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

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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 (L-SLND) was proposed to be an alternative to systematic lymph node dissection (SLND) for the treatment of early-stage NSCLC.

Methods and analysis The LobE-Specific lymph node diSsectiON trial is a single-institutional, randomised, double-blind and parallel controlled trial to investigate the feasibility of L-SLND 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 hypothesise that L-SLND (experimental group) is not inferior to SLND (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 anaesthesia (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.

Trial registration number This trial was registered in the Chinese Clinical Trial Registry, ChiCTR2100048415.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The LobE-Specific lymph node diSsectiON trial is a single-centre, randomised, double-blind and parallel controlled trial.
⇒ We investigate the feasibility of lobe-specific lymph node dissection (L-SLND) for clinical stage IA1-2 non-small cell lung cancer with ground-glass opacity components (≥50%).
⇒ We hypothesise that L-SLND is not inferior to systematic lymph node dissection in long-term survival.
⇒ The primary endpoint will be the 5-year disease-free survival and 5-year overall survival.
⇒ 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 randomised controlled study 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 tumour was located in the upper lobe and with a size of ≤2 cm, and the upper mediastinal lymph nodes were all negative when the tumour was located in the lower lobe and with a size of ≤2 cm.[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, randomised and parallel-controlled clinical trial to determine the preferred treatment between L-SLND and SLND for early-stage NSCLC. We hypothesised that L-SLND was not inferior to SLND in safety and long-term oncological results.

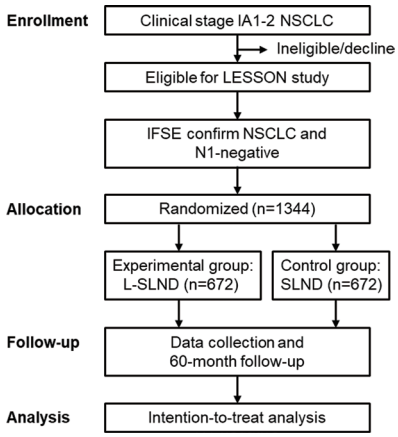

Figure 1 Scheme of the LobE-Specific lymph node diSsectiON (LESSON) trial. IFSE, intraoperative frozen section examination; L-SLND, lobe-specific lymph node dissection; NSCLC, non-small cell lung cancer; N1-negative, there is negative finding or no metastasis for the hilar lymph nodes; SLND, systematic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

METHODS

Protocol version

Protocol V.4.0, modified on 11 August 2022.

Trial design

This study is a single-institutional, randomised, 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 summarised 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% (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 randomisation 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 160/100 mm Hg; 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≥1.0 L; (3) the total bilirubin≤1.5×normal upper limit; (4) the alanine transaminase, aspartate aminotransferase ≤ 1.5×normal upper limit; (5) the creatinine≤1.25×normal upper limit and creatinine clearance rate≥60 mL/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 CT indicates peripheral tumour,[16 17] whose maximum diameter≤2 cm; the tumours are located in the upper lobe or lower lobe of the lung with unspecified laterality; the CT images indicate non-solid nodules or the lesions with ground-glass opacity components (consolidation-to-tumour ratio≤0.5 on CT images); the minimum diameter≤1 cm or the positron emission tomography/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 antitumour 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. Tumours located in the middle lobe.
6. Small cell lung cancer.
7. Patients have a history of unilateral thoracic surgery.
8. Women 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 6 months.
13. Tumours with potential pleura involvement on CT images.

Randomisation, allocation concealment and blinding

A random number table would be produced via SPSS software (V.22.0) by an independent randomisation 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 (L-SLND) and systematic lymph node dissection (SLND) in the LobE-Specific lymph node diSsectiON trial

	L-SLND	SLND
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 PS. Then the follow-up would be performed every 6 months for the first 24 months postoperatively. We would take the history and physical examination (H&P), focusing on the PS and weight loss and require the patients to receive CT of the chest. Whether CT of the chest 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 tumour 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 anaesthesia (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

Table 2 The timeline of data collection and postoperative follow-up in the LobE-Specific lymph node diSsectiON trial

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

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

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. X^2 test or Fisher's exact test is conducted to compare the categorical data between groups; the independent sample t-test, Mann-Whitney non-parametric U test or one-way analysis of variance 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 (online supplemental file 1).

ETHICS AND DISSEMINATION

This trial was approved by the ethics committee on biomedical research, West China Hospital of Sichuan University (2021-332, (online supplemental file 2) on 16 May 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 tumour 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 6 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.

Contributors WH and H-YD contributed to the conceptualisation of the study and drafting of the manuscript and took full responsibility for the content, including the data and analysis. WH, H-YD, Z-ZR, XT and D-XZ contributed to recruitment and

data curation. WH. H-YD, KX and Y-FW contributed to the formal analysis. WH, H-YD and QZ contributed to the revision of the manuscript. WH, H-YD, Z-ZR, KX, Y-FW, XT, D-XZ and QZ contributed to the approval of the final manuscript. H-YD and QZ contributed to supervision and project administration.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

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Author note Dr Weijia Huang and Dr Han-Yu Deng contributed equally to the study and shared co-first authorship.

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REFERENCES

1 Bray F, Ferlay J, Soerjomataram I. GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;2018:394–424.
2 Chen W, Zheng R, Baade PD, *et al*. Cancer statistics in China, 2015. *CA Cancer J Clin* 2016;66:115–32.
3 Gadgeel SM, Ramalingam SS, Kalemkerian GP. Treatment of lung cancer. *Radiol Clin North Am* 2012;50:961–74.
4 Deng H-Y, Wang Y-C, Ni P-Z, *et al*. Radiotherapy, lobectomy or sublobar resection? A meta-analysis of the choices for treating stage I non-small-cell lung cancer. *Eur J Cardiothorac Surg* 2017;51:203–10.
5 Howington JA, Blum MG, Chang AC. *American College of Chest Physicians Evidence-Based Clinical Practice Guidelines*. Chest. In: *Treatment of Stage I and II Non-small Cell Lung Cancer: Diagnosis and Management of Lung Cancer*. . *3rd ed*, 2013: 143. e278S–313.
6 Okada M, Tsubota N, Yoshimura M, *et al*. Proposal for reasonable mediastinal lymphadenectomy in bronchogenic carcinomas: role of subcarinal nodes in selective dissection. *J Thorac Cardiovasc Surg* 1998;116:949–53.
7 Asamura H, Nakayama H, Kondo H, *et al*. Lobe-specific extent of systematic lymph node dissection for non-small cell lung carcinomas according to a retrospective study of metastasis and prognosis. *J Thorac Cardiovasc Surg* 1999;117:1102–11.
8 Deng H-Y, Qin C-L, Li G, *et al*. Can lobe-specific lymph node dissection be an alternative to systematic lymph node dissection in treating early-stage non-small cell lung cancer: a comprehensive systematic review and meta-analysis? *J Thorac Dis* 2018;10:2857–65.
9 Deng H-Y, Zhou J, Wang R-L, *et al*. Lobe-Specific lymph node dissection for clinical early-stage (cIA) peripheral non-small cell lung cancer patients: what and how? *Ann Surg Oncol* 2020;27:472–80.
10 Han H, Chen H. Selective lymph node dissection in early-stage non-small cell lung cancer. *J Thorac Dis* 2017;9:2102–7.
11 Lardinois D, De Leyn P, Van Schil P, *et al*. Ests guidelines for intraoperative lymph node staging in non-small cell lung cancer. *Eur J Cardiothorac Surg* 2006;30:787–92.
12 Deng H-Y, Zhou Q. ASO author reflections: Lobe-Specific lymph node dissection for early-stage non-small cell lung cancer: a long way to go in the era of minimally invasive thoracic surgery. *Ann Surg Oncol* 2020;27:470–1.
13 Zhao Y, Mao Y, He J, *et al*. Lobe-specific lymph node dissection in clinical stage Ia Solid-dominant non-small-cell lung cancer: a propensity score matching study. *Clin Lung Cancer* 2021;22:e201–10.
14 Nagashima K. *A sample size determination tool for the log-rank test of non-inferiority*. Available: https://nshi.jp/en/js/twosurvyrni/ [Accessed 16 May 2021].
15 Goldstraw P, Chansky K, Crowley J, *et al*. The IASLC lung cancer staging project: proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer. *J Thorac Oncol* 2016;11:39–51.
16 Rusch VW, Asamura H, Watanabe H, *et al*. The IASLC lung cancer staging project: a proposal for a new international lymph node map in the forthcoming seventh edition of the TNM classification for lung cancer. *J Thorac Oncol* 2009;4:568–77.
17 Casal RF, Vial MR, Miller R, *et al*. What exactly is a centrally located lung tumor? results of an online survey. *Ann Am Thorac Soc* 2017;14:118–23.
18 Shin SH, Jeong DY, Lee KS, *et al*. Which definition of a central tumour is more predictive of occult mediastinal metastasis in nonsmall cell lung cancer patients with radiological N0 disease? *Eur Respir J* 2019;53:1801508.
19 Clopper CJ, Pearson ES. The use of confidence or FIDUCIAL limits illustrated in the case of the binomial. *Biometrika* 1934;26:404–13.