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Clinical Research

Outcomes of Completion Lobectomy for Locoregional Recurrence after Sublobar Resection in Patients with Non-small Cell Lung Cancer

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Background: This retrospective study aimed to determine the treatment patterns and the surgical and oncologic outcomes after completion lobectomy (CL) in patients with locoregionally recurrent stage I non-small cell lung cancer (NSCLC) who previously underwent sublobar resection.
Methods: Data from 36 patients who initially underwent sublobar resection for clinical, pathological stage IA NSCLC and experienced locoregional recurrence between 2008 and 2016 were analyzed.
Results: Thirty-six (3.6%) of 1,003 patients who underwent sublobar resection for NSCLC experienced locoregional recurrence. The patients' median age was 66.5 (range, 44–77) years at the initial operation, and 28 (77.8%) patients were men. Six (16.7%) patients underwent segmentectomy and 30 (83.3%) underwent wedge resection as the initial operation. The median follow-up from the initial operation was 56 (range, 9–150) months. Ten (27.8%) patients underwent CL, 22 (61.1%) underwent non-surgical treatments (chemotherapy, radiation, concurrent chemoradiation therapy), and 4 (11.1%) did not receive treatment or were lost to follow-up after recurrence. Patients who underwent CL experienced no significant complications or deaths. The median follow-up time after CL was 64.5 (range, 19–93) months. The 5-year overall survival (OS) and post-recurrence survival (PRS) were higher in the surgical group than in the non-surgical ($p<0.001$) and no-treatment groups ($p<0.001$).
Conclusion: CL is a technically demanding but safe procedure for locoregionally recurrent stage I NSCLC after sublobar resection. Patients who underwent CL had better OS and PRS than patients who underwent non-surgical treatments or no treatments; however, a larger cohort study and long-term surveillance are necessary.

Keywords: Completion lobectomy, Non-small cell lung cancer, Sublobar resection, Pulmonary resection

Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide, and surgical resection is the gold-standard treatment for early-stage lung cancer. The standard treatment for stage I non-small cell lung cancer (NSCLC) has traditionally been pulmonary lobectomy and mediastinal lymph node dissection [1]. However, evidence suggests that sublobar resection could offer comparable oncologic outcomes for certain patients [2-4]. As chest computed tomography (CT) becomes more widely available and the detection of peripheral small-sized tumors rises, the number of sublobar resection procedures for early-stage lung cancer is anticipated to increase [5].

Sublobar resection for early-stage lung cancer preserves pulmonary function without compromising overall survival (OS) [3-6]. However, the potential risk of recurrence after sublobar resection is a concern [5,7,8]. In particular,

locoregional recurrence can occur due to difficulties in achieving sufficient surgical margins and hilar lymph node dissection [5]. In the recent JCOG (Japan Clinical Oncology Group) 0802 trial, significantly more locoregional recurrences occurred in patients who underwent segmentectomy (11%) than in patients who underwent lobectomy (5%) [4].

The proper management of patients with locoregional recurrences after sublobar resection has not been established. Completion lobectomy (CL) is defined as resection of the remaining pulmonary lobe after wedge resection or segmentectomy [9-11]. CL is a potential surgical option for locoregional recurrence. However, performing CL after sublobar resection in the same lobe or hemithorax may be complicated by severe adhesions around the hilar structures, especially the pulmonary artery [12,13]. Only a few studies, which included a low number of patients, have reported the outcomes of CL after locoregional recurrence [9,12-15]. Therefore, the purpose of this study was to determine the surgical and oncologic outcomes of CL in patients with locoregionally recurrent stage I NSCLC.

Methods

Patients

Data from a prospectively maintained institutional database of patients who underwent sublobar resection for NSCLC between January 2008 and December 2016 at Samsung Medical Center were retrospectively analyzed. Of the 1,003 clinical and pathological stage IA patients who underwent sublobar resection for NSCLC, 360 patients (36%) underwent anatomical segmentectomy, and 643 patients (64%) underwent wedge resection. Seventy-four patients (7.4%) experienced recurrence. After excluding patients with distant metastasis, data from 36 patients with locoregional recurrence were analyzed; 10 of these patients underwent CL (Fig. 1). Recurrence in the stump was defined as local recurrence. Metastasis in the ipsilateral hilar or mediastinal lymph nodes was defined as regional recurrence. Distant recurrence was defined as recurrence at any other site [10].

The 36 patients who experienced locoregional recurrence were categorized into 3 groups. The surgical group included 10 patients who underwent CL. The non-surgical group included 22 patients who received chemotherapy, radiation, or concurrent chemoradiotherapy (CCRT). The remaining 4 patients were not treated or were lost to follow-up and were categorized into the no-treatment group (Fig. 1). The indications for CL and other non-surgical treatments were as follows: in cases where locoregional recurrence was suspected after sublobar resection, we initially performed imaging tests such as CT or positron emission tomography. Currently, the National Comprehensive Cancer Network guidelines recommend re-resection or radiotherapy in the event of locoregional recurrence. Since surgical resection is preferred when possible [16], we assessed the possibility of surgical resection based on the imaging findings. If surgical resection was possible, we evaluated the patient's general condition and cardiopulmonary function to determine whether the patient would be able to tolerate CL. In cases where the patient was considered not feasible for surgery, we opted for non-surgical treatments through a multidisciplinary discussion. CL was performed using either video-assisted thoracoscopic surgery (VATS) or a thoracotomy approach. The surgical approach was determined by the surgeon's preference. The surgical and oncologic outcomes after CL were investigated, followed by survival outcomes

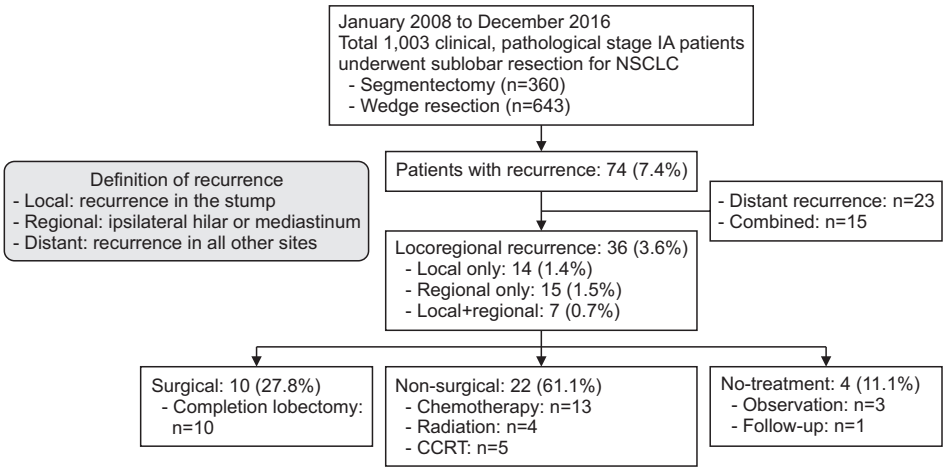

Fig. 1. Flow diagram of patient selection and patients' categorization according to treatment options. NSCLC, non-small cell lung cancer; CCRT, concurrent chemoradiotherapy.

in the 3 groups.

Data on the following perioperative outcomes were obtained and evaluated: initial operation, pathology, initial pathologic stage, recurrence pattern, recurrence interval between initial operation and CL, forced expiratory volume in 1 second (FEV1) before CL, surgical approach, surgical procedure, operative time for CL, intraoperative blood loss, hospital days, surgical margin, postoperative complications, and pathologic stage after CL. Complications were graded using the Clavien-Dindo classification [17].

Statistical analyses

Continuous variables were compared using the Student t-test or Kruskal-Wallis test, and categorical variables were compared using the chi-square or Fisher exact tests. OS was defined as the time from the initial surgery to the time of death or censoring. Post-recurrence survival (PRS) was defined as the time from locoregional recurrence to the time of death or censoring. Survival was estimated using the Kaplan-Meier method and analyzed using the log-rank test. All statistical tests were 2-sided, with a significance level of 0.05. Statistical analyses were performed using IBM SPSS ver. 26.0 (IBM Corp., Armonk, NY, USA).

Ethical statement

The study was approved by the institutional review board of Samsung Medical Center (2023-05-113), and the requirement for patient consent was waived due to the retrospective nature of the study.

Results

Characteristics of patients with locoregional recurrence

The baseline characteristics of the 36 patients who experienced locoregional recurrence are summarized in Table 1. The median age at the time of initial sublobar resection was 66.5 years, and 28 patients (77.8%) were men. Six (16.7%) and 30 (83.3%) patients underwent segmentectomy and wedge resection as the initial operation, respectively. Thirteen patients (36.1%) underwent mediastinal lymph node dissection as the initial sublobar resection, 6 patients (16.7%) underwent mediastinal lymph node sampling, and 1 patient (2.8%) underwent mediastinal lymph node biopsy. Twenty-five patients (69.4%) had adenocarcinoma, 10 patients (27.8%) had squamous cell carcinoma, and 1 patient (2.8%) had basaloid carcinoma. The median follow-up time after the initial operation was 56 months (range, 9–150 months).

Table 1. Baseline characteristics of patients (N=36)

Characteristic	Value
Age at initial operation (yr)	66.5 (44–77)
Sex	
Male	28 (77.8)
Female	8 (22.2)
Initial operation	
Segmentectomy	6 (16.7)
Wedge resection	30 (83.3)
Mediastinal lymph node	
Mediastinal lymph node dissection	13 (36.1)
Mediastinal lymph node sampling	6 (16.7)
Mediastinal lymph node biopsy	1 (2.8)
Not done	16 (44.4)
Initial pathology	
Adenocarcinoma	25 (69.4)
Squamous cell carcinoma	10 (27.8)
Others	1 (2.8)
Follow-up time from the initial operation (mo)	56 (9–150)

Values are presented as median (range) or number (%).

For the 36 patients with locoregional recurrence, the median age at the time of recurrence was 68.5 years (range, 44–79 years), and the median disease-free interval (DFI) from the initial sublobar resection to the locoregional recurrence was 18 months (range, 4 to 60 months). Fourteen patients (38.9%) had only local recurrence, 15 patients (41.7%) had only regional recurrence, and 7 patients (19.4%) had both local and regional recurrence. To treat recurrence, 10 patients (27.8%) underwent CL, 13 patients (36.1%) underwent chemotherapy, 4 patients (11.1%) underwent radiation therapy, and 5 patients (13.9%) underwent CCRT. Three patients (8.3%) were observed but received no treatment for unknown reasons. One patient (2.8%) was lost to follow-up. The median post-recurrence follow-up time was 28 months (range, 0–102 months) (Table 2).

Surgical outcomes for completion lobectomy

Table 3 shows the operative outcomes for the 10 patients who underwent CL for locoregional recurrence after the initial sublobar resection. The median age at recurrence was 71.5 years (range, 58–78 years). Eight patients underwent wedge resection, and 2 patients underwent segmentectomy as the initial operation. All patients had stage IA disease. The median DFI from the initial operation to recurrence was 35 months (range, 10–44 months). All pa-

Table 2. Characteristics of recurrent disease (N=36)

Variable	Value
Age at time of recurrence (yr)	68.5 (44–79)
Disease-free interval from initial operation to recurrence (mo)	18 (4–60)
Recurrence pattern	
Local only	14 (38.9)
Regional only	15 (41.7)
Locoregional	7 (19.4)
Treatment for recurrence	
Completion lobectomy	10 (27.8)
Chemotherapy	13 (36.1)
Radiation	4 (11.1)
CCRT	5 (13.9)
Observation	3 (8.3)
Loss to follow-up	1 (2.8)
Post-recurrence follow-up time (mo)	28 (0–102)

Values are presented as median (range) or number (%).
CCRT, concurrent chemoradiotherapy.

tients underwent initial sublobar resection with VATS.

In patients who underwent CL, the median operative time was 244.5 minutes (range, 177–382 minutes), the median blood loss was 200 mL (range, 50–400 mL), and the median hospital stay was 9 days (range, 7–25 days). R0 resection was achieved in every CL. Three patients experienced postoperative morbidities (atrial fibrillation), with a Clavien-Dindo classification of II. No in-hospital deaths occurred.

Adhesions around the hilar structures were identified in 8 of 10 patients who underwent CL. The severity of the adhesions varied. Parenchymal air leaks developed and the lung parenchyma was reinforced using sutures or fibrin glue in 4 cases. Additionally, the bronchial stump was reinforced using pericardial fat or additional sutures in 2 patients. During CL, suspicious nodules in other lobes or surrounding structures were found in 6 patients, and additional precision excisions, en-bloc wedge resections, or biopsy procedures were conducted.

VATS was performed in 3 patients, with no thoracotomy conversion, and intentional thoracotomies were performed in 7 patients. The median operation time was 237.0 minutes for VATS and 247.0 minutes for thoracotomies. The median blood loss amounts were 50 mL and 200 mL for VATS and thoracotomies, respectively. The median hospital stays were 13 days for patients who underwent VATS and 9 days for those who underwent thoracotomy.

Oncologic and survival outcomes

The 36 patients with locoregional recurrence were categorized into 3 groups according to the treatment after locoregional recurrence (Fig. 1). The surgical group consisted of 10 patients who underwent CL. The non-surgical group included 22 patients who were treated with chemotherapy, radiation therapy, or CCRT. The no-treatment group included 4 patients who underwent no treatment or were lost to follow-up. The median age at initial sublobar resection, the median age at recurrence, the median FEV1 (L) at initial sublobar resection, and the median DFI were compared, and no significant differences were detected.

As shown in Fig. 2A, the Kaplan-Meier OS curves for the treatment groups after locoregional recurrence were significantly different; the 5-year OS was 33.3% for the entire cohort, 60.0% for the surgical group, 27.3% for the non-surgical group, and 0% for the no-treatment group ($p<0.001$). As shown in Fig. 2B, the Kaplan-Meier curves for 5-year PRS were also significantly different depending on the treatment group ($p<0.001$); the 5-year PRS was 44.4% for the entire cohort, 80.0% for the surgical group, 36.4% for the non-surgical group, and 0% for the no-treatment group.

Although the 5-year PRS for the surgical group was 80%, 2 patients died within 5 years after the CL. One patient died 39 months after CL without recurrence. Another patient underwent VATS right middle lobe (RML) wedge resection for the initial surgery, and both local and regional recurrences occurred after 40 months. This patient underwent completion RML lobectomy with mediastinal lymph node dissection via a thoracotomy; during surgery, a metastatic pleural nodule was completely removed. The patient received palliative chemotherapy and died 19 months after CL.

Two other patients experienced recurrence after CL. One patient underwent VATS right lower lung (RLL) basal segmentectomy with mediastinal lymph node dissection as an initial sublobar resection, followed by completion RLL lobectomy for local recurrence 44 months after the initial surgery. However, multiple metastatic nodules in the RML were suspected on chest CT 51 months post-CL. The patient decided to only receive regular follow-up and is still alive 14 months after the second recurrence. Another patient underwent VATS left lower lobe (LLL) wedge resection and mediastinal lymph node sampling for the initial surgery. Fourteen months after the initial surgery, the patient underwent completion LLL lobectomy with mediastinal lymph node dissection via thoracotomy for local recur-

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Table 3. Perioperative data of patients who underwent completion lobectomy (N=10)

No.	Sex	Rec age (yr)	Initial operation (sublobar resection)				Rec pattern	DFI (mo)	Completion lobectomy									
			Initial operation	Mediastinal LN	Path-ology	pStage			FEV1 (L)	Ap-proach	Adhe-sion	Mediastinal LN	Operation time (min)	Blood loss (mL)	Hospital days	Margin	Compli-cation	pStage
1	M	72	WR (RUL)	Biopsy	SqCC	pT1aN0M0 (IA)	Local	43	2.69	Open	-	Dissection	282	400	9	R0	-	pT2aN0M0 (IB)
2	M	71	WR (LUL)	Sampling	SqCC	pT1aN0M0 (IA)	Local	33	1.85	Open	Diffuse tight	Dissection	247	200	9	R0	-	pT2aN0M0 (IB)
3	M	74	WR (RUL)	Dissection	ADC	pT1aN0M0 (IA)	Local	26	2.3	VATS	Focal tight	Dissection	237	50	8	R0	A.fib	pT1aN0M0 (IA)
4	F	65	Seg (RLL)	Dissection	ADC	pT1aN0M0 (IA)	Local	44	2.06	Open	-	-	242	300	7	R0	-	pT1aNxM0 (IA)
5	M	67	WR (LUL)	-	ADC	pT1aNxM0 (IA)	Local	37	2.68	VATS	Diffuse tight	Dissection	382	400	25	R0	A.fib	pT2aN0M0 (IB)
6	F	63	Seg (LLL)	Dissection	ADC	pT1aN0M0 (IA)	Local	41	1.94	Open	Focal tight	-	179	100	7	R0	-	pT1aN0M0 (IA)
7	F	72	WR (RLL)	-	ADC	pT1bNxM0 (IA)	Local	16	1.47	VATS	Focal loose	Dissection	177	50	13	R0	A.fib	pT2aN0M0 (IB)
8	F	73	WR (RML)	-	ADC	pT1aNxM0 (IA)	Local + regional	40	1.99	Open	Focal tight	Dissection	317	200	12	R0	-	pT1bN0M1a (IVA)
9	F	58	WR (RLL)	Sampling	ADC	pT1aN0M0 (IA)	Local + regional	10	2.01	Open	Focal loose	Dissection	283	200	9	R0	-	pT1aN2M0 (IIIA)
10	M	78	WR (LLL)	Sampling	ADC	pT1aN0M0 (IA)	Local	14	1.92	Open	Focal tight	Dissection	185	50	9	R0	-	pT2aN0M0 (IB)

Rec, recurrence; LN, lymph node; DFI, disease-free interval; FEV1, forced expiratory volume in 1 second; M, male; F, female; WR, wedge resection; RUL, right upper lobe; SqCC, squamous cell carcinoma; LUL, left upper lobe; ADC, adenocarcinoma; VATS, video-assisted thoracoscopic surgery; A.fib, atrial fibrillation; Seg, segmentectomy; RLL, right lower lobe; LLL, left lower lobe; RML, right middle lobe.

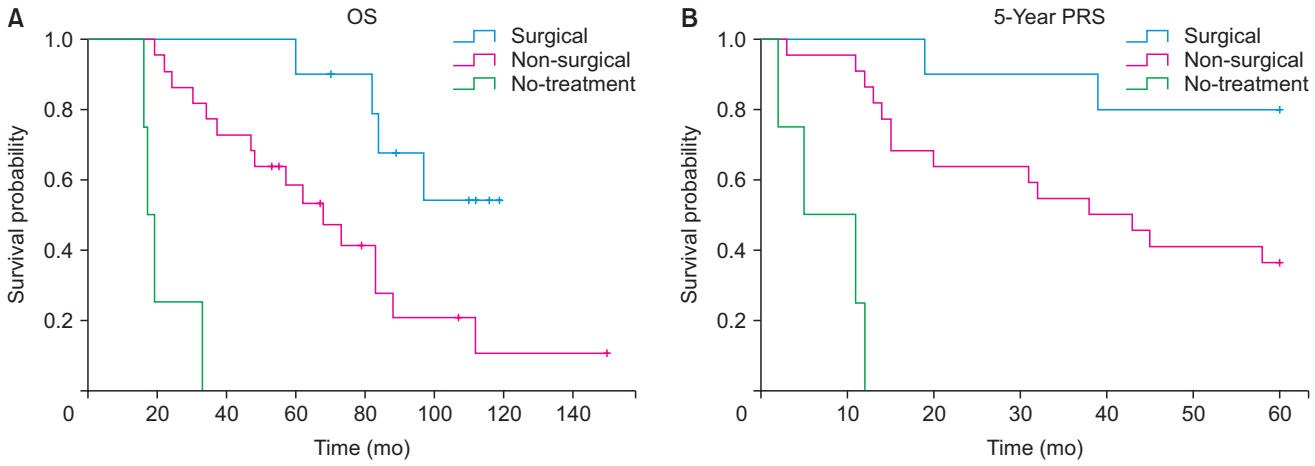

Fig. 2. Survival curves according to the treatment options, including (A) overall survival (OS) and (B) 5-year post-recurrence survival (PRS).

rence. Regional recurrence in the left upper lobe (LUL) was detected 20 months post-CL, and the patient underwent LUL wedge resection via thoracotomy again. However, multiple brain, lung, and pleural metastases occurred 27 months after the LUL wedge resection (47 months post-CL). The patient received palliative chemotherapy and Gamma Knife (Elekta AB, Stockholm, Sweden) radiosurgery and died 70 months post-CL due to coronavirus disease 2019 infection.

Discussion

To the best of our knowledge, this study included the largest number of patients who underwent CL for locoregional recurrences after sublobar resection [12,13,15]. Previous studies on CL included patients who underwent surgery not only for recurrence, but also for other reasons, such as complications, and included fewer than 10 patients. The results of this study demonstrate that CL for locoregionally recurrent stage I NSCLC after sublobar resection is a technically demanding but safe procedure.

Sublobar resection is a treatment option for early-stage NSCLC [2-4]. The use of sublobar resection is increasing because the early detection of suspicious ground-glass nodules with low-dose CT screening is increasing. However, sublobar resection is associated with a higher incidence of locoregional recurrence, and only a limited number of studies have described the surgical outcomes of CL for locoregional recurrence after sublobar resection. CL is a technically demanding procedure due to the dense adhesions around hilar structures [9,12-14]. Additionally, more severe adhesions around the hilum occur 5 weeks after the initial surgery, which can make CL more challenging to perform [14].

This study showed that CL for locoregional recurrence of NSCLC after sublobar resection was a feasible and safe procedure. The median operation time was approximately 240 minutes, and the median blood loss was 200 mL for the 10 CL cases performed at our institution. Eight patients had adhesions around hilar structures, especially along the former staple line or pleural space due to the previous sublobar resection. Four cases required reinforcement of the lung parenchyma because of air leaks, and 2 cases required bronchial stump reinforcement, indicating that CL is not a simple procedure. However, we observed favorable outcomes; the median hospital stay was only 9 days, and no deaths occurred. Although some patients experienced postoperative complications, all cases were classified as minor (Clavien-Dindo grade II).

Regarding the surgical approach, VATS is a viable option for performing CL. However, previous studies have shown that VATS CL is challenging due to the presence of hilar adhesions [9,12,13]. Severe hilar adhesions and fibrosis are more likely when CL is performed in the upper lobes, and a thoracotomy approach is often required [12,15]. The occasional use of taping and/or clamping of the main pulmonary artery may prevent catastrophic bleeding when the pulmonary artery is difficult to expose and divide [9,13]. In this study, 3 patients underwent CL through VATS without thoracotomy conversion, while the remaining 7 patients underwent CL via intended thoracotomy. The operation times (237.0 minutes versus 247.0 minutes) were shorter and blood loss (50 mL versus 200 mL) was lower for CL performed via VATS than for CL performed via thoracotomy.

When recurrence is suspected, tissue confirmation and

evaluation of the extent of recurrence are important for selecting the appropriate treatment. However, confirmation through non-surgical methods is challenging for locoregional recurrence. In such cases, CL provides simultaneous tissue confirmation and surgical treatment. Diaphragmic pleural seeding was discovered during the CL procedure in 1 case, indicating that surgical exploration may be useful for accurate staging.

We acknowledge that our comparison may not be perfect, insofar as we compared survival outcomes after CL with outcomes after non-surgical treatment or no treatment. In this study, the 5-year OS (60.0%) and PRS (80.0%) in patients who underwent CL were better than the OS and PRS in patients who underwent non-surgical treatment or received no treatment (OS: 27.5% and 0.0%; p<0.001, PRS: 36.4% and 0.0%; p<0.001). Although the survival rate was significantly higher among patients who underwent CL in this study, the possibility of differences in other general conditions and case selection should be taken into consideration. Larger cohort studies with sufficient patient numbers are needed in the future.

Several limitations to this study should be acknowledged. First, the study included a limited number of patients, which may impact the generalizability of the findings. Second, the patients who underwent CL may have had more favorable general conditions, leading to selection bias in this study. Third, this study was conducted at a single institution, and the quality of surgery, surgeon's proficiency, and other factors may differ from other centers. Additionally, this study was retrospective, which may limit the validity of the results. Further studies with larger populations and longer-term surveillance are necessary to confirm the findings of this study and address these limitations.

In conclusion, CL for locoregionally recurrent stage I NSCLC after sublobar resection is a technically demanding but safe procedure. VATS CL can be performed with comparable feasibility and safety. However, some patients experienced recurrence after CL, and long-term surveillance is necessary to ensure optimal patient outcomes.

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Author contributions

Conceived and designed the analysis: CEL, SYP. Collected the data: CEL. Contributed data or analysis tools: JY, YJJ, JL, JHC, HKK, YSC, JK, YMS. Performed the analysis: CEL. Wrote the paper: CEL, SYP. Final approval of the manuscript: all authors.

Conflict of interest

Corresponding author Seong Yong Park, M.D., Ph.D., serves as an associate editor of the Journal of Chest Surgery, while co-author Junghee Lee, M.D., Ph.D., is a member of the journal's editorial board. Hong Kwan Kim, M.D., Ph.D., was previously an editorial board member. None of them participated in the peer reviewer selection, evaluation, or decision-making process for this article. No other potential conflicts of interest relevant to this article were reported.

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