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Original Article / Özgün Makale

Long-term results of sleeve lobectomy with continuous suture technique in non-small cell lung cancer

Küçük hücreli dışı akciğer kanserinde sürekli sütür tekniği ile sleeve lobektominin uzun dönem sonuçları

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ABSTRACT

Background: This study aims to investigate the operation-related complications, recurrence frequency, morbidity, mortality and survival rates as well as variables effective on survival of patients undergoing bronchial sleeve lobectomy due to primary non-small cell lung cancer.

Methods: A total of 85 patients (80 males, 5 females; mean age 59.9±8.4 years; range, 35 to 77 years) of bronchial sleeve lobectomy operated with the same surgical technique by the same team in our clinic between May 2007 and November 2015 were analyzed retrospectively. Survival and 30- and 90-day mortality rates were analyzed. Variables effective on survival rate were evaluated statistically. Complications related to bronchial anastomosis and the frequency of local recurrence in postoperative period were investigated.

Results: Twenty-five patients (29.4%) received neoadjuvant therapy and two of these patients (8%) developed complication in the anastomosis line. Local recurrence rate in the postoperative follow-up was 16.5%. Mean duration of follow-up was 35±29.9 months, median survival was 65.2 months, and five-year survival rate was 50.9%. Thirty- and 90-day mortality rates were 1.2% and 2.4%, respectively. In univariate analysis, patients with larger tumors, N2 disease, or those who underwent extended surgery had statistically significantly worse survival rates (p=0.001, p=0.002, and p=0.0001, respectively). In the Cox regression analysis, variables effective on survival were presence of extended surgery and node status (p=0.03 and p=0.012, respectively).

Conclusion: Sleeve lobectomy can be achieved with acceptable anastomotic complications, good survival and low mortality rates using continuous suture technique. When performed due to oncological reasons, its long-term results are not different from pneumonectomy.

Keywords: Local recurrence; morbidity; mortality; non-small cell lung cancer; sleeve lobectomy; surgical technique.

ÖZ

Amaç: Bu çalışmada primer küçük hücreli dışı akciğer kanseri nedeniyle bronşiyal sleeve lobektomi uygulanan hastaların ameliyata bağlı komplikasyonları, nüks sıklığı, morbidite, mortalite ve sağkalım oranları ile sağkalım üzerinde etkili değişkenler araştırıldı.

Çalışma planı: Mayıs 2007 ve Kasım 2015 tarihleri arasında kliniğimizde aynı ekip tarafından aynı cerrahi teknik ile ameliyat edilen toplam 85 bronşiyal sleeve lobektomi hastası (80 erkek, 5 kadın; ort. yaş 59.9±8.4 yıl; dağılım, 35-77 yıl) retrospektif olarak analiz edildi. Sağkalım ve 30 ve 90 günlük mortalite oranları analiz edildi. Sağkalım oranı üzerinde etkili değişkenler istatistiksel olarak değerlendirildi. Bronş anastomozuna bağlı komplikasyonlar ve ameliyat sonrası dönemde lokal nüks sıklığı araştırıldı.

Bulgular: Yirmi beş hasta (%29.4) neoadjuvan tedavi gördü ve bu hastaların ikisinde (%8) anastomoz hattında komplikasyon gelişti. Ameliyat sonrası takipte lokal nüks oranı %16.5 idi. Ortalama takip süresi 35±29.9 ay, median sağkalım 65.2 ay ve beş yıllık sağkalım oranı %50.9 idi. Otuz ve 90 günlük mortalite oranları sırasıyla %1.2 ve %2.4 idi. Tek değişkenli analizde; daha büyük tümörlü, N2 hastalıklı veya uzatılmış cerrahi uygulanan hastalar istatistiksel olarak anlamlı derecede daha kötü sağkalım oranlarına sahipti (sırasıyla, p=0.001, p=0.002 ve p=0.0001). Cox regresyon analizinde sağkalım üzerinde etkili değişkenler uzatılmış cerrahi varlığı ve nodül durumu idi (sırasıyla, p=0.03 ve p=0.012).

Sonuç: Sleeve lobektomi sürekli sütür tekniği kullanılarak kabul edilebilir anastomotik komplikasyonlar, iyi sağkalım ve düşük mortalite oranları ile gerçekleştirilebilir. Onkolojik nedenlerle yapıldığında, uzun dönem sonuçları pnömonektomiden farklı değildir.

Anahtar sözcükler: Lokal nüks; morbidite; mortalite; küçük hücreli dışı akciğer kanseri; sleeve lobektomi; cerrahi teknik.

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Sleeve lobectomy is a bronchoplastic procedure that preserves pulmonary function in central tumors of the lung and provides a surgical alternative to pneumonectomy.[1] However, it is technically more challenging than pneumonectomy. Segmental resection, reconstruction and angioplastic procedures can be performed on pulmonary artery with bronchial sleeve resection.[2] Bronchial sleeve lobectomy was first described by Sir Clement Price Thomas[3] in 1947 as a parenchyma-preserving surgery for a carcinoid tumor in the right main bronchus. This technique was first applied by Allison[4] in 1954 because of bronchogenic carcinoma. Bronchoplasty techniques can be applied to both main bronchi and all five major lobe bronchi. Anastomosis can be performed with separate sutures, as well as with continuous suture technique that can be completed in shorter time and with similar success.[5]

Bronchoplastic procedures are suitable for approximately 5-8% of patients with resectable pulmonary malignancy.[6] The greatest benefit of increase in this rate is that it would reduce pneumonectomies.[7] It is known that pneumonectomy, particularly right pneumonectomy, is associated with significant morbidity and mortality.[1] In this study, we aimed to investigate the operation-related complications, recurrence frequency, morbidity, mortality and survival rates as well as variables effective on survival of patients undergoing bronchial sleeve lobectomy due to primary non-small cell lung cancer (NSCLC).

PATIENTS AND METHODS

A total of 85 patients (80 males, 5 females; mean age 59.9±8.4 years; range, 35 to 77 years) of bronchial sleeve lobectomy operated with the same surgical technique by the same team in University of Health Sciences, Dr. Suat Seren Chest Diseases and Surgery Training and Research Hospital between May 2007 and November 2015 were analyzed retrospectively. Data including age, histology, lymph node metastasis, tumor size, tumor status, neoadjuvant therapy and adjuvant therapy were obtained from hospital records, operation reports, patient charts, and national survival database. Patients were evaluated with regard to mortality rate, survival rate, analysis of variables effective on survival, complications related to bronchial anastomosis, and local recurrence frequency in the postoperative period. The study protocol was approved by the University of Health Sciences, Dr. Suat Seren Chest Diseases and Surgery Training and Research Hospital Ethics Committee (No: 49109414-806.02.02-E.1669). A written informed consent was obtained from each patient. The study was conducted in accordance with the principles of the Declaration of Helsinki.

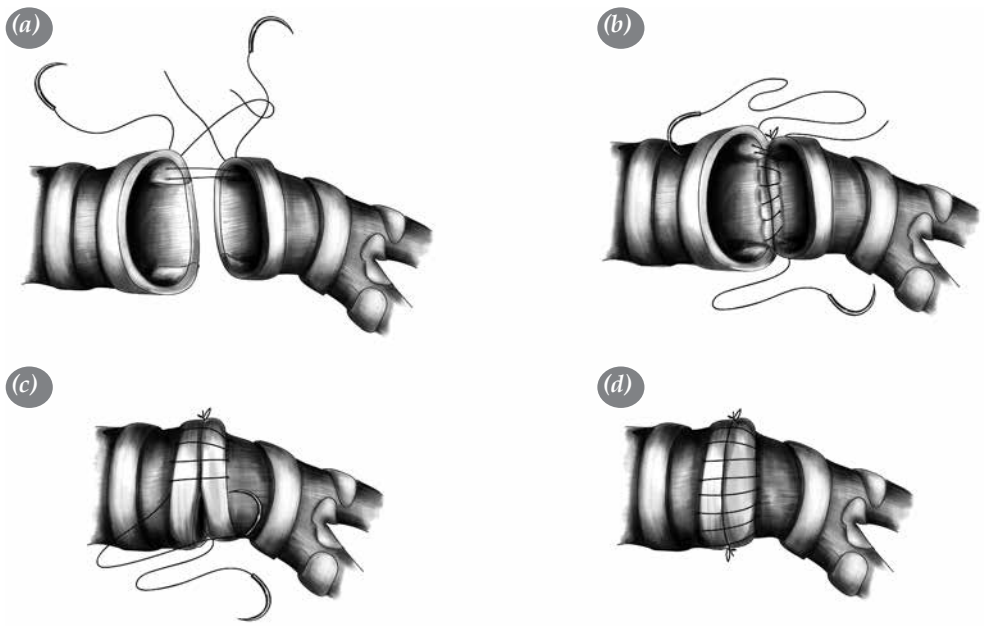

Figure 1. Illustration of sleeve anastomosis by continuous suture technique with two separate sutures. **(a)** Two separate sutures are placed on margin of main bronchus and on margin of remaining bronchus. **(b)** Bronchial membranous part is continuously sutured using one of the sutures. **(c)** Anterior portion of bronchial anastomosis is completed by continuous suture technique with other suture. **(d)** Final result of sleeve anastomosis.

Preoperative assessment included posteroanterior chest X-ray, thoracic, and upper abdominal computed tomography (CT), fiberoptic bronchoscopy (FOB), positron emission tomography, cranial magnetic resonance imaging or CT, pulmonary function tests and blood gas analysis as standard procedure. For eligible patients, transthoracic fine-needle aspiration biopsy and mediastinal lymph node staging with endobronchial ultrasonography and/or mediastinoscopy were performed.

Surgical technique

During the operation, anesthesiologists conducted double-lumen intubation, arterial and central venous pressure monitorization and epidural analgesia as standard procedure. The serratus anterior muscle was preserved and posterolateral thoracotomy was performed. To achieve a complete resection, additional procedures such as intrapericardial procedures, left atrium, diaphragm, or chest wall resection were

Table 1. General characteristics and survival values of patients with sleeve lobectomy

	n	%	Five-year survival	Median survival	*p*
Overall	85	100	50.9	65.2	
Gender					0.56
Female	5	5.9	66.7	65.2	
Male	80	94.1	49.8	56.7	
Age (year)					0.38
<60	42	49.4	58.1	-	
≥60	43	50.6	43.9	53.9	
Side					0.84
Left	24	28.2	47.9	53.9	
Right	61	71.8	51.9	-	
Extended resection					**0.001**
Absent	64	75.3	58	-	
Present	21	24.7	23.3	29.3	
Neoadjuvant therapy					
Absent	60	70.6	43.7	55.3	0.75
Present	25	29.4	61.6	-	
Adjuvant therapy					
Absent	49	57.6	50.8	65.2	0.95
Present	36	42.4	53.3	-	
Histology					
Squamous	75	88.2	53.6	65.2	0.71
Non-squamous	10	11.8	28.9	55.3	
Tumor size					**0.002**
≤3 cm	49	57.6	67.5	-	
>3 cm	36	42.4	23.6	37.5	
pT					0.57
0-1	13	15.3	60	-	
2	41	48.2	55.2	65.2	
3	31	36.5	41.3	55.3	
N disease					**0.0001**
N_0/N_1	72	84.7	56.9	-	
N_2	13	15.3	14.7	25.8	
Operation					
Right upper	55	64.7	50.2	-	
Left upper	12	14.1	50.5	65.2	
Left lower	12	14.1	45.7	37.8	
Bilobectomy	6	7.1	75	-	

pT: Pathological T Stage; N: Nodal.

performed when necessary. These additional procedures were defined as extended resection. Each patient underwent systematic mediastinal and hilar lymph node dissection. Main procedure in bronchial sleeve resection is reimplantation of the remaining bronchial structure after resection of bronchial segment to the main bronchus. The resection margins are assessed by a pathologist using the frozen-section procedure. A part of the main bronchus was removed with the lesion including the lobe. Dividing the inferior pulmonary ligament is performed to release the tension of bronchial anastomosis. Sutures are placed on margin of the main bronchus and on margin of the remaining bronchus. Normally, we used to perform bronchial anastomosis with monofilament absorbable 3/0 and 4/0 sutures. Suturation begins with two independent sutures from the cartilaginous section at both ends and cartilaginous sections are bonded with continuous suturing. The suture gaps on the main bronchial side can be wider than on the remaining bronchial side to eliminate possible diameter discrepancies. After the cartilaginous section is sutured, anastomosis of the membranous section is completed with continuous suturing using the second suture which was bonded with the first suture at the beginning, and both sutures are spliced together at the end. As a result, anastomosis is completed with two separate continuous sutures (Figure 1). The anastomosis is not covered with any soft tissue wrap. After the completion of the anastomosis, it is checked by ventilating the lung up with a maximum airway pressure of 30 cm of water.

The discharged patients were followed-up in the outpatient setting. All complications and mortalities were recorded. Local recurrence was defined as recurrence of disease at the bronchoplasty site or in lymph nodes in the ipsilateral hilum or in the mediastinum. All other sites of failure, including the contralateral hilum, were considered distant recurrences. Operative mortality was defined as death occurring within 30 days of the operation, or death directly related to the procedure even if it occurred more than 30 days after the operation.

Statistical analysis

Statistical analysis was performed using the SPSS version 16.0 software (SPSS Inc., Chicago, IL, USA). Descriptive data were expressed in mean, standard deviations and percentages for qualitative variables. The Fisher's exact two-tailed test, Pearson's chi-square test, and binary logistic regression test were used to determine factors affecting mortality and survival. Survival was defined as the interval between date of surgery and date of death or last follow-up. Survival analysis was performed using the Kaplan-Meier method. Survival comparison was made using the log-rank test and Cox's regression analysis. A p value of <0.05 was considered statistically significant.

RESULTS

Of the patients operated due to NSCLC in our clinic, 261 patients underwent pneumonectomy, 1,041 lobectomy and 85 bronchial sleeve lobectomy between May 2007 and November 2015.

Of the 85 bronchial sleeve lobectomy patients, 25 (29.4%) received neoadjuvant and 36 (42.4%) received adjuvant chemotherapy. The most common resection performed was right upper sleeve lobectomy with 55 patients (64.7%). When postoperative final diagnoses were examined, 75 patients (88.2%) were found to have squamous cell carcinoma (Table 1).

During the first week, FOB was performed to check the anastomosis line on the patients who underwent bronchoplastic procedure. In addition, in follow-ups, the anastomosis line was checked through FOB when bronchial complication was clinically or radiologically suspected. After bronchoplastic procedure, complication was detected in seven patients (8.2%). Two (8%) of these were the patients receiving neoadjuvant therapy. Two of the anastomotic complications were hemoptyses due to bronchial hemorrhage, two were stenoses, one was fistula, one was obstruction and one was atelectasis (Table 2). Recurrence was observed in 25 patients (29.4%). Eleven (12.9%) of these had distant, 12 (14.1%) had local, and two (2.4%) had both local and distant recurrence. Only five (5.9%) of the local recurrences were in the bronchoplasty area.

Tumor was smaller than 3 cm in 49 patients (57.6%) and larger than 3 cm in 36 patients (42.4%). Five-year

Table 2. Complications related to bronchoplastic procedure

Complication related to surgical procedure	n	%
Absent	78	91.8
Present	7	8.2
Hemorrhage	2	2.35
Stenosis	2	2.35
Fistula	1	1.17
Obstruction	1	1.17
Atelectasis	1	1.17

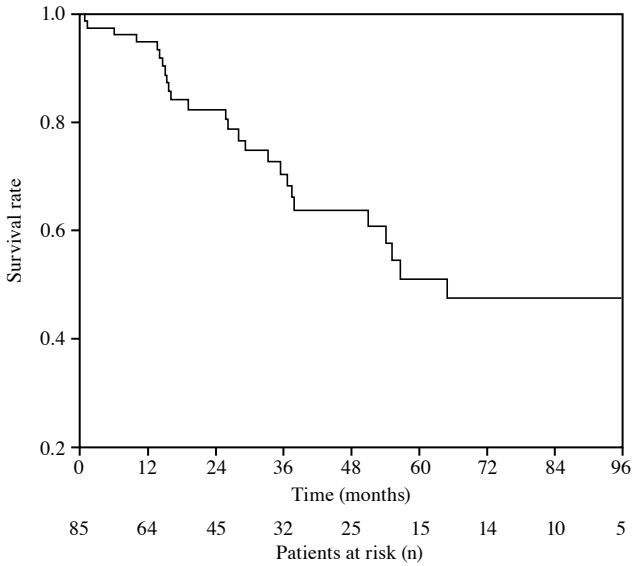

Figure 2. Overall survival graphic of patients having sleeve lobectomy (five-year survival 50.9%).

survival was 67.5% for tumors smaller than 3 cm and 23.6% for those larger than 3 cm, and the difference between the two groups was statistically significant (p=0.002).

Thirteen patients (15.3%) had mediastinal lymph node metastasis (N2). The mean five-year survival was 50.9%. While five-year survival was 14.7% in patients with N2 disease, it was 56.9% in 72 patients (84.7%) who did not have N2 disease. There was a statistically significant difference between the two groups (p=0.0001).

Table 3. Variables effective on survival according to Cox regression model

Variables	*p*	Risk ratio
Extended resection		
Absent	0.03	2.6
Present		
N disease		
N0 and N1	0.012	3.5
N2		

Extended resection was performed on 21 patients (24.7%), which was found to have a statistically significantly adverse effect on survival (p=0.03).

Mortality was observed in one patient within the first postoperative 30 days (1.2%) and between 30-90 days in the other (2.4%).

When all patients were considered, the mean duration of follow-up was 35±29.9 months, median survival time was 65.2 months, and five-year survival rate was 50.9% (Figure 2). In the Cox regression analysis, the variables effective on survival, extended resection and node status, were found to be statistically significant (p=0.03 and p=0.012, respectively; risk ratio: 2.6 and 3.5, respectively) (Table 3).

Table 4. Local recurrence, operative mortality and survival after sleeve lobectomy for bronchogenic carcinoma

First author	No. of patients	Local recurrence	30-day operative mortality	5-year survival
	n	%	%	%
Shi et al.[24] (Review)	1316	14.4	2.9	48.9
Tedder et al.[6] (Review)	614	12.5	5.5	40
Okada et al.[12]	60	8	0	48
Tronc et al.[25]	184	22	1.6	52
De Leyn et al.[7]	77	18	3.9	45.6
Hanagiri et al.[1]	24	NA	0	70
Ludwig et al.[10]	116	NA	4.3	39
Kim et al.[26]	49	32.6	6.1	53.7
Deslauriers et al.[9]	184	22	1,6	52
Yildizeli et al.[27]	218	4.6	4.1	53
Kutlu and Goldstraw[19]	100	4.1	2	NA
Present study	85	16.5	1.2	50.9

NA: Not available.

DISCUSSION

Sleeve lobectomy has been developed as an alternative to pneumonectomy in lung cancer patients with limited respiratory reserve for the preservation of healthy pulmonary tissue distal to the tumor. In addition to this, because of its lower mortality and morbidity rates than pneumonectomy, it is also performed on patients with adequate respiratory reserve. In the literature, the rate of sleeve resection varies between 5-8% in resectable pulmonary malignancies.[6] This rate was 6.1% in our series.

The first step of deciding on sleeve resection is bronchoscopy. In bronchoscopy, biopsy samples can be taken from the proximal and distal areas of the intended surgical margins to determine the tissue diagnosis and the extent of bronchial resection. However, the final decision is always established during the operation by evaluating the macroscopic lesion and frozen section (F/S) of the cross-section. In order to minimize the risk of recurrence, it is recommended to check essentially with F/S examination during operation.[8]

In reports comparing sleeve lobectomy with pneumonectomy, it has been shown that sleeve lobectomy has higher survival rates with lesser complications and lower postoperative mortality.[9-12] In a NSCLC series including 60 pneumonectomy and 60 sleeve lobectomy cases, Okada et al.[12] reported that postoperative mortality and complication rates were higher in the pneumonectomy group. In the same series, five- and 10-year survival rates were superior in the group of sleeve lobectomy. It was stated that sleeve lobectomy should be performed instead of pneumonectomy in NSCLC where complete resection could be achieved, with less postoperative risk than pneumonectomy.[13] In sleeve lobectomy, postoperative mortality has been reported to be in the range of 0-6.1% and five-year survival was between 39-70% (Table 4). The mean five-year survival rate of our study was 50.9%. Mediastinal lymph node metastasis appears to be the most important negative prognostic factor affecting long-term survival of sleeve resections. Van Schil et al.[14] reported that after sleeve lobectomy, survival of N2 disease was significantly shorter than N0 and N1 disease. Naruke[15] reported a five-year survival rate of 50% for N0, 46% for N1, and 33% for N2 in a series of 111 cases with sleeve resection. In addition, N2 disease was an important predictive value in distant recurrences.[16] Therefore, the role of sleeve resections in patients with N2 disease has not been properly defined yet. In our series, N2 disease was found to affect survival negatively. The five-year survival rates were 56.9% in N0/N1 and 14.7% in N2. According to our results, other important variables negatively affecting survival were tumor size and extended resection. Five-year survival was significantly lower in patients with tumors larger than 3 cm and in those undergoing extended resections. Surprisingly, unlike some other reports, survival was superior in patients receiving neoadjuvant therapy in our series; however, the difference was not statistically significant.[17]

The most frightening complication of sleeve resections is separation of the anastomotic line in the early period. Some thoracic surgeons, therefore, are hesitant to use the continuous suture technique. Other major complications are bronchial stenosis, granulomas in the suture line and bronchovascular fistula. Such complications can lead to other problems such as atelectasis, hemoptysis, respiratory failure, pneumonia or pneumothorax. Anastomotic complications can be prevented through careful dissection, preservation of blood flow and precise anastomosis. In a report presented by Bayram et al.,[5] two different anastomosis techniques were compared and there was no difference in anastomotic healing. They also showed that the continuous suture method is completed in shorter time than the interrupted technique. Nowadays, considering that sleeve resections are being performed using thoracoscopic methods, like many surgical techniques, the continuous suture technique, which is completed in shorter time with similar reliability, has grown in importance.[18] Kutlu and Goldstraw[19] discussed the differences between the interrupted technique and the continuous suture technique in the context of the literature and emphasized that the results were similar.

Several studies have been conducted specifically to investigate the effect of neoadjuvant therapy on anastomotic complications. While some studies suggest that neoadjuvant therapy does not have any negative effect,[17,20,21] some studies have reported that it increases the complications.[22] In our series, bronchial anastomotic complications occurred in two (8%) of 25 patients who received neoadjuvant therapy, and five (8.3%) of 60 patients who did not receive neoadjuvant therapy. Due to the similar complication rates in both groups, we suppose that neoadjuvant therapy does not have any negative effect on anastomotic healing and that sleeve lobectomy can be performed safely after induction therapy. We believe that it is not necessary to support the anastomosis line with living tissue flaps in these patients. However, due to different opinions on this subject, there is a need for randomized prospective studies to better evaluate the effect of neoadjuvant therapy on anastomotic healing. In the literature, the

rate of bronchopleural fistula varies between 1-14% in sleeve resections and 2-10% in pneumonectomies.[10] This rate was 1.17% in our patients. Our choice for bronchial anastomosis is absorbable suture material. In Van Schil's study,[14] 28 patients with non-absorbable suture material (polypropylene) and 105 patients with absorbable material (polyglactine) were evaluated in terms of bronchostenosis. It was concluded that pneumonectomy was needed more in the group using non-absorbable suture material, due to bronchostenosis, although the difference was not statistically significant.

Local recurrence is a serious problem in patients undergoing sleeve resection due to bronchial carcinoma. Local recurrence rate ranges from 4.6-32.6% in the literature (Table 4). In our series, local recurrence after sleeve lobectomy was 16.5%. Of these, 5.9% were on the bronchial suture line and 10.6% were non-bronchial local recurrence. Recurrence on the suture line may be related to not obtaining enough bronchial surgical margin to be able to perform sleeve lobectomy other than pneumonectomy.[6] In a study comparing local recurrence in sleeve lobectomy with that in pneumonectomy, this rate was 22% for sleeve lobectomy and 35% for pneumonectomy.[9] However, there are also publications reporting the exact opposite.[23] These different outcomes may be due to the lack of the exact definition of local recurrence in most studies.

The main limitation of this study is the non-randomized and retrospective nature. Unknown confounding variables and imbalance between patient characteristics may have caused bias in the results. Moreover, because all patients were from a single center, the results are not necessarily generalizable to other populations. Lastly, further research is required with larger samples and longer follow-ups.

In conclusion, sleeve lobectomy can be safely performed using continuous suture technique with minimal parenchymal loss, low mortality and low local recurrence, including patients receiving neoadjuvant therapy. In addition, long-term outcomes are oncologically similar to pneumonectomy and it provides better quality of life. For this reason, we believe that sleeve lobectomy should be preferred as a surgical alternative to pneumonectomy in each technically feasible case.

Declaration of conflicting interests

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