Comparison between Wedge Resection and Segmentectomy for Ground Glass Opacity-dominant Early Stage Non-Small Cell Lung Cancer (TSCI 002): Study protocol for a randomized controlled trial

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Study protocol

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Abstract

Background: Currently, there are no universally recognized criteria to choose between segmentectomy and wedge resection. However, compared with segmentectomy, wedge resection is more accessible, less invasive, preserves more pulmonary tissues and presents a faster post-operative recovery process, which in turn, result in a higher quality of life. We hypothesize that wedge resection could be a potential alternative to anatomic segmentectomy for patients with very early non-small cell lung cancer (NSCLC), and we plan to conduct the first randomized trial comparing the effectiveness and safety of wedge resection and segmentectomy to guide the surgical decision. Methods: We plan to conduct a prospective, multicentre, randomized, open, parallel control and non-inferiority verification adopted study. Patients from 21 sites of China who satisfy all the inclusion criteria and do not fall into any of the exclusion criteria are qualified to be included in this study. They will then be randomly allocated into two groups: lung wedge resection + hilar and mediastinal lymph node resection / sampling (study group) and segmentectomy + hilar and mediastinal lymph node resection/sampling (control group). A recruitment period of no more than two years is anticipated. The primary endpoint of the study is 5-year disease-free survival (DFS) between the two groups. The secondary endpoints are 3-year DFS, 5-year overall survival （OS）, 30-day morbidity and mortality rates, and pulmonary function. Discussion: This is a multi-centre, randomized, open, parallel control, and non-inferiority verification adopted study to evaluate whether lung wedge resection and segmentectomy are equivalent in long-term oncological efficacy in patients with ground glass opacity (GGO)-dominant early stage peripheral non-small cell lung cancer.

Background

Lung cancer is a malignant tumour with the highest incidence and mortality in the world[1]. With the generalized application of CT scanning in lung cancer screening, the probability of detecting early-stage lung cancer is continuously increasing, and the mortality of lung cancer has significantly decreased[2]. Surgical resection is still the best option for the treatment of early-stage non-small cell lung cancer (NSCLC). One randomized controlled trial (RCT) comparing sublobectomy (wedge resection and segmentectomy) and lobectomy indicated that sublobectomy has a higher local recurrence rate and a lower overall survival (OS) rate than lobectomy[3]. Thereafter, lobectomy was regarded as the standard procedure for early-stage NSCLC. However, due to the limited pre-operative staging measurements and clinical underdiagnosis, a large portion of the population underwent wedge resection, causing bias in the study. Currently, with advancements of surgical techniques and more accurate preoperative staging, an increasing studies have shown that sublobectomy can achieve the same outcome compared with lobectomy for early stage NSCLC[4-9].

Currently, there are no universally recognized criteria for selecting between segmentectomy and wedge resection. Compared with segmentectomy, wedge resection is more accessible, less invasive, preserves more pulmonary tissues and yields a faster post-operative recovery process, which in turn result in a higher quality of life. However, the indications of wedge resection still need further improvement. Recent

studies revealed that NSCLC with components of ground glass opacity (GGO) showed high consistency in clinical, radiological and pathological characteristics. With the increase in the solid components of the tumour, the malignancy also increases correspondingly[10-15]. A maximal diameter ≤2 cm and the GGO component proportion ≥75% were considered as reliable parameters indicating non-invasive tumours, i.e., carcinoma in situ or microinvasive carcinoma, extremely low invasiveness, nearly no pleural or vascular infiltration, and no lymph node metastasis[11, 15-18]. One recent study indicated that wedge resection was an appropriate procedure for the treatment of tumours with diameters ≤2 cm and GGO component proportions ≥75%, with a 5-year OS as high as 98.6%[19]. This is inconsistent with other studies that also showed that the five-year OS rate was nearly 100% after surgical resection [16, 18, 20, 21]. Therefore, tumour diameter ≤2 cm and GGO component proportion ≥75% may potentially be used as indicators in favour of choosing wedge resection in the treatment of patients with early-stage NSCLC.

This study aims to evaluate whether lung wedge resection + hilar and mediastinal lymph node resection/sampling and segmentectomy + hilar and mediastinal lymph node resection/sampling are equivalent in the long-term oncological efficacy in the treatment of peripheral NSCLC with diameter ≤2 cm and GGO component proportion ≥75% through a prospective, randomized, and controlled design.

Methods

Trial design

The is a prospective, multicentre, randomized, open, parallel control, and non-inferiority verification adopted study. The patients will be recruited from 21 participating hospitals in China and then randomly divided into two parallel groups. All 21 sites were requested to finish the patient recruiting process within two years. Five years after the last case recruited is the cut-off time to evaluate the primary endpoint (5-year DFS).

The study was registered at ClinicalTrials.gov and reported according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines[22], including the SPIRIT Figure (Fig. 1) and SPIRIT Checklist (Additional file 1).

Eligibility criteria and patient consent

According to the inclusion and exclusion criteria described below, all patients referred to the participated centres will be thoroughly assessed by a dedicated investigator to determine their eligibility. Each patient will be introduced to the trial by an investigator and receive an explanation of the study protocol. Specific informed consent regarding participation in the trial, randomization, and explanation of the surgery will be obtained before enrolment. The study will be carried out following the Helsinki Declaration and was approved by Ethics Committees of West China Hospital.

Diagnostic criteria

- ASLC/ UICC 2017, 8th version of the pulmonary carcinoma staging system will be adopted in this study.
- Definition of peripheral-type: the tumour is derived beyond the segmental bronchus.
- Pulmonary GGO is diagnosed through imaging, but the pulmonary tumour cannot be ruled out.

Inclusion criteria

- 18 years ≤ age ≤ 75 years
- Chest enhanced thin layer high-resolution CT examination: 5 mm < nodule ≤20 mm; ground grass opacity accounts for ≥ 75%
- Preoperative clinical evaluation reveals no hilar, mediastinal lymph node or remote metastasis
- The lesion is located at 1/3 of the peri-pulmonary region
- R0 resection is anticipated in both study groups, in which the subjects received lung wedge resection + hilar and mediastinal lymph node resection/sampling or segmentectomy + hilar and mediastinal lymph node resection
- The pulmonary function test indicates that FEV1 is ≥ 1 L and greater than or equal to 50% of the predicted value
- Preoperative ECOG performance status score is 0/1
- ASA score is I-III
- Patients who are willing to participate in this study and give written informed consent before any study-related procedures are performed

Exclusion criteria

- Quit smoking for less than two weeks
- Multiple pulmonary GGO nodules indicating multiple primary cancers
- The lesion is located at the middle lobe of the right lung
- The lesion is located between two segments, and a simultaneous segmentectomy is required
- Female patients who are pregnant or lactating at the time of screening
- Serious mental illness
- History of other malignant diseases within five years
- History of unstable angina pectoris or myocardial infarction within six months, and severe stenosis in the main branches of the coronary artery as shown by coronarography
- History of cerebral infarction or cerebral haemorrhage within six months
- History of receiving systemic steroids within one month
- Patients are unsuitable for participation in the study at the discretion of investigators

Study Grouping

Study subjects were randomly allocated to group A (study group) and group B (control group).

Group A (study group)

- Group of lung wedge resection + hilar and mediastinal lymph node resection/sampling.
- Pulmonary wedge resection: tumour margin ≥1.5 cm away from the margin of the surgical staples is required.
- Lymph node resection / sampling: following latest guidelines.

Group B (control group)

- Group of segmentectomy + hilar and mediastinal lymph node resection/sampling.
- Pulmonary segmentectomy: the requirement of specimen margins is the same for the pulmonary wedge resection. The requirement for bronchial incisal margin is that the specimens of the bronchial stump are collected and submitted for tests after resection of the surgical staples at the distal end of the segmental bronchus (no mandatory requirement is imposed for the intraoperative examination of bronchial incisal margins).
- Lymph node resection/sampling: following the latest guidelines.

Definition of endpoints and outcome measures

Primary endpoint

- 5-year DFS: Defined as the time interval from randomization to the earliest onset of any of the following events within five years: tumour recurrence, metastasis, or death caused by any reason.

Secondary endpoints

- 3-year DFS: Defined as the time interval from randomization to the earliest onset of any of the following events within three years: tumour recurrence, metastasis, or death caused by any reason.
- 5-year OS rate: Defined as the time interval from randomization to death from any cause within five years.
- 30-day morbidity and mortality rates: Including intraoperative death, all dead patients within 30 days at the end of surgery (no matter whether the cause of death has a causal relationship with the surgery), the deaths of patients with clear evidence and deaths with a direct causal relationship with the first surgery within 31 days or more after the surgery. The number of patients in each group receiving the surgical treatment is used as the denominator, and the patients in the corresponding group who conform to the conditions above are used as the numerator to obtain a ratio, which is the operative mortality.

Randomization

Central randomization.

The statisticians in the Chinese Cochrane Center use central randomization system to the complete randomization. When patients are included in the study, the clinical trial units will notify the Chinese Cochrane Center through E-mail or telephone. After the information of the included patients is confirmed, the Center responds to the number of groups in which the patients are included. After each participating centre receives the group information of the selected subjects, the subjects will then be divided into either group A or group B in strict accordance with the information. After that, the group number cannot be changed. If any of the patients cannot be randomly allocated due to their own reasons, this patient will be counted as a deleted case or a dropout, and the patient will not be re-included in the study.

Sample Size Estimation

The sample size was calculated by PASS 11 software (NCSS, LLC, Kaysville, UT, USA) based on the 5-year DFS of patients. The mean (or median) value of DFS of the subjects in group B (segmentectomy + hilar and mediastinal lymph node resection/sampling) is approximately 70 months, and the DFS of clinical significance is six months d (i.e., 6 months). Therefore, the mean (or median) value of DFS of the subjects in group A (study group, segmentectomy + hilar and mediastinal lymph node resection/sampling) is set as 64 months, and the standard deviation of the two groups is set as 24 months. As a=0.05 (one-sided) as the size of test, the power of test is set as 80%, and a balanced design is adopted (i.e., the subject ratio in the study group and the control group is 1:1). The maximal dropout rate and rate of loss to follow-up was set to 15%. Based on this, the sample size in each group should be 691 subjects, and 1392 subjects are needed in the two groups.

Data Management

Data management is composed of six strict steps:

- The investigators input the data into the case report form timely, completely, and correctly according to the subject's original observation records.
- The case report forms examined by the monitors shall be submitted to the clinical research data managers after the verification and signing of the monitors.
- The data managers verify the data again before recording, notify the monitors in good time in case of problems, and require the investigators to provide answers.
- The data managers input the data twice.
- The data managers shall work together with the principal investigators to set the contents for the data range examination and logic examination according to the range and mutual relationship of various indices in the case report form.
- The original case report forms shall be filed according to the numerical sequence after the data recording and verification is completed according to the requirements, and they shall be filed in the retrieval catalogues for future checks.

Statistical Analysis

Statisticians prepare the statistical analysis plan, the version is finalized before the database is locked and it consists of multiple forms. The contents of principal analysis include inter-group comparability analysis, effectiveness analysis and safety analysis. The following indicators are used for the descriptive analysis of enumeration data: mean, standard deviation, median, interquartile range, maximum and minimum. The following indicators are used for the descriptive analysis of measurement data: ratio, constituent ratio or RR. As for the statistical inference, correct hypothesis test methods are selected according to the suitable conditions of the statistical methods, and confidence intervals can be used if necessary. $P<0.05$ (i.e., $a=0.05$) means that the inter-group difference is statistically significant. Statistical analysis will be performed using SAS 9.4 software (SAS, Cary, NC, USA).

Follow-ups

Follow-up cycle and precautions

Each study site arranges follow-up visit specialists to follow up the patients included in the study. The patients are followed up at 1, 6, 12, 18, 24, 30, 36, 42, 48, 54, and 60 months after the operation.

It is recommended in this study that the above examinations are carried out at the study sites where the patients receive surgery, but the follow-up activities at other hospital are not ruled out. If the follow-up work is conducted at another hospital, it should be a tertiary referral hospital, and the follow-up specialists should track them and record the results of the examinations.

All the examination results are taken into consideration, and the postoperative survival status of all patients is evaluated to determine whether the tumour is recurrent or metastatic (it is better to obtain the pathological diagnosis).

If the patients refuse to receive follow-up visits according to the above plan, they should be recorded as those lost to follow-up visits, and they should be recorded in the CRFs.

Postoperative adjunctive therapies

No adjuvant therapy is postoperatively needed for the T1a-T1bN0M0 patients according to the China Primary Pulmonary Carcinoma Diagnostic and Therapeutic Regulations (2015 version) and NCCN Non-small cell Lung Cancer Guideline 2017.v8. Unless recurrence or metastasis is proven, adjuvant therapies, such as chemotherapy, radiotherapy, biologically targeted therapy, specific immunotherapy and cellular therapy, cannot be performed after the operation. After the operation, it is acceptable for patients to receive traditional Chinese medicine or nonspecific immunotherapy (thymopentin, thymalfasin and thymic peptide α1), and concomitant medicines/treatments should be recorded in the CRFs.

Reporting of adverse events

In case of the occurrence of “severe adverse events” or “unintended adverse events”, the study directors of each participating unit submit the reports to the study committee / PI. The reported pattern is presented

by the study committee to each participating unit before the start of the study.

The reports are submitted by the provincial (municipal) health departments where the study site belongs according to the related laws and regulations. The reports are submitted by the general directors of the medical institutions according to the severe adverse events as described in the ethical guidelines in the clinical study. Similar reporting procedures are finished according to the regulations related to the medical institutions. The study directors of each participating unit have the obligation and responsibility to give emergency handling to any patient who experiences any adverse event to ensure the patient's safety.

Discussion

This is a multi-centre, randomized, open, parallel control, and non-inferiority study to evaluate whether lung wedge resection + hilar and mediastinal lymph node resection/sampling and segmentectomy + hilar and mediastinal lymph node resection/sampling are equivalent in terms of long-term oncological efficacy in subjects with ground glass opacity (GGO) dominant early stage (including Tis) peripheral non-small cell lung cancer.

Lung cancer has the highest incidence and mortality rate in the world. For early-stage NSCLC, surgical resection is the first-choice treatment. Lobectomy and sublobectomy (wedge resection and segmentectomy) are both utilized based on different tumour stages. One randomized controlled study [2] compared sublobectomy and lobectomy and showed that sublobectomy had a higher local recurrence rate and a lower overall survival rate than lobectomy. Of note, due to the limited pre-operative staging measurements and clinical underdiagnosis, a large portion of the population underwent wedge resection, causing significant bias. Recently, an increasing number of studies have revealed that, for early-stage non-invasive NSCLC, sublobectomy can achieve the same oncological efficacy as lobectomy[23-26]. Therefore, sublobectomy is a now seen as an alternative for early-stage non-invasive NSCLC.

However, the selection between wedge resection and segmentectomy for early-stage, non-invasive NSCLC remains controversial. In a recent meta-analysis, Liu and colleagues found that, for stage I NSCLC, segmentectomy had comparable survival benefits as lobectomy, while the outcome of wedge resection was inferior to that of lobectomy.[27] However, the authors failed to compare the outcome of stage Ia NSCLC patients, who were considered to be optimal candidates for sublobectomy[28]. In a retrospective analysis, Altorki and colleagues found that wedge resection and segmentectomy were comparable oncological procedures when including Ia NSCLC patients.[29] The result was supported by a meta-analysis that included 3184 patients from nine studies[30] In addition, a recent study illustrated that tumour size and the GGO component proportion are the most essential reference indicators for choosing the appropriate surgical treatment, with tumour diameter $\leq$2 cm and GGO component proportion $\geq$75% being reliable indicators for wedge resection.[31] However, this study was a retrospective study with a relatively small sample size. Later on, the Lung Cancer Surgical Study Group of the Japan Clinical Oncology Group (JCOG) conducted a non-randomized study (JCOG0804) to explore the efficacy and safety of wedge resection for radiologically determined non-invasive NSCLC[32]. Although the study was a

prospective study with higher evidence level, a randomized controlled study is still needed to draw a definitive conclusion.

In summary, compared with segmentectomy, wedge resection is more accessible, less invasive, preserves more pulmonary tissues and yields a faster post-operative recovery process, which in turn result in a higher quality of life. In this clinical trial, we will mainly focus on comparing 5-year DFS between group A and group B and analysing our secondary study endpoints (3-year DFS, 5-year OS, 10-year OS, 30-day morbidity and mortality rates, and pulmonary function). Furthermore, we will also pay attention to adverse effects to measure the safety of different surgical procedures. We expect to find better primary and secondary endpoints and fewer adverse events in group A (study group).

Trial Status

The study registered on ClinicalTrials.gov (NCT02718365). West China Hospital Ethical Committee has approved the study protocol (version 2.0, 2017.8.28) on November 8th, 2017 (reference number 2017310). The study opened for recruitment in December 2017, and we plan to finish the recruitment in December 2020.

Abbreviations

GGO: ground glass opacity; DFS: disease-free survival; OS: overall survival; IASLC/ UICC: International Association for Study of Lung Cancer/ Union for International Cancer Control; FEV1: Forced expiratory volume in one second; ECOG: Eastern Cooperative Oncology Group; ASA: American Society of Anesthesiologists; CRF: Case Report Form; ITTP: Intent-to-treat population; MITTP: Modified intent-to-treat population; LOCF: last observation carry forward; PPP: Per-protocol population; SAP: Safety analysis population; SOP: Standard Operating Procedures; BN: baseline number

Declarations

Acknowledgments

Not applicable.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

HL, QP, FL and CWL conceived the study, participated in its design and coordination, and helped draft the manuscript; FL, QP, LM and LXL are responsible for the operations, LM, JDM and LP performed the sample size calculation and designed the statistical analysis protocol; LXL designed and financially supported the study.

Ethics approval and consent to participate

Central ethical approval has been confirmed from the ethics committee of West China Hospital (ref approval no. 2017310) and we will not begin recruiting at other centres in the trial until local ethical approval has been obtained. Written informed consent will be obtained from all study participants before participating in the trial.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

	STUDY PERIOD												
	Enrolment	Allocation	Follow up										
TIMEPOINT**	*3-7 days before surgery*	surgery	1 month	*6 months*	*12 months*	*18 months*	*24 months*	*30 months*	*36 months*	*42 months*	*48 months*	*54 months*	*60 months*
ENROLMENT:													
Eligibility screen	X												
medical history	X												
Obtaining informed consent	X												
Allocation		X											
INTERVENTIONS:													
Wedge resection		X											
Segmentectomy		X		X		X							
ASSESSMENTS:													
Blood test	X	X	←	→	→	→	→	→	→	→	→	→	→
chest X ray			X										
Chest CT scan	X			←	→	→	→	→	→	→	→	→	→
PET/CT scan or abdominal CT +head CT +bone scintigraphy	X				X		X		X		X		X
Pulmonary function	X		X	X	X								

Figure 1

Standard protocol items: recommendation for interventional trials (SPIRIT) figure.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SPIRITchecklist.doc