Original Article
Efficacy and safety of thoracoscopic resection for early-stage non-small cell lung cancer

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Abstract: Objective: To explore the efficacy and safety of thoracoscopic resection for early-stage non-small cell lung cancer (NSCLC). Methods: A total of 110 patients with early-stage NSCLC admitted to Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology between August 2017 and December 2019 were enrolled and retrospectively analysed. Among them, 60 patients receiving thoracoscopic resection for lung cancer (LC) were assigned to the research group (Res group) and another 50 patients treated with routine open radical resection for LC were included in the control group (Con group). The following items of the two groups were evaluated and compared: treatment efficacy, operation indexes, VAS score, lung function, lung capacity, complications, 2-year tumour-free survival rate, 2-year survival rate, and quality of life (QoL). Results: The Res group showed significantly better efficacy, and lower incidence of complications and VAS score than the Con group. In addition, patients in the Res group experienced less intraoperative blood loss, earlier anal exhaust, shorter hospital stay and indwelling time of drainage tube as well as less drainage volume. Furthermore, better recovery in pulmonary function and lung capacity, and significantly higher 2-year tumour-free survival rate, 2-year survival rate as well as postoperative QoL were noted in the Res group compared with the Con group. Conclusion: Thoracoscopic resection for LC is effective in the treatment of patients with early-stage NSCLC. It can substantially shorten the hospital stay and indwelling time of drainage tube and reduce drainage volume and blood loss, with high safety.

Keywords: Thoracoscopic resection for lung cancer, early-stage non-small cell lung cancer, efficacy, safety

Introduction

Non-small cell lung cancer (NSCLC) is a common malignant tumour that accounts for approximately 80% of all lung cancer (LC) cases [1], which can be classified into squamous cell carcinoma, adenocarcinoma, etc., with the characteristics of slow diffusion and metastasis as well as long growth and division time of cancer cells. For patients with middle and advanced-stage NSCLC, 5-year survival can hardly be ensured, so it is of great importance to make early diagnosis and treatment [2, 3]. Compared with small cell cancer, NSCLC cells grow and divide more slowly, and spread and metastasize later, leading to concealment of early symptoms [4]. Currently, even early-stage NSCLC is classified as a common malignant tumor, with an annually growing incidence, posing a threat to the life of patients. Surgery

remains the mainstay of treatment for NSCLC [5].

Surgical therapy is the preferred option against early-stage NSCLC and the only possible cure for the disease [6]. In patients with early-stage NSCLC, most lymph nodes do not metastasize due to limited lesion location. Early-stage NSCLC is mostly a carcinoma in situ or micro-invasive carcinoma, especially in cases with increased small nodules and frosted-glass-like shadows. The early-stage NSCLC can be treated by radical resection that allows for the elimination of lesions and surrounding lymph nodes with a cure rate of 100% [7]. There are many ways to implement radical resection for LC. Previously, open radical resection for LC was commonly used, which can completely remove the diseased tissues of LC. However, this procedure has been gradually abandoned due to its

great damage to the lungs and the possibility of increasing complications caused by frequent contact between thoracic organs and air in addition to more bleeding [8, 9]. With the continuous development of modern endoscopic technology, thoracoscopic resection for LC has been gradually applied in treatment of NSCLC, bringing great benefits to patients with early-stage NSCLC. It can significantly reduce pain and blood loss, and increase the safety profile of surgery, with higher acceptance by patients [10].

In order to further analyze the efficacy and safety of thoracoscopic resection for early-stage NSCLC, 110 patients with early-stage NSCLC were enrolled for a comparative study to understand the effect of thoracoscopic resection on clinical efficacy and patient prognosis.

Materials and methods

Clinical data

A total of 110 patients with early-stage NSCLC admitted to the Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology during August 2017 and December 2019 were enrolled and their clinical data were retrospectively analysed. Among them, there were 61 male patients and 49 female patients with an average age of (61.22±4.23) years old. 60 patients treated by thoracoscopic resection for LC were assigned to the research group (Res group), and another 50 patients receiving routine open radical resection for LC were included in the control group (Con group).

Inclusion criteria: (1) Patients meeting the diagnostic criteria for early-stage NSCLC developed by the World Health Organization (WHO) based on imaging and pathologic examination [11]; (2) Patients with TNM stage I or II; (3) Patients with complete case data preservation.

Exclusion criteria: (1) Patients with coagulation abnormalities; (2) Patients with mental diseases or consciousness disorders; (3) Patients unable to communicate due to language or cognition dysfunction; (4) Patients with other major somatic diseases; (5) Patients who had received chemotherapy or radiotherapy before operation; (6) Patients with a life expectancy less than 6 months; (7) Patients with abnormal liver or kidney function; (8) Lactating and pregnant women; (9) Patients with other tumors.

All patients signed the informed consent before participating in the study. The study was approved by the Ethics Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (TJ-IRB-20220329) and was conducted in conformity with the *Declaration of Helsinki*.

Treatment methods

Both groups were anesthetized by double-lumen endotracheal catheter intubation. Each patient maintained a 90° recumbent position on the unaffected side, and the lung of the unaffected side was ventilated and let to lean forward slightly. Upper limbs of the operation side were suspended from the anesthesia head frame, and the skin was disinfected and covered with a disinfection towel.

The Con group was given traditional thoracotomy. A surgical incision was made at the 5th intercostal space with a length of approximately 25 cm. Then, an electric knife was used to cut open the subcutaneous and thoracic muscles successively, as well as the latissimus dorsi and intercostal muscles, through which a distractor was used to stretch the intercostal space into the chest, so that the resection range covered all the lung lobes where the tumor would be removed. Lymph nodes were also dissected. Then 0.9% sodium chloride injection was used to rinse the patient's chest. After confirmation of complete hemostasis, closed thoracic drainage, instrument counting, dressing and incision suture were performed. Antibiotics were given for 3-4 days after the operation to prevent infection.

The Res group received thoracoscopic resection for LC. Specifically, the patient was asked to lie on the unaffected side and treated with combined intravenous and inhalation anesthesia after skin preparation and draping. With a thoracoscope, the blood vessels and bronchi were ligated under one-lung ventilation so that the pulmonary lobes could be removed. A 1 cm cannula was placed in the 7th intercostal space of the midaxillary line, and the 8th intercostal space of the posterior axillary line was selected to create a 2 cm incision. The 4th intercostal space of the anterior axillary line was

selected to make a 4 cm incision. Then, an oval forceps was carefully and slowly placed from the patient's incision, pulling the lungs backward to fully expose the pulmonary veins. During excision of the pulmonary lesions, the pulmonary veinwas treated first and then the hilum was treated from front to back. During the removal of the lower lobe, the patient's pulmonary ligaments was first treated, and the pulmonary veins was mechanically closed. The lesion was removed by anatomical lobectomy, and the lymph nodes around the lesion were effectively cleared. After that, a thoracic drainage tube was accurately placed according to the resection of the patient. Finally, the patient's pleura and intercostal muscles were carefully closed under the direct vision of the thoracoscope, and the incision was sutured. Postoperative antibiotics were given for 3-4 days to prevent infection.

Outcome measures

(1) The short-term efficacy of the two groups within 6 months after surgery was evaluated based on the Response Evaluation Criteria in Solid Tumours (RECIST 1.0) developed by the WHO [12]. The effective rate of treatment = complete remission (CR) + partial remission (PR). The evaluation criteria were as follows: CR: the tumour lesion completely disappeared for ≥4 weeks; PR: the reduction of lesion volume was ≥50%; stable disease (SD): during 4 weeks, the lesion volume was reduced <50% or increased <25%, with no new lesions found; progressive disease (PD): the lesion volume increased >25% or new lesions were found. (2) The intraoperative blood loss, time to anal exhaust, and length of hospital stay of the two groups were recorded and compared. Less intraoperative blood loss and shorter hospital stay indicate better performance of the surgery. (3) The indwelling times of the drainage tube and total drainage volume of the two groups were evaluated and compared. (4) The pain degree of two groups before and 3 days after operation was evaluated using the Visual Analogue Scale (VAS). On a 10-point scale, lower scores indicate milder pain. (5) The pulmonary function indexes including forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV1) of the two groups before surgery and at 1 month after surgery were evaluated. More significant postoperative improve-

ment of pulmonary function indexes indicates better performance of the surgery. (6) Lung volume-related indicators, including total lung capacity (TLC) and residual volume (RV), were compared between the two groups before surgery and one month after surgery. (7) The incidence of complications in the two groups during hospitalization was recorded and compared, including pulmonary atelectasis, incision infection, pneumothorax and thoracic infection. (8) The tumor-free survival (TFS) rate and 2-year survival rate of the two groups were compared. Each patient was regularly followed up by re-examination in hospitals, telephone, and SMS until patient death or December 31, 2021, whichever occurred first. (9) At 6 months after surgery, patients' quality of life (QoL) was assessed using the EORTC Core Quality of Life Questionnaire (QLQ-C30) [13] from the dimensions of body function, role function, emotional function, cognitive function, and social function. Higher scores indicate better QoL.

Statistical analysis

In this study, data were analyzed by SPSS18. 0 (IBM) and visualized using GraphPad Prism 8. The Chi-square test and independent samples t-test were adopted to analyze counted data and measured data, respectively. The log-rank test was used for survival analysis, and the Kaplan-Meier was used for drawing of survival curves. P<0.05 was considered a significant difference.

Results

Comparison of general data

There was no significant difference in general data such as gender, age and smoking history between the two groups (P>0.05), suggesting the two groups were comparable (**Table 1**).

Comparison of efficacy between the two groups

The number of patients with CR, PR, SD, and PD in the Res group was 27, 27, 5, and 1, respectively, while the numbers in Con group was 13, 20, 12, and 5, respectively. Therefore, the Res group showed a notably higher total effective rate than the Con group (90.00% *vs.* 66.00%, **Table 2**).

Table 1. General data [n (%)]

Factor	Research group (n=60)	Control group (n=50)	t/X^2	P
Gender			0.443	0.506
Male	35 (58.33)	26 (52.00)		
Female	25 (41.67)	24 (48.00)		
Age (years)			0.060	0.807
≤61	31 (51.67)	27 (54.00)		
>61	29 (48.33)	23 (46.00)		
BMI (kg/m^2)			0.121	0.728
≤23	28 (46.67)	25 (50.00)		
>23	32 (53.33)	25 (50.00)		
Smoking history			0.216	0.642
Yes	42 (70.00)	37 (74.00)		
No	18 (30.00)	13 (26.00)		
Clinical stage			0.185	0.667
Stage I	36 (60.00)	32 (64.00)		
Stage II	24 (40.00)	18 (36.00)		
Pathologic type			0.097	0.923
Squamous carcinoma	17 (28.33)	14 (28.00)		
Adenocarcinoma	23 (38.33)	18 (36.00)		
Other	20 (33.33)	18 (36.00)		
Tumour location			0.019	0.881
Left lung	32 (53.33)	26 (52.00)		
Right lung	28 (46.67)	24 (48.00)		

Table 2. Comparison of efficacy between the two groups [n (%)]

Efficacy	Research group (n=60)	Control group (n=50)	X^2	P-value
Complete remission	27 (45.00)	13 (26.00)	-	-
Partial remission	27 (45.00)	20 (40.00)	-	-
Stable disease	5 (8.33)	12 (24.00)	-	-
Progressive disease	1 (1.67)	5 (10.00)	-	-
Total effective rate	54 (90.00)	33 (66.00)	9.499	0.002

Table 3. Comparison of intraoperative blood loss, time to anal exhaust, and hospital stay between the two groups

Item	Research group (n=60)	Control group (n=50)	t	P-value
Intraoperative blood loss (ml)	26.1±1.26	81.12±3.22	121.7	<0.001
Time to anal exhaust (h)	23.84±1.18	56.15±2.41	91.56	<0.001
Hospital stay (d)	7.05±0.65	16.28±1.54	42.17	<0.001

Comparison of intraoperative blood loss, time to anal exhaust, and length of hospital stay between the two groups

According to the results, the Res group showed significantly less intraoperative blood loss and experienced earlier anal exhaust and shorter hospital stay than the Con group (all P<0.05, **Table 3**).

Comparison of indwelling time of drainage tube and total drainage volume between the two groups

It was found that the indwelling time of drainage tube was shorter and the total drainage volume was less in the Res group compared with the Con group (both P<0.05, **Table 4**).

Comparison of VAS scores between the two groups before and 3 days after surgery

Before surgery, no significant difference was observed in VAS scores between the two groups (P>0.05); while 3 days after surgery, the VAS score decreased in both groups compared with that before treatment, and was lower in the Res group compared with the Con group (P<0.05, **Table 5**).

Comparison of pulmonary function indexes between the two groups before surgery and at 1 month after surgery

Before surgery, the two groups showed no significant difference in pulmonary function indexes (all P>0.05). After surgery, FVC and FEV$_1$ improved significantly in both groups, with a better improvement in the Res group compared to the Con group (P<0.05, **Figure 1**).

Comparison of lung volume indexes between the two groups before and 1 month after surgery

No significant difference was observed in various lung volume indexes between the two

Table 4. Comparison of indwelling time of drainage tube and total drainage volume between the two groups

Item	Research group (n=60)	Control group (n=50)	t	P-value
Indwelling time of drainage tube (d)	5.13±0.76	7.14±0.41	16.77	<0.001
Total drainage volume (ml)	1013.11±38.29	1253.4±54.85	26.96	<0.001

Table 5. Comparison of VAS scores before and after surgery between the two groups

Time	Research Group n=60	Control Group n=50	t	P
Before surgery	4.36±0.4	4.3±0.42	0.766	0.446
3 days after surgery	2.34±0.36	3.3±0.37	13.75	<0.001

groups before surgery (P>0.05). After surgery, TLC and RV of both groups were decreased, and those of the Res group were significantly higher compared with the Con group (P>0.05, **Figure 2**).

Comparison of the incidence of complications between the two groups during hospitalization

The Res group showed an incidence of adverse reactions of 6.67%, including 2 patients with pulmonary atelectasis and 2 patients with incision infection. In the Con group, there were 4 cases of pulmonary atelectasis, 4 cases of incision infection, 3 cases of pneumothorax, and 3 cases of thoracic infection, with an incidence of adverse reactions of 28.00%. Therefore, the incidence of adverse reactions in the Res group was significantly lower than that of the Con group (P<0.01, **Table 6**).

Comparison of 2-year TFS rate and 2-year survival rate between the two groups

The Res group showed a 2-year TFS rate of 83.33% (50/60), which was 62% (31/50) in the Con group, indicating the 2-year TFS rate of the Res group was significantly higher than that of the Con group (P<0.05). The Res group showed a 2-year overall survival (OS) rate of 88.33% (53/60), and that was 72.00% (36/50) in the Con group, indicating a 2-year OS rate of the Res group that was significantly higher than that of the Con group (P<0.05, **Figure 3**).

Comparison of QoL between the two groups after surgery

Compared with the Con group, the QoL of the Res group in body function, role function, emo-

tional function, cognitive function, and social function were all significantly improved (all P<0.05, **Table 7**).

Discussion

NSCLC is a common malignant tumor in clinical scenarios with complicated pathogenesis, that is associated with smoking, ionizing radiation, air pollution, heredity, and occupational environment [14]. Instead of obvious chest pain, patients with early-stage NSCLC mainly suffer stuffy and vague pain. Capillary breakage is accompanied by a small amount of bleeding, and its mix with sputum will cause intermittent bloody phlegm. In addition, most patients with NSCLC will develop low fever and cough, which can be temporarily relieved by medication, but the recurrence rate is high [15]. Most patients are likely to ignore the disease at the early stage and pay attention to it only when the disease has progressed to the middle and late stages with obviously body reduction and aggravated symptoms such as dyspnea and hemoptysis, missing the optimal timing for treatment [16]. Therefore, timely and effective therapy is crucial for patients with early-stage NSCLC. In patients with early-stage NSCLC, most do not get lymph node metastasis due to limited lesion location. As mentioned earlier, early-stage NSCLC is mostly early carcinoma in situ or micro-invasive carcinoma, especially in cases with increases of small nodules and frosted-glass-like shadows, which can be treated by radical resection to remove the lesions and the surrounding lymph nodes so that patients may get a 100% complete cure [17, 18].

Surgery is the preferred option for clinical treatment of early-stage NSCLC [19]. Despite certain efficacy, traditional thoracotomy has many disadvantages and is highly traumatic for patients. For thoracotomy, a 20-30 cm incision should be made from the side chest of the patient to the back, and the chest wall muscles such as latissimus dorsi and serratus anterior muscle should be cut off. In addition, thoracot-
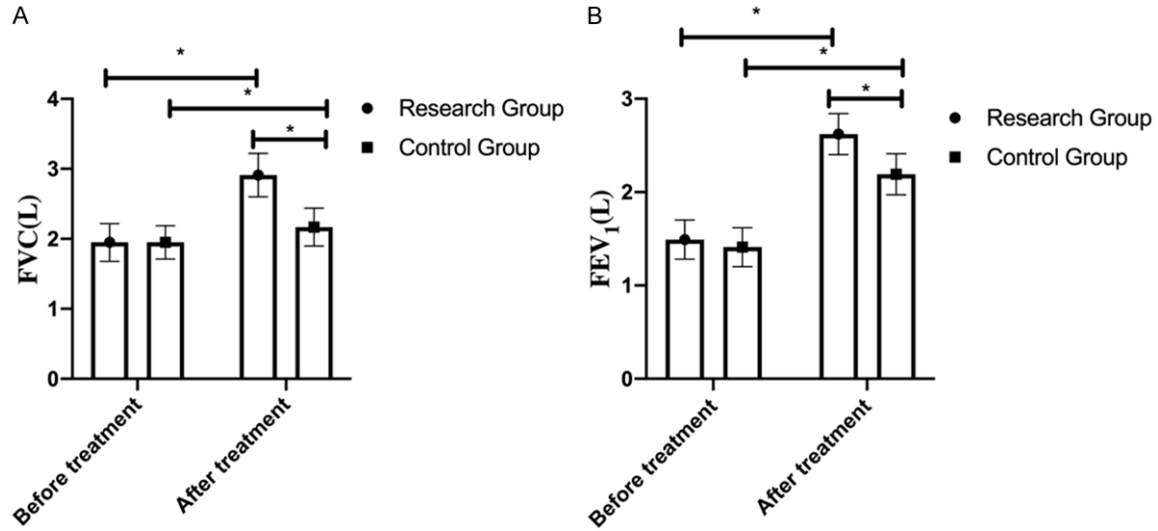
Figure 1. Comparison of pulmonary function indexes between the two groups before surgery and 1 month after surgery. A: Comparison of FVC; B: Comparison of FEV1. * indicates P<0.05.
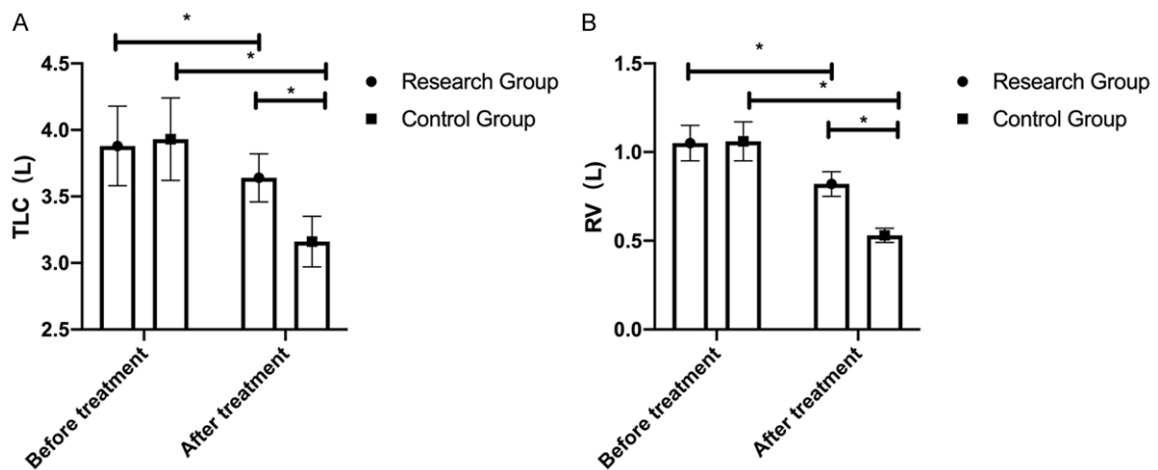
Figure 2. Comparison of lung volume indexes between the two groups before surgery and 1 month after surgery; A: Comparison of TLC; B: Comparison of RV. * indicates P<0.05.

**Table 6.** Comparison of incidence of adverse reactions between the two groups [n (%)]

Complication	Research group (n=60)	Control group (n=50)	χ^2	*P*-value
Pulmonary atelectasis	2 (3.33)	4 (8.00)	-	-
Incision infection	2 (3.33)	4 (8.00)	-	-
Pneumothorax	0	3 (6.00)	-	-
Thoracic infection	0	3 (6.00)	-	-
Incidence of complications	4(6.67)	14 (28.00)	9.069	0.003

omy requires the removal of one or two ribs of the patient to fully expose the tumour tissue to the field of vision, resulting in massive bleeding, severe pain and upper limb and shoulder movement disorder, and consequently an unfavourable prognosis and poor QoL [20, 21].

In recent years, with the constant progress made in thoracoscopic surgery techniques and the maturity of surgical anesthesia, thoracoscopic resection for LC has gradually replaced the traditional thoracotomy
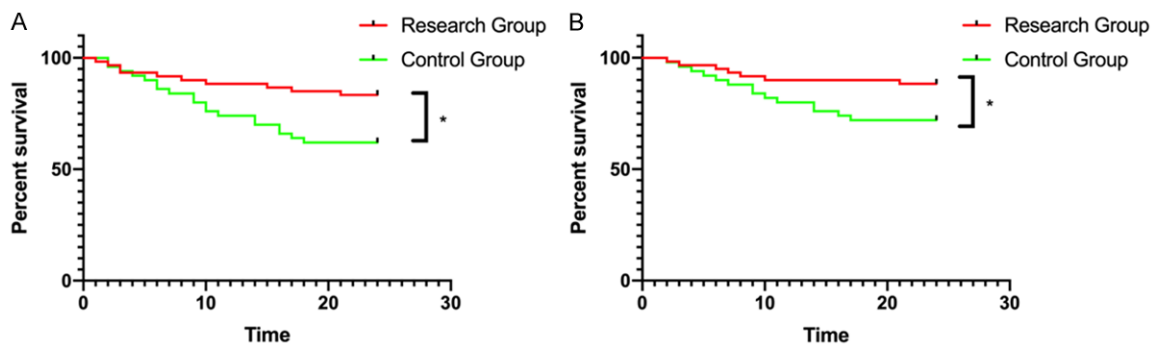
Figure 3. Comparison of 2-year TFS rate and 2-year survival rate between the two groups. A: Comparison of 2-year TFS rate. B: Comparison of 2-year survival rate. * indicates P<0.05.

Table 7. Comparison of QoL between the two groups

Factor	Research group (n=60)	Control group (n=50)	t	P-value
Body function	72.75±2.06	62±2.35	25.56	<0.001
Role function	73.44±2.17	60.81±2.54	28.13	<0.001
Emotional function	73.66±2.29	60.46±2.61	28.25	<0.001
Cognitive function	73.59±2.05	61.09±2.43	29.27	<0.001
Social function	73.26±2.38	61.28±1.97	28.39	<0.001

[22]. This procedure is performed under a clearer vision provided by a thoracoscope, with smaller incision, less intraoperative bleeding, milder pain, lower postoperative infection rate of incision, and faster recovery, contributing to a higher clinical acceptance [23]. In our study, the Res group outperformed the Con group with significantly better surgery outcomes, less intraoperative blood loss, earlier anal exhaust, shorter hospital stay, and indwelling time of drainage tube, as well as less total drainage volume. VAS score results also determined a significantly lower VAS score in the Res group compared with the Con group 3 days after surgery. The results can be explained by the following reasons: Thoracoscopic surgery causes a small incision and does not pull the ribs of patients too much, which can reduce the muscle injury of patients, and avoid the destruction of intercostal nerves, thus lowering the degree of injury in patients. In addition, under thoracoscopic surgery, the surgical field of vision is clear, which contributes to reduced intraoperative bleeding. Moreover, thoracoscopic surgery can accurately separate lymph nodes while avoiding destroying too many capillaries to reduce the massive loss of lymph fluid, thus reducing thoracic drainage fluid and facilitating

the removal of drainage tubes as soon as possible, which helps patients recover as soon as possible and shortens the hospital stay [24].

In our study, the postoperative pulmonary function of both groups was improved, but the improvement in the Res group was more significant. In addition, surgical treatment had an effect on the lung volume of both groups of patients, but the lung volume-related indexes of the Res group were better when compared with the Con group. Moreover, the Res group showed a higher 2-year TFS rate and experienced significantly higher QoL than the Con group at 6th months postoperatively. The reasons may be as follows: LC itself impairs the patient's lung function, and thoracotomy, which removes a large area of the patient's chest muscles, is likely to cause scarring and chest pain. Also, the intercostal nerve and thoracic dorsal nerve are damaged during the operation, and the ribs of patients are severed, which can destroy the integrity of thoracic cavity. All the above procedures damage the physiological function of patients' respiratory movement and cause restrictive ventilation dysfunction [25]. However, in thoracoscopic surgery, it is not necessary to cut patient's ribs, but only to separate the muscles along the muscle fibers of pectoralis major and serratus anterior muscle, which has less damage to respiratory muscles and is conducive to rapid chest opening and closure. In addition, the application of double-lumen tracheal intubation during surgery leads to collapse to the patient's lung on the affected side so that it is not easy to squeeze and pull the lung tissue

[26]. As a result, the respiratory movement of the patient is less affected and the stress response is relieved. In this study, the Res group showed better postoperative pulmonary function indexes than the Con group. More importantly, the incidence of complications in the Res group was significantly lower. The main reason is that thoracoscopic surgery contributes to less pain in patients after surgery, as well as early cough and sputum removal, which is conducive to reducing the incidence of complications such as pulmonary infection and atelectasis, alleviating postoperative pain, and improving patients' QoL [27].

In sum, for early-stage NSCLC, thoracoscopic resection can not only reduce blood loss, but also effectively reduce the occurrence of complications, thus shortening the hospital stay and reducing the economic burden of patients, which is worthy of clinical application. However, this study also has certain limitations. First, due to the small sample size, relevant conclusions of this study need to be further analyzed in follow-up studies. Second, in addition to surgical factors, it is also necessary to further analyze other factors that can lead to differences in the prognosis of patients. We will conduct in-depth large-sample, multi-center studies in the future to comprehensively analyze the effect of thoracoscopic radical resection for LC on patients with early-stage NSCLC.

Disclosure of conflict of interest

None.

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References

[1] Jonna S and Subramaniam DS. Molecular diagnostics and targeted therapies in non-small cell lung cancer (NSCLC): an update. Discov Med 2019; 27: 167-170.

[2] Broderick SR. Adjuvant and neoadjuvant immunotherapy in non-small cell lung cancer. Thorac Surg Clin 2020; 30: 215-220.

[3] Pennell NA, Arcila ME, Gandara DR and West H. Biomarker testing for patients with advanced non-small cell lung cancer: real-world issues and tough choices. Am Soc Clin Oncol Educ Book 2019; 39: 531-542.

[4] Sankar K, Gadgeel SM and Qin A. Molecular therapeutic targets in non-small cell lung cancer. Expert Rev Anticancer Ther 2020; 20: 647-661.

[5] Arbour KC and Riely GJ. Systemic therapy for locally advanced and metastatic non-small cell lung cancer: a review. JAMA 2019; 322: 764-774.

[6] Aokage K, Yoshida J, Hishida T, Tsuboi M, Saji H, Okada M, Suzuki K, Watanabe S and Asamura H. Limited resection for early-stage non-small cell lung cancer as function-preserving radical surgery: a review. Jpn J Clin Oncol 2017; 47: 7-11.

[7] Wu Y, Xu M and Ma Y. Fast-track surgery in single-hole thoracoscopic radical resection of lung cancer. J BUON 2020; 25: 1745-1752.

[8] Mimae T and Okada M. Are segmentectomy and lobectomy comparable in terms of curative intent for early stage non-small cell lung cancer? Gen Thorac Cardiovasc Surg 2020; 68: 703-706.

[9] Suzuki S and Goto T. Role of surgical intervention in unresectable non-small cell lung cancer. J Clin Med 2020; 9: 3881.

[10] Huang W, Liu J, Liang W, Shao W, Lan Z, Jiang L, Mo L, Gonzalez-Rivas D and He J. Outcome and safety of radical resection in non-small cell lung cancer patients via glasses-free 3-Dimensional video-assisted thoracoscope versus 2-dimensional video-assisted thoracoscope. Surg Innov 2018; 25: 121-127.

[11] Osmani L, Askin F, Gabrielson E and Li QK. Current WHO guidelines and the critical role of immunohistochemical markers in the subclassification of non-small cell lung carcinoma (NSCLC): moving from targeted therapy to immunotherapy. Semin Cancer Biol 2018; 52: 103-109.

[12] Kim JH. Comparison of the RECIST 1.0 and RECIST 1.1 in patients treated with targeted agents: a pooled analysis and review. Oncotarget 2016; 7: 13680-13687.

[13] Husson O, de Rooij BH, Kieffer J, Oerlemans S, Mols F, Aaronson NK, van der Graaf WTA and van de Poll-Franse LV. The EORTC QLQ-C30 summary score as prognostic factor for survival of patients with cancer in the "Real-World": results from the population-based PROFILES registry. Oncologist 2020; 25: e722-e732.

[14] Rafei H, El-Bahesh E, Finianos A, Nassereddine S and Tabbara I. Immune-based therapies for non-small cell lung cancer. Anticancer Res 2017; 37: 377-387.

[15] Hsu ML and Naidoo J. Principles of immunotherapy in non-small cell lung cancer. Thorac Surg Clin 2020; 30: 187-198.

[16] Nagano T, Tachihara M and Nishimura Y. Molecular mechanisms and targeted therapies including immunotherapy for non-small cell lung cancer. Curr Cancer Drug Targets 2019; 19: 595-630.

[17] Patel SA and Weiss J. Advances in the treatment of non-small cell lung cancer: immunotherapy. Clin Chest Med 2020; 41: 237-247.

[18] Aoki MN, Amarante MK, de Oliveira CEC and Watanabe MAE. Biomarkers in non-small cell lung cancer: perspectives of individualized targeted therapy. Anticancer Agents Med Chem 2018; 18: 2070-2077.

[19] Tandberg DJ, Tong BC, Ackerson BG and Kelsey CR. Surgery versus stereotactic body radiation therapy for stage I non-small cell lung cancer: a comprehensive review. Cancer 2018; 124: 667-678.

[20] Bott MJ, Yang SC, Park BJ, Adusumilli PS, Rusch VW, Isbell JM, Downey RJ, Brahmer JR, Battafarano R, Bush E, Chaft J, Forde PM, Jones DR and Broderick SR. Initial results of pulmonary resection after neoadjuvant nivolumab in patients with resectable non-small cell lung cancer. J Thorac Cardiovasc Surg 2019; 158: 269-276.

[21] Nagasaka M, Uddin MH, Al-Hallak MN, Rahman S, Balasubramanian S, Sukari A and Azmi AS. Liquid biopsy for therapy monitoring in early-stage non-small cell lung cancer. Mol Cancer 2021; 20: 82.

[22] He T, Cao J, Xu J, Lv W and Hu J. Minimally invasive therapies for early stage non-small cell lung cancer. Zhongguo Fei Ai Za Zhi 2020; 23: 479-486.

[23] McMurry TL, Shah PM, Samson P, Robinson CG and Kozower BD. Treatment of stage I non-small cell lung cancer: what's trending? J Thorac Cardiovasc Surg 2017; 154: 1080-1087.

[24] Sanchez-Lorente D, Guzman R, Boada M, Guirao A, Carriel N and Molins L. N2 disease in non-small-cell lung cancer: straight to surgery? Future Oncol 2018; 14: 13-16.

[25] Gaudet MA and D'Amico TA. Thoracoscopic lobectomy for non-small cell lung cancer. Surg Oncol Clin N Am 2016; 25: 503-513.

[26] Ikeda N. Updates on minimally invasive surgery in non-small cell lung cancer. Curr Treat Options Oncol 2019; 20: 16.

[27] Nelson DB, Mehran RJ, Mitchell KG, Rajaram R, Correa AM, Bassett RL Jr, Antonoff MB, Hofstetter WL, Roth JA, Sepesi B, Swisher SG, Walsh GL, Vaporciyan AA and Rice DC. Robotic-assisted lobectomy for non-small cell lung cancer: a comprehensive institutional experience. Ann Thorac Surg 2019; 108: 370-376.