignant tumors. In recent years, with the gradual development oftherapeutic modalities such as targeted therapy and immunotherapy, the overall survival oflung cancer patients have improved significantly. However, late tumor staging at the time of diagnosis often leaves patients with only pneumonectomy, which affects the prognosis with a higher rate ofpostoperative complications than lobectomy, poorer quality oflife, and the possible loss ofthe opportunity to continue adjuvant therapy.

Our group proposes to conduct this single-arm prospective clinical study to investigate the feasibility, safety, and prognosis ofthe conversion from pneumonectomy to lobectomy after neoadjuvant or induction therapy in patients with operable non-small cell lung cancer.

Study Objective： Primary objective: to investigate the feasibility of switching to lobectomy after neoadjuvant/induced chemoimmunotherapy in patients with operable non-small cell lung cancer requiring pneumonectomy at first diagnosis (R0 resection rate oflobectomy).

Secondary objective: to investigate the perioperative and long-term outcomes of patients with operable non-small cell lung cancer who were evaluated to undergo pneumonectomy at first diagnosis and switched to neoadjuvant or induction chemoimmunotherapy and subsequent lobectomy.

Study population: 50 cases

1） Patients voluntarily participated in this study, had good compliance, could cooperate with the trial requirements to complete observation and follow-up, and signed the informed consent form;

2） Be over 18 and under 75 years ofage, and is open to both men and women;

3） Pathologically confirmed non-small cell lung cancer and clinical stage T2-4N0-2, potentially need pneumonectomy, neoadjuvant, or induction Chemo-immunotherapy

4） ASA rating: I-III.

5） Cardiac function assessment was adequate for radical lung cancer surgery with normal liver and kidney function.

Study unit/location： This is a multicenter study with 4 centers proposed to participate in.

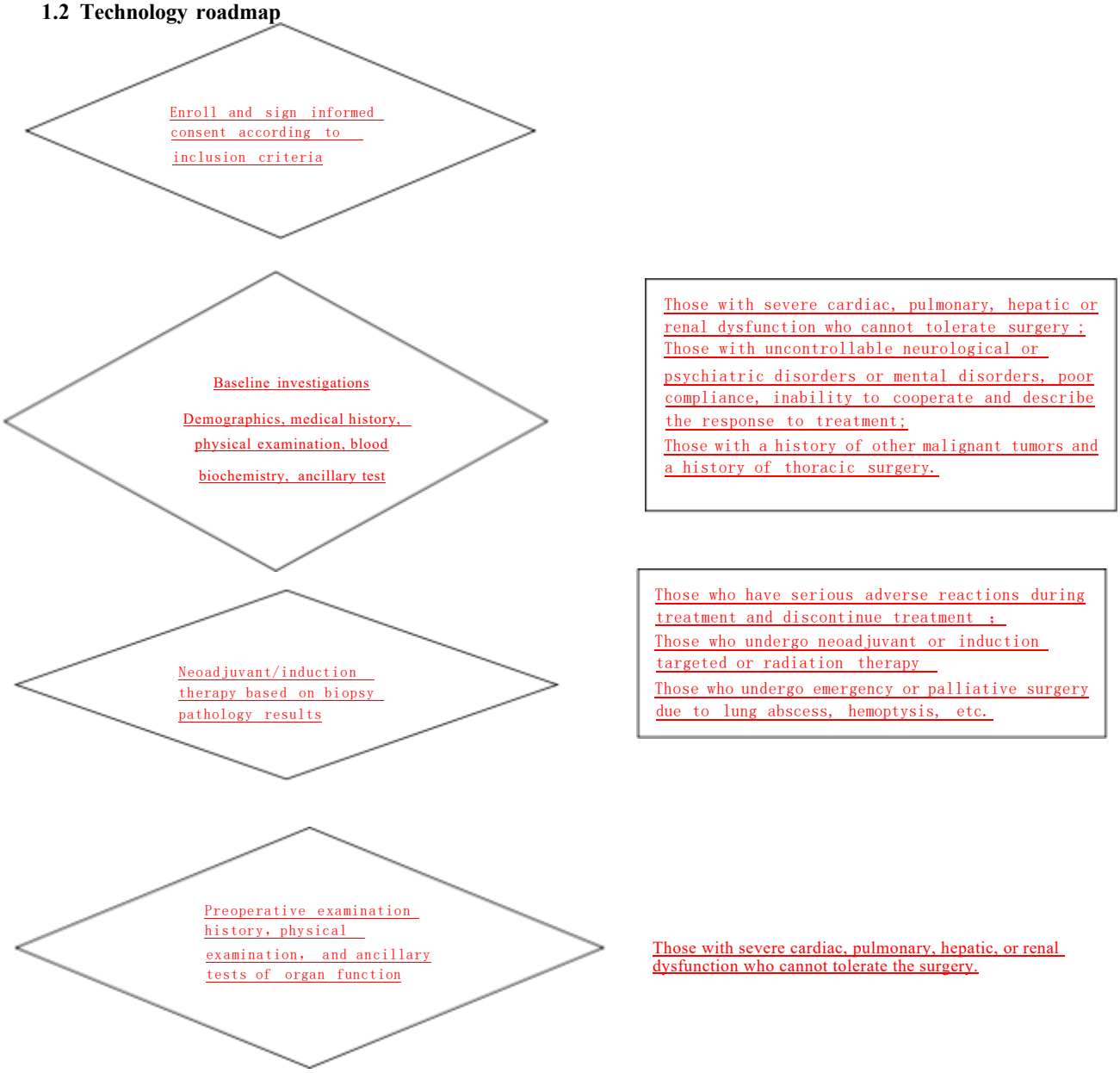
Study interventions： Patients enrolled will further undergo relevant examinations (including chest enhancement CT, PET-CT (optional), cranial MR, bronchoscopy, cardiac ultrasound, pulmonary function, electrocardiogram, and blood tests) and be checked for contraindications to surgery, then be evaluated whether be

amenable to surgical treatment after multidisciplinary discussion (Department of thoracic surgery, department of respiratory medicine, department of radiology). Open or minimally invasive radical lung cancer surgery and systematic lymph node dissection will be performed on eligible patients. The perioperative complications, lymph node dissection, R0 clearance rate, 3-year event-free survival rate, overall and disease-free survival time, quality of life, and pulmonary function will be recorded and analyzed.

Study duration： 5 years

Duration of subject participation : 3 years

1.2 Technology roadmap



2. Background of the Study

2.1 Significance of the study

Lung cancer is one of the most common malignant tumors worldwide, and the number of new lung cancer cases is expected to be as high as 1.8 million worldwide in 2019 [1]. The mortality rate of lung cancer is the highest among malignant tumors, and one-fifth of all malignant tumor deaths worldwide are due to lung cancer [1].

In recent years, lobectomy is no longer the only option for some early-stage lung cancer patients. Sub-lobe resection can achieve better protection of lung function with the same prognosis. Meanwhile, with the gradual development of targeted therapy, immunotherapy and other treatment modalities, more patients benefit from preoperative tumor downstaging. However, pneumonectomy is still preferred as the first choice for operable patients with tumors invading the main pulmonary artery and main bronchus, even achieving tumor downstaging after neoadjuvant therapy. Pneumonectomy is often associated with higher rates of perioperative complications and mortality than lobectomy, and a higher proportion of patients undergoing total pneumonectomy are lost to postoperative adjuvant therapy, which may have an impact on long-term survival. There is currently no evidence to support the decision to convert to lobectomy in this population.

We propose to conduct a single-arm prospective clinical study to investigate the feasibility, safety, perioperative and long-term outcomes of surgery (converting to lobectomy of pneumonectomy) in patients with locally progressive operable non-small cell lung cancer after neoadjuvant therapy.

2.2 Background

For operable early lung cancer, sub-lobe resection has been demonstrated to achieve similar oncologic outcomes compared with lobectomy [2, 3], while preserving the lung function. Pneumonectomy remains the standard surgical procedure for patients whose surgical strategies are pneumonectomy initially, although tumor downstaging after neoadjuvant therapy. More evidence is needed to determine whether the extent of surgical resection can be reduced for these patients.

Although pneumonectomy ensures a good R0 clearance rate, it is associated with a higher rate of perioperative complications and mortality than lobectomy. 355 patients with pneumonectomy were retrospectively analyzed by Gregory D. Jones' team [4], and the mortality rates were 3.7%, 4.5%, and 6.8% at in-hospital, 30 days, and 90 days, respectively, for non-oncological causes. 30- and 90-day readmission rates were 13% and 19%, respectively. The rate of readmission within 30 and 90 days was 13% versus 19%, with cardiopulmonary complications being the most common cause. In retrospective studies [5-8], the 30-day complication and mortality rates for total lung resection were 30% and 5%-8%, compared with 4%-10% and 0%-3% for lobectomy. In addition, the 90-day mortality rate after total lung resection can be 1-2 times higher than the 30-day mortality rate [9-10]. A controlled study published in the Annals of Surgery in 2022 [11] compared postoperative

complications and mortality rates between pneumonectomy and lobectomy by propensity score matching, and showed that the complication rates of grade III or higher and mortality at 90 days were significantly higher in the group of pneumonectomy than lobectomy (21% vs. 13% and 6.9% vs. 1.9%, respectively), The three complications with the highest rates were hypoxemic respiratory failure, bronchopleural fistula, and intrathoracic hemorrhage. In addition, cardiovascular complications were significantly higher in the pneumonectomy group.

Marc Riquet's team [12] retrospectively analyzed the 10-year survival of 1466 patients undergoing pneumonectomy, and the 5-year and 10-year survival rates were 32% and 19%, respectively. In the analysis of risk factors affecting long-term survival, the investigators found that patients' general physical status and tumor biology were closely related to prognosis, and that the occurrence of nonfatal postoperative complications independently increased the long-term risk of death, which was considered to be indicative of the fragility of patients' general physical status. The investigators compared the long-term survival of patients in the lobectomy versus pneumonectomy groups using propensity score analysis. Cumulative nonneoplastic mortality at 2 years was twice as high in the pneumonectomy group as in the lobectomy group (21% versus 11%), and cumulative nonneoplastic mortality at 5 years was 24% versus 13% in the pneumonectomy group and 2% in the lobectomy group, with the risk of nonneoplastic death increasing by 9% in pneumonectomy group versus 2% in lobectomy group over the postoperative period. The risk of non-tumor death increased by 9% in the total pneumonectomy group and by 2% in the lobular group at 1-2 years. The most common causes of death in both groups were pneumonia and myocardial infarction, both of which were significantly higher in the pneumonectomy group. These non-oncologic deaths are attributable to the impaired general health status of patients after pneumonectomy. A prospective controlled cohort study by Ulrik Sartipy's team [13] found that patients in the pneumonectomy group had a more pronounced decrease in strength scores than those in the lobectomy group (-32% vs. -17%). Recovery from this decline in strength scores was different between the two groups, with Bram Balduyck's team [14] finding that strength scores in patients who underwent lobectomy returned to baseline levels within 1 month after surgery, which supports the idea that adjuvant therapy is often initiated in the first month after surgery, whereas in patients who underwent pneumonectomy, strength scores did not return to baseline levels after 1 year of follow-up. The physical strength scores did not return to baseline after 1 year of follow-up. Patients with pneumonectomy were more likely to have dyspnea, pain, and shoulder dyskinesia than those with lobectomy. Because of the decline in general physical status and strength scores, a significant proportion of patients undergoing pneumonectomy did not receive postoperative adjuvant therapy. In the study by Filippo Lococ's team [15], nearly half of the patients did not receive postoperative adjuvant therapy, although the benefit of postoperative adjuvant chemotherapy on long-term survival has been demonstrated in clinical studies [16]. Recent advances in neoadjuvant/adjuvant combination of immuno- and chemotherapy [17] have

increased the rate of long-term survival benefit in patients with operable lung cancer, whereas the loss of access to adjuvant therapy in pneumonectomy patients potentially compromises their long-term survival benefit.

According to the existing clinical studies, patients after pneumonectomy face higher perioperative complications and mortality, and their long-term survival is impaired due to the loss of adjuvant therapy or non-tumor factors, and their quality of life scores are also lower. Taking into account the high efficiency and downstaging rate of neoadjuvant therapy for lung cancer, strict patient screening was performed to reduce surgical trauma while ensuring R0 resection (from pneumonectomy to lobectomy/sleeve lobectomy after neoadjuvant therapy). Reduce perioperative complications and mortality in this population and increase the proportion of postoperative adjuvant therapy for potential long-term survival benefits and improved quality of life. Prospective evidence is lacking. Therefore, our group would like to conduct this single-arm prospective clinical study to explore the safety, feasibility, and long-term outcome of reducing the scope of surgery after neoadjuvant therapy for locally progressive NSCLC, in order to lay the foundation for further research and clinical application.

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2.3 Expected results of the research

1) Expected to publish 2-3 papers in SCI/EI indexedjournals.

2) Expected to participate in international academic conferences 1-2 times, national

conferences 3-4 times.

2.4 Risk/benefit assessment

2.4.1 Known potential risks

Radical lung cancer surgery is a widely practiced treatment for early stage lung cancer, including pneumonectomy, double lobectomy, sleeve lobectomy and lobectomy or segmental resection, etc. The common potential risks are perioperative complications, including intraoperative or postoperative bleeding, persistent air leakage, lung infections, pleural effusions, and an increase in the rate of local recurrence.

2.4.2 Known Potential Benefits

Narrowing surgical resection in cases that do well on neoadjuvant or induced chemoimmunotherapy preserves lung function, potentially reducing the risk of perioperative complications, and death. It protects the patient's general state of health, reduces the incidence of long-term non-tumor deaths, maintains a high physical strength score, facilitates adjuvant therapy follow-up, and may result in a long-term survival benefit for the patient.

2.4.2 Assessment of potential risks/benefits

It has been shown in retrospective studies that total pneumonectomy is only performed when lobectomy is difficult to achieve R0 resection and is associated with higher perioperative complications and mortality than lobectomy, with a significant impact on the patient's general state of health and strength scores, which may contribute to impaired long-term survival. In patients who do well on neoadjuvant or induction therapy, conversion to lobectomy can potentially reduce the incidence of perioperative adverse events, reduce the risk of immediate and long-term non-tumor death, protect the patient's general health and strength scores, and increase the patient's chances of receiving postoperative adjuvant therapy, thereby reducing the risk of tumor-related death.

Risk-minimizing measures: Select patients with good results of neoadjuvant or induction therapy according to strict admission criteria, review the tracheoscopic biopsy before surgery to clarify the status of the bronchus to be preserved, take frozen pathology to clarify the status of the nearest incision margins during the surgery to decide the actual surgical method, and maintain adjuvant therapy after the surgery to minimize the possibility of increasing the risk of local recurrence. Postoperatively, the patient's vital signs, drainage, and air leakage were closely observed to ensure perioperative safety.

Preoperative and intraoperative reassessment

1 Bronchoscopic biopsy of bronchial mucosa to be preserved/EBUS to assess the condition of the outer wall of the preserved bronchus.

2 In cases of main pulmonary artery invasion prior to neoadjuvant therapy, intraoperative

freezing is performed to assess the status ofthe arterial wall at the site oforiginal invasion.

3 For cases with transverse fissure invasion, pulmonary fissure margins were frozen for pathologic evaluation.

3. Information on the principal investigator

3.1 Name, qualifications, and contact information of the principal investigator

Name:Li Hecheng
Sex:Male
Age: 48 years old
Specialty:Thoracic Surgery
Title:ChiefPhysician
Administrative Position:ChiefofDepartment
GCP Training:Yes
Contact:lihecheng2000@hotmail.com(E-mail);13917113402(Mobile)

No.	Name	Gender（M/F）	Age（y）			GCP（Y/N）	
1	ZX.Yin	M	37		Thoracic	Y	Sub-I,CRC
2	XF.Zhang	M	28		Thoracic	Y	Sub-I,CRC
3	RS.Jin	M	37		Thoracic	Y	Sub-I,CRC
4	XY.Chen	M	38		Thoracic	Y	Sub-I
5	NC.Zhang	M	36		Thoracic	Y	Sub-I
6	SJ.Yu	M	30		Thoracic	Y	Sub-I
7	YQ.Cao	F	26		Thoracic	Y	Sub-I
8	CQ.Li	M	38		Thoracic	Y	Sub-I
9	DP.Han	M	38		Thoracic	Y	Sub-I
10	YJ.Zhang	M	38		Thoracic	Y	Sub-I
11	K.Chen	M	38		Thoracic	Y	Sub-I
12	HL.Du	M	42		Thoracic	Y	Sub-I

4. Aims of the study

Primary objective: to investigate the feasibility of conversion to lobectomy after neoadjuvant/induced chemoimmunotherapy in patients with operable non-small cell lung

cancer who are required to undergo pneumonectomy at first diagnosis (R0 resection rate).

Secondary objective: to investigate the perioperative and long-term outcomes of patients with operable non-small cell lung cancer who were evaluated to undergo pneumonectomy at first diagnosis and switched to neoadjuvant or induction chemoimmunotherapy and subsequent lobectomy.

5. Research design

5.1 Overall design

In this single-arm, open-label, multicenter, prospective clinical trial, 50 cases of operable non-small-cell lung cancer requiring pneumonectomy were proposed to be enrolled. Patients will be treated with neoadjuvant or inductive combination therapy of immuno- and chemo- by evaluation from multidisciplinary discussion (Department of Thoracic Surgery, department of Respiratory Medicine, department of Radiology), than undergo open or minimally invasive radical surgery for lung cancer and systematic lymph node dissection. Peri-operative complications, lymph node dissection, R0 resection rate, and postoperative short-term and long-term efficacy outcomes will be recorded and evaluated.

Participating centers:

1 Ruijin Hospital, Shanghai Jiao Tong University School ofMedicine, Shanghai, China

2 Shanghai General Hospital of Shanghai Jiao Tong University School ofMedicine

3 The Ninth People's Hospital of Shanghai Jiao Tong University School ofMedicine

4 Huadong Hospital, Fudan University Medical College, Shanghai, China

5.2 Defining study endpoints

The study is completed if the subject completes all phases of the study according to the protocol, if he or she is no longer being examined, or if the last subject has had the last follow-up visit.

A subject completes the study if he or she completes all phases of the study, including the last follow-up visit or the last treatment or examination specified in the protocol.

Primary study endpoints

- Tumor R0 resection rate (lobectomy)

Secondary study endpoints

- Overall survival (OS, unit:month)
- Disease-free survival (DFS, unit: month)
- Surgical Evaluation Indicators.
  - Surgical time (unit: minutes), intraoperative bleeding (unit: ml), intraoperative blood transfusion (unit: ml)
  - Incidence of intraoperative accidents
  - Lymph node dissection: total number of lymph node dissection (unit: one), number of lymph node dissection stations (intrapulmonary,hilar and ipsilateral

mediastinal lymph nodes), and the number of lymph nodes cleared at each station (unit: one).

- Perioperative, 30-day, 90-day complication rates, mortality rates
- Quality of Survival and Pulmonary Function Evaluation at Admission, Discharge, 30 Days, and 90 Days
  - Quality of Life Score: Scored using the short form-36 (SF-36) and recorded on a 100-point scale.
  - Resting oxygen saturation (unit: percentage)
  - Lung function: Tidal volume, Vital capacity, Forced vital capacity, first second vital capacity.
  - Tidal volume, Vital capacity, Forced Expiratory Volume In 1s, all in ml.

5.3 Determination of sample size

This study is a prospective observational clinical study, and the purpose of the study is to evaluate the feasibility and long-term outcome of pnuemonectomy to lobectomy after neoadjuvant or induction chemoimmunotherapy for locally progressive non-small cell lung cancer. Due to the lack of previous reference data, the sample size was not calculated based on hypothesis testing, and 50 patients were enrolled.

6 Study population

6.1 Inclusion criteria

The study subjects should meet the following criteria:

1) The patients voluntarily participate in the study, have good compliance, can cooperate with the requirements of the experiment to complete the observation and follow-up, and sign the informed consent form.

2) Aged over 18 years old, under 75 years old; male and female are not limited;

3) Pathologically confirmed non-small cell lung cancer with clinical stage T2-4N0-2, resectable non-small cell lung cancer, potentially needing pneumonectomy and receiving neoadjuvant or induction therapy.

4) ASA score: Grade I-III;

5) The cardiopulmonary function evaluation can meet the requirements for radical lung cancer surgery, and the liver and kidney functions are normal.

6.2 Exclusion Criteria

Subjects meeting any ofthe following criteria will be excluded from this study;

1) Those with serious cardiac, pulmonary, hepatic, and renal dysfunctions, unable to tolerate the surgery;

2) Those with uncontrollable neurological or psychiatric diseases or mental disorders, poor compliance, and being unable to cooperate and describe the treatment response.

3)Those who are going to undergo emergency surgery or palliative surgery due to lung

abscess or hemoptysis.

4) Those who have been treated, or are undergoing neoadjuvant or induction radiotherapy or targeted therapy.

5) Those who have a combined history of other malignant tumors

6) Those who have a history of thoracic surgery

7) Those who are pregnant or breastfeeding women

8) Patients of childbearing age who refuse to use contraception.

6.3 Recruitment

Source of study subjects: outpatients

Recruitment location: Thoracic Surgery and Respiratory Medicine Clinic of participant centers.

Recruitment method: Through WeChat public number, departmental website and other online channels to publish recruitment information.

The researchers conducted a study on the lungs of patients attending outpatient clinics. After preliminary evaluation of lung cancer patients in the outpatient clinic of Ruijin Hospital and identification of those who are potentially eligible for enrollment, as well as improvement of chest CT, PET-CT （ optional ） , cardiac ultrasound, lung function and other auxiliary examinations, and after it is clear that they are eligible for enrollment, subjects will be informed of the study and will sign an informed consent form.

Measures to strengthen the compliance of the study subjects: The researchers contacted the study subjects or their families through the Internet or telephone, informing them of the schedule of the treatment program and reminding them of the follow-up visits.

6.4 Methods of Study Subject Allocation

This study is a single-arm clinical trial and does not involve the allocation of study subjects to the enrollment group.

7. Research interventions

7.1 Giving the research intervention

7.1.1 Description of the research intervention

After the patients were enrolled in the group, further relevant examinations (bronchoscopy, chest enhanced CT, PET-CT (optional), cranial MR, cardiac ultrasound, pulmonary function, electrocardiogram, and blood test) were completed, contraindications to surgery were ruled out, and they were evaluated to receive neoadjuvant/induced chemo-immuntherapy after multidisciplinary discussion (thoracic surgery, respiratory medicine, pathology). After completion of treatment, the patient is reassessed and discussed multidisciplinaryly for surgical feasibility. Open or minimally invasive (thoracoscopic-assisted, robotic-assisted) radical lung cancer surgery with systemic lymph node dissection is performed, including

pneumonectomy, lobectomy, combined lobectomy, and sleeve lobectomy (with or without pulmonary angioplasty/sleeve). Based on the surgical pathology and guidelines, the postoperative adjuvant treatment and follow-up plan was individualized after multidisciplinary discussion.

7.1.2 Dosage and method of administration

No drug trials were involved in this study.

7.1.3 Methods of establishing, preserving, and unblinding test drug codes and breaking the blind in emergency situations

This study does not involve blinding.

7.1.4 Items and number of clinical and laboratory examinations to be conducted

Postoperative follow-up in January, follow-up in March, follow-up every three months thereafter, and follow-up every six months after one year postoperatively, with blood routine, biochemistry, tumor indexes, and chest CT examination at each follow-up. In the first year after surgery, head MR was performed every half a year and PET-CT （optional ） was repeated every year; after one year after surgery, head MR was performed every half a year and PET-CT（optional） was performed every year.

7.2 Preparation/handling/storage/responsibility

7.2.1 Responsibility

No drug trials were involved in this study.

7.2.2 Composition, appearance, packaging and labeling

This study did not involve drug testing.

7.2.3 Product storage and stability

This study does not involve drug testing.

7.2.4 Preparation

This study does not involve drug trials.

7.3 Measures to reduce bias: randomization and blinding

This study was a single-arm study and did not involve randomization grouping and blinding.

7.4 Follow-up and compliance

The patients will be followed up in one and three months after surgery. Then every three months in first year, every six months after one year of operation, with blood routine, biochemistry, tumor indexes, and chest CT examination at each visit. Within one year after surgery, head MR was performed every six months and PET-CT was performed at one year, and after one year after surgery, head MR was performed every six months and PET-CT was performed every year.

The researchers will contact the study participants or their families via the Internet or telephone to inform them of the treatment schedule and remind them of follow-up visits.

7.5 Commitment to research intervention

During the perioperative period, relevant complications and examination test results were recorded by the treating doctors and nursing staff, and after discharge, a specialized After discharge from the hospital, specialists will be assigned to conduct follow-up visits and record them in the case report form (CRF).

		screening period	Peri-operative period	Follow-up							
				3 months	**6** months	**9** months	**1** year	**1.5** years	**2** years	**2.5** years	**3** years
Informed consent		×									
Base-line		×									
Inclusion/exclusion		×									
Test	Physical Examination	×	×								
	Complete Blood Count	×	×	×	×	×	×	×	×	×	×
	Blood Biochemical Analysis	×	×	×	×	×	×	×	×	×	×
	Tumor Bio-marker	×	×	×	×	×	×	×	×	×	×
	Chest CT	×	×	×	×	×	×	×	×	×	×
	PET-CT	×					×		×		×
	Cephalic MR	×									

8. Discontinuation of the research intervention and discontinuation/withdrawal of research subjects

8.1 Discontinuation of the research intervention

The investigator should consider discontinuing the study intervention if the subject develops. 1) patients with serious unintended adverse reactions or complications that do not improve significantly after symptomatic treatment and cannot be continued. patients who are unable to continue the study intervention.

2) Patients who are unable to tolerate the study intervention for non-treatment related reasons.

3) Laboratory test values that, in the judgment of the investigator, are clinically significant. After discontinuation of the study intervention, patients may continue to complete other parts of the treatment regimen, including chemotherapy, radiotherapy, targeted therapy, immunotherapy, etc., and will be treated in accordance with the study protocol. therapy, targeted therapy, immunotherapy, etc., and will be scheduled for examination and follow-up according to the study protocol.

8.2 Suspension/withdrawal of research subjects

The researcher may discontinue or withdraw a research subject if the subject is.

1) pregnancy

2) apparent noncompliance with the study intervention.

3) if clinical side effects, abnormal laboratory tests, or other clinical conditions occur that make continued participation in the study is no longer in the best interest ofthe subject.

4) Disease progression such that discontinuation ofthe study intervention is warranted.

5) The subject meets the exclusion criteria (emerging or confirmed).

6) the subject is unable to receive the study intervention for a certain period oftime.

The reason for discontinuation/withdrawal of the subject from the study should be documented on the case report form, and subjects who signed the informed consent, were randomized, but did not receive the study intervention will be replaced. Subjects who signed informed consent, were randomized, received the study intervention and were subsequently withdrawn will or will not be replaced.

8.3 Loss of Follow-Up

Subjects will be followed up for a period of 3 years. Lost visits will be considered to occur when the subject stops scheduled follow-up visits, fails to complete the procedures specified in the study, or cannot be contacted by the investigator.

The investigator will follow the established follow-up plan, complete telephone and outpatient follow-up regularly, and communicate with the subject on a regular basis to minimize lost visits.

9. Evaluation of study outcomes

9.1 Evaluation of primary and secondary outcomes

Primary Study Endpoints

R0 Resection rate (lobectomy): the proportion of patients with complete tumor removal by lobectomy, as evaluated by thepathologic findings ofpostoperative lung cancer specimens;

Secondary study endpoints

1) Lymph node dissection:Record the total number of lymph node dissection, the number of stations of lymph node dissection, and the number of lymph node dissection at each station during the operation, and evaluate them according to the pathologic results.

2) Perioperative indicators:Record the duration of surgery, intraoperative bleeding, the incidence of intraoperative accidents, evaluated by surgical records and perioperative clinical manifestations, laboratory tests, physical examination;.

3) Postoperative short-term efficacy indicators: record the length of postoperative hospitalization (days), survival within 30 days after surgery, and evaluate through postoperative follow-up;

4) Perioperative complication rate: Evaluated by clinical manifestations, laboratory tests, and physical examination.

5) 3-year disease-free survival rate: defined as the proportion of patients without tumor recurrence or metastasis 3 years after surgery, evaluated by postoperative follow-up.

6) 3-year overall survival rate: defined as the proportion ofpatients who are still alive 3 years after surgery, and evaluated by postoperative follow-up.

9.2 Safety and other evaluations

The main methods of safety evaluation of the study intervention include.

1) Clinical presentation;

2) Physical examination;

3) Vital signs (e.g., temperature, pulse, blood pressure);

4) Routine blood and blood biochemistry tests.

9.3 Adverse Events and Serious Adverse Events

9.3.1 Definition of Adverse Events (AE)

This refers to all adverse medical events that occur after a subject has undergone radical lung cancer surgery, which may be manifested by signs, symptoms, disease, or abnormal laboratory tests, but are not necessarily causally related to the trial intervention.

9.3.2 Definition of Serious Adverse Event (SAE)

means an adverse medical event resulting in death, life-threatening, permanent or serious disability or loss of function, the need for hospitalization of the subject, or prolonged hospitalization after the subject has undergone radical lung cancer surgery. A serious adverse event (SAE) is defined as an adverse medical event resulting in death, life-threatening, permanent or serious disability or loss of function, hospitalization or prolonged hospitalization after radical lung cancer surgery.

9.3.3 Classification of adverse events

9.3.3.1Severity of the incident

1) Mild: Symptoms and signs are easily tolerated by the patient. Symptoms may be ignored or disappear when the patient is distracted.

2) Moderate: Symptoms cause discomfort but are tolerable. They cannot be ignored and interfere with concentration.

3) Severe: Symptoms interfere with daily activities.

9.3.3.2Relevance to research interventions

1) Unrelated: A condition that occurs in a subject that is clearly related to other factors such as the subject's clinical status, treatment, or concomitant medications.

2) Unlikely to be related: What happens to the subject is likely to be caused by other factors such as the subject's clinical condition, treatment, or concomitant medications, but not by a known response to the intervention.

3) Possibly Related: What happens to the subject is sometimes related to the intervention or is a known response, but may also result from other factors such as the subject's clinical condition, treatment, or concomitant medications.

4) Likely Related: The subject has a condition that is sometimes related to the intervention, is a known response, and cannot be explained by other factors such as the subject's clinical status, treatment, or concomitant medications.

5) Highly Likely to be Relevant: The subject is experiencing a condition that is sometimes

related to the intervention, is a known response, and cannot be explained by other factors such as the subject's clinical status, treatment, or concomitant medications. There may also be one or more of the following: i) immediate onset after the intervention; ii) improvement after discontinuation of the intervention; iii) reoccurrence after a second intervention; iv) a positive reaction at the site ofthe intervention.

9.3.3.3Anticipation

Investigators should confirm that adverse events are expected or unanticipated, and that adverse events may be considered unanticipated iftheir nature, severity, or

frequency are not consistent with the risk information described for previous study interventions, they may be considered unintended.

9.3.4 Timing, frequency, follow-up and regression of adverse event assessment

Time and frequency of adverse event assessment: assessed every three days during hospitalization, and once at each follow-up visit after discharge.

Follow-up of adverse events: The investigator should follow up the adverse events; observe the final regression until the symptoms disappear or stabilize; the investigator should follow up the results with the principal investigator and the ethics committee.

All adverse events should be collected on a case report form (CRF), which should include a description of the event, time of occurrence, physician's assessment of severity, relationship to the study intervention, and time to resolution/stabilization ofthe event.

9.3.5 Adverse event reporting

Adverse events should be promptly recorded on the Case Report Form (CRF) and regularly reported to the Principal Investigator, Ethics Committee:.

1) description ofthe adverse event; and

2) the time ofoccurrence and duration; and

3)Whether the adverse event was serious or unintended.

4) the mode ofonset; and

5) evaluation of severity; and
6)regression; and

7)Measures taken in response to the adverse event.

9.3.6 Reporting of Serious Adverse Events

Serious adverse events should be promptly documented on a Case Report Form (CRF) and reported within 24 hours to the Principal Investigator, Ethics Committee.

1)the description ofthe adverse event;
2)time ofoccurrence and duration;

3)whether the adverse event was serious or unintended;
4)mode ofonset;

5)assessment ofseverity;
6)regression;

7)Measures taken in response to the adverse event.

10. Statistical analysis

10.1 General methodology

All statistical analyses were performed using R software, and hypothesis tests were standardized using two-sided tests, giving the test statistic and its corresponding p-value. $p<0.05$ was considered statistically significant, and 95% confidence intervals were set as required.

Statistical description: All indicators are described according to their nature. Qualitative indicators are expressed as frequencies and percentages of categories; metrics provide the number of cases, mean, standard deviation, median, minimum and maximum values.

Statistical inference: For overall survival time and disease-free survival time, overall survival curves and disease-free survival curves were plotted using the Kaplan-Meier method; risk differences between survival and disease-free survival were assessed using the Log-Rank test; multivariate analyses were performed using the Cox proportional risk model to assess the effect of subgrouping (surgical modality) and other prognostic factors on survival and disease-free survival. survival and disease-free survival. The t-test was used for measures that were normally distributed, and the rank-sum test was used for measures that were not normally distributed; the chi-square test was used for between-group comparisons of count data, and the Fisher exact probability method was used when necessary.

10.2 Analysis of Primary and Secondary Study Endpoints

Primary Endpoints

Overall survival time (in months): Overall survival curves were plotted using the Kaplan-Meier method; the difference in survival risk between the two groups was assessed using the Log-Rank test with 95% confidence intervals; multivariate analyses were performed using the Cox proportional risk model to assess the effect of subgrouping (surgical procedure) and other prognostic factors on the survival risk, and 95% confidence intervals were given for each factor. A multivariate analysis using the Cox proportional risk model was performed to assess the effect of grouping factors (surgical modality) and other prognostic factors on survival risk with 95% confidence intervals for each factor.

Secondary endpoints

Disease-free survival time (in months): Disease-free survival curves were plotted using the Kaplan-Meier method; differences in the risk of disease-free survival between the two groups were assessed using the Log-Rank test with 95% confidence intervals; multivariate analyses were performed using the Cox proportional risk model to assess the effect of subgrouping factors (surgical procedure) and other prognostic factors on the risk of disease-free survival, with 95% confidence intervals for each factor. A multivariate analysis using the Cox proportional risk model was performed to assess the effect of grouping factors (surgical modality) and other prognostic factors on the risk of disease-free survival with 95% confidence intervals for each factor.

- Surgical evaluation indicators.
  - Surgical time (unit: minutes), intraoperative bleeding (unit: ml), intraoperative blood transfusion (unit: ml): all quantitative data not conforming to normal distribution, calculate the median, 25% quartile, 75% quartile, the minimum value, the maximum value, and analyze the difference between the two groups by using the rank sum test.
  - Incidence of intraoperative accidents: count data, using chi-square test to analyze the difference between the two groups.
  - Lymph node dissection: the total number of lymph node dissection (unit: one) and the number of lymph node dissection at each station (unit: one) were non-normally distributed measurements, and the difference between the two groups was analyzed using the rank-sum test; the number of stations of lymph node dissection (intrapulmonary, hilar, and ipsilateral mediastinal lymph nodes) was count data, and the difference between the two groups was analyzed using the chi-square test. Differences between the two groups were analyzed using the chi-square test.
  - Tumor R0 resection rate: count data, using the chi-square test to analyze the difference between the two groups.
- Perioperative, 30-day, and 90-day complication rates, and mortality rates: were count data, and differences between the two groups were analyzed using the chi-square test.
- Quality of Survival and Cardiorespiratory Function Evaluation at Admission, Discharge, 30 Days, and 90 Days
  - Quality of Life Score SF-36 Scale: Percentage, as a non-normally distributed measure, use rank sum test to analyze the difference between the two groups.
  - Resting oxygen saturation (in percent): a non-normally distributed measure, differences between the two groups were analyzed using the rank-sum test.
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Lung function: Tidal volume, Vital capacity, Forced vital capacity, Forced Expiratory Volume In 1s, all in ml: were normally distributed measures and analyzed using the student The differences between the two groups were analyzed using the student-t test with 95% confidence intervals.

10.3 Safety analysis

Adverse events were coded, calculated, and expressed using severity, frequency, and association with intervention. Adverse events leading to Adverse events leading to discontinuation of the study intervention should be listed separately from serious adverse events arising from the treatment.

10.4 Descriptive analysis at baseline

Descriptive statistics were used to analyze the demographic characteristics and laboratory indicators ofthe study population at baseline.

10.5 Subgroup analysis

For the primary study endpoints grouped by age, sex or other demographic,

clinicopathologic characteristics, and surgical treatment modalities, a Subgroup analysis was performed.

11. Supporting documentation and considerations

11.1 Informed consent process

Informed consent should be completed before the subject agrees to participate in the study and continue throughout the study. The informed consent form is approved by the Ethics Committee and should be read by the subject. The researcher will explain the research process and answer questions from the subject; the subject will be informed of the possible risks and their rights. Subjects will be allowed to discuss their participation with their family or guardian before agreeing to participate. The researcher must tell the subject that participation in the study is voluntary and that he or she may withdraw from the study at any time. A copy of the informed consent form may be provided to the participant to keep. The rights and welfare of research subjects will be protected, and it is emphasized that the quality of their medical care will not be compromised by their refusal to participate in the study.

11.2 Privacy

Subjects' personal information in the study will be kept confidential. Identifying information will not be disclosed outside of the research team unless permission is granted. Subjects' files will be kept in locked filing cabinets and will be accessible only to researchers. To ensure that the study is conducted in accordance with the regulations, access to the subjects' personal data at the research unit will be provided by government authorities or the Ethics Review Committee, as required.

11.3 Collection and use of specimens and data

Study data will be obtained by the investigator and stored in the custody of the Department of Thoracic Surgery, Ruijin Hospital. If the study is completed, the retained clinical information and other data may be used for future studies with the consent of the study participants.

Storage location:Thoracic Surgery Ward, 4th and 7th floor, Building 6, Ruijin Hospital.

11.4 Quality control and quality assurance

In order to ensure that this trial is conducted in strict accordance with the clinical study protocol, clinical investigators and clinical sponsors should operate in strict accordance with the requirements of the study protocol throughout the clinical trial, and make sure that the test procedures are standardized, the test data are accurate and the conclusions of the study are reliable. The specific requirements are as follows.

1) Investigators must be physicians trained in clinical trials and work under the guidance of senior professionals;

2) The clinical ward inspection before the trial must meet the standardized requirements and ensure that the resuscitation equipment is complete;

3) Research centers must strictly follow the study protocol and truthfully fill in the case observation form;

4) Supervisors should follow the operating procedures, supervise the conduct of the clinical

trial, confirm that all data are recorded and reported correctly and completely, and that all case report forms are filled out correctly and are consistent with the original information to ensure that the trial is conducted in accordance with the clinical research protocol. Ensure that the trial is carried out in accordance with the clinical study protocol.

5) Ensure that the investigator can be contacted at any time by telephone, fax or e-mail.

6) In case of serious adverse events, the study should be suspended ifnecessary.

11.5 Data processing and record keeping

11. 5.1 Data collection and management

Completion and handover of the case report form (CRF): All relevant information of the case should be recorded in the CRF by the treating physician according to the trial protocol, and ensure that the data are recorded in a timely, complete, accurate, and truthful manner. the CRF should not be altered, and if there is a mistake that needs to be corrected, the correction should be signed and dated. The completed CRF must be reviewed and signed by the clinical investigator. If there is any doubt, the investigator must decide whether to make changes or not, and no further changes should be made to the CRF after confirmation. The completed CRF should be handed over to the data manager for data entry and management. All processes should be documented.

Data entry and modification: A designated data manager is responsible for this process. Establish a database system specific to this test. Data entry will be performed after training of the data entry personnel and will be done by two people independently using the double entry method.

Generation and resolution of questions: If the data manager has any questions during the CRF review, data entry, or any part of the data review process, he/she should fill out a question form and return it to the supervisor. The researcher should provide a written answer to the question on the question form, sign it, and return it to the data manager to correct the data; the data manager does not have the authority to modify the original data. The query form should be kept in a safe place.

Data Audit: This is the process of checking and evaluating the data in the database. This process is a special task of the data manager, who should report on the process of data management and general information, case enrollment and completion (including the list of shedding subjects), items involved in determining the population for statistical analysis, and issues that need to be discussed and resolved (inclusion/exclusion criteria checking, completeness checking, logical consistency checking, outlier data checking, and time-window checking, etc.), and should be verified by the principal investigator, Statistical analysts.

Database locking: After reviewing the data and confirming that the database has been created correctly, the principal investigator and the statistical analyst will lock the database. In principle, the data should not be modified after locking, but if there is a problem, it can only be corrected in the statistical analysis program after confirmation by the study leader. All modifications should be documented and explained. Data security should be guaranteed, and unrelated personnel should not have access to or modify the data, and the data should be backed up.

11. 5.2 Research data retention

After the completion of the clinical trial, the investigator will organize the clinical trial data and original records and within three months The investigator shall organize the clinical trial data and original records and submit them to the office of the clinical trial organization for archiving within three months. The minimum period of retention of data after the completion of clinical trials is 10 years.

Data destruction should be licensed by the Clinical Trial Organization of Ruijin Hospital.

11.6 Publication and Data Sharing Conventions

This clinical trial is a multicenter study and data are shared within each participating center.

11.7 Declaration of conflict of interest

There are no relevant conflicts of interest.