


ORIGINAL ARTICLE

Video-assisted thoracic surgery is an optimal alternative to conventional thoracotomy for reoperations for ipsilateral pulmonary lesions

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Keywords

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Abstract

Background: Ipsilateral pulmonary reoperation is empirically considered a contraindication of video-assisted thoracic surgery (VATS) because of intrapleural adhesion and the destruction of anatomical structures caused by previous surgery. The purpose of this study was to present our experience of the use of VATS for ipsilateral reoperations.

Methods: The medical records of patients who underwent VATS reoperation or re-thoracotomy between January 2006 and March 2017 were retrospectively reviewed. Data were compared to assess the feasibility and safety of VATS for ipsilateral reoperations.

Results: The study enrolled 64 patients, including 36 patients who underwent attempted ipsilateral VATS reoperations (VATS group) and 28 who underwent conventional re-thoracotomy as a control with clinicopathological characteristics similar to those in the VATS group. Intrapleural severe adhesions were detected in 28 (77.8%) and 22 (78.6%) patients in the VATS and re-thoracotomy groups, respectively ($P = 0.906$), and their dissection required a longer period in the VATS group ($P = 0.014$). VATS reoperations were converted to re-thoracotomy or video-assisted mini re-thoracotomy in three patients because of bleeding or difficulty in dissecting hilar structures. There were no significant differences in resection methods, time to reoperation, intraoperative blood loss, or drainage time between the two groups. However, patients in the VATS group had a shorter hospital stay ($P < 0.01$) and fewer complications ($P = 0.042$).

Conclusion: VATS is an optimal alternative to re-thoracotomy for ipsilateral pulmonary lesions, regardless of intrapleural adhesions and the destruction of anatomical structures caused by former operations in selected patients.

Introduction

Video-assisted thoracoscopic surgery (VATS) has shown superiority over thoracotomy, especially in patients with early-stage non-small-cell lung cancer (NSCLC).¹ Although VATS is a safe and effective method for treating early-stage lung cancer, studies have proposed relative contraindications of VATS, including: (i) dense pleural adhesions, (ii) central-type tumors that may necessitate sleeve resection, (iii) giant lymphadenopathy, (iv) preoperative radiation therapy or chemotherapy, and (v) tumor infiltration into the chest wall.² Therefore, the use of VATS for

ipsilateral reoperations is challenging because of the potential for intrapleural adhesions. Intrapleural adhesions occur frequently between pulmonary vessels and bronchial stumps, in the thoracic apex or the chest wall. The dissection of intrapleural adhesions may lead to errhysis or major bleeding. Furthermore, secondary changes of the hilum occurring after the first operation, especially scar formation in the pulmonary trunks, pose an obstacle for the recognition and isolation of anatomical structures. Because of these two potential complications, VATS is rarely used in reoperations for ipsilateral pulmonary lesions.

Technical advances have led to an increase in the indications for VATS. Conversely, many of the contraindications to VATS have been eliminated in recent years with the evolution of the VATS technique, including: (i) preoperative neoadjuvant therapy, (ii) sleeve resection, and (iii) reoperations for recurrent pneumothorax.^{3–7} Therefore, VATS may become a potentially optimal alternative to thoracotomy in reoperations, whereas the safety and feasibility of ipsilateral VATS reoperations needs to be further evaluated. No studies on VATS reoperations for ipsilateral pulmonary lesions have been published to date. In the present study, we summarized our single center experience with ipsilateral VATS reoperations by comparing patients who underwent ipsilateral re-thoracotomy with those who underwent VATS reoperation.

Methods

Study population

We retrospectively reviewed the records of 77 consecutive patients who underwent ipsilateral reoperations between January 2006 and March 2017 at Shanghai Pulmonary Hospital. Thirteen cases were excluded because: (i) the types of resection were not attempted by VATS, including sleeve resection and intrapericardial pneumonectomy; and (ii) the patients underwent reoperation for bronchopleural fistula repair or hemostasis and not for pulmonary resection. The inclusion criteria were: (i) patients who underwent sublobectomy or lobectomy in the first operation, (ii) either sublobectomy or lobectomy was performed in the reoperation, and (iii) the surgical margin of the lobar bronchus was not affected based on preoperative computed tomography (CT) scanning if lobectomy was performed in the reoperation.

Informed consent was waived because of the retrospective nature of the study, and the review of medical records was approved by the Medical College Review Board of Tongji University, Shanghai, China.

Preoperative evaluation

Patients with an Eastern Cooperative Oncology Group (ECOG) score of 0–2 were considered suitable for reoperations. All reoperation patients underwent routine preoperative evaluation. Chest contrast CT scans and bronchoscopy were performed to assess operability and the range of resection. Abdominal sonography, head magnetic resonance imaging, and bone scintigraphy were used to rule out metastasis. Electrocardiogram and lung function tests were also prescribed to ensure operative safety.

The selection of candidates for VATS reoperation was based mainly on the experience of the surgeon. Generally,

patients were selected as candidates for VATS reoperation according to the following criteria: localized ipsilateral pulmonary lesions detected by CT examination, no calcified or enlarged lymph nodes near pulmonary arteries and veins, adequate cardiopulmonary reserve, obvious failure of medical treatment, and the hilar structures involved in the reoperation were intact in the first operation. In addition, VATS reoperation was attempted by an expert surgeon for patients who requested minimally invasive surgery. The extent of pulmonary resection was determined by imaging features, the location of the lesion, the range of the lung involved in the emerging lesion, the degree of lung function, and the extent of the underlying disease. Lobectomy was the first choice in patients with invasive lesions and adequate cardiopulmonary function, whereas sublobectomy was considered in those with noninvasive lesions or insufficient cardiopulmonary function reserve.

Surgical procedures

Patients were placed in the lateral decubitus position and ventilation was established for the contralateral lung through a double-lumen endotracheal tube. Re-thoracotomy was performed through a conventional posterolateral muscle-sparing thoracotomy. VATS was performed through an access incision with three ports or less. An observation port was created in the seventh or eighth intercostal space (depending on the patient's thoracic configuration) in the midaxillary line to explore the intrathoracic conditions and confirm the viability of the technique. One or two operation ports were made according to the surgeon's preference and the individual situation regarding ongoing reoperations. Usually one anterior incision (approximately 3 cm long) was made over the third or fourth intercostal space without rib spreading, with or without another port below the scapular vertex in the sixth or seventh intercostal space to assist in manipulation. The present VATS technique for reoperation did not differ considerably from that used for routine cancer cases, except for the manipulation of severe adhesions and alterations in hilar structures, and the port locations were not changed even if adhesions were expected. The handling experience and technique are described in detail in the discussion section. Antibiotic therapy was routinely commenced intraoperatively and continued until the white blood cell count returned to normal levels. All specimens were pathologically confirmed as pulmonary lesions.

Data collection and statistical analysis

Patient data are presented as the median with range for quantitative variables or frequencies for qualitative variables. Patient characteristics and perioperative data were

compared using the Student's *t* and χ^2 tests with SPSS version 20.0 (IBM Corp., Armonk, NY, USA). Statistical significance was defined as a *P* value < 0.05.

Results

General information

Overall, 64 patients (35 men, 29 women) who underwent consecutive operations for ipsilateral pulmonary lesions in our hospital were enrolled in the study. The average age of all recruited patients was 59 years (95% confidence interval 56.8–61). Of the 64 patients, 23 had ipsilateral pulmonary lesions on the left lung and 41 on the right. General information on the patients included in the study is shown in Table S1. Ipsilateral VATS reoperation was attempted in 36 patients (VATS group), whereas conventional re-thoracotomy was performed in 28 (re-thoracotomy group).

Table 1 shows the baseline characteristics of the patients in the two groups. There were no significant differences in patient characteristics including age, gender, and pulmonary function. There were no significant differences in the

surgical manipulation of different lobes and mediastinal lymph nodes in the first operation, and the average tumor size in reoperations was also similar.

Perioperative conditions

In the VATS group, the presenting symptoms were a cough in 6 patients (16.7%), sputum in 4 (11.1%), chest pain in 2 (5.5%), and no symptoms in 24 patients (66.7%) whose ipsilateral pulmonary lesions were found by routine CT examinations. No patients required emergency procedures (e.g. massive hemorrhage), and all operations were performed electively. The tumor locations and surgical procedures are listed in Table 2. VATS cases that were converted to thoracotomy or video-assisted mini thoracotomy were included in the VATS group.

There were no significant differences between the two groups in surgical location, resection method, and lymphadenectomy during reoperation (Table 3), and the rates of malignant lesions were also similar. Thoracic surgeons usually detect intrathoracic adhesions in reoperation patients. In the VATS group, extensive pleural adhesion was

Table 1 Characteristics of patients who underwent VATS reoperation and re-thoracotomy

| Characteristics | VATS (<i>n</i> = 36) | Re-thoracotomy (<i>n</i> = 28) | <i>P</i> |
|--|-----------------------|---------------------------------|----------|
| Gender, male | 16/36 | 19/28 | 0.062 |
| Age, years (mean) | 60.1 ± 8.9 | 57.2 ± 7.5 | 0.167 |
| FEV1 predicted (%) | 80.9 ± 5.9 | 81.7 ± 5.1 | 0.577 |
| Tumor size in reoperations (cm) | 2.7 ± 1.7 | 2.9 ± 1.3 | 0.712 |
| Average interval between operations (months) | 24.1 ± 19.2 | 31.8 ± 28.8 | 0.209 |
| Duration of detected ipsilateral lesions (months) | 3.8 ± 3.1 | 4.7 ± 4.0 | 0.787 |
| Surgical procedures in first operation | | | |
| Thoracotomy/VATS | 7/29 | 20/8 | < 0.01 |
| Lobectomy/sublobectomy | 27/9 | 25/3 | 0.146 |
| No/SLND/LNS | 8/20/8 | 1/21/6 | 0.089 |
| Surgical locations in first operations | | | |
| Upper lobe/middle and lower lobe | 17/19 | 18/10 | 0.174 |
| Left/right sides | 11/25 | 12/16 | 0.309 |
| Adjuvant therapy after first operations | | | |
| No | 31 | 22 | 0.723 |
| Chemotherapy only | 4 | 5 | |
| Target therapy | 1 | 1 | |
| Ratio of malignant lesions in first operations (%) | 97.2 | 100 | 0.462 |
| Surgical procedures in reoperations | | | |
| Lobectomy/sublobectomy | 19/17 | 18/10 | 0.355 |
| Surgical location in reoperations | | | |
| Upper lobe/middle and lower lobe | 14/22 | 10/18 | 0.795 |
| Lymphadenectomy in reoperations | | | |
| No | 17 | 10 | 0.468 |
| Systematic lymph node dissection | 7 | 9 | |
| Lymph node sampling | 12 | 9 | |
| Ratio of malignancy lesions in reoperations (%) | 91.9 | 96.4 | 0.118 |

FEV1, Forced expiratory volume in one second; LNS, lymph node sampling; SLND, systematic lymph node dissection; VATS, video-assisted thoracoscopic surgery.

Table 2 Surgical sites and procedures in the VATS and re-thoracotomy groups

| Primary location in first operation | 1st surgical procedure | 2nd surgical procedure | Re-thoracotomy group (n = 28) | VATS group (n = 36) |
|-------------------------------------|------------------------|------------------------|-------------------------------|----------------------|
| Upper lobe | Lob | Lob | 10 | 6 (2 mini, 1 conver) |
| | Lob | Sublob | 5 | 5 |
| | Sublob | Lob | 2 | 5 |
| Middle/lower lobe | Lob | Lob | 6 | 5 |
| | Lob | Sublob | 4 | 11 |
| | Sublob | Lob | 1 | 2 |
| | Sublob | Sublob | 0 | 2 |
| Total | | | 28 | 36 |

Conver, conversion from VATS to thoracotomy; lob, lobectomy; mini, video-assisted mini thoracotomy; sublob, sublobectomy; VATS, video-assisted thoracoscopic surgery.

observed in 11 patients (30.6%), and dense adhesions in 17 cases (47.2%). The dissection of intrathoracic adhesions required a median of 1.3 ± 0.5 hours (range: 0.5–2.5) in the VATS group, which was significantly longer than the 1.0 ± 0.5 hours required in the re-thoracotomy group ($P = 0.014$). However, the total time required for reoperations was similar between the groups ($P = 0.562$). As indicated in the perioperative data in Table 3, intraoperative blood loss did not differ significantly between the two groups ($P = 0.316$), but patients in the VATS group showed a tendency toward reduced blood loss. Patients in the VATS group had equal postoperative drainage time ($P = 0.294$) as those in the re-thoracotomy group.

Intraoperative or postoperative transfusions were required in three patients (8.3%) in the VATS group who had either severe adhesions ($n = 2$) or a bronchopleural fistula after the first operation ($n = 1$). Despite the

successful ipsilateral VATS reoperation in 33 cases, failure occurred in three cases in the initial stage of attempting the VATS reoperation. One case was converted from VATS to open thoracotomy because of intraoperative bleeding secondary to the dissection of dense adhesions, and two patients underwent video-assisted mini thoracotomy because of difficulty in dissecting the bronchus and pulmonary arteries affected by the destruction of hilar structures in the first operation. The three converted cases had undergone upper lobectomy in the first operation, of which two had undergone thoracotomy on the left side and one on the right.

No perioperative deaths occurred in either group. In the VATS group, six patients developed postoperative complications compared to 11 in the re-thoracotomy group ($P = 0.042$). Although intrapleural adhesions developed in 28 patients in the VATS group, persistent air leakage of

Table 3 Perioperative information of the patients in whom ipsilateral VATS and re-thoracotomy reoperations were attempted

| Variables | VATS group (n = 36) | Re-thoracotomy (n = 28) | P |
|---|---------------------|-------------------------|--------|
| Surgical procedures in reoperations | | | |
| Lobectomy/sublobectomy | 19/17 | 18/10 | 0.355 |
| No/SLND/LNS | 17/7/12 | 10/9/9 | 0.468 |
| Surgical location in reoperations | | | |
| Upper lobe/middle and lower lobe | 14/22 | 10/18 | 0.795 |
| Ratio of malignancy lesions in reoperations (%) | 91.9 | 96.4 | 0.118 |
| Volume of intraoperative blood loss (ml) | 354.2 ± 211.6 | 432.1 ± 396.1 | 0.316 |
| Time of reoperation (hours) | 3.7 ± 1.0 | 3.4 ± 0.9 | 0.562 |
| Time of dissecting adhesions (hours) | 1.3 ± 0.5 | 1.0 ± 0.4 | 0.014 |
| Intrathoracic adhesions (%) | | | |
| No | 8 (22.2) | 6 (21.4) | 0.906 |
| Severe intrapleural adhesions | 28 (77.8) | 22 (78.6) | |
| Postoperative drainage time (days) | 5.7 ± 4.0 | 7.1 ± 6.1 | 0.294 |
| Duration of hospital stay (days) | 11.0 ± 5.4 | 20.4 ± 9.5 | < 0.01 |
| Postoperative complications (cases) | 6 | 11 | 0.042 |
| Persistent air leak > 2 weeks | 2 | 4 | |
| Brochopleural fistula | 1 | 1 | |
| Pulmonary embolism | 1 | 1 | |
| Pneumonia | 1 | 3 | |
| Empyema | 1 | 2 | |
| Total complication rate (%) | 16.7 | 39.3 | |

LNS, lymph node sampling; SLND, systematic lymph node dissection; VATS, video-assisted thoracoscopic surgery.

> 2 weeks was only observed in two patients who were treated by pleurodesis. A postoperative pulmonary embolism was detected by CT pulmonary angiography in one patient in the VATS group after lobectomy. This patient was treated successfully with low molecular weight heparin prescribed for anticoagulation. Bronchopleural fistula was observed in one patient and managed by postural drainage. The other two patients in the VATS group with empyema and pneumonia were managed by conservative therapy and recovered well. As shown in Table 3, the duration of hospital stay was lower in the VATS group than in the re-thoracotomy ($P < 0.01$).

Postoperative pathology

Postoperative histology is shown in Table 4. Adenocarcinoma was the most common histologic type ($n = 36$, 56.3%). No differences were apparent in the surgical margin ($P = 0.115$) or sampled lymph node stations ($P = 0.295$). No significant differences were detected in pathologic N status ($P = 0.679$) between the groups. The pathologic stage was also comparable between reoperations and first operations ($P = 0.076$ and 0.769 , respectively).

Discussion

Video-assisted thoracoscopic surgery is currently considered an optimal choice for thoracic surgery, although it was conventionally considered technically challenging for

ipsilateral reoperations. The underlying reason was the difficulty associated with the dissection of severe adhesions and the potential complications, such as bleeding. Although VATS reoperation for recurrent primary spontaneous pneumothorax after VATS has been reported,^{7,8} the present study is the first to demonstrate that VATS reoperation is feasible in patients with a history of ipsilateral tumor surgery. The data presented in Table 1 indicate no significant differences in baseline information between patients undergoing VATS reoperation and those undergoing re-thoracotomy. However, surgeons might be inclined to attempt VATS reoperation in patients with a previous history of VATS.

The most common difficulty associated with ipsilateral reoperations was the dissection of adhesions. Usually there were dense adhesions between the remnant lung and chest wall incision. Dissection along the extrapleural plane is a useful technique to manage pleural adhesions. An extrapleural plane needs to be created, mainly by blunt dissection if the utility port overlaps with a previous incision with formation of dense adhesions. An incision in the muscle layer of the chest wall facilitates visualization of the extrapleural space by rotating the angles of the thoracoscope. After placement of the incision protection sleeve, the remnant adhesions around the incision should be dissected carefully. Adhesions may exist in the seventh or eighth intercostal space if a chest tube was placed after the first operation; therefore, observation by thoracoscope through the port in the fourth intercostal space is

Table 4 Postoperative pathology of the patients in whom ipsilateral reoperations were attempted

| Postoperative pathology | VATS group ($n = 36$) | Re-thoracotomy ($n = 28$) | P |
|---|-------------------------|-----------------------------|-------|
| Histologic type in reoperations (%) | | | |
| Benign lesions | 3 (8.3) | 1 (2.7) | 0.211 |
| Squamous carcinoma | 5 (13.9) | 10 (35.7) | |
| Adenocarcinoma | 24 (66.7) | 14 (50.0) | |
| Others | 4 (13.9) | 3 (10.7) | |
| Average surgical margin (cm) | 1.7 ± 0.4 | 1.9 ± 0.5 | 0.115 |
| LN stations sampled (median, IQR) | 3 (0:4) | 3 (0:5) | 0.295 |
| Pathologic N status in reoperations (%) | | | |
| N0 | 24 (66.7) | 20 (71.4) | 0.372 |
| N1 | 2 (5.6) | 4 (14.3) | |
| N2 | 1 (2.7) | 1 (3.6) | |
| Nx | 6 (16.7) | 2 (7.2) | |
| Pathologic stages in first operations (%) | | | |
| I | 28 (77.8) | 23 (82.1) | 0.679 |
| II | 4 (11.1) | 4 (14.3) | |
| III | 1 (2.7) | 0 (0) | |
| Pathological stages in reoperations (%) | | | |
| 0 | 4 (11.2) | 3 (8.3) | 0.102 |
| I | 18 (50) | 14 (50) | |
| II | 2 (5.6) | 7 (25.0) | |
| III | 2 (5.6) | 1 (3.6) | |
| Unknown | 4 (11.2) | 0 (0) | |

IQR, interquartile range; LN, lymph nodes.

important to avoid unwanted lung damage during single-utility-port VATS. The presence of adhesions at the thoracic apex, a common complication during the lysis of adhesions, required extra caution to avoid damage to adjacent tissues, especially the phrenic nerve, vagus, and superior vena cava. Regarding adhesions in the anteroinferior thorax, it was important to refer to the experience gained from uniportal VATS, in which the thoracoscope and surgical instruments were inserted in the same direction to avoid the mirror reflex in resolving adhesions. Another practical technique was to bend the long-handle electro-tome to achieve proper angles for the dissection of adhesions. Because of technical advances, VATS operations are becoming feasible and safe for selected patients.⁹ Therefore, adhesions alone should no longer be a contraindication to VATS reoperations.

In certain cases, surgeons failed to perform complete VATS. Conversions from complete VATS to open surgery have been described in a few studies, with an incidence of 6.5–23%.^{6,10–15} Approximately 24% of conversions are related to intense adhesions and massive intraoperative bleeding.^{10–12} In the present study, the three cases of conversion in our initial attempted VATS reoperation were related to intraoperative bleeding ($n = 1$) and difficulty dissecting the bronchial and pulmonary arteries affected by destruction of the hilar structures during the first surgeries ($n = 2$), which are consistent with previous studies. The most challenging intraoperative complication was major bleeding. The best way to manage bleeding is to prevent it; therefore, patient selection and operative manipulation should be performed with caution to avoid complications. In a case series reported by Puri *et al.*, patients who underwent successful and uneventful VATS lobectomy were more likely to be female, negative current smokers, and at low T and N stages.¹¹ Gonzalez-Rivas *et al.* reported that a previous history of infectious and inflammatory disease, and CT evidence of hilar tumor or calcified lymph nodes increased the risk of intraoperative bleeding.¹⁶ If bleeding occurs, the first step is to stay calm and immediately compress the hilum to control the bleeding using sponge sticks. Minor bleeding or oozing can usually be controlled by direct compression. However, persistent bleeding may require suture or metallic clips. In general, major bleeding caused by injury to the main pulmonary artery requires urgent conversion from VATS to thoracotomy.^{17,18}

Because any maneuvers affecting normal hilar structures during first operations could result in the formation of dense adhesions and difficulty in vessel dissection, information on hilum and mediastinal lymph nodes needs to be carefully collected before scheduling VATS reoperations. Watanabe *et al.* described their experience of dissection of complex hilar structures in which the main pulmonary

artery was divided following a double ligation with a 1–0 silk suture before lobectomy.¹⁷ This technique is effective for preventing bleeding, and can be performed in patients with dense hilar adhesions or lymphadenopathy. In patients showing scar formation in hilar structures secondary to previous operations, specific surgical strategies are necessary, especially to manipulate the pulmonary vein before the artery. The anatomy of pulmonary veins usually remains relatively intact after the first operation, and they are therefore easier for surgeons to handle. Because accurate recognition of the space between the target bronchus and the pulmonary arteries is difficult, the stapler line may become an effective landmark of the bronchial stump. It is dangerous to perform blunt dissection between the target bronchus and arteries with scar formation, which may lead to massive intraoperative bleeding from arteries. To avoid uncontrollable intraoperative bleeding, two methods are currently used: (i) temporary blockade of the arterial trunk, and (ii) the bronchus-before-artery maneuver. We recommend cutting down the distal bronchus as the first step, followed by sharp dissection along the bronchus to avoid injury to vessels. After handling the bronchus, it becomes easier to remove the target lung tissue with staplers. In our experience with the three converted cases that underwent upper lobectomy in the first operation, recognition and dissection of arterial trunks was difficult because of scar formation when the upper hilum was previously manipulated, and extra caution and experience were required. However, if the initial lobectomy involved the middle or lower lobe, the upper hilar and mediastinal structures should be relatively intact and allow safe VATS reoperation. Furthermore, in cases in which station 4 (tracheobronchial) nodes were removed, left complete thoracoscopic resection subsequent to upper lobectomy would be difficult to perform.

Lymph node dissection or sampling is required for lung cancer surgery. Commonly, lymph node sampling is performed during reoperation if systemic lymph node dissection was performed in the first operation. Interference of the lymph nodes was the main reason for conversion to thoracotomy from VATS lobectomy, which prolonged operative duration and increased the blood loss during surgery.^{19,20} In a study by Li *et al.*, among 27 cases requiring conversion to open thoracotomy, 18 (66.7%) were associated with lymph node involvement, including eight cases of lymph node metastases and 10 cases of calcified lymph node adhesions.¹³ In our experience, lymph node involvement was not an absolute contradiction to VATS. In cases in which systemic lymph node dissection was necessary, a wise choice was to clamp and dissect the distal bronchial stump followed by sharp dissection to manage benign adhesions and to compensate for the increased risk of intraoperative bleeding during VATS. In addition, VATS

can provide illumination and clearly magnified images with anatomic details deep in the body, which is helpful for lymph node dissection.²¹

The present study had several limitations. First, the selection of patients was limited and the clinical data may have been biased because the purpose was to demonstrate the feasibility of ipsilateral VATS reoperations, especially the differences between thoracotomy and VATS in first operations in the two groups. Second, the sample size was relatively small because few patients underwent second operations for ipsilateral pulmonary lesions. Third, the surgeons' preferences may have influenced the selection of the surgical procedures.

In conclusion, VATS is an optimal alternative to rethoracotomy for ipsilateral pulmonary lesions, regardless of intrapleural adhesions and the destruction of anatomical structures caused by former operations in selected patients.

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Disclosure

No authors report any conflict of interest.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Table S1. General information of the patients included in the study