Feasibility and effectiveness of thoracoscopic pulmonary segmentectomy for non-small cell lung cancer

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Abstract
The outcomes of minimally invasive thoracoscopic pulmonary segmentectomy for non-small cell lung cancer (NSCLC) still need to be defined. This study aimed to investigate the feasibility and effectiveness of thoracoscopic pulmonary segmentectomy in patients with early peripheral NSCLC.

This was a retrospective study of patients with early peripheral NSCLC admitted between January 2013 and January 2017. Patients were divided into the segmentectomy and lobectomy groups (40/group), according to the surgery they underwent. Blood loss, operation time, removal of drainage tube time, inflammatory response after operation, postoperative complications, postoperative lung function, local recurrence, and survival were compared.

Blood loss and removal of drainage tube time were not significantly different between the 2 groups (all \( P > .05 \)). Operation time in the segmentectomy group was longer than in the lobectomy group (\( P < .001 \)). The postoperative interleukin-6, procalcitonin, and C-reactive protein changes in the segmentectomy group were significantly lower than in the lobectomy group (all \( P < .001 \)). The pulmonary function at 2 weeks was significantly reduced in the 2 groups (all \( P < .001 \)), but it was better in the segmentectomy group than in the lobectomy group (all \( P < .05 \)). The 1- and 3-year local recurrence disease-free, and overall survival rates were not significantly different between the 2 groups (all \( P > .05 \)). The multivariable analysis could not identify any factor associated with local recurrence or survival (all \( P > .05 \)).

Thoracoscopic pulmonary segmentectomy and lobectomy are both acceptable for the treatment of early peripheral NSCLC, but segmentectomy was associated with lower postoperative inflammation and better postoperative pulmonary function than lobectomy.

Abbreviations: CRP = C-reactive protein, CT = computed tomography, FEV1 = forced expiratory volume in 1 second, FEV1% = percentage of forced expiratory volume in 1 second, FVC = forced vital capacity, IL-6 = interleukin-6, NSCLC = non-small cell lung cancer, PCT = procalcitonin.

Keywords: non-small cell lung cancer, survival, thoracoscopic pulmonary lobectomy, thoracoscopic pulmonary segmentectomy

1. Introduction
Lung cancer is one of the malignant tumors with the highest incidence and mortality rates, with about 1,100,000 new cases every year.\[^{[1]}\] About 85% to 90% of all cases are non-small cell lung cancer (NSCLC).\[^{[1,2]}\] Most patients are men \( > 65 \) years of age, and 85% to 90% of the cases of NSCLC are caused by cigarette smoking.\[^{[2,3]}\] In China, NSCLC is the first cause of cancer-related death.\[^{[4]}\]

According to the NCCN, patients with early NSCLC (stage I-II, ie, with negative mediastinal lymph nodes) and who can withstand surgery should be considered for surgery and lymph node dissection.\[^{[5]}\] Sublobar resection (segmentectomy and wedge resection) is appropriate in selected patients.\[^{[6,7]}\] Sleeve lobectomy can reduce mortality compared with pneumonectomy.\[^{[8]}\] Neoadjuvant chemotherapy does not improve survival for stage I-II NSCLC, whereas adjuvant chemotherapy and radiotherapy may improve patient outcome.\[^{[9]}\]

Thoracoscopic minimally invasive pulmonary lobectomy is characterized by a small incision, fast recovery, and a small impact on postoperative lung function.\[^{[7,8,9]}\] It has become the standard surgical procedure for the treatment of malignant lung tumors.\[^{[5]}\] Recently, it has been reported that for patients with early peripheral NSCLC, minimally invasive thoracoscopic pulmonary segmentectomy could improve lung function and achieve good efficacy in patients with stage 1A NSCLC.\[^{[11]}\] Patients with small nodules showing ground-glass opacity\[^{[12]}\] patients with benign lung disease, and patients with small NSCLC.\[^{[13,14]}\]

Nevertheless, the outcomes of minimally invasive thoracoscopic pulmonary segmentectomy still need to be defined in a wide selection of patients. Therefore, this study aimed to...
investigate the feasibility and effectiveness of thoracoscopic pulmonary segmentectomy in patients with early peripheral NSCLC. The results could provide additional choices for surgery in those patients.

2. Material and methods

2.1. Study design and patients

This was a retrospective study of the patients with early peripheral NSCLC admitted to the People’s Hospital of Yuxi City between January 2013 and January 2017. The study was approved by the ethics committee of the People’s Hospital of Yuxi City. The need for individual consent was waived by the committee because of the retrospective nature of the study.

The inclusion criteria were: ≥18 years of age; with surgical indication, no other primary tumor, no metastasis, and no obvious absolute surgical contraindication; and postoperative pathology confirmed the cancer as stage pTlaN0M0, clinical TNM stage I. The exclusion criteria were: active tuberculosis or tuberculosis cavity; extensive pleural adhesion; previous chest surgery; no lung function data at 1 day before or 2 weeks after surgery; or no survival data at 1 and 3 years.

The surgical indications were (1+2 or 1+3 had to be met): pulmonary space-occupying lesion and irregular margin with burr and with lobulated shape found in preoperative thin-section computed tomography (CT); malignant tumor confirmed by preoperative fiberoptic bronchoscopy brushing, bronchus lavage, or biopsy; and malignant tumor was confirmed by percutaneous lung puncture under CT guidance.

The patients who underwent pulmonary segmentectomy were frequency-matched 1:1 based on age and sex with those who underwent pulmonary lobectomy.

2.2. Surgery in the two groups

All patients were operated by the same surgeon (20 years of experience in thoracic surgery) under general anesthesia. Through dual-lumen tracheal intubation, the diseased lung was collapsed. The patients were placed in the lateral position. An incision of 3 cm was made in the 3rd or 4th intercostal space at the anterior axillary line. An incision of 1.5 cm was made in the 7th intercostal space at the mid-axillary line. An incision of 1.5 cm was made in the 8th intercostal space at the posterior axillary line as the auxiliary operation port. Hook-wire localization was performed under CT guidance before surgery for patients with pulmonary ground-glass opacity or small nodules that were difficult to observe intraoperatively.

Pulmonary wedge resection refers to placing long vascular forceps on both sides of the lung lesion and using a thoracoscopic cutter to remove the tumor. It was performed for pathological diagnosis using frozen sections. If the result of the pathological examination was malignancy, surgery (lobectomy or segmentectomy) was continued based on the location of the tumor.

2.3. Segmentectomy

Segmentectomy was performed routinely after pulmonary wedge resection. The tumor was resected with a >2-cm margin. An intrathoracic drain was placed in the 7th intercostal space at the mid-axillary line after surgery.

2.4. Lobectomy

Wedge resection was performed, followed by routine pulmonary lobectomy after the pathological examination suggested malignancy. An intrathoracic drain was placed in the 7th intercostal space at the mid-axillary line after surgery. Regarding lymph nodes, the dissection range of mediastinal lymph node on the right side included the 2, 3, 4, 7, 8, 9, 10, and 11 groups; on the left side, the dissection included the 4, 5, 6, 7, 8, 9, 10, and 11 groups.

2.5. Data collection

Intraoperative blood loss, operation time, removal of thoracic drainage tube time, inflammatory biomarkers (interleukin 6 [IL-6], procalcitonin [PCT], C-reactive protein [CRP]) 3 days after surgery, and postoperative complications (postoperative pulmonary air leakage, pulmonary infection, and incision infection) were extracted from the medical charts. Lung function changes at 2 weeks were compared: forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), and percentage of forced expiratory volume in 1 second (FEV1%) at 1 day before surgery and 2 weeks after surgery. Recurrence was observed by CT at 12 and 36 months.

Postoperative complications referred to the occurrence of any condition or disease that resulted from the operation. Surgery-related infection included pulmonary infection that occurred immediately after surgery (mostly due to a preexisting chronic infection, aspiration, or atelectasis), and pulmonary infection that occurred at a later stage (mostly ventilator-associated pneumonia). The disease-free survival rate was defined as the proportion of patients still alive and without a positive test indicating disease recurrence at 1 and 3 years. The overall survival rate was defined as the proportion of patients still alive at 1 and 3 years.

2.6. Statistical analysis

SPSS 22.0 (IBM, Armonk, NY) was used to analyze the data. Continuous data are expressed as means ± standard deviations and were analyzed using the Student t test. Categorical data are expressed as proportions and were analyzed using the χ² or Fisher exact test. Demographic and clinical factors thought to potentially affect survival based on the literature and experience (surgical method, age, sex, pathological type, TNM stage, family history, and smoking history) were entered as independent variables in a multivariable logistic regression analysis, with overall survival or disease-free survival as the dependent variable. Two-sided P values <.05 were considered statistically significant.

3. Results

3.1. Characteristics of the patients

Forty patients underwent thoracoscopic pulmonary segmentectomy (segmentectomy group) during the study period and were frequency-matched with 40 patients who underwent thoracoscopic pulmonary lobectomy (lobectomy group). In the segmentectomy group, there were 25 (62.5%) men and 15 (37.5%) women. The patients were 42 to 73 years of age (59.7 ± 9.5 years). Thirteen (32.5%) patients had adenocarcinoma, and 27 (67.5%) had squamous cell carcinoma. Fourteen (35.0%) patients smoked. In the lobectomy group, there were 23 (57.5%) men and 17 (42.5%) women. They were 45 to 73
Intraoperative blood loss, mL 222 ± 46 vs 220 ± 45, <.001). The operation time in the segmentectomy group was longer than in the lobectomy group (185 ± 43 vs 122 ± 18 min, <.001). The length of stay was shorter in the segmentectomy group than in the lobectomy group (6.6 ± 1.2 vs 10.7 ± 1.5 days, <.001). The IL-6, PCT, and CRP levels 3 days after surgery in the segmentectomy group were significantly lower than in the lobectomy group (all P < .001). There were no significant differences in postoperative pulmonary air leakage, postoperative pulmonary infection, and the occurrence of postoperative incision infection between the 2 groups (all P > .05) (Table 2).

### Table 2

**Operative characteristics.**

|                         | Segmentectomy group (n = 40) | Lobectomy group (n = 40) | P       |
|-------------------------|------------------------------|--------------------------|---------|
| Intraoperative blood loss, mL | 222 ± 46                     | 220 ± 45                 | .900    |
| Time of operation, min   | 185 ± 43                     | 122 ± 18                 | <.001   |
| Sampled lymph nodes, n/patient | 7.7 ± 2.2                   | 8.2 ± 2.2                | .312    |
| Removal of drainage tube time, days | 5.0 ± 1.5                   | 5.1 ± 1.3                | .754    |
| Length of stay, days     | 6.6 ± 1.2                    | 10.7 ± 1.5               | <.001   |
| IL-6, ng/L               | 9.37 ± 2.85                  | 15.0 ± 4.58              | <.001   |
| PCT, ng/L                | 1.70 ± 0.76                  | 3.10 ± 1.39              | <.001   |
| CRP, ng/L                | 38.32 ± 9.84                 | 64.15 ± 15.05            | <.001   |
| Pulmonary air leakage, n (%) | 6 (15.0)                    | 2 (5.0)                  | .649    |
| Pulmonary infection, n (%) | 8 (20.0)                     | 6 (15.0)                 | .483    |
| Postoperative incision infection, n (%) | 4 (10.0)               | 2 (5.0)                  | .402    |
| Readmission, n (%)       | 0                           | 0                        | —       |

*CRP = C-reactive protein, IL-6 = interleukin 6, PCT = procalcitonin.

#### 3.2. Operative data

No operation was converted to thoracotomy. There were no significant differences in intraoperative blood loss, removal of thoracic drainage tube time between the 2 groups, and the numbers of sampled lymph nodes (both P > .05). The operation time in the segmentectomy group was longer than in the lobectomy group (185 ± 43 vs 122 ± 18 min, <.001). The length of stay was shorter in the segmentectomy group than in the lobectomy group (6.6 ± 1.2 vs 10.7 ± 1.5 days, <.001). The IL-6, PCT, and CRP levels 3 days after surgery in the segmentectomy group were significantly lower than in the lobectomy group (all P < .001). There were no significant differences in postoperative pulmonary air leakage, postoperative pulmonary infection, and the occurrence of postoperative incision infection between the 2 groups (all P > .05) (Table 2).

#### 3.3. Lung function reduction at 2 weeks

Before surgery, there were no differences between the 2 groups in pulmonary function (Table 1 and Fig. 1). Compared with the lung function (FVC; FEV1; FEV1%) before surgery, the function at 2 weeks was significantly reduced in the 2 groups (all P < .001), but was better in the segmentectomy group than in the lobectomy group (FVC: P < .001; FEV1: P < .001; FEV1%: P = .027) (Fig. 1).

#### 3.4. One- and 3-year survival

There was no readmission. The 1- and 3-year local recurrence rate, disease-free survival, and overall survival were not significantly different between the 2 groups (P > .05) (Table 3).

#### 3.5. Multivariable analysis

The surgical method, age, sex, pathological type, TNM stage, family history, and smoking history were not independently associated with local recurrence or survival (all P > .05) (Tables 4–6).

#### 4. Discussion

The outcomes of minimally invasive thoracoscopic pulmonary segmentectomy for NSCLC still need to be defined in a wide selection of patients. This study aimed to investigate the feasibility and effectiveness of thoracoscopic pulmonary segmentectomy in...
patients with early peripheral NSCLC. The results suggest that thoracoscopic pulmonary segmentectomy and lobectomy are both acceptable for the treatment of early peripheral NSCLC, but segmentectomy was associated with lower postoperative inflammation and better postoperative pulmonary function than lobectomy.

The pathogenesis of lung cancer is very complex, and no preventive action can reduce the incidence of lung cancer except avoiding smoking.\[17,18\] Once NSCLC occurs, only surgery and, in some cases, chemotherapy, targeted therapy, and radiation therapy can improve outcomes.\[19\] Video-assisted thoracoscopic lobectomy has been widely used.\[19,20\] It has been reported that for early peripheral NSCLC, thoracoscopic pulmonary lobectomy and thoracotomy have no significant difference in the improvement of lung function or survival.\[21\]

Compared with thoracoscopic pulmonary lobectomy, thoracoscopic pulmonary segmentectomy is a more elaborate and complicated surgery in which pulmonary segment vessels and bronchi are dissociated and processed along through a small incision (3–4 cm) without an expander.\[11,14,22,23\] It has been hypothesized that for patients with early peripheral NSCLC with lesion <2 cm (stage IA), thoracoscopic pulmonary segmentectomy could reduce the loss of lung function and improve the postoperative quality of life.

In the present study, the operation time in the segmentectomy group was higher than in the lobectomy group. The main reason is probably that pulmonary segmentectomy needs a precise understanding of the distribution of the pulmonary vessels and location of pulmonary segment bronchi. The complicated dissection and structural variation of the vessels and bronchi require high operative technique. Thus, operation time was longer than for pulmonary lobectomy. On the other hand, regarding postoperative inflammatory biomarkers, pulmonary segmentectomy was significantly better than pulmonary lobectomy. The possible reason is that the resected pulmonary tissues were smaller, and the incision was smaller, which significantly reduced the occurrence of postoperative inflammation. Nevertheless, there was no significant difference in the postoperative complications between the 2 groups, suggesting that the differences in inflammation were subclinical.

Importantly, the comparison of the changes in lung function between the 2 groups indicated that the lung function indices (FVC, FEV1, and FEV1%) were reduced at 2 weeks compared with baseline in the 2 groups, which is to be expected, but the reduction was smaller with pulmonary segmentectomy than with pulmonary lobectomy. It has been reported that pulmonary segmentectomy has a small change on the lung function of patients with early peripheral NSCLC, and is conducive to protecting postoperative lung function.\[11,14,22,23\]

There are many studies on the postoperative survival rate of patients with early peripheral NSCLC after thoracoscopic pulmonary segmentectomy. Pulmonary lobectomy could not significantly improve the 5-year survival rate of patients.\[5,11–14,22,23\] The present study showed that the 2 surgical procedures did not lead to significant differences in 1- and 3-year survival rates.

The present study has limitations. It was a retrospective study with a small sample and from a single center, and the follow-up was short. Importantly, there was no randomization, and an inherent selection bias for the type of surgery might exist. The patients without follow-up data at 1 and 3 years were excluded, which could lead to some bias. Frequency matching was used to match the two groups, but propensity score matching would have been better. This approach was not possible in the present study.

### Table 3

| Local recurrence and survival at 1 and 3 years. | Segmentectomy group (n = 40) | Lobectomy group (n = 40) | P |
|---|---|---|---|
| Local recurrence rates |  |  |  |
| 1-year | 1 (2.5%) | 2 (5%) | .582 |
| 3-year | 7 (17.5%) | 6 (15%) | .290 |
| Disease-free survival rates |  |  |  |
| 1 y | 38 (95.0%) | 37 (92.5%) | .644 |
| 3 y | 29 (72.5%) | 30 (75.0%) | .620 |
| Overall survival rates |  |  |  |
| 1 y | 40 (100%) | 40 (100%) | 1.000 |
| 3 y | 37 (92.5%) | 35 (87.5%) | .179 |

### Table 4

#### Multivariable logistic regression of local recurrence at 3 years.

| OR (95% CI) | P |
|---|---|
| Sex | 0.205 (0.038–1.090) | .063 |
| Female vs male |  |  |
| Age | 0.992 (0.926–1.062) | .813 |
| Pathological type |  |  |
| Adenocarcinoma vs squamous cell carcinoma | 0.958 (0.255–3.600) | .950 |
| TNM stage |  |  |
| IA2 vs IA1 | 1.971 (0.499–7.792) | .333 |
| Surgical method |  |  |
| Lobectomy vs segmentectomy | 0.779 (0.200–3.033) | .719 |
| Smoking |  |  |
| No vs yes | 0.990 (0.212–4.620) | .989 |
| Family history |  |  |
| No vs yes | 0.836 (0.223–3.128) | .790 |

\* 95\% CI=95\% confidence interval, OR=odds ratio.

\* The 8th edition TNM stage classification for lung cancer was used.
because of the limited number of available controls (lobectomy). A recent study of robotic anatomic segmentectomy describes the learning curve associated with segmentectomy with cutoff values and proficiency at 21 and 46 procedures.\cite{12,13} Since the present study included 40 cases of segmentectomy, it is possible that the data do not represent the true success of segmentectomy. Nevertheless, the present study may suggest that segmentectomy does not result in worse outcomes than lobectomy. However, the cases included here were not operated using a robot, but by a surgeon with >20 years in thoracic surgery. A prospective trial should overcome these limitations.

Based on the available data, thoracoscopic pulmonary segmentectomy and lobectomy are both acceptable for the treatment of early peripheral NSCLC, but segmentectomy was associated with lower postoperative inflammation and better postoperative pulmonary function than lobectomy. There was no difference in 3-year survival between the 2 procedures.

### Author contributions

Mingsheng Ma, Fan He contributed to the conception of the study; Xiangyang Lv, Sizeng Dong contributed significantly to analysis and manuscript preparation; Mingsheng Ma, Xiaoyan Wang performed the data analyses and wrote the manuscript; Chao Liu, Cuiping Zhou, helped perform the analysis with constructive discussions.

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