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One-stage versus two-stage video-assisted thoracic surgery for synchronous bilateral pulmonary nodules: protocol for a single center, non-randomized clinical trial (OTVATS-1)

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Abstract

Background Previous retrospective studies demonstrated both one-stage and two-stage video-assisted thoracic surgery (VATS) for bilateral pulmonary nodules were safe and feasible in selected patients. However, prospective data is still lacking. The purpose of this trial is to prospectively compare the prognostic and perioperative outcomes between one-stage and two-stage VATS for synchronous bilateral pulmonary nodules.

Methods We conduct a prospective clinical trial to investigate the surgical outcomes of one-stage and two-stage VATS for patients with synchronous bilateral pulmonary nodules. This trial plan to enroll 198 patients from a single institution during a period of 5 years. The primary outcome is 5-year overall survival. Secondary outcomes include 5-year disease free survival, 3-year overall survival, 3-year disease free survival, overall complications rate, 30-day mortality, pain score after surgery, surgical time, blood loss in the operation, duration of chest tube, length of stay, and quality of life score after surgery.

Discussion To our knowledge, this study is the first prospective registered clinical trials to compare the clinical outcomes after one-stage or two-stage VATS for synchronous bilateral non-small cell lung cancer.

Trail registration This study underwent review by the Ethics Committee of China-Japan Friendship Hospital under No. 2023-KY-061-1. It has been officially registered with the China Clinical Trial Registry, TRN: ChiCTR2300071198 and registration date is May. 8, 2023.

Keywords Bilateral pulmonary nodules, Thoracoscopic surgery, One-stage, Two-stage

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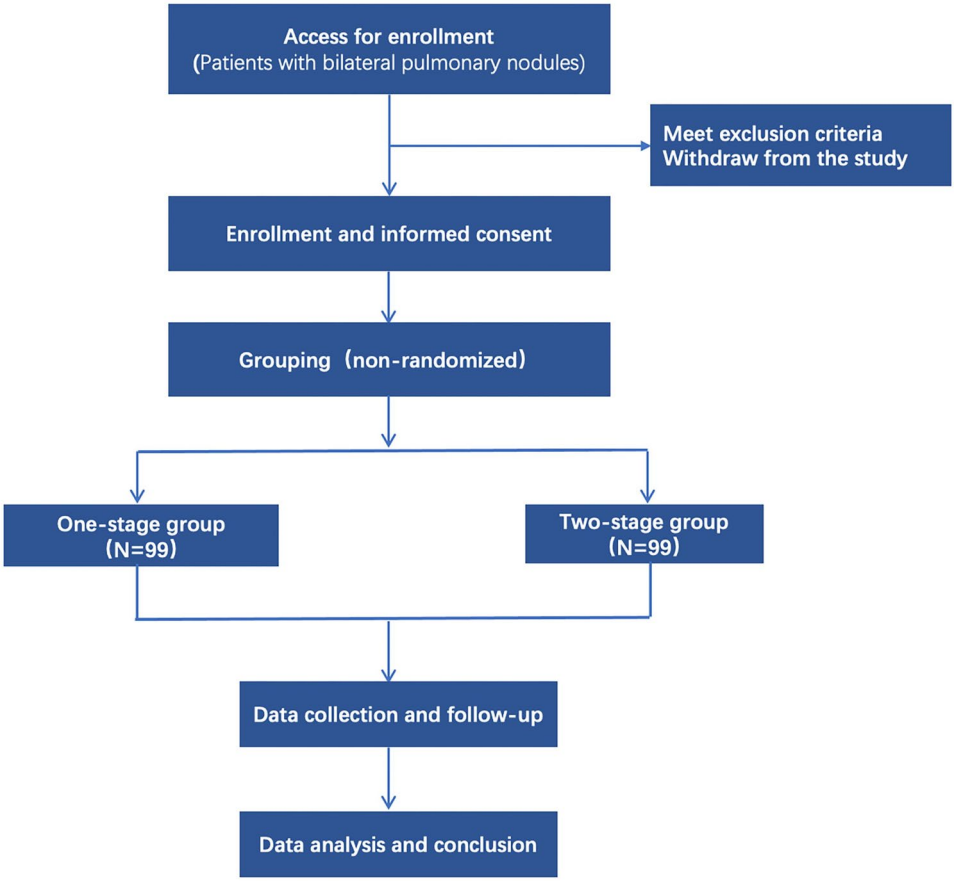

Fig. 1 Study flowchart

Background

Due to the popularization of high-resolution computed tomography (HRCT), an increasing number of synchronous multiple pulmonary nodules (SMPNs) have been identified [1, 2], among which bilateral pulmonary nodules account for a large proportion [3]. Surgical resection remains the mainstay of treatment for SMPNs suspected to be malignant [4]. For bilateral pulmonary nodules, the surgical options including one-stage and two-stage procedure.

Until now, the optimal surgical methods for synchronous bilateral lung cancer is still debated [5]. One-stage surgery for bilateral pulmonary lesions was traditionally considered to be associated with high risk and morbidity [6]. However, with the rapid development and wide application of thoracoscopic minimally invasive techniques, several studies have demonstrated the safety of performing bilateral thoracoscopic lung surgery simultaneously [7–9]. What's more, the simultaneous surgical resection of bilateral lung lesions processes potential survival benefits for patients [10]. Two-stage procedure seems to be more suitable for patients with poor pulmonary functions, and the interval between two surgeries is usually more than 4 weeks. However, the second operation may be postponed due to the complications of the first operation, fearing of another operation, as well as social and economic factors.

This single center, prospective non-randomized clinical trial (OTVATS-1) aims to investigate and compare the surgical outcomes of one-stage and two-stage VATS for patients with synchronous bilateral pulmonary nodules.

Methods/design

Study design

OTVATS-1 is a single center, prospective non-randomized clinical trial to compare the perioperative and long term outcomes between one-stage and two-stage VATS for patients with synchronous bilateral pulmonary nodules. It has been officially registered with the China Clinical Trial Registry (ChiCTR2300071198). As the formulation of surgical strategies for bilateral lesions are influenced by several factors including the location and stage of the lesions, the patients' willing and physical condition, as well as the habits of the surgeons, so this study is designed as a non-randomized clinical trial (Fig. 1).

The trial started in May 2023; the estimated recruiting time is to December 2025 and the estimated study completion date is December 2030. This report follows the

Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist (Supplementary material 1) [11], which is a comprehensive 27-item guideline designed to improve the quality and completeness of protocols for clinical trials. The main items including objectives, hypotheses, trial design, statistical methods, and monitoring methods.

Objectives

The primary objective of OTVATS-1 is to compare the clinical outcomes after one-stage or two-stage VATS for synchronous bilateral non-small cell lung cancer (NSCLC). The secondary objective is to compare the quality of life of patients after one-stage or two-stage VATS for synchronous bilateral NSCLC.

Outcome and measurements

Primary endpoint

The primary outcome is 5-year overall survival (5-year OS). OS events are defined as the time between the date at diagnosis and the date of death (from any cause).

Secondary outcomes include

(1) 5-year disease free survival (DFS), and 3-year DFS. DFS events are defined as the time from surgery to recurrence of tumor or death from any cause.
(2) Postoperative complications include: air leakage, pleura effusion, pulmonary infection, pulmonary embolism, postoperative bleeding, chylothorax, atrial fibrillation, pulmonary embolism and wound infection. The postoperative complications are described according to the Clavien-Dindo classifications [12]. Complications of grades I-II will be categorized as minor and those with grades III-IV will be categorized as major complications.
(3) 30-day mortality.
(4) Visual Analogue Scale (VAS)(1–10) or numeric rating score (NRS)(1–10) will be used to evaluate the postoperative pain at following times: postoperative day 1,2,3 and at weeks 1, 4, 24 and 48. For two-stage group, the date of the first operation will be taken as the starting point.
(5) Quality of life (QoL) will be evaluated at following times: pre-operative < 5 days, and at weeks 1, 4, 24, and 48 postoperatively. The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) version 3.0 [13] and the EORTC Quality of Life Questionnaire in Lung Cancer (EORTC QLQ-LC13) [14] will be used. For two-stage group, the date of the first operation will be taken as the starting point.
(6) Surgical time is defined as time from incision until closure (minutes).
(7) Blood loss in the operation (ml).
(8) Duration of chest tube and length of stay (day).

For two-stage group, the complication rate, surgical time, blood loss, duration of chest tube and length of stay are defined as the sum of two stage operations.

Follow-up protocol

After surgery, follow-up visits will be conducted every 3 to 6 months for a duration of 2 years. During this period, in addition to routine physical examinations, a chest CT scan, abdominal CT or ultrasound, a head MRI, and bone scan will be performed to assess recurrence or metastasis. For the next 3 to 5 years, follow-up visits are recommended annually, with the relevant examination frequency also advised to be once per year. For patients beyond 5 years post-surgery, an annual follow-up visit is recommended.

Eligibility criteria

Inclusion criteria

All enrolled patients should meet the following criteria:

1. 18 to 80 years old (including cut-off value) at the time of signing the informed consent.
2. Surgical intervention is needed for bilateral pulmonary lesions according to the guidelines for the diagnosis and treatment of pulmonary nodules, clinical stage T1-2N0-1M0 (8th edition of National Comprehensive Cancer Network).
3. American Society of Anesthesiologists classification (ASA) stage: I-III.
4. Indications for minimally invasive surgery.
5. Normal preoperative evaluation.
6. Sign the informed consent.

Exclusion criteria

Patients are excluded if they meet any of the following criteria:

1. Underwent adjuvant therapy before surgery.
2. Pathologically confirmed benign.
3. History of other malignant tumor.
4. Small cell lung cancer.
5. Pathologically confirmed metastatic tumor.

Surgical procedures

Double-lumen endotracheal intubation with single-lung ventilation was performed for both groups, and the patient was placed in the lateral decubitus position. A 3–4 cm incision was made through the fourth or fifth interspace in the anterior axillary line as operative hole, while a 1–2 cm incision was made through the seventh or eighth interspace in the middle axillary line

for endoscopic hole. In one-stage bilateral VATS, the operation usually started from the side with less invasive resection, such as wedge resection and segmentectomy. After the first side procedure was finished and the chest tube was placed, the patients were rotated to the opposite side for the second resection. Simultaneous bilateral lobectomy was avoided. If the first operation ended with lobectomy and the other side was also scheduled for lobectomy, or the single-lung ventilation could not be maintained for the second side, the surgical plan will be changed to two-stage. The surgical principles of two-stage procedure were in accordance with one-stage surgery. The interval between two operations in two-stage group at least 1 month, which also depend on the physical recovery after the first surgery.

Statistics

The statistical analysis will be performed with SPSS (version 23. Inc., Chicago, IL, USA). Categorical data will be compared using chi-square tests or Fisher's exact tests. Student t test or the Wilcoxon rank sum test will be applied to analyze continuous variables. Statistical significance will be set at $p < 0.05$.

Confounding variables

Possible differences between one-stage and two-stage groups will be adjusted for the following confounding variables to minimise bias: surgeon experience, tumor heterogeneity, patient comorbidities, and surgical interval in two stage group. The multivariate analysis will help to eliminate differences between the patients. Subgroup analyses will be performed stratified by pathological stage and surgical approach.

Calculation of sample size

According to the results of previous studies, the 5-year OS of patients who underwent one-stage surgery for bilateral non-small cell lung cancer was set as 62%, while the 5-year OS in two-stage group was set as 41% [10]. The sample size was calculated using the PASS V.2021 software, and Log-rank Test was performed. Variables are determined as follows: two-sided hypothesis, power = 0.8, $\alpha = 0.05$. Power > 0.8 is defined as meaningful to detect the effect size. Considering a possible dropout rate of 10%, the total sample size is 198 in this trial ($n = 99$ in each group).

Data statement

Case Report Form (CRF) will be utilized for data collect and record. CRFs and the informed consent will be stored in a clinical trial filing cabinet. All Principal Investigators will be given access to the cleaned data sets, and all data sets will be password-protected. The IRB will oversee the intra-study data sharing process, with input from the Data Management Subcommittee. Patients with significant missing data will be excluded. Missing data in quality of life assessments will be handled using the last-observation-carried-forward (LOCF) method.

Ethics and dissemination

This study was approved by the Ethics Committee of China-Japan Friendship Hospital (ethical approval ID: 2023-KY-061-1). Informed consent will be obtained from all participants. The surgical strategy, potential risks, benefits and adverse events of this trial will be fully informed to the participants.

The interventions in our trial are one-stage and two-stage VATS for bilateral NSCLC, which are mature procedures and routinely performed in clinical practice. We consider that our treatments will not cause additional harm to the participants. Throughout the data collection, data will be processed and limited to those necessary to complete the purposes of this study. Findings will be published in peer-reviewed journals and presented at international conferences.

Interim data and preliminary analysis

Until December 2024, 49 patients were enrolled in the two-stage group and 16 patients were enrolled in the one-stage group. There was no tumor recurrence or death in either group. The complications rates were comparable between the one-stage and the two-stage groups (18.8% vs. 22.4%, $p = 1.000$).

Discussion

To the best of our knowledge, this is the first prospective trial comparing the perioperative and long-term outcomes between one-stage and two-stage VATS for patients with bilateral multiple pulmonary nodules. Although the safety and efficacy of one-stage VATS for bilateral pulmonary lesions has been demonstrated by several retrospective studies [9, 15], prospective evidence is still lacking.

It is common conclusion that performing bilateral VATS in one stage associated with higher pain intensity and poorer quality of life. However, previous studies have not quantitatively compared pain scores and quality of life for the two procedures. In order to get quantitative results, pain score and quality of life of the patients who underwent one-stage and two-stage VATS will be prospectively assessed in this study.

Overall survival is generally considered the most important endpoint for the oncology clinical trial [16]. In two-stage group, patients usually need to wait for at least one months before the second operation, and the interval may be extended for a variety of other reasons including complication happens in the first operation, the fear of the second operation, social or economic factors. It can

be seen that one-stage procedure possess potential benefit in preventing tumor progression.

The recruitment timeline of this study spans five years, and there are potential challenges in patients retention. Patients may lose interest or motivation to continue participating in the trial during the long-term follow up. The transportation issues or scheduling conflicts may make it difficult for patients to attend follow-up visits. Several strategies will be employed to ensure follow-up adherence. Personalized communication can help maintain their interest and commitment. We will offer flexible scheduling options to accommodate patients' schedules and personal commitments. This can include evening or weekend appointments, remote monitoring options, and telemedicine consultations, which can reduce the need for in-person visits and increase patient convenience.

As a single-center study, the results obtained may not directly translate to other settings due to inherent differences in patient demographics, clinical practices, and resource availability across various healthcare environments. To address these limitations, future research should consider multi-center trials that include diverse populations and healthcare systems. The demographic characteristics of this study population will be compared with national or international benchmarks to evaluate the general applicability.

This study has some limitations. First, this study is a single center trial, and the results obtained may not directly translate to other settings due to inherent differences in patient demographics, clinical practices, and resource availability across various healthcare environments. The demographic characteristics of the study population could be compared with national or international benchmarks to evaluate the general applicability. Second, considering surgical strategy for bilateral pulmonary nodules usually depend on the location of the lesions, physical condition of patient, as well as the willing of surgeon and patient, so grouping is not randomized in this study. The non-randomized design would introduce a risk of selection bias. Several strategies could be implemented to mitigate this limitation including stratified analysis based on patient characteristics; enhanced patient population homogeneity; and matched study participants in two groups. In the follow-up study, multicenter randomized clinical trial will be conducted in appropriate population.

In general, the purpose of this clinical trial is to improve the survival of patients with bilateral NSCLC. This trial will provide objective evidence on the choice of surgical strategy for patients with bilateral multiple pulmonary nodules.

Abbreviations and acronyms

VATS	Video-assisted thoracic surgery
IRB	Institutional Review Board
HRCT	High-resolution computed tomography
SMPNs	Synchronous multiple pulmonary nodules
OS	Overall survival
DFS	Disease free survival
CRF	Case Report Form
NSCLC	Non-small cell lung cancer
ASA	American Society of Anesthesiologists classification

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12893-024-02753-0.

Supplementary Material 1

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Author contributions

Yu Han: study design and article writing; Weixun Zhang and Peihang Xu: made substantial contributions to the design of the study; Zhoujunyi Tian and Yang Hao: article writing; Jin Zhang and Tai Ren: the sample size calculation; Chaoyang Liang: quality control and editing. All authors have read and approved the final manuscript.

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Data availability

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

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of China-Japan Friendship Hospital (IRB 2023-KY-061-1). Informed consent will be obtained from all participants before enrollment, ensuring they understand the study's purpose, procedures, risks, and benefits. Participants will be informed of their right to withdraw from the study at any time, and confidentiality of their data will be strictly protected.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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