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LobE-Specific lymph node diSsectiON for clinical early-stage non-small cell lung cancer: protocol for a randomized controlled trial (the LESSON Trial)

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Title

LobE-Specific lymph node diSsectiON for clinical early-stage non-small cell lung cancer: protocol for a randomized controlled trial (the LESSON Trial)

Running head

Lobe-specific lymph node dissection for NSCLC

Authors

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ABSTRACT

Introduction: Lung cancer was the most common malignancy and the leading cause of cancer-related death either in China or worldwide, and surgery is still the preferred treatment for early-stage non-small cell lung cancer(NSCLC). The pattern of lymph node metastasis might be lobe-specific, and thus, lobe-specific lymph node dissection was proposed to be an alternative to systematic lymph node dissection for the treatment of early-stage NSCLC.

Methods and analysis: The LESSON trial is a single-institutional, randomized, double-blind, and parallel controlled trial to investigate the feasibility of lobe-specific lymph node dissection in clinically diagnosed stage IA1-2 NSCLC. We hypothesize that lobe-specific lymph node dissection(experimental group) is not inferior to systematic lymph node dissection(control group) and intend to include 672 participants for the experimental group and 672 participants for the control group with a follow-up duration of 60months. The primary outcomes are 5-year disease-free survival and 5-year overall survival. The secondary outcomes are metastatic lymph node ratio, postoperative complication incidence and mortality, duration of operation, duration of anesthesia(min), the volume of bleeding(ml), the volume of drainage. The intention-to-treat analysis would be performed in the trial.

Ethics and dissemination: This trial was approved by the Ethics Committee on Biomedical Research, West China Hospital of Sichuan University(2021-332). Informed consent would be obtained from all participants. Dissemination activities would include academic conference presentations and peer-reviewed publications. This trial was

registered in the Chinese Clinical Trial Registry(Trial Registration number: ChiCTR2100048415).

Strengths and Limitations of This Study:

1. The LESSON trial is a randomized, double-blind, and parallel controlled trial.
2. It investigates the feasibility of lobe-specific lymph node dissection for clinical-stage IA1-2 non-small cell lung cancer, for which we hypothesize is not inferior to systematic lymph node dissection.
3. This study might provide some suggestions in clinical practice on lymph node dissection for early-stage non-small cell lung cancer.
4. This trial would be conducted in a single institution instead of in multiple centers.

INTRODUCTION

Lung cancer was the most common malignancy and the main cause of cancer-related death either in China or worldwide[1, 2]. Lung cancer is mainly composed of small cell lung cancer and non-small cell lung cancer(NSCLC), which accounts for about 85% of all histological types of lung cancer[3]. With the advances in the technology of lung cancer screening, more and more early-stage NSCLC was likely to be diagnosed[4]. At present, surgery is still the preferred treatment for early-stage NSCLC, and current guidelines suggest that anatomical lung resection with systematic lymph node dissection or lymph node sampling is the standard treatment for clinical stage I NSCLC[5]. Since previous researches indicated that the pattern of lymph node

metastasis might be lobe-specific, lobe-specific lymph node dissection was proposed to be an alternative to systematic lymph node dissection for the treatment of early-stage NSCLC[6, 7].

In our previous study, we conducted a meta-analysis to compare the safety and efficacy between lobe-specific lymph node dissection and systemic lymph node dissection in the treatment of early-stage NSCLC. Our findings implied that compared with systemic lymph node dissection, the occurrence of postoperative complications in lobe-specific lymph node dissection decreased significantly but was comparable in long-term survival, indicating that lobe-specific lymph node dissection might be an alternative to systemic lymph node dissection[8, 9]. However, there is no explicit and precise definition of the lobe-specific lymph node dissection and the dissecting range of lymph nodes in previous cohort studies and practice guidelines[10, 11]. The role of lobe-specific lymph node dissection and the explicit dissecting range remains to be further studied and established, and a well-designed and conducted randomized controlled study(RCT) might provide some suggestions to clinical instructions[12].

As shown in our previous retrospective study, the subcarinal and lower mediastinal lymph nodes were all negative when the tumor was located in the upper lobe and with a size of ≤2cm, and the upper mediastinal lymph nodes were all negative when the tumor was located in the lower lobe and with a size of ≤2cm[9]. It reminded us that the lobe-specific lymph node metastasis pattern might be noticed, and the lobe-specific lymph node dissection might be practical, with similar long-term survival and fewer postoperative complications[13]. Therefore, we conducted a double-blind, randomized,

and parallel-controlled clinical trial to determine the favorable treatment between lobe-specific lymph node dissection(L-SLND) and systematic lymph node dissection(SLND) for treatment of early-stage NSCLC. We hypothesized that lobe-specific lymph node dissection was not inferior to systematic lymph node dissection in safety and long-term oncological results.

METHODS

Protocol version

Protocol V3.0, modified May 16, 2021.

Trial design

This study is a single-institutional, randomized, double-blind, and parallel controlled trial conducted in Lung Cancer Center, West China Hospital, Sichuan University. Patients would be enrolled since August 2021, and it would be operated until July 2024.

Sample size

According to the summarized survival rate of early-stage NSCLC in prior researches, we assumed that the 5-year overall survival(OS) rate was 70% among the total population of lobe-specific lymph node dissection group and the systemic lymph node dissection group, and the non-inferiority threshold of 5-year OS rate was 6%(hazard ratio[HR]=1.25), with a unilateral α of 0.05 and a certainty of 0.8. The recruiting duration is 36 months, and the duration of follow-up is 60 months. In this way, the

sample size is 1344 cases as calculated by the Log-rank test[14], in which 672 cases are for the experimental group and 672 cases for the control group.

Study population

This trial plans to include 1344 patients with clinically diagnosed stage IA1-2 NSCLC, and the trial schema of the patient pathway is shown in Figure 1. The staging is referred to the American Joint Committee on Cancer(the eighth edition)[15, 16].

The included patients are required to meet all of the following inclusion criteria:

1. Patient aged 18-80 years old;

2. The preoperative blood pressure is controlled below 160/100mmHg; the blood glucose is controlled between 5.6 and 11.2 mmol/L; the major organs' function is within normality, including cardiac, pulmonary, hepatic, and nephritic function: (1) the cardiac function examination indicates a Goldman index rated 1-2; (2) the pulmonary function examination indicates an estimated postoperative forced expiratory volume in the first second(FEV_1) ≥1.0L; (3) the total bilirubin ≤ 1.5×normal upper limit; (4) the alanine transaminase(ALT), aspartate aminotransferase(AST) ≤ 1.5×normal upper limit; (5) the creatinine ≤ 1.25×normal upper limit, and creatinine clearance rate ≥ 60ml/min;

3. The primary preoperative clinical diagnosis is non-small cell lung cancer, including adenocarcinoma, squamous cell carcinoma, large cell carcinoma, and other histological types;

4. The thin-layer computed tomography(CT) indicates peripheral tumor[16, 17], whose maximum diameter ≤2cm; the tumors are located in the upper lobe or lower lobe of the

lung with unspecified laterality; the CT imaging indicates nonsolid nodules; the minimum diameter ≤ 1cm or the positron emission tomography/computed tomography(PET/CT) indicates no mediastinal lymph node metastasis; the clinical staging is cT1a-1bN0M0 (cIA1-2);

5. The Eastern Cooperative Oncology Group performance status(PS) score of 0-1;

6. All preoperative examinations are completed within 28 days preoperatively;

7. Patients who can comprehend this study and sign an informed consent form.

Patients with any of the following exclusion criteria would be ruled out:

1. Patients who have received preoperative anti-tumor treatment, including prior radiotherapy, chemotherapy, target therapy, and immunotherapy;

2. Patients have a history of other malignancies;

3. Patients are diagnosed a secondary malignancy when included;

4. Centrally located lung cancer[17, 18];

5. Tumors located in the middle lobe;

6. Small cell lung cancer;

7. Patients have a history of unilateral thoracic surgery;

8. Females with pregnancy or lactation;

9. Patients with interstitial pneumonitis, pulmonary fibrosis, or severe emphysema;

10. Uncontrollable active bacterial infection or fungal infection;

11. Severe mental disease;

12. Patients have a history of severe cardiac disease, cardiac failure, myocardial

infarction, or angina within six months.

Randomization, allocation concealment, and blinding

A random number table would be produced via SPSS software(version 22.0; IBM Corp, Armonk, NY, USA) by an independent randomization committee before research, which is confidential to researchers(and related personnel) and patients. A random number selected from the random number table would be allocated into an opaque envelope. An opaque envelope with a random number would be assigned to each patient who is included in the research. The researcher would unfold the envelope and get a random number, according to which the patient would be grouped. The trial is double-blind, and the researcher and the participant would be blinded to the allocation. The allocation would be unblinded when an emergency occurs, and the participant would be withdrawn from the trial.

Interventions

Patients in the experimental group would receive lobe-specific lymph node dissection[9]. We would dissect the upper mediastinal lymph node for lung cancer of the upper lobe, subcarinal and lower mediastinal lymph node for lung cancer of lower lobe, and upper mediastinal and subcarinal lymph node for lung cancer of the middle lobe(Table 1). Patients in the control group would receive systematic lymph node dissection, including upper mediastinal, subcarinal, and lower mediastinal lymph nodes.

When participants are diagnosed with mediastinal lymph node metastasis,

postoperative adjuvant therapy would be conducted to decrease the risk of recurrence and metastasis, including target therapy, radiotherapy, and chemotherapy.

The overall follow-up duration would be last for 60 months for each patient(Table 2). The first postoperative follow-up would be on the 30 days postoperatively, and we would focus on the postoperative complications and performance status. Then the follow-up would be performed every six months for the first 24 months postoperatively. We would take the history and physical examination(H&P), focusing on the performance status and weight loss, and require the patients to receive chest CT. Whether the chest CT was contrast-enhanced CT or non-contrast-enhanced CT was determined by the surgeon. The H&P and low-dose non-contrast-enhanced CT would be performed annually in the following 36 months.

Outcomes

The primary outcomes are 5-year disease-free survival(DFS) and 5-year OS. The DFS is defined as the duration(days) from the date of operation to the date of tumor recurrence, and the OS is defined as the duration(days) from the date of operation to the date of death of any cause. The secondary outcomes are metastatic lymph node ratio, postoperative complication incidence, and mortality(≤30days), duration of operation(day), duration of anesthesia(min), the volume of bleeding(ml), the volume of drainage(ml). The metastatic lymph node ratio is defined as the ratio of the number of positive lymph nodes divided by all dissected lymph nodes

Data collection, management, monitoring, and analysis

The data collection and management were achieved by researchers under the guidance of the Data Management Committee of Lung Cancer Center of West China Hospital. All adverse events would be documented in detail and handled properly, which would also be reported to the Data Management Committee and Ethics Committee of West China Hospital of Sichuan University. The principal investigators would periodically review the reported adverse events and evaluate the corresponding subjects' risk and benefit.

The intention-to-treat principle would be performed, and participants would be allocated to the assigned group. Chi-square test or Fisher's exact test is conducted to compare the categorical data between groups; the independent sample t-test or Mann-Whitney nonparametric U test or one-way analysis of variance(ANOVA) test is performed to compare the continuous data between groups; the survival analysis is conducted to compare the long-term prognosis between two groups; bilateral P-value <0.05 is considered statistically significant[19].

Patients or public involvement

Patients and the public would not be involved in the design, or conduct, or reporting, or dissemination plans of the research. All participants would sign the informed consent and be involved in the follow-up.

ETHICS AND DISSEMINATION

This trial(Version 3.0) was approved by the Ethics Committee on Biomedical Research, West China Hospital of Sichuan University(2021-332) on May 16, 2021, and registered in the Chinese Clinical Trial Registry(ChiCTR2100048415). The LESSON study would be performed in accordance with the Declaration of Helsinki. All participants would learn the outline of this trial and sign the informed consent, who could also have the right to opt out without medical care being affected, and the tumor specimens would not be collected. A regulatory team from the Ethics Committee of West China Hospital of Sichuan University would review all research data every six months, including data records, medical documents, and electronic case report forms. Important protocol modifications would be reported to the Ethics Committee. The principal investigators would guarantee the participants' right to withdraw from this trial in an emergency to ensure their safety. All research data would be carefully stored and only available for the researchers and monitoring panels. The corresponding result of the trial would be published in academic conference presentations and peer-reviewed publications.

Author contributions: W. H. and H. D. contribute to the conceptualization of the study and drafting of the manuscript and took full responsibility for the content, including the data and analysis. W. H., H. D., Z. R., X. T., and D. Z. contribute to the recruitment and data curation. W. H., H. D., K. X., and Y. W. contribute to the formal analysis. W. H., H. D., and Q. Z. contribute to the revision of the manuscript. W. H., H. D., Z. R., K. X., Y. W., X. T., D. Z., and Q. Z. contribute to the approval of the final manuscript. H. D. and Q. Z. contribute to supervision and project administration.

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Supplementary data: e-Doc 1, The trial approval from the Ethics Committee on Biomedical Research, West China Hospital of Sichuan University(2021-332).

Abbreviations

ALT, alanine transaminase

ANOVA, analysis of variance

AST, aspartate aminotransferase

CT, computed tomography

DFS, disease-free survival

DL_{CO}, carbon monoxide diffusing capacity

FEV_1, forced expiratory volume in the first second

H&P, history and physical examination

HR, hazard ratio

NSCLC, non-small cell lung cancer

OS, overall survival

PET/CT, positron emission tomography/computed tomography

PS, performance status

RCT, randomized controlled study

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Figure legends

Figure 1 Scheme of the LESSON Trial. **Abbreviation:** NSCLC, non-small cell lung cancer; L-SLND, lobe-specific lymph node dissection; SLND, systematic lymph node dissection.

Table 1 The dissected lymph nodes in lobe-specific lymph node dissection and systematic lymph node dissection in the LESSON Trial

	Lobe-specific lymph node dissection	Systematic lymph node dissection
Left lung		
Upper lobe	4L, 5, 6	4L, 5, 6, 7,8,9
Lower lobe	7, 8, 9	4L, 5, 6, 7, 8, 9
Right lung		
Upper lobe	2R, 4R	2R, 4R, 7,8,9
Lower lobe	7, 8, 9	2R, 4R, 7, 8, 9

Table 2 The timeline of data collection and postoperative follow-up in the LESSON Trial

Timepoint	**Preoperative**	**Day of surgery**	**Before discharge**	**Postoperative (follow-up)**		
	Baseline			30 days	6, 12, 18, 24 months	3, 4, 5 years
Eligibility	√					
H&P	√		√	√	√	√
Blood test	√		√	√	√	√
Chemistry profile	√		√	√	√	√
Tumor marker	√		√	√	√	√
Chest CT/CECT	√				√	
Chest LDCT						√
Metastatic LNR		√				
Postoperative complication incidence				√		
Postoperative mortality				√		

Duration of operation	√	
Duration of anesthesia	√	
Volume of bleeding	√	
Volume of drainage		√

Abbreviation: H&P, medical and physical examination; CT, computed tomography; CECT, contrast-enhanced computed tomography; LDCT, low-dose computed tomography; LNR, lymph node rate.

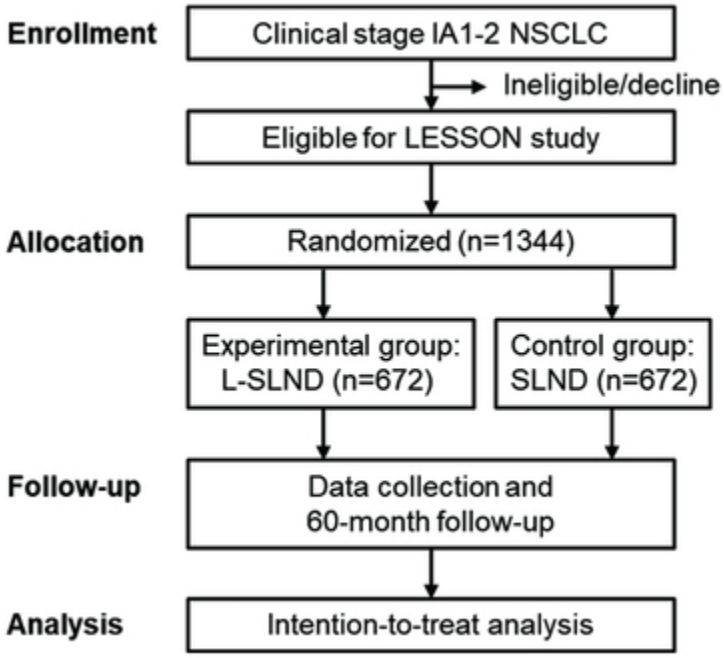

Figure 1 Scheme of the LESSON Trial. Abbreviation: NSCLC, non-small cell lung cancer; L-SLND, lobe-specific lymph node dissection; SLND, systematic lymph node dissection.

15x13mm (600 x 600 DPI)

四川大学华西医院生物医学伦理审查委员会
Ethics Committee on Biomedical Research, West China Hospital of Sichuan University

四川大学华西医院生物医学伦理审查委员会批件

2021年审(332)号

科室（专业）：肺癌中心	项目负责人姓名及职称：邓汉宇/讲师	
项目名称	肺叶特异性淋巴结清扫术在早期非小细胞肺癌中的可行性研究	
研究方案	版本号：V3.0	版本日期：2021年5月16日
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审查意见：

1. 研究者资质符合伦理要求。
2. 研究方案及知情同意书基本符合伦理要求。

审查结果：■批准 □修改后批准 □修改后再审 □不批准 □暂停或者终止研究
持续审查频率： □3 个月/3months ■6 个月/6months □1 年/1year □不适用/NA

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本批件有效期为一年，逾期未实施的，则自行废止。

根据国际医学期刊编辑委员会（ICMJE）要求，所有在人体中和采用取自人体的标本进行的临床研究均应注册。请接到伦理批件的研究者务必在临床研究开始前到中国临床研究注册中心注册，请使用我院公共账号(请发邮件到临床研究管理部邮箱hxlcyjglb@163.com申请，联系电话：85422851)登陆以下网址进行临床研究注册： http://www.chictr.org.cn,临床研究项目注册成功后产生的唯一注册号请及时发送邮件到伦理办公室（huaxilunli@163.com），是伦理跟踪审查的必查项目。

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主任委员（签名）：[illegible]

2021年7月20日

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Keywords:	Respiratory tract tumours < ONCOLOGY, Cardiothoracic surgery < SURGERY, Thoracic surgery < SURGERY

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ABSTRACT

Introduction: Lung cancer was the most common malignancy and the leading cause of cancer-related death in China or worldwide, and surgery is still the preferred treatment for early-stage non-small cell lung cancer(NSCLC). The pattern of lymph node metastasis was found potentially lobe-specific, and thus, lobe-specific lymph node dissection was proposed to be an alternative to systematic lymph node dissection for the treatment of early-stage NSCLC.

Methods and analysis: The LESSON trial is a single-institutional, randomized, double-blind, and parallel controlled trial to investigate the feasibility of lobe-specific lymph node dissection in clinically diagnosed stage IA1-2 NSCLC with ground-glass opacity components(≥50%). The intraoperative frozen section examination of surgical tissues confirms the histological type of NSCLC. We hypothesize that lobe-specific lymph node dissection(experimental group) is not inferior to systematic lymph node dissection(control group) and intend to include 672 participants for the experimental group and 672 participants for the control group with a follow-up duration of 60 months. The primary outcomes are 5-year disease-free survival and 5-year overall survival. The secondary outcomes are metastatic lymph node ratio, postoperative complication incidence and mortality, duration of operation, duration of anesthesia(min), the volume of bleeding(ml), and drainage volume. The intention-to-treat analysis would be performed in the trial.

Ethics and dissemination: This trial was approved by the Ethics Committee on Biomedical Research, West China Hospital of Sichuan University(2021-332). Informed

consent would be obtained from all participants, and dissemination activities would include academic conference presentations and peer-reviewed publications. This trial was registered in the Chinese Clinical Trial Registry(Trial Registration number: ChiCTR2100048415).

Strengths and Limitations of This Study:

1. The LESSON trial is a single-center, randomized, double-blind, and parallel controlled trial.
2. We investigate the feasibility of lobe-specific lymph node dissection for clinical-stage IA1-2 non-small cell lung cancer with ground-glass opacity components(≥50%).
3. We hypothesize that lobe-specific lymph node dissection is not inferior to systematic lymph node dissection in long-term survival.
4. The primary endpoint will be the 5-year disease-free survival and 5-year overall survival.
5. The separation of investigators who handled data curation and formal analyses and surgeons could ensure the success of trial blinding.

INTRODUCTION

Lung cancer was the most common malignancy and the main cause of cancer-related death in China or worldwide[1, 2]. Lung cancer is mainly composed of small cell lung cancer and non-small cell lung cancer(NSCLC), accounting for about 85% of all histological types of lung cancer[3]. With the advances in lung cancer screening technology, more and more early-stage NSCLC is likely to be diagnosed[4]. At present, surgery is still the preferred treatment for early-stage NSCLC, and current guidelines suggest that anatomical lung resection with systematic lymph node dissection(SLND) or lymph node sampling is the standard treatment for clinical stage I NSCLC[5]. Since previous research indicated that the pattern of lymph node metastasis might be lobe-specific, lobe-specific lymph node dissection(L-SLND) was proposed to be an alternative to SLND for the treatment of early-stage NSCLC[6, 7].

In our previous research, we conducted a meta-analysis to compare the safety and efficacy between L-SLND and SLND in treating early-stage NSCLC. Our findings implied that compared with SLND, the occurrence of postoperative complications in L-SLND decreased significantly but was comparable in long-term survival, indicating that L-SLND might be an alternative to SLND[8, 9]. However, there is no explicit and precise definition of the L-SLND and the dissecting range of lymph nodes in previous cohort studies and practice guidelines[10, 11]. The role of L-SLND and its explicit dissecting range remain to be further studied and established, and a well-designed and conducted randomized controlled study(RCT) might provide some suggestions to clinical instructions[12].

As shown in our previous retrospective study, the subcarinal and lower mediastinal lymph nodes were all negative when the tumor was located in the upper lobe and with a size of ≤2cm, and the upper mediastinal lymph nodes were all negative when the tumor was located in the lower lobe and with a size of ≤2cm[9]. It reminded us that the lobe-specific lymph node metastasis pattern might be noticed, and the L-SLND might be practical, with comparable long-term survival and fewer postoperative complications[13]. Therefore, we conducted a double-blind, randomized, and parallel-controlled clinical trial to determine the preferred treatment between L-SLND and SLND for early-stage NSCLC. We hypothesized that L-SLND was not inferior to SLND in safety and long-term oncological results.

METHODS

Protocol version

Protocol V3.0, modified May 16, 2021.

Trial design

This study is a single-institutional, randomized, double-blind, and parallel controlled trial conducted in Lung Cancer Center, West China Hospital, Sichuan University. Patients had been enrolled since August 2021, and it would be operated until July 2024. The study with active follow-up would be operated until July 2026.

Sample size

According to the summarized survival rate of early-stage NSCLC in prior research, we assumed that the 5-year overall survival(OS) rate was 70% among the total population of the L-SLND group and SLND group. The non-inferiority threshold of the 5-year OS rate was 6%(hazard ratio[HR]=1.25), with a unilateral α of 0.05 and a certainty of 0.8. The recruiting duration is 36 months, and the duration of follow-up is 60 months. In this way, the sample size is 1344 cases as calculated by the Log-rank test[14], in which 672 cases are for the experimental group and 672 cases for the control group. We are dedicated to requiring the enrolled patients to be in active follow-up and offer some allowance to those patients to reduce the risk of participants loss and enable the trial to reach the target sample size.

Study population

This trial intends to include 1344 patients with clinically diagnosed stage IA1-2 NSCLC, and the trial schema of the patient pathway is shown in Figure 1. These preliminary eligible patients would be enrolled in the study cohort and participate in randomization after intraoperative frozen section examination conformity of NSCLC. The staging is referred to the American Joint Committee on Cancer(the eighth edition)[15, 16].

The included patients are required to meet all of the following inclusion criteria:

1. Patient aged 18-80 years old;

2. The preoperative blood pressure is controlled below 160/100mmHg; the blood glucose is controlled between 5.6 and 11.2 mmol/L; the major organs' function is within normality, including cardiac, pulmonary, hepatic, and nephritic function: (1) the cardiac

function examination indicates a Goldman index rated 1-2; (2) the pulmonary function examination indicates an estimated postoperative forced expiratory volume in the first second(FEV_1) ≥1.0L; (3) the total bilirubin ≤ 1.5×normal upper limit; (4) the alanine transaminase(ALT), aspartate aminotransferase(AST) ≤ 1.5×normal upper limit; (5) the creatinine ≤ 1.25×normal upper limit, and creatinine clearance rate ≥ 60ml/min;

3. The primary preoperative clinical diagnosis highly suggested NSCLC, including adenocarcinoma, squamous cell carcinoma, large cell carcinoma, and other histological types; the clinical staging is T1a-1bN0M0 (IA1-2);

4. The thin-layer computed tomography(CT) indicates peripheral tumor[16, 17], whose maximum diameter ≤2cm; the tumors are located in the upper lobe or lower lobe of the lung with unspecified laterality; the CT images indicate nonsolid nodules or the lesions with ground-glass opacity components (consolidation-to-tumor ratio ≤0.5 on CT images); the minimum diameter ≤1cm or the positron emission tomography/computed tomography(PET/CT) indicates no mediastinal lymph node metastasis;

5. The intraoperative frozen section examination of surgical tissues and hilar lymph nodes confirms the histological type of NSCLC and negative diseases of N1 lymph nodes pathologically;

6. The Eastern Cooperative Oncology Group performance status(PS) score of 0-1;

7. All preoperative examinations are completed within 28 days preoperatively;

8. Patients who can comprehend this study and sign an informed consent form.

Patients with any of the following exclusion criteria would be ruled out:

1. Patients who have received preoperative anti-tumor treatment, including prior radiotherapy, chemotherapy, target therapy, and immunotherapy;

2. Patients have a history of other malignancies;

3. Patients diagnosed a secondary malignancy when included;

4. Centrally located lung cancer, defined as the inner one-third of the hemithorax adopted by drawing concentric lines from the midline[17, 18];

5. Tumors located in the middle lobe;

6. Small cell lung cancer;

7. Patients have a history of unilateral thoracic surgery;

8. Females with pregnancy or lactation;

9. Patients with interstitial pneumonitis, pulmonary fibrosis, or severe emphysema;

10. Uncontrollable active bacterial infection or fungal infection;

11. Severe mental disease;

12. Patients have a history of severe cardiac disease, cardiac failure, myocardial infarction, or angina within six months;

13. Tumors with potential pleura involvement on CT images.

Randomization, allocation concealment, and blinding

A random number table would be produced via SPSS software(version 22.0; IBM Corp, Armonk, NY, USA) by an independent randomization committee before research, confidential to researchers and patients. A random number selected from the random number table would be allocated into an opaque envelope, and a random number in the

envelope would be assigned to each enrolled patient. The researcher would unfold the envelope and get a random number, according to which the patient would be grouped. The trial is double-blind, and the researcher and the participant would be blinded to the allocation. The allocation would be unblinded when an emergency occurs, and the participant would be withdrawn from the trial.

Interventions

All patients would receive complete lymph node dissection for N1 lymph nodes. As for the mediastinal lymph nodes, patients in the experimental group would receive L-SLND[9]. We would completely dissect the upper mediastinal lymph node for lung cancer of the upper lobe, and the subcarinal and lower mediastinal lymph node for lung cancer of the lower lobe(Table 1). Patients in the control group would receive SLND, including upper mediastinal, subcarinal, and lower mediastinal lymph nodes. We would dissect at least three mediastinal nodal stations(including subcarinal lymph nodes) and a total of six lymph nodes during SLND[11]. Intraoperative frozen section examination of the suspected mediastinal lymph nodes in the L-SLND group would be performed to detect the possible lymph node metastasis, and in the case of positive lymph node metastasis on the frozen section, SLND would be performed intraoperatively.

When participants are diagnosed with pathological lymph node metastasis, postoperative adjuvant treatment would be conducted to reduce the risk of recurrence and metastasis, including target therapy and chemotherapy. Adjuvant radiotherapy would be considered in those who receive L-SLND or have positive mediastinal lymph

nodes.

The overall follow-up duration would be last for 60 months for each patient(Table 2). The first postoperative follow-up would be on the 30 days postoperatively, and we would focus on the postoperative complications and performance status. Then the follow-up would be performed every six months for the first 24 months postoperatively. We would take the history and physical examination(H&P), focusing on the performance status and weight loss, and require the patients to receive chest CT. Whether the chest CT was contrast-enhanced CT or non-contrast-enhanced CT was determined by the surgeon. The H&P and low-dose non-contrast-enhanced CT would be performed annually in the following 36 months.

Outcomes

The primary outcomes are 5-year disease-free survival(DFS) and 5-year OS. The DFS is defined as the duration(days) from the date of operation to the date of tumor recurrence, and the OS is defined as the duration(days) from the date of operation to the date of death of any cause. The secondary outcomes are metastatic lymph node ratio, postoperative complication incidence and mortality(≤30days), duration of operation(day), duration of anesthesia(min), the volume of bleeding(ml), and the volume of drainage(ml). The metastatic lymph node ratio is defined as the ratio of the number of positive lymph nodes divided by all dissected lymph nodes.

Data collection, management, monitoring, and analysis

The data collection and management were achieved by researchers under the guidance of the Data Management Committee of Lung Cancer Center of West China Hospital. All adverse events would be documented in detail and handled properly, which would also be reported to the Data Management Committee and Ethics Committee of West China Hospital of Sichuan University. The principal investigators would periodically review the reported adverse events and evaluate the related subjects' risk and benefit.

The intention-to-treat principle would be performed, and participants would be allocated to the assigned group. Chi-square test or Fisher's exact test is conducted to compare the categorical data between groups; the independent sample t-test, Mann-Whitney nonparametric U test, or one-way analysis of variance(ANOVA) test is performed to compare the continuous data between groups; the survival analysis compares the long-term survival between two groups via the Kaplan-Meier method and log-rank test; a bilateral *P*-value <0.05 is considered statistically significant[19].

Patients or public involvement

Patients and the public would not be involved in the research's design, conduct, reporting, or dissemination plans. All participants would sign the informed consent and be involved in the follow-up(e-Doc 1).

ETHICS AND DISSEMINATION

This trial(Version 3.0) was approved by the Ethics Committee on Biomedical Research, West China Hospital of Sichuan University(2021-332, e-Doc 2) on May 16, 2021, and

registered in the Chinese Clinical Trial Registry(ChiCTR2100048415). The LESSON study would be performed following the Declaration of Helsinki. All participants would learn the outline of this trial and sign the informed consent, who could also have the right to opt-out without medical care being affected, and the tumor specimens would not be collected. A regulatory team from the Ethics Committee of West China Hospital of Sichuan University would review all research data every six months, including research data, medical records, and electronic case report forms. Important protocol modifications would be reported to the Ethics Committee. The principal investigators would guarantee the participants' right to withdraw from this trial in an emergency to ensure their safety. All research data would be carefully stored and only available for the researchers and monitoring panels. The corresponding result of the trial would be published in academic conference presentations and peer-reviewed publications.

Author contributions: W. H. and H. D. contributed to the conceptualization of the study and drafting of the manuscript and took full responsibility for the content, including the data and analysis. W. H., H. D., Z. R., X. T., and D. Z. contributed to recruitment and data curation. W. H., H. D., K. X., and Y. W. contributed to the formal analysis. W. H., H. D., and Q. Z. contributed to the revision of the manuscript. W. H., H. D., Z. R., K. X., Y. W., X. T., D. Z., and Q. Z. contributed to the approval of the final manuscript. H. D. and Q. Z. contributed to supervision and project administration.

Competing interests: The authors declare no conflict of interest.

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Supplementary data: e-Doc 1, an example of the patient consent form; e-Doc 2, the trial approval from the Ethics Committee on Biomedical Research, West China Hospital of Sichuan University(2021-332).

Abbreviations

ALT, alanine transaminase

ANOVA, analysis of variance

AST, aspartate aminotransferase

CT, computed tomography

DFS, disease-free survival

DL_{CO}, carbon monoxide diffusing capacity

FEV_1, forced expiratory volume in the first second

H&P, history and physical examination

HR, hazard ratio

NSCLC, non-small cell lung cancer

OS, overall survival

PET/CT, positron emission tomography/computed tomography

PS, performance status

RCT, randomized controlled study

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Figure legends

Figure 1 Scheme of the LESSON Trial. **Abbreviation:** NSCLC, non-small cell lung cancer; IFSE, intraoperative frozen section examination; N1-negative, there is negative finding or no metastasis for the hilar lymph nodes; L-SLND, lobe-specific lymph node dissection; SLND, systematic lymph node dissection.

Table 1 The dissected lymph nodes in lobe-specific lymph node dissection and systematic lymph node dissection in the LESSON Trial

	Lobe-specific lymph node dissection	**Systematic lymph node dissection**
Left lung		
Upper lobe	4L, 5, 6	4L, 5, 6, 7,8,9
Lower lobe	7, 8, 9	4L, 5, 6, 7, 8, 9
Right lung		
Upper lobe	2R, 4R	2R, 4R, 7,8,9
Lower lobe	7, 8, 9	2R, 4R, 7, 8, 9

Table 2 The timeline of data collection and postoperative follow-up in the LESSON Trial

Timepoint	**Preoperative**	**Day of surgery**	**Before discharge**	**Postoperative (follow-up)**		
	Baseline			30 days	6, 12, 18, 24 months	3, 4, 5 years
Eligibility	√					
H&P	√		√	√	√	√
Blood test	√		√	√	√	√
Chemistry profile	√		√	√	√	√
Tumor marker	√		√	√	√	√
Chest CT/CECT	√				√	
Chest LDCT						√
Metastatic LNR		√				
Postoperative complication incidence				√		
Postoperative mortality				√		

Duration of operation	√	
Duration of anesthesia	√	
Volume of bleeding	√	
Volume of drainage		√

Abbreviation: H&P, medical and physical examination; CT, computed tomography; CECT, contrast-enhanced computed tomography; LDCT, low-dose computed tomography; LNR, lymph node rate.

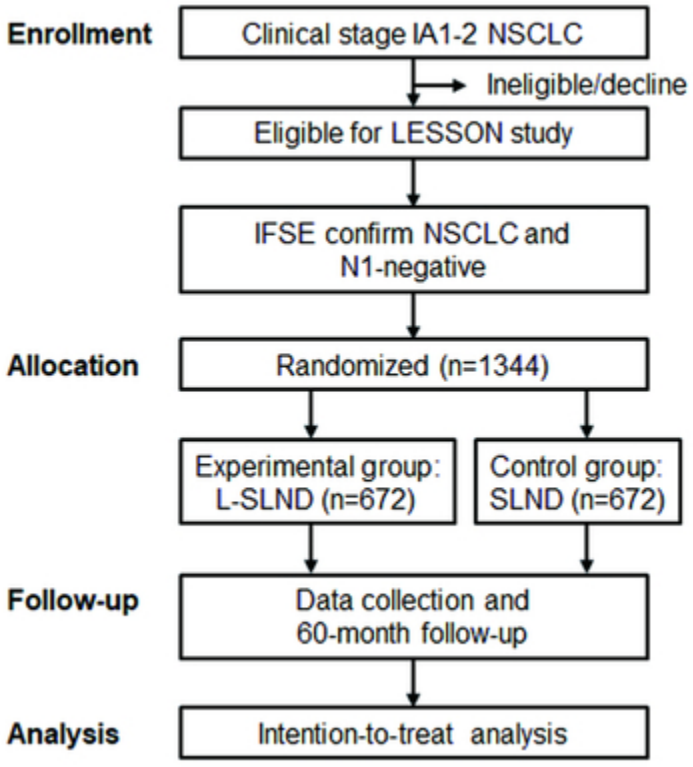

Figure 1 Scheme of the LESSON Trial. Abbreviation: NSCLC, non-small cell lung cancer; IFSE, intraoperative frozen section examination; N1-negative, there is negative finding or no metastasis for the hilar lymph nodes; L-SLND, lobe-specific lymph node dissection; SLND, systematic lymph node dissection.

15x16mm (600 x 600 DPI)

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肺叶特异性淋巴结清扫术在早期非小细胞肺癌中的可行性研究方案知情同意书

尊敬的受试者

我们邀请您参加四川大学华西医院 SCI 经费支持下批准开展的“肺叶特异性淋巴结清扫术在早期非小细胞肺癌中的可行性研究方案”课题研究。本研究将在四川大学华西医院开展，估计将有 1300 名受试者自愿参加。本研究已经得到四川大学华西医院生物医学伦理审查委员会的审查和批准。

1. 为什么要开展本项研究？

肺癌已成为中国乃至全世界最常见的恶性肿瘤和癌症相关死亡的主要原因。肺癌主要由小细胞肺癌和非小细胞肺癌组成，非小细胞肺癌占所有肺癌的约 85%。随着医学筛查方法的进步，越来越多的早期非小细胞肺癌被发现。目前，手术仍然是早期非小细胞肺癌的首选治疗方案，最近的指南都建议解剖性肺切除术和系统性淋巴结清扫或系统性淋巴结采样作为治疗临床 I 期非小细胞肺癌标准治疗方案。然而，最近，由于先前的文献提示非小细胞肺癌中的淋巴结转移模式被认为是肺叶特异性的，因此有学者提出了肺叶特异性淋巴结清扫作为系统性淋巴结清扫治疗早期非小细胞肺癌的替代方案。在我们的前期研究中，通过将所有最新证据研究汇集在一起来进行全面的荟萃分析，以比较肺叶特异性淋巴结清扫和系统性淋巴结清扫在治疗早期非小细胞肺癌中的作用。我们的研究发现与系统性淋巴结清扫相比，肺叶特异性淋巴结清扫的术后并发症的发生风险显著降低且不会影响患者的长期肿瘤学结果，因此肺叶特异性淋巴结清扫可以替代系统性淋巴结清扫作为治疗早期非小细胞肺癌的淋巴结清扫方案。然而，在以往的队列研究和临床指南中，并没有关于肺叶特异性淋巴结清扫清扫范围一致而确切的定义，因此肺叶特异性淋巴结清扫在早期非小细胞肺癌中的清扫范围仍待进一步研究和确立，需要进一步的研究去确定肺叶特异性淋巴结清扫的治疗作用以及肺叶特异性淋巴结清扫清扫范围的精确定义。因此，本新技术课题组拟行以下探究方案来开创性地提出早期非小细胞肺叶特异性淋巴结清扫术的新技术理念：根据我们开创性提出的早期非小细胞肺癌肺叶特异性淋巴结清扫的方案，开展前瞻性随机对照研究，对于肺叶特异性淋巴结清扫术和系统性淋巴结清扫术在治疗早期非小细胞肺癌中的效果，为肺叶特异性淋巴结清扫术作为早期非小细胞肺癌治疗可选方案之一提供决定性依据。

2. 如果参加研究，您需要做什么？

如果您同意参与这项研究，我们将对每位受试者进行编号，建立病历档案。由于临床诊断或治疗需要，您将会被随机分配进入系统性淋巴结清扫术组或肺叶特异性淋巴结清扫术组，手术中切除的组织除供临床常规病理检查，术后按照标准的复查随访方案进行随访汇报总结。您的病例报告（个人基本信息除外）会发表于全球性的网站和期刊上，印刷版本和网络版本会供医生、媒体、大众阅读。

3. 可供选择的诊疗方案有哪些？

目前可供选择的早期肺癌的淋巴结清扫方式包括：系统性淋巴结清扫术或淋巴结采样术

4. 哪些人不宜参加研究？

1. 在手术前已行抗肿瘤治疗（放疗、化疗、靶向治疗、免疫治疗）的患者；2. 既往有其他恶性肿瘤病史的患者；3. 入组时合并第二原发癌的患者；4. 中央型肺癌；5. 小细胞肺癌；6. 既往有单侧开胸手术病史；7. 怀孕或处于哺乳期的妇女；8. 间质性肺炎、肺纤维化或严重肺气肿；9. 难以控制的活动性细菌或真菌感染；10. 严重的精神疾病；11. 近 6 个月内有严重心脏病、心力衰竭、心肌梗塞或心绞痛发作史。

5. 参加研究有哪些风险？

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Ethics Committee on Biomedical Research, West China Hospital of Sichuan University

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2021年审(332)号

科室（专业）：肺癌中心	项目负责人姓名及职称：邓汉宇/讲师	
项目名称	肺叶特异性淋巴结清扫术在早期非小细胞肺癌中的可行性研究	
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知情同意书	版本号：V3.0	版本日期：2021年5月16日
招募广告	无	

审查意见：

1. 研究者资质符合伦理要求。
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LobE-Specific lymph node diSsectiON for clinical early-stage non-small cell lung cancer: protocol for a randomized controlled trial (the LESSON Trial)

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Title

LobE-Specific lymph node diSsectiON for clinical early-stage non-small cell lung cancer: protocol for a randomized controlled trial (the LESSON Trial)

Running head

Lobe-specific lymph node dissection for NSCLC

Authors

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ABSTRACT

Introduction: Lung cancer was the most common malignancy and the leading cause of cancer-related death in China or worldwide, and surgery is still the preferred treatment for early-stage non-small cell lung cancer(NSCLC). The pattern of lymph node metastasis was found potentially lobe-specific, and thus, lobe-specific lymph node dissection was proposed to be an alternative to systematic lymph node dissection for the treatment of early-stage NSCLC.

Methods and analysis: The LESSON trial is a single-institutional, randomized, double-blind, and parallel controlled trial to investigate the feasibility of lobe-specific lymph node dissection in clinically diagnosed stage IA1-2 NSCLC with ground-glass opacity components(≥50%). The intraoperative frozen section examination of surgical tissues confirms the histological type of NSCLC. We hypothesize that lobe-specific lymph node dissection(experimental group) is not inferior to systematic lymph node dissection(control group) and intend to include 672 participants for the experimental group and 672 participants for the control group with a follow-up duration of 60 months. The primary outcomes are 5-year disease-free survival and 5-year overall survival. The secondary outcomes are metastatic lymph node ratio, postoperative complication incidence and mortality, duration of operation, duration of anesthesia(min), the volume of bleeding(ml), and drainage volume. The intention-to-treat analysis would be performed in the trial.

Ethics and dissemination: This trial was approved by the Ethics Committee on Biomedical Research, West China Hospital of Sichuan University(2021-332). Informed

consent would be obtained from all participants, and dissemination activities would include academic conference presentations and peer-reviewed publications. This trial was registered in the Chinese Clinical Trial Registry(Trial Registration number: ChiCTR2100048415).

Strengths and Limitations of This Study:

1. The LESSON trial is a single-center, randomized, double-blind, and parallel controlled trial.
2. We investigate the feasibility of lobe-specific lymph node dissection for clinical-stage IA1-2 non-small cell lung cancer with ground-glass opacity components(≥50%).
3. We hypothesize that lobe-specific lymph node dissection is not inferior to systematic lymph node dissection in long-term survival.
4. The primary endpoint will be the 5-year disease-free survival and 5-year overall survival.
5. The challenge of this trial is to ensure the complete follow-up of the numerous participants.

INTRODUCTION

Lung cancer was the most common malignancy and the main cause of cancer-related death in China or worldwide[1, 2]. Lung cancer is mainly composed of small cell lung cancer and non-small cell lung cancer(NSCLC), accounting for about 85% of all histological types of lung cancer[3]. With the advances in lung cancer screening technology, more and more early-stage NSCLC is likely to be diagnosed[4]. At present, surgery is still the preferred treatment for early-stage NSCLC, and current guidelines suggest that anatomical lung resection with systematic lymph node dissection(SLND) or lymph node sampling is the standard treatment for clinical stage I NSCLC[5]. Since previous research indicated that the pattern of lymph node metastasis might be lobe-specific, lobe-specific lymph node dissection(L-SLND) was proposed to be an alternative to SLND for the treatment of early-stage NSCLC[6, 7].

In our previous research, we conducted a meta-analysis to compare the safety and efficacy between L-SLND and SLND in treating early-stage NSCLC. Our findings implied that compared with SLND, the occurrence of postoperative complications in L-SLND decreased significantly but was comparable in long-term survival, indicating that L-SLND might be an alternative to SLND[8, 9]. However, there is no explicit and precise definition of the L-SLND and the dissecting range of lymph nodes in previous cohort studies and practice guidelines[10, 11]. The role of L-SLND and its explicit dissecting range remain to be further studied and established, and a well-designed and conducted randomized controlled study(RCT) might provide some suggestions to clinical instructions[12].

As shown in our previous retrospective study, the subcarinal and lower mediastinal lymph nodes were all negative when the tumor was located in the upper lobe and with a size of ≤2cm, and the upper mediastinal lymph nodes were all negative when the tumor was located in the lower lobe and with a size of ≤2cm[9]. It reminded us that the lobe-specific lymph node metastasis pattern might be noticed, and the L-SLND might be practical, with comparable long-term survival and fewer postoperative complications[13]. Therefore, we conducted a double-blind, randomized, and parallel-controlled clinical trial to determine the preferred treatment between L-SLND and SLND for early-stage NSCLC. We hypothesized that L-SLND was not inferior to SLND in safety and long-term oncological results.

METHODS

Protocol version

Protocol V3.0, modified May 16, 2021.

Trial design

This study is a single-institutional, randomized, double-blind, and parallel controlled trial conducted in Lung Cancer Center, West China Hospital, Sichuan University. Patients had been enrolled since August 2021, and it would be operated until July 2024. The study with active follow-up would be operated until July 2026.

Sample size

According to the summarized survival rate of early-stage NSCLC in prior research, we assumed that the 5-year overall survival(OS) rate was 70% among the total population of the L-SLND group and SLND group. The non-inferiority threshold of the 5-year OS rate was 6%(hazard ratio[HR]=1.25), with a unilateral α of 0.05 and a certainty of 0.8. The recruiting duration is 36 months, and the duration of follow-up is 60 months. In this way, the sample size is 1344 cases as calculated by the Log-rank test[14], in which 672 cases are for the experimental group and 672 cases for the control group. We are dedicated to requiring the enrolled patients to be in active follow-up and offer some allowance to those patients to reduce the risk of participants loss and enable the trial to reach the target sample size.

Study population

This trial intends to include 1344 patients with clinically diagnosed stage IA1-2 NSCLC, and the trial schema of the patient pathway is shown in Figure 1. These preliminary eligible patients would be enrolled in the study cohort and participate in randomization after intraoperative frozen section examination conformity of NSCLC. The staging is referred to the American Joint Committee on Cancer(the eighth edition)[15, 16].

The included patients are required to meet all of the following inclusion criteria:

1. Patient aged 18-80 years old;

2. The preoperative blood pressure is controlled below 160/100mmHg; the blood glucose is controlled between 5.6 and 11.2 mmol/L; the major organs' function is within normality, including cardiac, pulmonary, hepatic, and nephritic function: (1) the cardiac

function examination indicates a Goldman index rated 1-2; (2) the pulmonary function examination indicates an estimated postoperative forced expiratory volume in the first second(FEV_1) ≥1.0L; (3) the total bilirubin ≤ 1.5×normal upper limit; (4) the alanine transaminase(ALT), aspartate aminotransferase(AST) ≤ 1.5×normal upper limit; (5) the creatinine ≤ 1.25×normal upper limit, and creatinine clearance rate ≥ 60ml/min;

3. The primary preoperative clinical diagnosis highly suggested NSCLC, including adenocarcinoma, squamous cell carcinoma, large cell carcinoma, and other histological types; the clinical staging is T1a-1bN0M0 (IA1-2);

4. The thin-layer computed tomography(CT) indicates peripheral tumor[16, 17], whose maximum diameter ≤2cm; the tumors are located in the upper lobe or lower lobe of the lung with unspecified laterality; the CT images indicate nonsolid nodules or the lesions with ground-glass opacity components (consolidation-to-tumor ratio ≤0.5 on CT images); the minimum diameter ≤1cm or the positron emission tomography/computed tomography(PET/CT) indicates no mediastinal lymph node metastasis;

5. The intraoperative frozen section examination of surgical tissues and hilar lymph nodes confirms the histological type of NSCLC and negative diseases of N1 lymph nodes pathologically;

6. The Eastern Cooperative Oncology Group performance status(PS) score of 0-1;

7. All preoperative examinations are completed within 28 days preoperatively;

8. Patients who can comprehend this study and sign an informed consent form.

Patients with any of the following exclusion criteria would be ruled out:

1. Patients who have received preoperative anti-tumor treatment, including prior radiotherapy, chemotherapy, target therapy, and immunotherapy;

2. Patients have a history of other malignancies;

3. Patients diagnosed a secondary malignancy when included;

4. Centrally located lung cancer, defined as the inner one-third of the hemithorax adopted by drawing concentric lines from the midline[17, 18];

5. Tumors located in the middle lobe;

6. Small cell lung cancer;

7. Patients have a history of unilateral thoracic surgery;

8. Females with pregnancy or lactation;

9. Patients with interstitial pneumonitis, pulmonary fibrosis, or severe emphysema;

10. Uncontrollable active bacterial infection or fungal infection;

11. Severe mental disease;

12. Patients have a history of severe cardiac disease, cardiac failure, myocardial infarction, or angina within six months;

13. Tumors with potential pleura involvement on CT images.

Randomization, allocation concealment, and blinding

A random number table would be produced via SPSS software(version 22.0; IBM Corp, Armonk, NY, USA) by an independent randomization committee before research, confidential to researchers and patients. A random number selected from the random number table would be allocated into an opaque envelope, and a random number in the

envelope would be assigned to each enrolled patient. The researcher would unfold the envelope and get a random number, according to which the patient would be grouped. The trial is double-blind, and the researcher and the participant would be blinded to the allocation. The allocation would be unblinded when an emergency occurs, and the participant would be withdrawn from the trial.

Interventions

All patients would receive complete lymph node dissection for N1 lymph nodes. As for the mediastinal lymph nodes, patients in the experimental group would receive L-SLND[9]. We would completely dissect the upper mediastinal lymph node for lung cancer of the upper lobe, and the subcarinal and lower mediastinal lymph node for lung cancer of the lower lobe(Table 1). Patients in the control group would receive SLND, including upper mediastinal, subcarinal, and lower mediastinal lymph nodes. We would dissect at least three mediastinal nodal stations(including subcarinal lymph nodes) and a total of six lymph nodes during SLND[11]. Intraoperative frozen section examination of the suspected mediastinal lymph nodes in the L-SLND group would be performed to detect the possible lymph node metastasis, and in the case of positive lymph node metastasis on the frozen section, SLND would be performed intraoperatively.

Table 1 The dissected lymph nodes in lobe-specific lymph node dissection and systematic lymph node dissection in the LESSON Trial

	Lobe-specific lymph node dissection	Systematic lymph node dissection
Left lung		
Upper lobe	4L, 5, 6	4L, 5, 6, 7,8,9
Lower lobe	7, 8, 9	4L, 5, 6, 7, 8, 9
Right lung		
Upper lobe	2R, 4R	2R, 4R, 7,8,9
Lower lobe	7, 8, 9	2R, 4R, 7, 8, 9

When participants are diagnosed with pathological lymph node metastasis, postoperative adjuvant treatment would be conducted to reduce the risk of recurrence and metastasis, including target therapy and chemotherapy. Adjuvant radiotherapy would be considered in those who receive L-SLND or have positive mediastinal lymph nodes.

The overall follow-up duration would be last for 60 months for each patient(Table 2). The first postoperative follow-up would be on the 30 days postoperatively, and we would focus on the postoperative complications and performance status. Then the follow-up would be performed every six months for the first 24 months postoperatively. We would take the history and physical examination(H&P), focusing on the performance status and weight loss, and require the patients to receive chest CT. Whether the chest CT was contrast-enhanced CT or non-contrast-enhanced CT was determined by the surgeon. The H&P and low-dose non-contrast-enhanced CT would be performed annually in the following 36 months.

Table 2 The timeline of data collection and postoperative follow-up in the LESSON Trial

Timepoint	**Preoperative**	**Day of surgery**	**Before discharge**	**Postoperative (follow-up)**		
	Baseline			30 days	6, 12, 18, 24 months	3, 4, 5 years
Eligibility	√					
H&P	√		√	√	√	√
Blood test	√		√	√	√	√
Chemistry profile	√		√	√	√	√
Tumor marker	√		√	√	√	√
Chest CT/CECT	√				√	
Chest LDCT						√
Metastatic LNR		√				
Postoperative complication incidence				√		
Postoperative mortality				√		
Duration of operation		√				
Duration of anesthesia		√				
Volume of bleeding		√				
Volume of drainage			√			

Abbreviation: H&P, medical and physical examination; CT, computed tomography; CECT, contrast-enhanced computed tomography; LDCT, low-dose computed tomography; LNR, lymph node rate.

Outcomes

The primary outcomes are 5-year disease-free survival(DFS) and 5-year OS. The DFS is defined as the duration(days) from the date of operation to the date of tumor recurrence, and the OS is defined as the duration(days) from the date of operation to the date of death of any cause. The secondary outcomes are metastatic lymph node ratio, postoperative complication incidence and mortality(≤30days), duration of

operation(day), duration of anesthesia(min), the volume of bleeding(ml), and the volume of drainage(ml). The metastatic lymph node ratio is defined as the ratio of the number of positive lymph nodes divided by all dissected lymph nodes.

Data collection, management, monitoring, and analysis

The data collection and management were achieved by researchers under the guidance of the Data Management Committee of Lung Cancer Center of West China Hospital. All adverse events would be documented in detail and handled properly, which would also be reported to the Data Management Committee and Ethics Committee of West China Hospital of Sichuan University. The principal investigators would periodically review the reported adverse events and evaluate the related subjects' risk and benefit.

The intention-to-treat principle would be performed, and participants would be allocated to the assigned group. Chi-square test or Fisher's exact test is conducted to compare the categorical data between groups; the independent sample t-test, Mann-Whitney nonparametric U test, or one-way analysis of variance(ANOVA) test is performed to compare the continuous data between groups; the survival analysis compares the long-term survival between two groups via the Kaplan-Meier method and log-rank test; a bilateral *P*-value <0.05 is considered statistically significant[19].

Patients or public involvement

Patients and the public would not be involved in the research's design, conduct, reporting, or dissemination plans. All participants would sign the informed consent and

be involved in the follow-up(Supplementary File 1).

ETHICS AND DISSEMINATION

This trial(Version 3.0) was approved by the Ethics Committee on Biomedical Research, West China Hospital of Sichuan University(2021-332, Supplementary File 2) on May 16, 2021, and registered in the Chinese Clinical Trial Registry(ChiCTR2100048415). The LESSON study would be performed following the Declaration of Helsinki. All participants would learn the outline of this trial and sign the informed consent, who could also have the right to opt-out without medical care being affected, and the tumor specimens would not be collected. A regulatory team from the Ethics Committee of West China Hospital of Sichuan University would review all research data every six months, including research data, medical records, and electronic case report forms. Important protocol modifications would be reported to the Ethics Committee. The principal investigators would guarantee the participants' right to withdraw from this trial in an emergency to ensure their safety. All research data would be carefully stored and only available for the researchers and monitoring panels. The corresponding result of the trial would be published in academic conference presentations and peer-reviewed publications.

Author contributions: W. H. and H. D. contributed to the conceptualization of the study and drafting of the manuscript and took full responsibility for the content, including the data and analysis. W. H., H. D., Z. R., X. T., and D. Z. contributed to

recruitment and data curation. W. H., H. D., K. X., and Y. W. contributed to the formal analysis. W. H., H. D., and Q. Z. contributed to the revision of the manuscript. W. H., H. D., Z. R., K. X., Y. W., X. T., D. Z., and Q. Z. contributed to the approval of the final manuscript. H. D. and Q. Z. contributed to supervision and project administration.

Competing interests: The authors declare no conflict of interest.

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Supplementary data: Supplementary File 1, an example of the patient consent form; Supplementary File 2, the trial approval from the Ethics Committee on Biomedical Research, West China Hospital of Sichuan University(2021-332).

Abbreviations

ALT, alanine transaminase

ANOVA, analysis of variance

AST, aspartate aminotransferase

CT, computed tomography

DFS, disease-free survival

DL_{CO}, carbon monoxide diffusing capacity

FEV_1, forced expiratory volume in the first second

H&P, history and physical examination

HR, hazard ratio

NSCLC, non-small cell lung cancer

OS, overall survival

PET/CT, positron emission tomography/computed tomography

PS, performance status

RCT, randomized controlled study

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Figure legends

Figure 1 Scheme of the LESSON Trial. **Abbreviation:** NSCLC, non-small cell lung cancer; IFSE, intraoperative frozen section examination; N1-negative, there is negative finding or no metastasis for the hilar lymph nodes; L-SLND, lobe-specific lymph node dissection; SLND, systematic lymph node dissection.

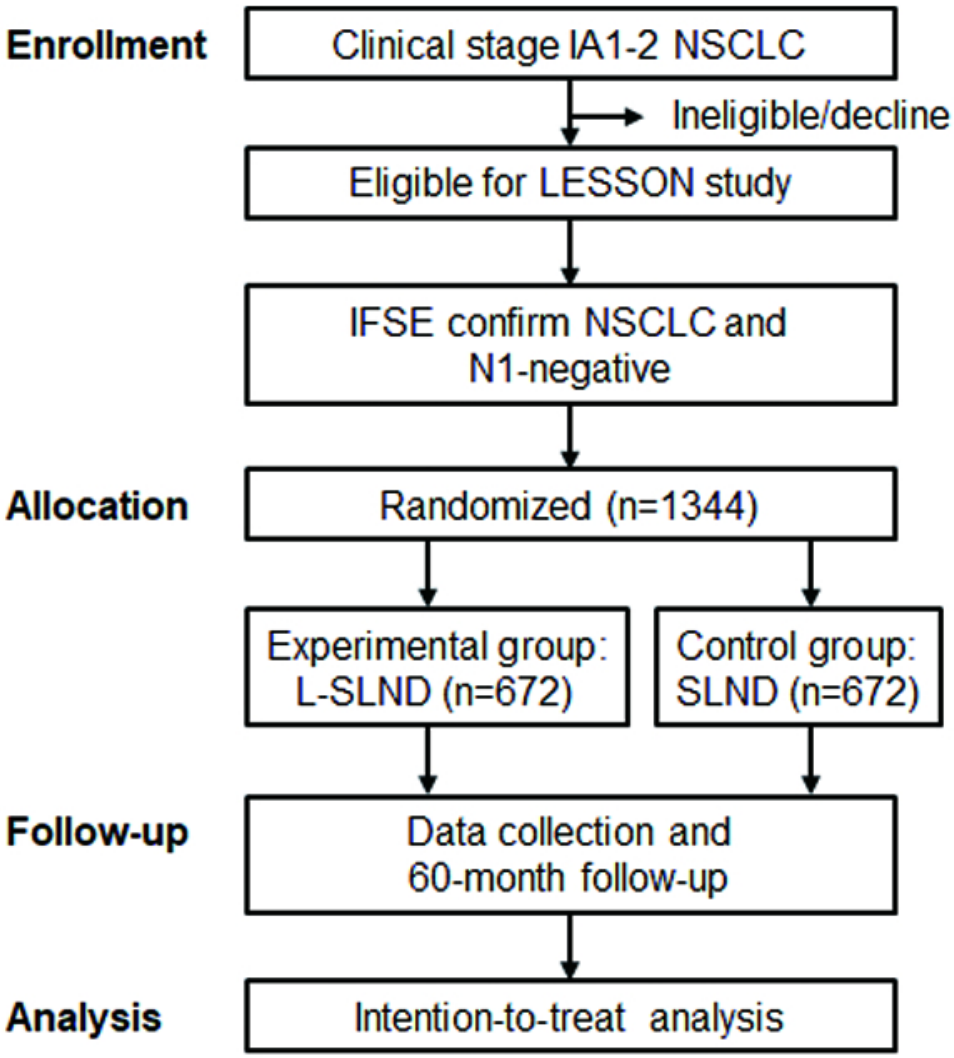

Figure 1 Scheme of the LESSON Trial. Abbreviation: NSCLC, non-small cell lung cancer; IFSE, intraoperative frozen section examination; N1-negative, there is negative finding or no metastasis for the hilar lymph nodes; L-SLND, lobe-specific lymph node dissection; SLND, systematic lymph node dissection.

肺叶特异性淋巴结清扫术在早期非小细胞肺癌中的可行性研究方案知情同意书

尊敬的受试者

我们邀请您参加四川大学华西医院 SCI 经费支持下批准开展的“肺叶特异性淋巴结清扫术在早期非小细胞肺癌中的可行性研究方案”课题研究。本研究将在四川大学华西医院开展，估计将有 1300 名受试者自愿参加。本研究已经得到四川大学华西医院生物医学伦理审查委员会的审查和批准。

1. 为什么要开展本项研究？

肺癌已成为中国乃至全世界最常见的恶性肿瘤和癌症相关死亡的主要原因。肺癌主要由小细胞肺癌和非小细胞肺癌组成，非小细胞肺癌占所有肺癌的约 85%。随着医学筛查方法的进步，越来越多的早期非小细胞肺癌被发现。目前，手术仍然是早期非小细胞肺癌的首选治疗方案，最近的指南都建议解剖性肺切除术和系统性淋巴结清扫或系统性淋巴结采样作为治疗临床 I 期非小细胞肺癌标准治疗方案。然而，最近，由于先前的文献提示非小细胞肺癌中的淋巴结转移模式被认为是肺叶特异性的，因此有学者提出了肺叶特异性淋巴结清扫作为系统性淋巴结清扫治疗早期非小细胞肺癌的替代方案。在我们的前期研究中，通过将所有最新证据研究汇集在一起来进行全面的荟萃分析，以比较肺叶特异性淋巴结清扫和系统性淋巴结清扫在治疗早期非小细胞肺癌中的作用。我们的研究发现与系统性淋巴结清扫相比，肺叶特异性淋巴结清扫的术后并发症的发生风险显著降低且不会影响患者的长期肿瘤学结果，因此肺叶特异性淋巴结清扫可以替代系统性淋巴结清扫作为治疗早期非小细胞肺癌的淋巴结清扫方案。然而，在以往的队列研究和临床指南中，并没有关于肺叶特异性淋巴结清扫清扫范围一致而确切的定义，因此肺叶特异性淋巴结清扫在早期非小细胞肺癌中的清扫范围仍待进一步研究和确立，需要进一步的研究去确定肺叶特异性淋巴结清扫的治疗作用以及肺叶特异性淋巴结清扫清扫范围的精确定义。因此，本新技术课题组拟行以下探究方案来开创性地提出早期非小细胞肺叶特异性淋巴结清扫术的新技术理念：根据我们开创性提出的早期非小细胞肺癌肺叶特异性淋巴结清扫的方案，开展前瞻性随机对照研究，对于肺叶特异性淋巴结清扫术和系统性淋巴结清扫术在治疗早期非小细胞肺癌中的效果，为肺叶特异性淋巴结清扫术作为早期非小细胞肺癌治疗可选方案之一提供决定性依据。

2. 如果参加研究，您需要做什么？

如果您同意参与这项研究，我们将对每位受试者进行编号，建立病历档案。由于临床诊断或治疗需要，您将会被随机分配进入系统性淋巴结清扫术组或肺叶特异性淋巴结清扫术组，手术中切除的组织除供临床常规病理检查，术后按照标准的复查随访方案进行随访汇报总结。您的病例报告（个人基本信息除外）会发表于全球性的网站和期刊上，印刷版本和网络版本会供医生、媒体、大众阅读。

3. 可供选择的诊疗方案有哪些？

目前可供选择的早期肺癌的淋巴结清扫方式包括：系统性淋巴结清扫术或淋巴结采样术

4. 哪些人不宜参加研究？

1. 在手术前已行抗肿瘤治疗（放疗、化疗、靶向治疗、免疫治疗）的患者；2. 既往有其他恶性肿瘤病史的患者；3. 入组时合并第二原发癌的患者；4. 中央型肺癌；5. 小细胞肺癌；6. 既往有单侧开胸手术病史；7. 怀孕或处于哺乳期的妇女；8. 间质性肺炎、肺纤维化或严重肺气肿；9. 难以控制的活动性细菌或真菌感染；10. 严重的精神疾病；11. 近 6 个月内有严重心脏病、心力衰竭、心肌梗塞或心绞痛发作史。

5. 参加研究有哪些风险？

对于您来说，所有的信息将是保密的。您的手术将由专业人员如外科医师操作。参加研究的风险与手术治疗风险等同，即：术中或者术后大出血：术中损伤神经、血管或邻近器官：手术切口并发症：血栓栓塞：呼吸系统并发症；循环系统并发症；尿路感染及肾衰：脑血管意外；肝功能不全等。

本研究中使用的研究治疗或操作可能会对您产生副作用，也可能不会。副作用可从轻度至非常严重不等，因人而异。参加本研究的所有患者都将被密切关注任何副作用。以下是关于副作用的要点：

- 部分风险可能很快消失，部分可能持续较长时间，部分可能一直存在。
- 一些风险可能严重，甚至可能导致死亡。

如果您注意或感觉到任何异常，请告知研究医生以便他/她能查看您是否出现了副作用。研究医生可能会治疗副作用或调整研究治疗，以减轻副作用。如果您住得很远或是由于其他原因而无法赶到研究中心，您需要前往您当地的卫生保健专业服务提供者或当地的急诊服务处。确保带上您的患者（身份识别）卡，此卡将在开始研究治疗时提供给您，以方便您与您的研究医生联系。

6. 参加研究有哪些可能的好处？

参加本项研究，您的病情有可能获得改善，本项研究还有助于确定哪种治疗方法可以更安全有效地治疗与您具有相似病情的其他病人。参加本研究可能无法改善您的健康状况。即使您没有直接获益，其他人可能从本研究得出的结果中获益。同时本研究会给予受试者补贴相应的交通和检查费：交通费：100 元/人；术后一月胸部 CT 检查补贴费：100 元/人。

7. 参加研究需要支付有关费用吗？

本研究参与的受试者无需支付相关费用，如果出现与研究相关的损伤时，将依据国家有关规定提供相应的治疗与赔偿。如果您觉得您因为参与本研究而受到了损害，请务必告诉您的研究医生。如果您由于参与本研究而受到损害，您将得到治疗。您的研究医生将向您解释治疗方案，并告诉您可以在哪里获得治疗。

请您严格遵从研究医生的指导，如果您在本研究过程中发生了损害/伤害，请立即与研究医生联系，研究医生将向您提供合理且必要的医疗诊治。如果您出现了与研究相关的损害/伤害，申办方将根据中国相关法律和法规向您赔付治疗该损害/伤害的合理且必要的费用，并提供适当的补偿。与研究相关的损害/伤害是指由于研究药物给药和/或研究方案中描述的研究操作的执行直接引起的，但不包括下列任何一项造成的损害/伤害：

- 与研究药物或研究方案规定的步骤不相关；
- 因您原有身体状况或基础疾病的自然进展所导致；
- 因医疗事故导致；
- 因您自己的疏忽、过错或故意的不当行为导致（例如未严格遵守本知情同意书、研究方案、研究医生或研究工作人员提供的指导）；

签署此知情同意书不会导致您失去任何合法权利。

8. 个人信息是保密的吗？

您的研究资料将保存在四川大学华西医院，研究者、研究主管部门、伦理审查委员会可查阅您的医疗记录。任何有关本项研究结果的公开报告将不会披露您的个人身份。我们将在

法律允许的范围内，尽一切努力保护您个人医疗资料的隐私和个人信息。

9. 我必须参加研究吗？

参加本项研究是完全自愿的，您可以拒绝参加研究，或在试验的任何阶段随时退出本研究而不会受到歧视和报复，其医疗待遇与权益不受影响。如果您决定退出本研究，请与您的医生联系，以便妥善诊疗疾病。

受试者声明：我已经阅读了上述有关本研究的介绍，我的研究人员已向我充分解释和说明了本研究的目的、操作过程以及参加本研究可能存在的风险和潜在的获益，并回答了我所有相关问题。自愿参加本研究。

我同意☐ 或拒绝☐ 除本研究以外的其他研究利用我的研究资料和生物标本。

受试者正楷姓名：_____

受试者签名：_____ 日期：__ __ __ __ 年 __ __ 月 __ __ 日

受试者的联系电话：_____ 手机号：_____

法定代理人正楷姓名：_____ （如适用）

与受试者关系：_____

法定代理人签名：_____ 日期：__ __ __ __ 年 __ __ 月 __ __ 日

需法定代理人签署的原因：_____

见证人正楷姓名：_____ （如适用）

见证人签名：_____ 日期：__ __ __ __ 年 __ __ 月 __ __ 日

需见证人签署的原因：_____

医生声明：我已对上述参加本研究的自愿者说明了该项研究的有关细节，并且为他/她提供一份签署过的知情同意书的原件。我确认已向受试者详细解释了本研究的情况，特别是参加本研究可能产生的风险与受益、免费与补偿、损害与赔偿、自愿与保密等伦理原则和要求。

医生签名：_____ 日期：__ __ __ __ 年 __ __ 月 __ __ 日

医生的联系电话：_____

四川大学华西医院生物医学伦理审查委员会 联系电话：028-85422654，028-85423237

四川大学华西医院生物医学伦理审查委员会
Ethics Committee on Biomedical Research, West China Hospital of Sichuan University

四川大学华西医院生物医学伦理审查委员会批件

2021年审(332)号

科室（专业）：肺癌中心	项目负责人姓名及职称：邓汉宇/讲师	
项目名称	肺叶特异性淋巴结清扫术在早期非小细胞肺癌中的可行性研究	
研究方案	版本号：V3.0	版本日期：2021年5月16日
知情同意书	版本号：V3.0	版本日期：2021年5月16日
招募广告	无	

审查意见：

1. 研究者资质符合伦理要求。
2. 研究方案及知情同意书基本符合伦理要求。

审查结果：■批准 □修改后批准 □修改后再审 □不批准 □暂停或者终止研究
持续审查频率： □3 个月/3months ■6 个月/6months □1 年/1year □不适用/NA

请遵循我国相关法律、法规和规章（《涉及人的生物医学研究伦理审查办法》等）以及WMA《赫尔辛基宣言》和CIOMS《人体生物医学研究国际道德指南》，遵循伦理审查委员会批准的方案和知情同意书开展临床试验（研究），保护受试者的健康与权利。

请严格执行《中华人民共和国人类遗传资源管理条例》（国令第717号），涉及我院人类遗传资源的采集、保藏、国际合作、材料出境等行为均需向国家科技部申请行政许可，信息对外提供或开放使用需向国家科技部申请备份备案，通过后方可实施相应活动。临床研究管理部作为全院人类遗传资源管理部门，咨询电话85422851。

在试验（研究）过程中，若变更主要研究者，对临床研究方案、知情同意书等的任何修改，请申请人提交修正案审查申请。

发生严重不良事件，请申请人及时提交严重不良事件报告；紧急报告之后，尽快提交详细的严重不良事件随访报告。

请递交年度和定期跟踪审查报告；当出现任何可能显著影响试验（研究）进行或增加受试者危险的情况时，请申请人及时向伦理审查委员会提交书面报告。

试验（研究）纳入了不符合纳入标准或符合排除标准的受试者，符合中止试验（研究）规定而未让受试者退出试验（研究），给予错误治疗或剂量，给予方案禁止的合并用药等没有遵从方案开展研究的情况；或可能对受试者的权益/健康、以及研究的科学性造成不良影响等违背伦理原则与规范的情况，请申办者/监查员/研究者提交违背方案报告。

申请人暂停或提前终止临床试验（研究），请及时提交暂停/终止试验（研究）报告。完成临床试验（研究），请申请人提交结题报告。

未经伦理审查批准,不能开展临床研究。

本批件有效期为一年，逾期未实施的，则自行废止。

根据国际医学期刊编辑委员会（ICMJE）要求，所有在人体中和采用取自人体的标本进行的临床研究均应注册。请接到伦理批件的研究者务必在临床研究开始前到中国临床研究注册中心注册，请使用我院公共账号(请发邮件到临床研究管理部邮箱hxlcyjglb@163.com申请，联系电话：85422851)登陆以下网址进行临床研究注册： http://www.chictr.org.cn,临床研究项目注册成功后产生的唯一注册号请及时发送邮件到伦理办公室（huaxilunli@163.com），是伦理跟踪审查的必查项目。

单位（章）：四川大学华西医院生物医学伦理审查委员会

主任委员（签名）：[illegible]

2021年7月20日