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

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Manuscripts

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4 **Title**

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

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16
17 Lobe-specific lymph node dissection for NSCLC
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50
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52

53
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4 21 **ABSTRACT**
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6 22 **Introduction:** Lung cancer was the most common malignancy and the leading cause
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9 23 of cancer-related death either in China or worldwide, and surgery is still the preferred
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11 24 treatment for early-stage non-small cell lung cancer(NSCLC). The pattern of lymph
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13
14 25 node metastasis might be lobe-specific, and thus, lobe-specific lymph node dissection
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16
17 26 was proposed to be an alternative to systematic lymph node dissection for the treatment
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19
20 27 of early-stage NSCLC.

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22 28 **Methods and analysis:** The LESSON trial is a single-institutional, randomized,
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25 29 double-blind, and parallel controlled trial to investigate the feasibility of lobe-specific
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28 30 lymph node dissection in clinically diagnosed stage IA1-2 NSCLC. We hypothesize
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31 31 that lobe-specific lymph node dissection(experimental group) is not inferior to
32
33 32 systematic lymph node dissection(control group) and intend to include 672 participants
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36 33 for the experimental group and 672 participants for the control group with a follow-up
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38 34 duration of 60months. The primary outcomes are 5-year disease-free survival and 5-
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41 35 year overall survival. The secondary outcomes are metastatic lymph node ratio,
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44 36 postoperative complication incidence and mortality, duration of operation, duration of
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46
47 37 anesthesia(min), the volume of bleeding(ml), the volume of drainage. The intention-to-
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49
50 38 treat analysis would be performed in the trial.

51 39 **Ethics and dissemination:** This trial was approved by the Ethics Committee on
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54 40 Biomedical Research, West China Hospital of Sichuan University(2021-332). Informed
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57 41 consent would be obtained from all participants. Dissemination activities would include
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60 42 academic conference presentations and peer-reviewed publications. This trial was

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4 43 registered in the Chinese Clinical Trial Registry(Trial Registration number:
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6 44 ChiCTR2100048415).
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46 **Strengths and Limitations of This Study:**

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

55 **INTRODUCTION**

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

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4 65 metastasis might be lobe-specific, lobe-specific lymph node dissection was proposed to
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6 66 be an alternative to systematic lymph node dissection for the treatment of early-stage
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9 67 NSCLC[6, 7].
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11 68 In our previous study, we conducted a meta-analysis to compare the safety and
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14 69 efficacy between lobe-specific lymph node dissection and systemic lymph node
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17 70 dissection in the treatment of early-stage NSCLC. Our findings implied that compared
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20 71 with systemic lymph node dissection, the occurrence of postoperative complications in
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23 72 lobe-specific lymph node dissection decreased significantly but was comparable in
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26 73 long-term survival, indicating that lobe-specific lymph node dissection might be an
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29 74 alternative to systemic lymph node dissection[8, 9]. However, there is no explicit and
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32 75 precise definition of the lobe-specific lymph node dissection and the dissecting range
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35 76 of lymph nodes in previous cohort studies and practice guidelines[10, 11]. The role of
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38 77 lobe-specific lymph node dissection and the explicit dissecting range remains to be
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41 78 further studied and established, and a well-designed and conducted randomized
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44 79 controlled study(RCT) might provide some suggestions to clinical instructions[12].
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46 80 As shown in our previous retrospective study, the subcarinal and lower mediastinal
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49 81 lymph nodes were all negative when the tumor was located in the upper lobe and with
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52 82 a size of ≤ 2 cm, and the upper mediastinal lymph nodes were all negative when the
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55 83 tumor was located in the lower lobe and with a size of ≤ 2 cm[9]. It reminded us that the
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58 84 lobe-specific lymph node metastasis pattern might be noticed, and the lobe-specific
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61 85 lymph node dissection might be practical, with similar long-term survival and fewer
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64 86 postoperative complications[13]. Therefore, we conducted a double-blind, randomized,

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4 87 and parallel-controlled clinical trial to determine the favorable treatment between lobe-
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6 88 specific lymph node dissection(L-SLND) and systematic lymph node dissection(SLND)
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9 89 for treatment of early-stage NSCLC. We hypothesized that lobe-specific lymph node
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11 90 dissection was not inferior to systematic lymph node dissection in safety and long-term
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14 91 oncological results.
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19 93 **METHODS**

22 94 **Protocol version**

25 95 Protocol V3.0, modified May 16, 2021.
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30 97 **Trial design**

32 98 This study is a single-institutional, randomized, double-blind, and parallel controlled
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34 99 trial conducted in Lung Cancer Center, West China Hospital, Sichuan University.
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37 100 Patients would be enrolled since August 2021, and it would be operated until July 2024.
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43 102 **Sample size**

45 103 According to the summarized survival rate of early-stage NSCLC in prior researches,
46
47 104 we assumed that the 5-year overall survival(OS) rate was 70% among the total
48
49 105 population of lobe-specific lymph node dissection group and the systemic lymph node
50
51 106 dissection group, and the non-inferiority threshold of 5-year OS rate was 6%(hazard
52
53 107 ratio[HR]=1.25), with a unilateral α of 0.05 and a certainty of 0.8. The recruiting
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56 108 duration is 36 months, and the duration of follow-up is 60 months. In this way, the
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4 109 sample size is 1344 cases as calculated by the Log-rank test[14], in which 672 cases are
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7 110 for the experimental group and 672 cases for the control group.
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112 **Study population**

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14 113 This trial plans to include 1344 patients with clinically diagnosed stage IA1-2 NSCLC,
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17 114 and the trial schema of the patient pathway is shown in Figure 1. The staging is referred
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20 115 to the American Joint Committee on Cancer(the eighth edition)[15, 16].
21

22 116 The included patients are required to meet all of the following inclusion criteria:

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25 117 1. Patient aged 18-80 years old;
26
27 118 2. The preoperative blood pressure is controlled below 160/100mmHg; the blood
28
29
30 119 glucose is controlled between 5.6 and 11.2 mmol/L; the major organs' function is within
31
32
33 120 normality, including cardiac, pulmonary, hepatic, and nephritic function: (1) the cardiac
34
35 121 function examination indicates a Goldman index rated 1-2; (2) the pulmonary function
36
37 122 examination indicates an estimated postoperative forced expiratory volume in the first
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39
40 123 second(FEV₁) ≥1.0L; (3) the total bilirubin ≤ 1.5×normal upper limit; (4) the alanine
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43 124 transaminase(ALT), aspartate aminotransferase(AST) ≤ 1.5×normal upper limit; (5) the
44
45 125 creatinine ≤ 1.25×normal upper limit, and creatinine clearance rate ≥ 60ml/min;
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47
48 126 3. The primary preoperative clinical diagnosis is non-small cell lung cancer, including
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51 127 adenocarcinoma, squamous cell carcinoma, large cell carcinoma, and other histological
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53 128 types;
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56 129 4. The thin-layer computed tomography(CT) indicates peripheral tumor[16, 17], whose
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59 130 maximum diameter ≤2cm; the tumors are located in the upper lobe or lower lobe of the
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4 131 lung with unspecified laterality; the CT imaging indicates nonsolid nodules; the
5
6 132 minimum diameter \leq 1cm or the positron emission tomography/computed
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9 133 tomography(PET/CT) indicates no mediastinal lymph node metastasis; the clinical
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12 134 staging is cT1a-1bN0M0 (cIA1-2);

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14 135 5. The Eastern Cooperative Oncology Group performance status(PS) score of 0-1;

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16
17 136 6. All preoperative examinations are completed within 28 days preoperatively;

18
19 137 7. Patients who can comprehend this study and sign an informed consent form.

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25 139 Patients with any of the following exclusion criteria would be ruled out:

26
27 140 1. Patients who have received preoperative anti-tumor treatment, including prior

28
29 141 radiotherapy, chemotherapy, target therapy, and immunotherapy;

30
31 142 2. Patients have a history of other malignancies;

32
33 143 3. Patients are diagnosed a secondary malignancy when included;

34
35 144 4. Centrally located lung cancer[17, 18];

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37 145 5. Tumors located in the middle lobe;

38
39 146 6. Small cell lung cancer;

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41 147 7. Patients have a history of unilateral thoracic surgery;

42
43 148 8. Females with pregnancy or lactation;

44
45 149 9. Patients with interstitial pneumonitis, pulmonary fibrosis, or severe emphysema;

46
47 150 10. Uncontrollable active bacterial infection or fungal infection;

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49 151 11. Severe mental disease;

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51 152 12. Patients have a history of severe cardiac disease, cardiac failure, myocardial

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4 153 infarction, or angina within six months.
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9 155 **Randomization, allocation concealment, and blinding**
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11 156 A random number table would be produced via SPSS software(version 22.0; IBM Corp,
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13
14 157 Armonk, NY, USA) by an independent randomization committee before research,
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17 158 which is confidential to researchers(and related personnel) and patients. A random
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19
20 159 number selected from the random number table would be allocated into an opaque
21
22 160 envelope. An opaque envelope with a random number would be assigned to each patient
23
24
25 161 who is included in the research. The researcher would unfold the envelope and get a
26
27 162 random number, according to which the patient would be grouped. The trial is double-
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29
30 163 blind, and the researcher and the participant would be blinded to the allocation. The
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32 164 allocation would be unblinded when an emergency occurs, and the participant would
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35 165 be withdrawn from the trial.
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40 167 **Interventions**
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43 168 Patients in the experimental group would receive lobe-specific lymph node
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45 169 dissection[9]. We would dissect the upper mediastinal lymph node for lung cancer of
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48 170 the upper lobe, subcarinal and lower mediastinal lymph node for lung cancer of lower
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51 171 lobe, and upper mediastinal and subcarinal lymph node for lung cancer of the middle
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53 172 lobe(Table 1). Patients in the control group would receive systematic lymph node
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55
56 173 dissection, including upper mediastinal, subcarinal, and lower mediastinal lymph nodes.
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58 174 When participants are diagnosed with mediastinal lymph node metastasis,
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4 175 postoperative adjuvant therapy would be conducted to decrease the risk of recurrence
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6 176 and metastasis, including target therapy, radiotherapy, and chemotherapy.
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9 177 The overall follow-up duration would be last for 60 months for each patient(Table
10
11 178 2). The first postoperative follow-up would be on the 30 days postoperatively, and we
12
13
14 179 would focus on the postoperative complications and performance status. Then the
15
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17 180 follow-up would be performed every six months for the first 24 months postoperatively.
18
19 181 We would take the history and physical examination(H&P), focusing on the
20
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22 182 performance status and weight loss, and require the patients to receive chest CT.
23
24 183 Whether the chest CT was contrast-enhanced CT or non-contrast-enhanced CT was
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26
27 184 determined by the surgeon. The H&P and low-dose non-contrast-enhanced CT would
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29
30 185 be performed annually in the following 36 months.
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34 35 187 **Outcomes**

36
37 188 The primary outcomes are 5-year disease-free survival(DFS) and 5-year OS. The DFS
38
39 189 is defined as the duration(days) from the date of operation to the date of tumor
40
41
42 190 recurrence, and the OS is defined as the duration(days) from the date of operation to
43
44
45 191 the date of death of any cause. The secondary outcomes are metastatic lymph node
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48 192 ratio, postoperative complication incidence, and mortality(≤ 30 days), duration of
49
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51 193 operation(day), duration of anesthesia(min), the volume of bleeding(ml), the volume of
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54 194 drainage(ml). The metastatic lymph node ratio is defined as the ratio of the number of
55
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57 195 positive lymph nodes divided by all dissected lymph nodes
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197 **Data collection, management, monitoring, and analysis**

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

205 The intention-to-treat principle would be performed, and participants would be
206 allocated to the assigned group. Chi-square test or Fisher's exact test is conducted to
207 compare the categorical data between groups; the independent sample t-test or Mann-
208 Whitney nonparametric U test or one-way analysis of variance(ANOVA) test is
209 performed to compare the continuous data between groups; the survival analysis is
210 conducted to compare the long-term prognosis between two groups; bilateral P-value
211 <0.05 is considered statistically significant[19].

213 **Patients or public involvement**

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

218 **ETHICS AND DISSEMINATION**

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4 219 This trial (Version 3.0) was approved by the Ethics Committee on Biomedical Research,
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6 220 West China Hospital of Sichuan University (2021-332) on May 16, 2021, and registered
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9 221 in the Chinese Clinical Trial Registry (ChiCTR2100048415). The LESSON study
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11 222 would be performed in accordance with the Declaration of Helsinki. All participants
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13
14 223 would learn the outline of this trial and sign the informed consent, who could also have
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16
17 224 the right to opt out without medical care being affected, and the tumor specimens would
18
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20 225 not be collected. A regulatory team from the Ethics Committee of West China Hospital
21
22 226 of Sichuan University would review all research data every six months, including data
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24
25 227 records, medical documents, and electronic case report forms. Important protocol
26
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28 228 modifications would be reported to the Ethics Committee. The principal investigators
29
30 229 would guarantee the participants' right to withdraw from this trial in an emergency to
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33 230 ensure their safety. All research data would be carefully stored and only available for
34
35
36 231 the researchers and monitoring panels. The corresponding result of the trial would be
37
38 232 published in academic conference presentations and peer-reviewed publications.

233

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

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5
6 242 any specific grant from funding agencies in the public, commercial, or not-for-profit
7
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9 243 sectors.

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11 244 **Supplementary data:** e-Doc 1, The trial approval from the Ethics Committee on
12
13
14 245 Biomedical Research, West China Hospital of Sichuan University(2021-332).
15
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19 247 **Abbreviations**

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21
22 248 ALT, alanine transaminase

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24 249 ANOVA, analysis of variance

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26 250 AST, aspartate aminotransferase

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28 251 CT, computed tomography

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30 252 DFS, disease-free survival

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32 253 DL_{CO}, carbon monoxide diffusing capacity

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34 254 FEV₁, forced expiratory volume in the first second

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36 255 H&P, history and physical examination

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38 256 HR, hazard ratio

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40 257 NSCLC, non-small cell lung cancer

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42 258 OS, overall survival

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44 259 PET/CT, positron emission tomography/computed tomography

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46 260 PS, performance status

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48 261 RCT, randomized controlled study

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4 321 **Figure legends**

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6 322 **Figure 1** Scheme of the LESSON Trial. **Abbreviation:** NSCLC, non-small cell lung
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9 323 cancer; L-SLND, lobe-specific lymph node dissection; SLND, systematic lymph node
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11 324 dissection.
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For peer review only

325 **Table 1** The dissected lymph nodes in lobe-specific lymph node dissection and
 326 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

328 **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				√		

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

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

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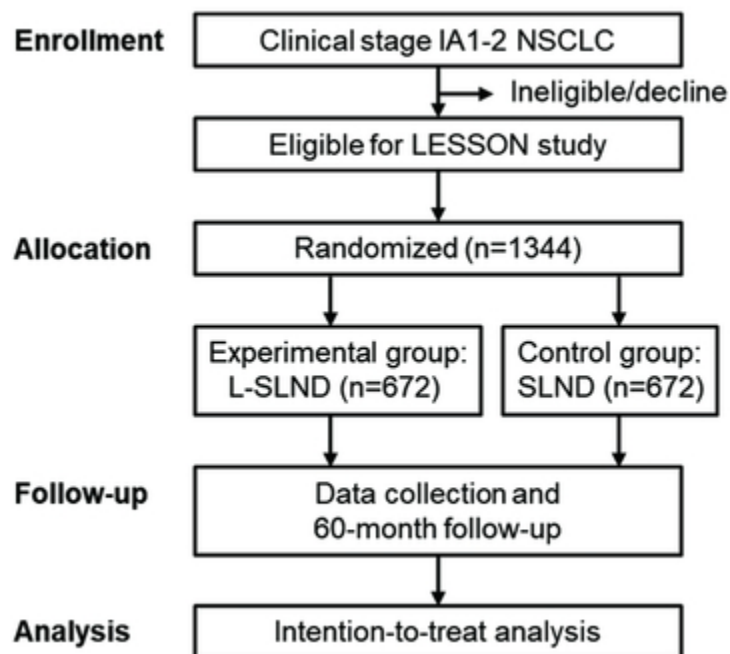


Figure 1 Scheme of the LESSON Trial. Abbreviation: NSCLC, non-small cell lung cancer; L-SLND, lobe-specific lymph node dissection; SLND, systematic lymph node dissection.

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。

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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。

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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) :

主任委员(签名) :

生物医学伦理
审查委员会

邓福林
2021年5月26日

BMJ Open

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

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Primary Subject Heading:	Surgery
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Keywords:	Respiratory tract tumours < ONCOLOGY, Cardiothoracic surgery < SURGERY, Thoracic surgery < SURGERY

SCHOLARONE™
Manuscripts

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4 **Title**

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

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16
17 Lobe-specific lymph node dissection for NSCLC
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21

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50
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53
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4 21 **ABSTRACT**
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6 22 **Introduction:** Lung cancer was the most common malignancy and the leading cause
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9 23 of cancer-related death in China or worldwide, and surgery is still the preferred
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11 24 treatment for early-stage non-small cell lung cancer(NSCLC). The pattern of lymph
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14 25 node metastasis was found potentially lobe-specific, and thus, lobe-specific lymph node
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17 26 dissection was proposed to be an alternative to systematic lymph node dissection for
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20 27 the treatment of early-stage NSCLC.

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22 28 **Methods and analysis:** The LESSON trial is a single-institutional, randomized,
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25 29 double-blind, and parallel controlled trial to investigate the feasibility of lobe-specific
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28 30 lymph node dissection in clinically diagnosed stage IA1-2 NSCLC with ground-glass
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31 31 opacity components($\geq 50\%$). The intraoperative frozen section examination of surgical
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34 32 tissues confirms the histological type of NSCLC. We hypothesize that lobe-specific
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37 33 lymph node dissection(experimental group) is not inferior to systematic lymph node
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40 34 dissection(control group) and intend to include 672 participants for the experimental
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43 35 group and 672 participants for the control group with a follow-up duration of 60 months.
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46 36 The primary outcomes are 5-year disease-free survival and 5-year overall survival. The
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49 37 secondary outcomes are metastatic lymph node ratio, postoperative complication
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52 38 incidence and mortality, duration of operation, duration of anesthesia(min), the volume
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55 39 of bleeding(ml), and drainage volume. The intention-to-treat analysis would be
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57
58 40 performed in the trial.

56 41 **Ethics and dissemination:** This trial was approved by the Ethics Committee on
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59 42 Biomedical Research, West China Hospital of Sichuan University(2021-332). Informed
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4 43 consent would be obtained from all participants, and dissemination activities would
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6 44 include academic conference presentations and peer-reviewed publications. This trial
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9 45 was registered in the Chinese Clinical Trial Registry(Trial Registration number:
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11 46 ChiCTR2100048415).

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17 48 **Strengths and Limitations of This Study:**

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19 49 1. The LESSON trial is a single-center, randomized, double-blind, and parallel
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21 50 controlled trial.
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24 51 2. We investigate the feasibility of lobe-specific lymph node dissection for clinical-
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26 52 stage IA1-2 non-small cell lung cancer with ground-glass opacity components($\geq 50\%$).
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29 53 3. We hypothesize that lobe-specific lymph node dissection is not inferior to systematic
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31 54 lymph node dissection in long-term survival.
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34 55 4. The primary endpoint will be the 5-year disease-free survival and 5-year overall
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36 56 survival.
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39 57 5. The separation of investigators who handled data curation and formal analyses and
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41 58 surgeons could ensure the success of trial blinding.
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59 INTRODUCTION

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

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

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4 81 As shown in our previous retrospective study, the subcarinal and lower mediastinal
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6 82 lymph nodes were all negative when the tumor was located in the upper lobe and with
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9 83 a size of ≤ 2 cm, and the upper mediastinal lymph nodes were all negative when the
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12 84 tumor was located in the lower lobe and with a size of ≤ 2 cm[9]. It reminded us that the
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14 85 lobe-specific lymph node metastasis pattern might be noticed, and the L-SLND might
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16 86 be practical, with comparable long-term survival and fewer postoperative
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18 87 complications[13]. Therefore, we conducted a double-blind, randomized, and parallel-
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20 88 controlled clinical trial to determine the preferred treatment between L-SLND and
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22 89 SLND for early-stage NSCLC. We hypothesized that L-SLND was not inferior to
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24 90 SLND in safety and long-term oncological results.
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32 92 **METHODS**

33 93 **Protocol version**

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37 94 Protocol V3.0, modified May 16, 2021.
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43 96 **Trial design**

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45 97 This study is a single-institutional, randomized, double-blind, and parallel controlled
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47 98 trial conducted in Lung Cancer Center, West China Hospital, Sichuan University.

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49 99 Patients had been enrolled since August 2021, and it would be operated until July 2024.

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51 100 The study with active follow-up would be operated until July 2026.
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58 102 **Sample size**

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4 103 According to the summarized survival rate of early-stage NSCLC in prior research, we
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6 104 assumed that the 5-year overall survival(OS) rate was 70% among the total population
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9 105 of the L-SLND group and SLND group. The non-inferiority threshold of the 5-year OS
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11 106 rate was 6%(hazard ratio[HR]=1.25), with a unilateral α of 0.05 and a certainty of 0.8.
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14 107 The recruiting duration is 36 months, and the duration of follow-up is 60 months. In
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17 108 this way, the sample size is 1344 cases as calculated by the Log-rank test[14], in which
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19 109 672 cases are for the experimental group and 672 cases for the control group. We are
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22 110 dedicated to requiring the enrolled patients to be in active follow-up and offer some
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25 111 allowance to those patients to reduce the risk of participants loss and enable the trial to
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28 112 reach the target sample size.
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33 114 **Study population**

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35 115 This trial intends to include 1344 patients with clinically diagnosed stage IA1-2 NSCLC,
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38 116 and the trial schema of the patient pathway is shown in Figure 1. These preliminary
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41 117 eligible patients would be enrolled in the study cohort and participate in randomization
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44 118 after intraoperative frozen section examination conformity of NSCLC. The staging is
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47 119 referred to the American Joint Committee on Cancer(the eighth edition)[15, 16].

48 120 The included patients are required to meet all of the following inclusion criteria:

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51 121 1. Patient aged 18-80 years old;
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54 122 2. The preoperative blood pressure is controlled below 160/100mmHg; the blood
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57 123 glucose is controlled between 5.6 and 11.2 mmol/L; the major organs' function is within
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60 124 normality, including cardiac, pulmonary, hepatic, and nephritic function: (1) the cardiac

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4 125 function examination indicates a Goldman index rated 1-2; (2) the pulmonary function
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6 126 examination indicates an estimated postoperative forced expiratory volume in the first
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9 127 second(FEV_1) $\geq 1.0L$; (3) the total bilirubin $\leq 1.5 \times$ normal upper limit; (4) the alanine
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11 128 transaminase(ALT), aspartate aminotransferase(AST) $\leq 1.5 \times$ normal upper limit; (5) the
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14 129 creatinine $\leq 1.25 \times$ normal upper limit, and creatinine clearance rate $\geq 60ml/min$;
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17 130 3. The primary preoperative clinical diagnosis highly suggested NSCLC, including
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19 131 adenocarcinoma, squamous cell carcinoma, large cell carcinoma, and other histological
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22 132 types; the clinical staging is T1a-1bN0M0 (IA1-2);
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25 133 4. The thin-layer computed tomography(CT) indicates peripheral tumor[16, 17], whose
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27 134 maximum diameter $\leq 2cm$; the tumors are located in the upper lobe or lower lobe of the
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30 135 lung with unspecified laterality; the CT images indicate nonsolid nodules or the lesions
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33 136 with ground-glass opacity components (consolidation-to-tumor ratio ≤ 0.5 on CT
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36 137 images); the minimum diameter $\leq 1cm$ or the positron emission tomography/computed
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38 138 tomography(PET/CT) indicates no mediastinal lymph node metastasis;
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41 139 5. The intraoperative frozen section examination of surgical tissues and hilar lymph
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43 140 nodes confirms the histological type of NSCLC and negative diseases of N1 lymph
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46 141 nodes pathologically;
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49 142 6. The Eastern Cooperative Oncology Group performance status(PS) score of 0-1;
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52 143 7. All preoperative examinations are completed within 28 days preoperatively;
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54
55 144 8. Patients who can comprehend this study and sign an informed consent form.
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146 Patients with any of the following exclusion criteria would be ruled out:

- 147 1. Patients who have received preoperative anti-tumor treatment, including prior
- 148 radiotherapy, chemotherapy, target therapy, and immunotherapy;
- 149 2. Patients have a history of other malignancies;
- 150 3. Patients diagnosed a secondary malignancy when included;
- 151 4. Centrally located lung cancer, defined as the inner one-third of the hemithorax
- 152 adopted by drawing concentric lines from the midline[17, 18];
- 153 5. Tumors located in the middle lobe;
- 154 6. Small cell lung cancer;
- 155 7. Patients have a history of unilateral thoracic surgery;
- 156 8. Females with pregnancy or lactation;
- 157 9. Patients with interstitial pneumonitis, pulmonary fibrosis, or severe emphysema;
- 158 10. Uncontrollable active bacterial infection or fungal infection;
- 159 11. Severe mental disease;
- 160 12. Patients have a history of severe cardiac disease, cardiac failure, myocardial
- 161 infarction, or angina within six months;
- 162 13. Tumors with potential pleura involvement on CT images.

164 **Randomization, allocation concealment, and blinding**

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

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4 169 envelope would be assigned to each enrolled patient. The researcher would unfold the
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6 170 envelope and get a random number, according to which the patient would be grouped.
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9 171 The trial is double-blind, and the researcher and the participant would be blinded to the
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11 172 allocation. The allocation would be unblinded when an emergency occurs, and the
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14 173 participant would be withdrawn from the trial.
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19 175 **Interventions**

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22 176 All patients would receive complete lymph node dissection for N1 lymph nodes. As for
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24 177 the mediastinal lymph nodes, patients in the experimental group would receive L-
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27 178 SLND[9]. We would completely dissect the upper mediastinal lymph node for lung
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30 179 cancer of the upper lobe, and the subcarinal and lower mediastinal lymph node for lung
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33 180 cancer of the lower lobe(Table 1). Patients in the control group would receive SLND,
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35 181 including upper mediastinal, subcarinal, and lower mediastinal lymph nodes. We would
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38 182 dissect at least three mediastinal nodal stations(including subcarinal lymph nodes) and
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40
41 183 a total of six lymph nodes during SLND[11]. Intraoperative frozen section examination
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43 184 of the suspected mediastinal lymph nodes in the L-SLND group would be performed to
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46 185 detect the possible lymph node metastasis, and in the case of positive lymph node
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48 186 metastasis on the frozen section, SLND would be performed intraoperatively.

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50 187 When participants are diagnosed with pathological lymph node metastasis,
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53 188 postoperative adjuvant treatment would be conducted to reduce the risk of recurrence
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56 189 and metastasis, including target therapy and chemotherapy. Adjuvant radiotherapy
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58
59 190 would be considered in those who receive L-SLND or have positive mediastinal lymph
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4 191 nodes.

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6 192 The overall follow-up duration would be last for 60 months for each patient(Table
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8
9 193 2). The first postoperative follow-up would be on the 30 days postoperatively, and we
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11
12 194 would focus on the postoperative complications and performance status. Then the
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15 195 follow-up would be performed every six months for the first 24 months postoperatively.
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17 196 We would take the history and physical examination(H&P), focusing on the
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19
20 197 performance status and weight loss, and require the patients to receive chest CT.
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22 198 Whether the chest CT was contrast-enhanced CT or non-contrast-enhanced CT was
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24
25 199 determined by the surgeon. The H&P and low-dose non-contrast-enhanced CT would
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27 200 be performed annually in the following 36 months.

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31 32 202 **Outcomes**

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35 203 The primary outcomes are 5-year disease-free survival(DFS) and 5-year OS. The DFS
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38 204 is defined as the duration(days) from the date of operation to the date of tumor
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41 205 recurrence, and the OS is defined as the duration(days) from the date of operation to
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44 206 the date of death of any cause. The secondary outcomes are metastatic lymph node
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47 207 ratio, postoperative complication incidence and mortality(≤ 30 days), duration of
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50 208 operation(day), duration of anesthesia(min), the volume of bleeding(ml), and the
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53 209 volume of drainage(ml). The metastatic lymph node ratio is defined as the ratio of the
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56 210 number of positive lymph nodes divided by all dissected lymph nodes.

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58 212 **Data collection, management, monitoring, and analysis**

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4 213 The data collection and management were achieved by researchers under the guidance
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6 214 of the Data Management Committee of Lung Cancer Center of West China Hospital.
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9 215 All adverse events would be documented in detail and handled properly, which would
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11 216 also be reported to the Data Management Committee and Ethics Committee of West
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14 217 China Hospital of Sichuan University. The principal investigators would periodically
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17 218 review the reported adverse events and evaluate the related subjects' risk and benefit.

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19 219 The intention-to-treat principle would be performed, and participants would be
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22 220 allocated to the assigned group. Chi-square test or Fisher's exact test is conducted to
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25 221 compare the categorical data between groups; the independent sample t-test, Mann-
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27 222 Whitney nonparametric U test, or one-way analysis of variance(ANOVA) test is
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30 223 performed to compare the continuous data between groups; the survival analysis
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33 224 compares the long-term survival between two groups via the Kaplan-Meier method and
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35 225 log-rank test; a bilateral P -value <0.05 is considered statistically significant[19].
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39 40 227 **Patients or public involvement**

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43 228 Patients and the public would not be involved in the research's design, conduct,
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46 229 reporting, or dissemination plans. All participants would sign the informed consent and
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48 230 be involved in the follow-up(e-Doc 1).

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51 52 53 232 **ETHICS AND DISSEMINATION**

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56 233 This trial(Version 3.0) was approved by the Ethics Committee on Biomedical Research,
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58 234 West China Hospital of Sichuan University(2021-332, e-Doc 2) on May 16, 2021, and
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4 235 registered in the Chinese Clinical Trial Registry(ChiCTR2100048415). The LESSON
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6 236 study would be performed following the Declaration of Helsinki. All participants would
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9 237 learn the outline of this trial and sign the informed consent, who could also have the
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11 238 right to opt-out without medical care being affected, and the tumor specimens would
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14 239 not be collected. A regulatory team from the Ethics Committee of West China Hospital
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17 240 of Sichuan University would review all research data every six months, including
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19 241 research data, medical records, and electronic case report forms. Important protocol
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21 242 modifications would be reported to the Ethics Committee. The principal investigators
22
23 243 would guarantee the participants' right to withdraw from this trial in an emergency to
24
25 244 ensure their safety. All research data would be carefully stored and only available for
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27 245 the researchers and monitoring panels. The corresponding result of the trial would be
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29 246 published in academic conference presentations and peer-reviewed publications.
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248 **Author contributions:** W. H. and H. D. contributed to the conceptualization of the
249 study and drafting of the manuscript and took full responsibility for the content,
250 including the data and analysis. W. H., H. D., Z. R., X. T., and D. Z. contributed to
251 recruitment and data curation. W. H., H. D., K. X., and Y. W. contributed to the
252 formal analysis. W. H., H. D., and Q. Z. contributed to the revision of the manuscript.
253 W. H., H. D., Z. R., K. X., Y. W., X. T., D. Z., and Q. Z. contributed to the approval
254 of the final manuscript. H. D. and Q. Z. contributed to supervision and project
255 administration.

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7
8
9 259 the public, commercial, or not-for-profit sectors.
10

11 260 **Supplementary data:** e-Doc 1, an example of the patient consent form; e-Doc 2, the
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14 261 trial approval from the Ethics Committee on Biomedical Research, West China
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17 262 Hospital of Sichuan University(2021-332).
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22 264 **Abbreviations**
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24 265 ALT, alanine transaminase
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27 266 ANOVA, analysis of variance
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30 267 AST, aspartate aminotransferase
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32 268 CT, computed tomography
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35 269 DFS, disease-free survival
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38 270 DL_{CO}, carbon monoxide diffusing capacity
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40 271 FEV₁, forced expiratory volume in the first second
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43 272 H&P, history and physical examination
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45 273 HR, hazard ratio
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48 274 NSCLC, non-small cell lung cancer
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50 275 OS, overall survival
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53 276 PET/CT, positron emission tomography/computed tomography
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56 277 PS, performance status
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58 278 RCT, randomized controlled study
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4 339 **Figure legends**

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6 340 **Figure 1** Scheme of the LESSON Trial. **Abbreviation:** NSCLC, non-small cell lung
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9 341 cancer; IFSE, intraoperative frozen section examination; N1-negative, there is negative
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11 342 finding or no metastasis for the hilar lymph nodes; L-SLND, lobe-specific lymph node
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14 343 dissection; SLND, systematic lymph node dissection.
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For peer review only

344 **Table 1** The dissected lymph nodes in lobe-specific lymph node dissection and
 345 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

347 **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				√		

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5	Duration of operation	√	
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8	Duration of anesthesia	√	
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11	Volume of bleeding	√	
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13	Volume of drainage		√
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16 348 **Abbreviation:** H&P, medical and physical examination; CT, computed tomography; CECT, contrast-enhanced computed tomography; LDCT,
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18 349 low-dose computed tomography; LNR, lymph node rate.
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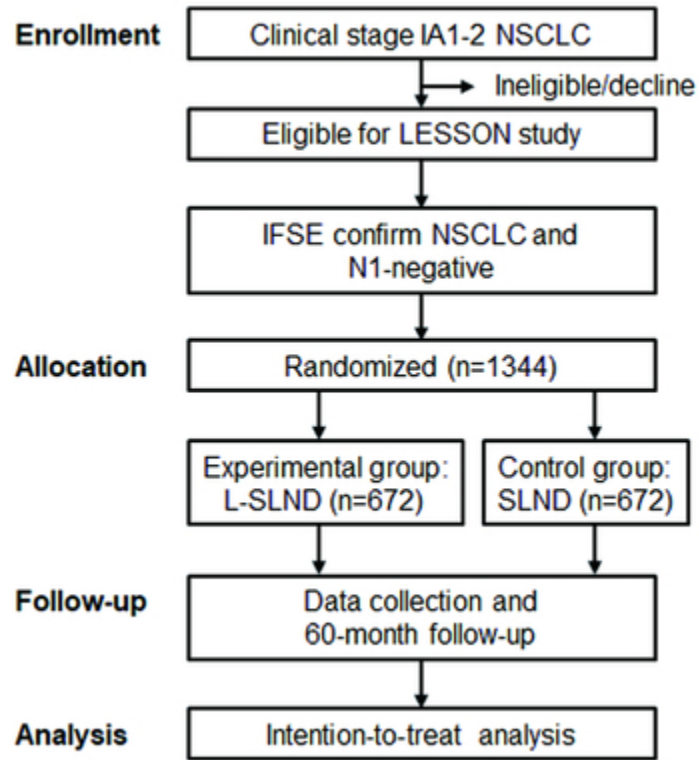


Figure 1 Scheme of the LESSON Trial. Abbreviation: NSCLC, non-small cell lung cancer; IFSE, intraoperative frozen section examination; N1-negative, there is negative finding or no metastasis for the hilar lymph nodes; L-SLND, lobe-specific lymph node dissection; SLND, systematic lymph node dissection.

15x16mm (600 x 600 DPI)

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,非小细胞肺癌占有所有肺癌的约 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,通过将最新证据研究汇集在一起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?

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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益处？

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。

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医生的联系电话： _____

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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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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

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生物医学伦理
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邓福林
2021年5月26日

BMJ Open

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

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Primary Subject Heading:	Surgery
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Keywords:	Respiratory tract tumours < ONCOLOGY, Cardiothoracic surgery < SURGERY, Thoracic surgery < SURGERY

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Manuscripts

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4 **Title**

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

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17 Lobe-specific lymph node dissection for NSCLC
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21

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52

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54
55
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4 22 **ABSTRACT**
5

6 23 **Introduction:** Lung cancer was the most common malignancy and the leading cause
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8
9 24 of cancer-related death in China or worldwide, and surgery is still the preferred
10
11 25 treatment for early-stage non-small cell lung cancer(NSCLC). The pattern of lymph
12
13
14 26 node metastasis was found potentially lobe-specific, and thus, lobe-specific lymph node
15
16
17 27 dissection was proposed to be an alternative to systematic lymph node dissection for
18
19
20 28 the treatment of early-stage NSCLC.

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22 29 **Methods and analysis:** The LESSON trial is a single-institutional, randomized,
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25 30 double-blind, and parallel controlled trial to investigate the feasibility of lobe-specific
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28 31 lymph node dissection in clinically diagnosed stage IA1-2 NSCLC with ground-glass
29
30
31 32 opacity components($\geq 50\%$). The intraoperative frozen section examination of surgical
32
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34 33 tissues confirms the histological type of NSCLC. We hypothesize that lobe-specific
35
36
37 34 lymph node dissection(experimental group) is not inferior to systematic lymph node
38
39
40 35 dissection(control group) and intend to include 672 participants for the experimental
41
42
43 36 group and 672 participants for the control group with a follow-up duration of 60 months.
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45
46 37 The primary outcomes are 5-year disease-free survival and 5-year overall survival. The
47
48
49 38 secondary outcomes are metastatic lymph node ratio, postoperative complication
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52 39 incidence and mortality, duration of operation, duration of anesthesia(min), the volume
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54
55 40 of bleeding(ml), and drainage volume. The intention-to-treat analysis would be
56
57
58 41 performed in the trial.

56 42 **Ethics and dissemination:** This trial was approved by the Ethics Committee on
57
58
59 43 Biomedical Research, West China Hospital of Sichuan University(2021-332). Informed
60

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4 44 consent would be obtained from all participants, and dissemination activities would
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6 45 include academic conference presentations and peer-reviewed publications. This trial
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8
9 46 was registered in the Chinese Clinical Trial Registry(Trial Registration number:
10
11 47 ChiCTR2100048415).
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17 49 **Strengths and Limitations of This Study:**

- 18
19 50 1. The LESSON trial is a single-center, randomized, double-blind, and parallel
20
21
22 51 controlled trial.
23
24 52 2. We investigate the feasibility of lobe-specific lymph node dissection for clinical-
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27 53 stage IA1-2 non-small cell lung cancer with ground-glass opacity components($\geq 50\%$).
28
29
30 54 3. We hypothesize that lobe-specific lymph node dissection is not inferior to systematic
31
32
33 55 lymph node dissection in long-term survival.
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35 56 4. The primary endpoint will be the 5-year disease-free survival and 5-year overall
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37
38 57 survival.
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40 58 5. The challenge of this trial is to ensure the complete follow-up of the numerous
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43 59 participants.
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60 INTRODUCTION

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

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

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4 82 As shown in our previous retrospective study, the subcarinal and lower mediastinal
5
6 83 lymph nodes were all negative when the tumor was located in the upper lobe and with
7
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9 84 a size of ≤ 2 cm, and the upper mediastinal lymph nodes were all negative when the
10
11
12 85 tumor was located in the lower lobe and with a size of ≤ 2 cm[9]. It reminded us that the
13
14 86 lobe-specific lymph node metastasis pattern might be noticed, and the L-SLND might
15
16
17 87 be practical, with comparable long-term survival and fewer postoperative
18
19 88 complications[13]. Therefore, we conducted a double-blind, randomized, and parallel-
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21
22 89 controlled clinical trial to determine the preferred treatment between L-SLND and
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24
25 90 SLND for early-stage NSCLC. We hypothesized that L-SLND was not inferior to
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27
28 91 SLND in safety and long-term oncological results.

92

93 **METHODS**

94 **Protocol version**

95 Protocol V3.0, modified May 16, 2021.

96

97 **Trial design**

98 This study is a single-institutional, randomized, double-blind, and parallel controlled
99 trial conducted in Lung Cancer Center, West China Hospital, Sichuan University.

100 Patients had been enrolled since August 2021, and it would be operated until July 2024.

101 The study with active follow-up would be operated until July 2026.

102

103 **Sample size**

1
2
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4 104 According to the summarized survival rate of early-stage NSCLC in prior research, we
5
6 105 assumed that the 5-year overall survival(OS) rate was 70% among the total population
7
8
9 106 of the L-SLND group and SLND group. The non-inferiority threshold of the 5-year OS
10
11
12 107 rate was 6%(hazard ratio[HR]=1.25), with a unilateral α of 0.05 and a certainty of 0.8.
13
14 108 The recruiting duration is 36 months, and the duration of follow-up is 60 months. In
15
16
17 109 this way, the sample size is 1344 cases as calculated by the Log-rank test[14], in which
18
19
20 110 672 cases are for the experimental group and 672 cases for the control group. We are
21
22 111 dedicated to requiring the enrolled patients to be in active follow-up and offer some
23
24
25 112 allowance to those patients to reduce the risk of participants loss and enable the trial to
26
27
28 113 reach the target sample size.
29

30 114

31 32 115 **Study population**

33
34
35 116 This trial intends to include 1344 patients with clinically diagnosed stage IA1-2 NSCLC,
36
37
38 117 and the trial schema of the patient pathway is shown in Figure 1. These preliminary
39
40
41 118 eligible patients would be enrolled in the study cohort and participate in randomization
42
43
44 119 after intraoperative frozen section examination conformity of NSCLC. The staging is
45
46
47 120 referred to the American Joint Committee on Cancer(the eighth edition)[15, 16].

48 121 The included patients are required to meet all of the following inclusion criteria:

- 49
50
51 122 1. Patient aged 18-80 years old;
52
53
54 123 2. The preoperative blood pressure is controlled below 160/100mmHg; the blood
55
56
57 124 glucose is controlled between 5.6 and 11.2 mmol/L; the major organs' function is within
58
59
60 125 normality, including cardiac, pulmonary, hepatic, and nephritic function: (1) the cardiac

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4 126 function examination indicates a Goldman index rated 1-2; (2) the pulmonary function
5
6 127 examination indicates an estimated postoperative forced expiratory volume in the first
7
8
9 128 second(FEV_1) $\geq 1.0L$; (3) the total bilirubin $\leq 1.5 \times$ normal upper limit; (4) the alanine
10
11 129 transaminase(ALT), aspartate aminotransferase(AST) $\leq 1.5 \times$ normal upper limit; (5) the
12
13
14 130 creatinine $\leq 1.25 \times$ normal upper limit, and creatinine clearance rate $\geq 60ml/min$;
15
16
17 131 3. The primary preoperative clinical diagnosis highly suggested NSCLC, including
18
19 132 adenocarcinoma, squamous cell carcinoma, large cell carcinoma, and other histological
20
21
22 133 types; the clinical staging is T1a-1bN0M0 (IA1-2);
23
24
25 134 4. The thin-layer computed tomography(CT) indicates peripheral tumor[16, 17], whose
26
27 135 maximum diameter $\leq 2cm$; the tumors are located in the upper lobe or lower lobe of the
28
29
30 136 lung with unspecified laterality; the CT images indicate nonsolid nodules or the lesions
31
32
33 137 with ground-glass opacity components (consolidation-to-tumor ratio ≤ 0.5 on CT
34
35 138 images); the minimum diameter $\leq 1cm$ or the positron emission tomography/computed
36
37
38 139 tomography(PET/CT) indicates no mediastinal lymph node metastasis;
39
40
41 140 5. The intraoperative frozen section examination of surgical tissues and hilar lymph
42
43 141 nodes confirms the histological type of NSCLC and negative diseases of N1 lymph
44
45
46 142 nodes pathologically;
47
48
49 143 6. The Eastern Cooperative Oncology Group performance status(PS) score of 0-1;
50
51 144 7. All preoperative examinations are completed within 28 days preoperatively;
52
53
54 145 8. Patients who can comprehend this study and sign an informed consent form.
55
56
57
58
59 147 Patients with any of the following exclusion criteria would be ruled out:
60

- 148 1. Patients who have received preoperative anti-tumor treatment, including prior
- 149 radiotherapy, chemotherapy, target therapy, and immunotherapy;
- 150 2. Patients have a history of other malignancies;
- 151 3. Patients diagnosed a secondary malignancy when included;
- 152 4. Centrally located lung cancer, defined as the inner one-third of the hemithorax
- 153 adopted by drawing concentric lines from the midline[17, 18];
- 154 5. Tumors located in the middle lobe;
- 155 6. Small cell lung cancer;
- 156 7. Patients have a history of unilateral thoracic surgery;
- 157 8. Females with pregnancy or lactation;
- 158 9. Patients with interstitial pneumonitis, pulmonary fibrosis, or severe emphysema;
- 159 10. Uncontrollable active bacterial infection or fungal infection;
- 160 11. Severe mental disease;
- 161 12. Patients have a history of severe cardiac disease, cardiac failure, myocardial
- 162 infarction, or angina within six months;
- 163 13. Tumors with potential pleura involvement on CT images.

165 **Randomization, allocation concealment, and blinding**

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

1
2
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4 170 envelope would be assigned to each enrolled patient. The researcher would unfold the
5
6 171 envelope and get a random number, according to which the patient would be grouped.
7
8
9 172 The trial is double-blind, and the researcher and the participant would be blinded to the
10
11 173 allocation. The allocation would be unblinded when an emergency occurs, and the
12
13
14 174 participant would be withdrawn from the trial.
15
16

17 175

19 176 **Interventions**

21
22 177 All patients would receive complete lymph node dissection for N1 lymph nodes. As for
23
24 178 the mediastinal lymph nodes, patients in the experimental group would receive L-
25
26
27 179 SLND[9]. We would completely dissect the upper mediastinal lymph node for lung
28
29
30 180 cancer of the upper lobe, and the subcarinal and lower mediastinal lymph node for lung
31
32
33 181 cancer of the lower lobe(Table 1). Patients in the control group would receive SLND,
34
35 182 including upper mediastinal, subcarinal, and lower mediastinal lymph nodes. We would
36
37
38 183 dissect at least three mediastinal nodal stations(including subcarinal lymph nodes) and
39
40
41 184 a total of six lymph nodes during SLND[11]. Intraoperative frozen section examination
42
43 185 of the suspected mediastinal lymph nodes in the L-SLND group would be performed to
44
45
46 186 detect the possible lymph node metastasis, and in the case of positive lymph node
47
48
49 187 metastasis on the frozen section, SLND would be performed intraoperatively.
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188 **Table 1** The dissected lymph nodes in lobe-specific lymph node dissection and
 189 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

190

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

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

205

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

207 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			√			

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

212 **Outcomes**

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

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4 218 operation(day), duration of anesthesia(min), the volume of bleeding(ml), and the
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6 219 volume of drainage(ml). The metastatic lymph node ratio is defined as the ratio of the
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9 220 number of positive lymph nodes divided by all dissected lymph nodes.
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13 14 222 **Data collection, management, monitoring, and analysis**

15
16
17 223 The data collection and management were achieved by researchers under the guidance
18
19 224 of the Data Management Committee of Lung Cancer Center of West China Hospital.
20
21
22 225 All adverse events would be documented in detail and handled properly, which would
23
24 226 also be reported to the Data Management Committee and Ethics Committee of West
25
26
27 227 China Hospital of Sichuan University. The principal investigators would periodically
28
29
30 228 review the reported adverse events and evaluate the related subjects' risk and benefit.

31
32 229 The intention-to-treat principle would be performed, and participants would be
33
34
35 230 allocated to the assigned group. Chi-square test or Fisher's exact test is conducted to
36
37
38 231 compare the categorical data between groups; the independent sample t-test, Mann-
39
40 232 Whitney nonparametric U test, or one-way analysis of variance(ANOVA) test is
41
42
43 233 performed to compare the continuous data between groups; the survival analysis
44
45
46 234 compares the long-term survival between two groups via the Kaplan-Meier method and
47
48 235 log-rank test; a bilateral P -value <0.05 is considered statistically significant[19].
49

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51 236

52 53 237 **Patients or public involvement**

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55
56 238 Patients and the public would not be involved in the research's design, conduct,
57
58 239 reporting, or dissemination plans. All participants would sign the informed consent and
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4 240 be involved in the follow-up(Supplementary File 1).
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9 242 **ETHICS AND DISSEMINATION**
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11 243 This trial(Version 3.0) was approved by the Ethics Committee on Biomedical Research,
12

13 244 West China Hospital of Sichuan University(2021-332, Supplementary File 2) on May
14

15 245 16, 2021, and registered in the Chinese Clinical Trial Registry(ChiCTR2100048415).
16
17

18 246 The LESSON study would be performed following the Declaration of Helsinki. All
19

20 247 participants would learn the outline of this trial and sign the informed consent, who
21

22 248 could also have the right to opt-out without medical care being affected, and the tumor
23

24 249 specimens would not be collected. A regulatory team from the Ethics Committee of
25

26 250 West China Hospital of Sichuan University would review all research data every six
27

28 251 months, including research data, medical records, and electronic case report forms.
29

30 252 Important protocol modifications would be reported to the Ethics Committee. The
31

32 253 principal investigators would guarantee the participants' right to withdraw from this
33

34 254 trial in an emergency to ensure their safety. All research data would be carefully stored
35

36 255 and only available for the researchers and monitoring panels. The corresponding result
37

38 256 of the trial would be published in academic conference presentations and peer-reviewed
39

40 257 publications.
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46 260 study and drafting of the manuscript and took full responsibility for the content,
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4 262 recruitment and data curation. W. H., H. D., K. X., and Y. W. contributed to the
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6 263 formal analysis. W. H., H. D., and Q. Z. contributed to the revision of the manuscript.
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9 264 W. H., H. D., Z. R., K. X., Y. W., X. T., D. Z., and Q. Z. contributed to the approval
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11 265 of the final manuscript. H. D. and Q. Z. contributed to supervision and project
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13
14 266 administration.

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27 271 Supplementary File 2, the trial approval from the Ethics Committee on Biomedical
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30 272 Research, West China Hospital of Sichuan University(2021-332).

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34 35 274 **Abbreviations**

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37 275 ALT, alanine transaminase

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39 276 ANOVA, analysis of variance

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41 277 AST, aspartate aminotransferase

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43 278 CT, computed tomography

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45 279 DFS, disease-free survival

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47 280 DL_{CO}, carbon monoxide diffusing capacity

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49 281 FEV₁, forced expiratory volume in the first second

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51 282 H&P, history and physical examination

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53 283 HR, hazard ratio

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4 284 NSCLC, non-small cell lung cancer
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6 285 OS, overall survival
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9 286 PET/CT, positron emission tomography/computed tomography
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12 287 PS, performance status
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14 288 RCT, randomized controlled study
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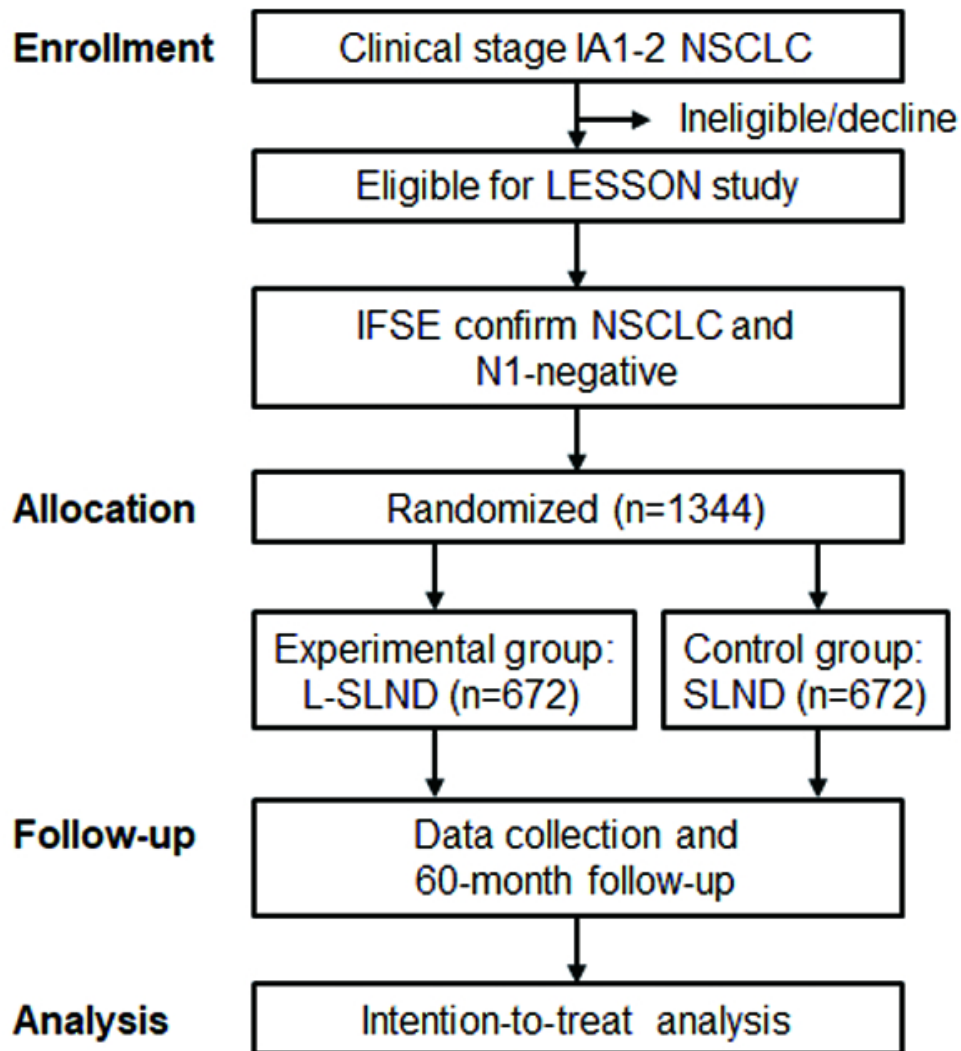
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4 348 **Figure legends**

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6 349 **Figure 1** Scheme of the LESSON Trial. **Abbreviation:** NSCLC, non-small cell lung
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9 350 cancer; IFSE, intraoperative frozen section examination; N1-negative, there is negative
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11 351 finding or no metastasis for the hilar lymph nodes; L-SLND, lobe-specific lymph node
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14 352 dissection; SLND, systematic lymph node dissection.
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For peer review only



41 Figure 1 Scheme of the LESSON Trial. Abbreviation: NSCLC, non-small cell lung cancer; IFSE, intraoperative
42 frozen section examination; N1-negative, there is negative finding or no metastasis for the hilar lymph
43 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,非小细胞肺癌占有所有肺癌的约 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,通过将最新证据研究汇集在一起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?

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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hxlcyjlb@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) :

主任委员(签名) :

生物医学伦理
审查委员会

邓福林
2021年5月26日