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Pneumonectomy for left-sided non-small cell lung cancer: analysis of 111 cases over 10 years

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Abstract

Background: Pulmonary resection is the preferred therapeutic option for non-small cell lung cancer (NSCLC). Despite the physiological insult, pneumonectomy (PN) may be unavoidable in patients with early-stage central tumors. This study aimed to analyze the management of early-stage left-sided NSCLC by PN.

Methods: This was a prospective observational study of patients with different stages of NSCLC who underwent left PN over a 10-year period. In-hospital morbidity and mortality and long-term survival were calculated.

Results: A total of 111 patients were enrolled (aged 46–80 years). Preoperatively, 53.2% of patients had stage IIIA, 32.4% stage IIB, and 14.4% had stage IIA disease. Postoperatively, the number of patients with stage IIA and IIB decreased while stage IIIA increased. All PNs were radical. The 5- and 10-year survival rates in stage IIA patients were 42.8% and14.2%, respectively, in stage IIB patients were 56.25% and 3.1%, and the 5-year survival in stage IIIA patients was 22. 5%. The overall 1-, 2-, 5-, and 10-year survival rates were 94.6%, 77.47%, 34.23%, and 2.7%, respectively.

Conclusions: The operative mortality, morbidity, and 5-year survival rates of patients with NSCLC after PN matched the international standards. Left PN might be unavoidable for patients with centrally located tumors.

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Introduction

Non-small cell lung cancer (NSCLC) remains the leading cause of cancer-related mortality in men and women, with a cumulative all-stage 5-year survival rate of around 20%.[1] The affected side influences the therapeutic algorithm and quality of life:[2,3] patients with right-lung NSCLC have a poorer quality of life than those with left lung cancer. This discrepancy can be explained by many factors, including the size of the right lung and its contribution to respiratory function. NSCLC of the right lung also has a tendency towards earlier invasion of the vital structures of the hilum, and less chance of successful curative resection.[3]

The recommended surgical treatment for most stages of NSCLC includes anatomical pulmonary resection combined with mediastinal lymph node dissection or sampling.[2] Video-assisted thoracoscopic surgery (VATS) resection via either multiple or single ports is considered to be cost-effective and associated with less perioperative morbidity and mortality.[4] The overall 5-year survival rate for patients with stage I NSCLC treated with lobectomy is 55% to 77%, compared with only 6% for non-operated patients. Administration of adjuvant chemotherapy after surgery may also prolong survival.[2,3]

Pneumonectomy (PN) is a valuable surgical option for patients with anatomically resectable NSCLC when lobectomy or sleeve resection (bronchoplastic or angioplastic) cannot provide the required safe margins.[5] However, PN is associated with significant morbidity and mortality in patients with lung cancer, and there have been conflicting reports concerning the risk factors associated with poor outcomes following PN.[4,5]

Most evidence suggests that right-sided lung resection is associated with increased complications and mortality due to the increased risk of broncho-pleural fistulae.[5] However, no study has focused on the short- and long-term outcomes of left PN (LPN) in patients with various stages of NSCLC. In the current study, we therefore aimed to determine the outcomes in a series of patients undergoing LPN.

Patients and methods

This was single-center, prospective, observational study. Patients undergoing elective PN for lung cancer from 1 January 2007 to 31 December 2017 at the Department of Surgery, College of Medicine, University of Sulaimani, were eligible for inclusion in the study. Patients underwent all necessary preoperative investigations including arterial blood gas analysis, pulmonary function testing, flexible fiberoptic bronchoscopy (Figure 1), and chest (Figure 2), upper abdomen, and brain computed tomography. Suspected distant metastasis was ruled out by abdominal ultrasonography and skeletal bone survey with or without positron emission tomography scans; however, the latter was not available in our center at the beginning of the study. Mediastinal staging was

Figure 1. Flexible fiberoptic bronchoscopic image showing left upper lobe tumor invading left lower lobe bronchus.

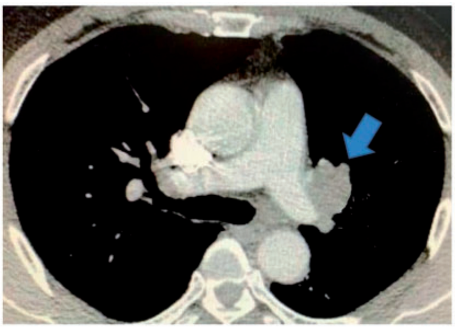

Figure 2. Chest computed tomography scan of a large T4 tumor with partial invasion of aortopulmonary window.

performed non-invasively. Noninvasive and/or invasive cardiac assessment was performed in all patients. Pre-, intra-, and postoperative details and outcome variables were collected by clinical assessment, patient inquiry, and review of any inpatient admissions. An information sheet (simulating a questionnaire) was designed containing detailed demographic and clinical features and information on various aspects of the patient's management from admission to discharge, as well as during the follow-up period.

We only included patients for whom PN was the intended primary procedure or who were scheduled for more limited lung resection but required on-table conversion to PN. We excluded all patients who underwent pleuro-PN, completion PN following previous lobectomy, and PN for benign disease.

Approval for this study was obtained from Sulaimani DOH Institutional Review Board (full name and number available on request; Act No. 491/3/2017) and the Ethics Committee of the Ministry of Health (#: 123/53/2/2017). Written informed consent was provided by all participants, including for the use of their operation photos and images for scientific publications only.

Patient scoring

Breathlessness was assessed and scored according to the MRC Breathlessness Scale.[6] Body mass index (BMI) was calculated according to the equation: BMI = weight in kilograms/(height in meters)^2 and patients were classified as having a subnormal body weight (<18.5) or healthy body weight (18.5–24.9), or as pre-obese (25–29.9), obesity I (30–34.9), obesity II (35–39.9), and obesity III (≥40). Performance status (PS) was scored according to the Zubrod or ECOG scale.[7] The American Society of Anesthesiologists (ASA) score was calculated for each patient.[8]

Indications and preparation for surgery

Surgery was recommended for patients with stage IA, IB, IIA, IIB, or IIIA NSCLC according to the 8th TNM classification. Patients were prepared according to the protocol for major pulmonary surgery. Smokers were asked to quit smoking for at least 2 weeks prior to surgery and any chest infections were treated. Two units of cross-matched blood were made available. No patients underwent VATS pneumonectomy in this study.

Thoracoscore

Probable in-hospital mortality of each patients was predicted using Thoracoscore[9] based on nine variables: age, sex, ASA score, PS classification, dyspnea score, priority of surgery, procedure class, diagnosis group, and co-morbidity score.

Surgery

All operations were done via selective one-lung ventilation through an advanced single-lumen endotracheal tube to the right main bronchus; no double lumen endotracheal intubation was used in this case series. Surgery was carried out via muscle-sparing postero-lateral thoracotomy. The standard technique was used in all cases.[10]

In this series, LPN was either or extended. No routine pleural space drainage was employed. Final pathological staging was made based on the results of histopathological examination of the resected specimen and mediastinal lymph nodes. In the case of a discrepancy between the histopathological results for the bronchoscopic biopsy and operative specimen, the latter results were adopted.

Result interpretations

The results of this study included intraoperative and postoperative events recorded by reviewing the patients' medical files. Complications were defined according to the Association of Surgeons of the Netherlands (ASN) as any state or event unfavorable to the patient's health, arising during admission or within 30 days after discharge that either caused unintentional injury or required additional treatment.[11] Pneumonia was diagnosed if there were clinical and radiological signs consistent with right lung pneumonia requiring antibiotics. Operative mortality included all intraoperative and in-hospital deaths at any postoperative day, or death outside the hospital within the first 30 days after the operation. Survival time was defined as the time from diagnosis until death or last follow-up.[11] Patients were mainly followed up by their referring physicians and our outpatient clinic; however, the operating surgeon was involved in the event of a surgical complication such as empyema or bronchopleural fistula.

Statistical analysis

The data were analyzed using SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics (means, numbers, and percentage) were calculated.

Results

This study enrolled 111 patients (90 men and 21 women; male:female ratio 4.3:1; mean age 61.5 ± 7.9 years; age range 46–80 years). The annual rate of LPN varied among years; it was relatively low in the first 3 years of the study, increased over the next 4 years, and declined thereafter, with an overall annual rate of 11.1 cases per year. Eithgy-nine right PNs (RPNs) were performed for lung cancer during the same period, giving an LPN:RPN ratio of 1.24:1.

In addition to a male predominance, most patients were in their sixth decade (n = 46, 41.4%) followed by the seventh decade (n = 39, 35.2%). The youngest patient was a 46-year-old man and the oldest was an 80-year-old man. Unresolved cough was the most common symptom (n = 97, 87.4%) and smoking was the main co-morbidity (n = 110, 99.1%). Most patients (n = 102, 91.9%) had a relatively good PS. ASA scores indicated that most patients (n = 89, 80.2%) suffered from mild systemic disease. Considering the different grades of breathlessness score, most patients (n = 100, 90.1%) performed well. Regarding BMI, no patient was underweight and all patients had either a normal or increased body weight. According to Thoracoscore values, many patients (n = 41, 37%) had a high or very high chance of dying within 30 days of surgery.

All patients in this series had visible endobronchial tumors. The endobronchial locations of the left lung cancers are shown in Table 1. The most common location was the left upper lobe bronchus invading the left main bronchus n = 54 (48.4%). Almost all patients (n = 110, 99.1%) had either a normal ejection fraction or mild left ventricular dysfunction.

More than half of the patients (n = 59, 53.2%) had stage IIIA and almost a third (n = 36, 32.4%) had stage IIB disease. Relatively few patients had very early disease (stage IB and IIA; n = 16, 14.4%). Notably, the number of patients with stage IIA and IIB disease decreased after surgery while the number with stage IIIA increased. However, there was no significant difference in Z scores between the preoperative and postoperative populations (Table 2).

All LPNs in this study were radical. Mediastinal lymph node removal was mostly (n = 102) complete and the other patients (n = 9) had sampling of multiple lymph node stations (5, 7, and 9) (Figure 3 and Figure 4). Surgery was uneventful in most patients (n = 104, 93.7%), with few significant intraoperative events (cardiac arrest; n = 1, bleeding from superior pulmonary vein; n = 2, transient supraventricular tachycardia; n = 3 and pulmonary edema; n = 1).

Table 1. Location of left lung cancers.

Site	n (%)
LUL invading MSB	54 (48.4)
LLL invading MSB	39 (35.2)
LMB >2 cm (for PN)	18 (16.2%)
Total	111 (100)

LUL, left upper lobe; MSB, main stem bronchus; LLL, left lower lobe; LMB, left main bronchus; PN, pneumonectomy.

Table 2. Preoperative (clinical) and final (pathological) staging.

Stage	Preoperative, n (%)	Final (pathological), n (%)
IB	1 (0.9)	1 (0.9)
IIA	15 (13.5)	7 (6.3)
IIB	36 (32.4)	32 (28.9)
IIIA	59 (53.2)	71 (63.9)
Total	111 (100)	111 (100)

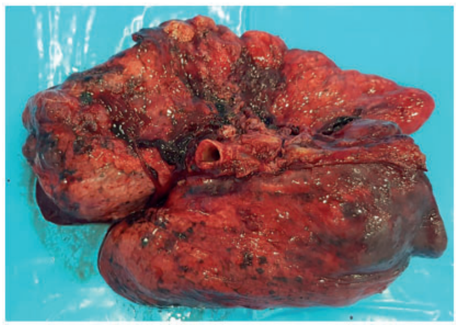

Figure 3. Left lung specimen.

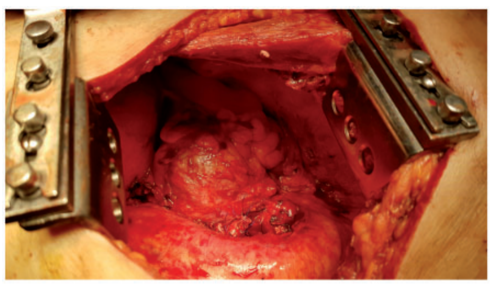

Figure 4. Post-pneumonectomy space and left mediastinum and dissected lymph nodes.

The mean duration of hospitalization was 9 days (range 5–28 days), with 51 patients (46%) staying in hospital for <1 week.

Almost two thirds of patients developed no postoperative complications. Surgical site infection was the leading complication (n = 22, 19.8%). Five patients (4.5%) required prolonged endotracheal intubation for >48 hours, and two of these five patients ultimately died. Other less frequent complications included atrial fibrillation, early empyema, pneumonia, bronchopleural fistula, deep vein thrombosis, urinary tract infection, and upper gastrointestinal bleeding (Table 3).

Five patients (4.5%) died within 30 days of surgery. All were men (mean age 65.8 years; range 54–78 years). Four out of five (80%) had stage IIIA disease and three (60%) had a high or very high Thoracoscore value. All five patients died of non-cancer-related causes. Notably, only one of 15 patients (6.7%) aged >70 years died in this period. In addition to these five patients, three (2.7%) died in the first postoperative year and six (5.4%) in the second year (Table 4). Most patients reached the end of the 2-year follow-up period uneventfully (n = 84, 75.7%).

Local recurrence at 1 year occurred in 4.5% of patients overall, of which about 45.6% occurred in patients with stage IIIA disease. These patients were treated with radiotherapy alone. The causes of early in-hospital death are detailed in Table 4.

Regarding long-term survival analysis, the 1-, 2-, 5-, and 10-year survival rates in patients with stage IB, IIA, IIB, and IIIA disease are shown in Table 5. The overall survival rates are shown in Table 5 and Figure 5.

Table 3. Postoperative complications.

Complication	n (%)
SSI	22 (19.8)
Prolonged intubation	5 (4.5)
AF	2 (1.8)
Empyema	3 (2.7)
Aspiration pneumonia	1 (0.9)
BPF	1 (0.9)
DVT	1 (0.9)
UTI	2 (1.8)
Upper GI bleeding (malena)	1 (0.9)
No complications	73 (66.7)
Total	111 (100)

SSI, surgical site infection; AF, atrial fibrillation; BPF, bronchopleural fistula; DVT, deep vein thrombosis; UTI, urinary tract infection; GI, gastrointestinal.

Discussion

There are currently no published studies in English focusing on LPN in patients with NSCLC. Although the current case series was relativity small, the duration of follow-up and homogeneity of the variables in most cases made the present study unique in this regard. The low rate of LPN at the beginning of this study could have been related to low patient referral, which then gradually increased. Damage to the right

Table 4. Details of patients who died early.

ID	Age, sex	Clinical stage	Thoracoscore	Final stage	Time & cause of death
10	78, M	IIIA	19.5 (very high)	IIIA	28 days, sepsis
31	54, M	IIIA	8.1 (very high)	IIIA	6 days, ACS
56	67, M	IIB	6.2 (high)	IIB	3 days, ACS
58	62, M	IIIA	3.1 (moderate)	IIIA	3 days, ACS
106	68, M	IIIA	5 (moderate)	IIIA	22 days, stroke

M, male; ACS, acute coronary syndrome.

Table 5. Long-term survival according to stage.

Stage	Number of patents in each stage	Surviving patients after 1 year, n (%)	Surviving patients after 2 years, n (%)	Surviving patients after 5 years, n (%)	Surviving patients after 10 years, n (%)
Stage IB	1	1 (100%)	1 (100%)	1 (100%)	1 (100%)
Stage IIA	7	7 (100%)	6 (85.7%)	3 (42.8%)	1 (14.2%)
Stage IIB	32	31 (96.85%)	30 (93.75%)	18 (56.25%)	1 (3.1%)
Stage IIIA	71	67 (94.3%)	49 (69.01%)	16 (22.5%)	0 (0%)
Total survival	111	106 (94.6)	86 (77.47%)	38 (34.23%)	3 (2.7)

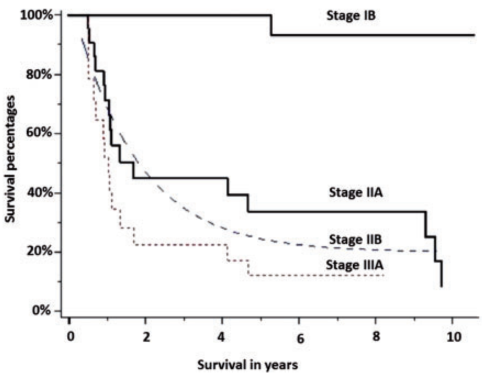

Figure 5. Kaplan–Meier survival estimate.

lung carries a higher physiological insult and is associated with higher morbidity and mortality, and fewer RPNs than LPNs were therefore carried out in our center and elsewhere.[12] The rate of LPN in the present study was higher than in many international studies (Table 6). There are several possible explanations for this: 1) a high rate of lung cancer and its early detection in the Kurdistan region compared with other parts of the country; 2) a higher percentage of early-stage lung cancer detection; 3) the influence of the civil war and internal people displacement; and 4) a high number of surgeons and early referral by multidisciplinary teams.

Male sex is a risk factor for lung cancer.[13–15] This may be because men start smoking at a younger age, and a long duration of smoking is required before the development of cancer. This may explain the high rates of lung cancer in sixth and seventh decades of life. However, patients who start smoking earlier in life are also more prone to develop lung cancer than those who start smoking later.[5,7,9]

Most patients in the current series (n = 102, 91.9%) had a relatively good PS, while ASA scores indicated that most (n = 89, 80.2%) were either healthy or had only mild systemic disease. This finding could be related to the stage of lung cancer in the study patients. This may be an important point in selecting patients for PN to obtain better long-term survival.

No patient in the current study was underweight and all patients had either normal or increased body weight. This could be because of the early stage of lung cancer in the studied patients. This observation was in accord with that of Faeh et al.[16]

No induction chemotherapy was implemented in the current patients because we and others[17] believe that induction chemotherapy might increase the rates of perioperative morbidity and mortality.

The Thoracoscore values in our series indicated that many patients (n = 41, 37%) had a high or very high chance of dying within 30 days of surgery. However, only five patients actually died within 30 days of surgery, suggesting that the Thoracoscore largely failed to predict operative mortality after PN in our group of LPN patients. This finding is in agreement with many other studies.[9,11,13]

Table 6. Hospital-based prevalence of pneumonectomy in other studies.

Reference, country	Prevalence	Comment
Present study, Iraq	11.1 cases per year	LPN
Aytekin et al.,[26] Turkey	5.7 cases per year	LPN
Parissis et al.[14]	16 cases per year	Both RPN and LPN
Thorsteinsson et al.,[18] Iceland	2.26 cases per year	LPN
Sartipy et al.,[27] Sweden	8 cases per year	Both RPN and LPN
Powell et al.,[5] UK	2–38 PN/center/year	Both RPN and LPN
Veen et al.,[11] Netherlands	10.6 cases per year	LPN

PN, pneumonectomy; LPN, left pneumonectomy; RPN, right pneumonectomy.

We systematically adopted either mediastinal lymph node sampling or dissection, which explains why the numbers of patients with stage IIA and IIB disease decreased while the number with stage IIIA increased. This increase could be due to a large number of occult N2 cases in our series. Such upstaging could be prevented by more extensive preoperative staging work-ups using positron emission tomography, endobronchial ultrasound, or mediastinoscopy; however, these are currently unavailable in our region.

In accordance with other studies,[3,5,11] about one third of our patients developed complications, though fortunately most of these complications were managed conservatively. Notably, prolonged intubation may indicate an inadequate pulmonary reserve necessitating longer ventilator support. The occurrence of atrial fibrillation was low in our study, in contrast to Thorsteinsson et al.[18] who reported a complication rate of 21%. This apparent discrepancy may be related to the good preoperative cardiac status of our patients, most of whom had normal cardiac function or mild LV dysfunction.

Early operative mortality in this series was 4.5%, which was lower than in some other studies, such as that of Parissis et al.[14] (8.5%). In contrast, Annessi et al.[15] reported an operative mortality of 1.4% to 2.5% which was almost half the rate in our study, while a study from Iceland[18] showed an operative mortality after PN of 3.9%, which was close to the current study.

Only 1 of 15 patients (6.7%) aged >70 years died during the current study, indicating that PN is safe even in older adult patients. This finding was in accord with Annessi et al.[18] who considered that although age was a risk factor for morbidity and mortality in patients undergoing PN, the risk was still acceptable.

Long-term survival analysis of patients with stage IIA disease revealed similar results to many other studies.[5,9,11,13] In contrast, the rates for stage IIB patients were slightly superior to other reports.[5,9,13,15,19] The long-term survival rates for patients with stage IIIA disease were also similar to many other studies that reported outcomes for heterogeneous lung cancers, unlike our series which only considered left-sided lung cancer.[5,15,19]

Long-term survival after PN for stage IIIA NSCLC was within an acceptable range in our case series. As noted above, no patients with stage IIIA NSCLC underwent induction chemotherapy because, in agreement with Shah et al.,[20] we believe that induction therapy may significantly increase the incidence of postoperative complications following PN.

Improving overall survival remains a major challenge in lung cancer management, especially in developing countries where late presentation limits improvements offered by new techniques. Lobectomy has now become the standard surgical option for lung cancer, and increasing numbers of patients with early and localized cancers are currently being managed by segmentectomy and sleeve lobectomy, resulting in significant reductions in perioperative morbidity and mortality and increased survival rates.[19,21] Clinical-stage analysis in our study showed a significantly larger proportion of locally advanced lung cancers, thus negating the performance of these parenchyma-preserving surgeries in most of our patients. Moreover, PN is often required to achieve complete resection with negative margins in patients with large and centrally located tumors.

Pneumonectomy has generally been criticized because of the potential related complications, leading to a shift to alternative treatments, most notably radiation therapy, as an alternative to surgery.[22]

Overall, most studies showed higher perioperative mortality associated with PN (5.9–6.2%) compared with lobectomy (1.5%–3.2%). However, perioperative mortality depended on the patient's age, the presence of comorbidities, use of induction therapy, surgical expertise, anesthesia care, and postoperative management, and not just on the type of surgery performed.[13,17–19] The similar perioperative outcomes of lobectomy and PN in our study might thus have been due to better patient selection, preoperative evaluation, and optimization prior to surgery.

Better patient selection is key to successful surgery. Appropriate selection has been facilitated by advances in the fields of radiology and nuclear medicine, which help to improve staging, assess resectability, and further plan appropriate multimodality treatments. Preoperative cardiopulmonary clinical evaluation with lung ventilation perfusion scan, diffusion capacity of lung for carbon monoxide, and stress echo might have helped to identify patients optimally fit to undergo radical surgery.[16,22–24]

Multimodality treatment is the preferred option in patients with stage IIIA NSCLC. Neoadjuvant treatment may convert some unresectable tumors to resectable ones without significantly affecting postoperative mortality, and complete resection is seen to be essential for increasing survival.[15,25] Most studies found no survival benefit in patients undergoing radical surgery after neoadjuvant therapy due to higher rates of complications and mortality with PN.[7,11] This prevented some patients from being offered the option of curative surgery. However, recent studies have reported that the mortality rate for PN was significantly lower (as low as 6%) than that seen in the intergroup 0139 trial (25%), indicating acceptable risks and preventing patients from being deprived of the potential survival benefits.[12,20–24] Other studies have focused on other factors affecting outcomes, such as different chemotherapy regimens and the responses to them, methods of staging and restaging, and anatomical and cardiopulmonary factors, as possible factors for selecting patients.[25]

In our series, that <30% of the patients received adjuvant therapy, together with factors such as tumor size, central location, the presence of peri-hilar lymph nodes, and post-therapy fibrosis, indicated a need for PN in 45.8% of cases. PN was considered to be safe and feasible even after neo-adjuvant therapy, given no increase in perioperative mortality. Previous studies demonstrated similar median overall survival in patients undergoing PN and lobectomy after neoadjuvant therapy, confirming the role of PN in multimodality management.[3,23,26,27]

This study had some limitations. It was a retrospective study of a small number of cases with a relatively short-term follow-up. However, the results may provide the basis for randomized trials re-evaluating the role of PN in patients with locally advanced cancers otherwise unfit for lobectomy, especially after neoadjuvant therapy. In addition, the study only enrolled cases of LPN, and the inclusion of a comparator group of patients with RPN in the same period would have been preferable. The results would also have been strengthened by comparing LPN with lesser left-sided pulmonary resections, such as sleeve resection and/or pulmonary lobectomies performed for lung cancers of comparable stages.

Conclusions

The current study demonstrated an operative mortality of 4.5% and morbidity rate of 33% after LPN, supporting the idea that LPN is associated with lower mortality and morbidity than RPN in tumors of comparable stages. Thoracoscore failed to accurately predict post-PN hospital mortality, and most patients survived the operation, despite having high or very high Thoracoscore results. The overall 5-year survival rate in our patients matched the previously reported rate (36.1% vs. 34.23%). Among the reported complications, atrial fibrillation was rare compared with previous reports, while the hospital-based prevalence of LPN was higher than in previous local and international studies.[5,9,13] Although PN is a major undertaking due to the loss of a lung, it might be unavoidable in patients with centrally located tumors.

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Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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