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Original Article

Long-term prognosis of patients with non-small cell lung cancer after bilobectomy and the associated risk factors

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Abstract: Objective: To determine the long-term outcomes associated with bilobectomy for non-small cell lung cancer (NSCLC) and to identify the associated risk factors. Methods: A cohort of 260 patients with NSCLC who underwent bilobectomy was enrolled in this study from June 2005 to January 2015 at our hospital. The clinical data of these patients were reviewed and analyzed retrospectively. All 260 patients were followed up from 12 months to 71 months with a median period of 54 months. Survival analysis were conducted to evaluate the 5-year and 10-year overall survival and disease-free survival, and the risk factors associated with prognosis were further identified. The risk factors associated to poor prognosis were confirmed by the Cox regression analysis. Results: Among 260 patients, there were 150 patients undergoing upper and middle bilobectomy and 110 patients receiving middle and lower bilobectomy. No patients died during surgery or within 30 days postoperatively. The complications within 30-day was 30.8%. Patients were followed-up from 12 months to 71 months with a median period of 54 months. Until the last follow-up (June 2016), a total of 116 deaths and 31 recurrences were reported. The 5- and 10-year overall survivals were 60% and 55.3%, respectively; the 5- and 10-year disease-free survivals were 50.8% and 43.5%, respectively. Cox regression analysis showed that clinical stage III and N2 disease were independent risk factors associated to poor prognosis. Conclusions: Bilobectomy is effective in the treatment of non-small cell lung cancer with a satisfactory long-term survival outcome.

Keywords: Bilobectomy, non-small cell lung cancer, prognosis, risk factors

Introduction

The common surgical methods of non-small cell lung cancer (NSCLC) in clinical treatment were bilobectomy and lobectomy. Then the bilobectomy has been considered to be associated with increased morbidity and mortality, and with decreased long-term survival and quality of life (QOL) compared with lobectomy in NSCLC. Bilobectomy was first reported in the treatment of bronchogenic carcinoma by Churchill in 1933 [1], but its features were not summarized until 1988 by Keller et al [2]. Bilobectomy is termed as the resection of two lobes of the right lung, including the middle lobe, which is a relatively uncommon surgical procedure in the treatment of NSCLC. Upper and lower bilobectomy, preserving the middle lobe, is not viable due to the marked mismatch between the size of the pleural cavity and that of the remaining lung [1]. Upper bilobectomy refers to the concomitant resection of the upper lobe, whereas lower bilobectomy refers to the concomitant resection of the lower lobe. Bilobectomy is thought to be an alternative option to pneumonectomy for primary lung cancer that achieves the balanced surgical effects of both curability and functional preservation. Furthermore, as right pneumonectomy has been reported to carry the highest risk of postoperative complications and mortality among all types of major pulmonary resections [2-5].

To date, information on the prognosis of NSCLC patients who received bilobectomy was very limited. It was reported that the morbidity and mortality post-bilobectomy were between that of lobectomy and pneumonectomy [6, 7]. However, most of the limited numbers of studies

were focused on the short-term outcomes such as the perioperative mortality and morbidity [8-10]. Long-term prognosis after bilobectomy has not been well studied, especially in NSCLC patients in Asia. Additionally, only a few studies that evaluate the long-term survival were conducted in America and European population [11-13, 15]. So there is a necessity to evaluate the long-term prognosis of NSCLC patients after bilobectomy, especially in Asian population.

In this study, a total of 260 patients with NSCLC who underwent bilobectomy were enrolled from June 2005 to January 2015 at our hospital. The clinical and follow-up data of these patients were reviewed and analyzed retrospectively. Survival analysis were conducted to evaluate the 5-year and 10-year overall survival and disease-free survival, and the risk factors associated with prognosis were further identified.

Material and methods

Patients

The inclusion criteria included: (1) patients who were diagnosed with NSCLC and confirmed pathologically; (2) patients who underwent bilobectomy as a radical treatment; (3) patients with complete clinical and follow-up data. The exclusion criteria included: (1) patients who were diagnosed with small cell lung cancer; (2) patients with distant metastasis.

Finally, a total of 260 patients with NSCLC who underwent bilobectomy were enrolled in this study from June 2005 to January 2015 at our hospital. For every patient enrolled, a complete diagnostic evaluation consisting of Bronchoscopy, chest, brain, and abdominal computed tomography (CT), ultrasounds of the liver, and a whole-body bone scan before surgery was performed to exclude the presence of distant metastasis. If necessary, the patients were examined with mediastinoscopy, positron emission tomography-CT. Patients with suspected mediastinal lymph node metastasis (N2 disease) underwent mediastinoscopic examination. When mediastinal lymph node metastasis was confirmed by mediastinoscopy, the patients were first treated with neoadjuvant therapy, after which they were assessed for surgical indications according to their response to neoadjuvant therapy.

This study complied with the Declaration of Helsinki, and was approved by the Ethics Committee of our institution. Written informed consent was waived because it was a retrospective study.

Information collection

Clinical and pathological information was obtained for the following: age, sex, the American Society of Anesthesiologists (ASA) score, surgical type, medical comorbidities, whether preoperative neoadjuvant therapy was applied, smoke status, surgical indications, histological tumor type, mediastinal lymph node metastasis, clinical stage, and surgical margin status. Mortality during the operation and 30 days postoperatively. Complications 30 days post operation, The clinical stage was classified according to tumor node metastasis (TNM) staging system of lung cancer (the 7th edition), which was proposed by the American Joint Committee on Cancer, the Union Internationale Contre le Cancer, and the International Association the American. Complications 30 days post operation were graded to be either major or minor using the Clavien-Dindo classification based on the following definitions: Grade 1: oral medication or bedside medical care required; Grade 2: intravenous medical therapy required; Grade 3: radiologic, endoscopic, or operative intervention required; Grade 4: chronic deficit or disability associated with the event; and Grade 5: death associated with surgical complication. Major complications were defined as grades 3, 4, and 5, and minor complications were classified as grades 1 and 2.

Follow-up

All patients were followed up until June 2016 by interviews in the outpatient settings and/or through telephone interviews, home visitations, or communication with family members. The patients were followed-up once every 3 months for the first year after surgery and were subsequently once every 4 months for the second year, once every 6 months for the third year, and once a year thereafter. The follow-up appointments included disease history, physical examination, routine laboratory tests, and brain/chest/abdominal CT scans. Patients with suspected bone metastases underwent bone scanning. Patients with suspected tumor recurrence were referred to our hospital. Locoregi-

Table 1. Clinical and pathological characteristics of patients undergoing bilobectomy

Characteristics	
Age (year)	62 (41-69)
Gender (n)	
Male	201
Female	59
FEV1 (%)	91 (73-116)
DLCO (mL/kPa.s)	79 (39-97)
Comorbidity (n)	
COPD	6
Hypertension	13
Diabetes Mellitus	7
Stable angina	6
Chronic atrial fibrillation	1
Chronic renal inadequacy	2
Number of comorbidity (n)	
0	230
1	25
2	3
3	2
ASA score (n)	
I	226
II	31
III	3
Neoadjuvant therapy (n)	
Yes	31
No	229
Surgical type (n)	
Upper-middle bilobectomy	150
Middle-lower bilobectomy	110
Smoking status (n)	
Nonsmoker	56
Past smoker	161
Active smoker	43
Histological type (n)	
Adenocarcinoma	146
Squamous cell carcinoma	102
Large cell carcinoma	12
Mediastinal lymph node metastasis (N2 disease)	
Yes	26
No	234
Clinical stage (n)	
IB	71
IIA	76
IIB	30
IIIA	83
Residual tumor (n)	
R0	241
R1	19

EV1: forced expiratory volume in 1 second. DLCO: diffusing capacity of carbon monoxide.

onal recurrence was defined if it occurred in (1) the bronchial stump or cut end of the lung parenchyma, (2) the ipsilateral pleura and/or chest wall, or (3) the ipsilateral hilar and/or mediastinal lymph nodes. Recurrence was defined as distant if it occurred in a separate lobe of the ipsilateral lung, contralateral thorax, supraclavicular lymph nodes, or in a distant organ. If distant recurrences were uncovered by systemic survey within a month after the detection of locoregional recurrence, these were defined as concurrent distant and locoregional recurrence. Disease-free survival (DFS) was calculated as the duration from the date of surgery to the date of first evidence of local recurrence, distant metastasis, or diagnosis of a second primary tumor or cancer-related mortality. Overall survival (OS) was calculated as the time from the date of surgery to the date of death from any cause.

Statistical analysis

SPSS 19.0 software (IBM company. Chicago, IL) was used for the statistical analysis. The survival analysis was conducted by using the Kaplan-Meier method and comparisons were performed using Log-rank tests. Univariate Cox regression analysis was used to identify the potential risk factors associated with the overall survival and disease-free survival. Subsequently, the factors with $P<0.05$ in the univariate analysis were included in the multivariate Cox regression analysis to determine the independent prognostic factors and explore their effects. All P values presented are 2-sided, and a $P<0.05$ was considered statistically significant.

Results

Patient characteristics

A total of 260 patients with NSCLC who underwent bilobectomy in our hospital between June 2005 and January 2015 were enrolled in this study, including 201 males and 59 females. At the time of surgery, the age of the patients was 41-69 years old with a median age of

Table 2. Indications of bilobectomy

Type of bilobectomy	*n*	Indication of bilobectomy
Upper and middle bilobectomy	93	Involvement of the minor fissure
	57	Double synchronous primary cancer
Lower and middle bilobectomy	67	Internal or external involvement of the bronchus intermedius
	26	Double synchronous primary cancer
	17	Invasion of the anterior part of the major fissure

Table 3. Perioperative complications and mortality

Variable	Data
Complications (n)	80
ARDS	6
Pulmonary embolism	3
Bronchopleural fistula	3
Respiratory failure	5
Prolonged air leak	20
Atrial arrhythmia	7
Atelectasis	16
Pleural effusion	8
Pneumonia	6
Acute coronary syndrome	6
Patients with major complications (n/%)	16
Patients with minor complications (n/%)	64

62 years (**Table 1**). Among all the patients, there were 30 patients with medical comorbidities, including 25 patients with one medical comorbidity, 3 patients with two medical comorbidities and 2 patients with three medical comorbidities. There were 150 patients undergoing upper-middle bilobectomy and 110 patients receiving middle-lower bilobectomy. There were 31 patients who received neoadjuvant therapy before surgery. For histological tumor type, there were 146 patients with adenocarcinoma, 102 patients with squamous cell carcinoma, and 12 patients with large cell carcinoma. Additionally, there were 71 patients in clinical stage IB, 76 patients in clinical stage IIA, 30 patients in clinical stage IIB, and 83 patients in clinical stage IIIA. The surgical margin status was R0 in 241 patients, and R1 in 19 patients. The surgical indications are shown in **Table 2**.

Perioperative complications and mortality

In this study, no patients died during the surgery or within 30 days postoperatively. Complications within 30 days post-operation are shown in **Table 3**. The total incidence of complications was 30.8%, with 6.2% major complications and 24.6% minor complications.

The long-term survival rate and prognostic factors

Patients were followed-up from 12 months to 71 months with a median period of 54 months. Until the last follow-up (June 2016), a total of 116 deaths (109 patients died from tumor recurrence, 5 patients died from ischemic stroke and 2 patients died from acute coronary syndrome) and 31 recurrences were reported. The 5- and 10-year overall survival rates were 60% and 55.3%, respectively; the 5- and 10-year disease-free survival rates were 50.8% and 43.5%, respectively (**Figures 1** and **2**).

To determine the risk factors associated with the survival, we firstly conducted the univariate Cox regression analysis, and the results showed that clinical stage III (P=0.013) and N2 disease (P=0.023) were negatively associated with overall survival. And age >65 years (P=0.021), TNM stage III (P=0.019), and N2 disease (P=0.031) were all negatively associated with disease-free survival. Then, multivariate Cox regression analysis was conducted and the results indicated that clinical stage III and N2 disease were independent risk factors associated with both overall survival and disease-free survival, indicating clinical stage III and N2 disease were independent predictors of poor prognosis (**Tables 4** and **5**).

Discussion

It was reported that, bilobectomy presented a higher rates of postoperative complications and mortality by comparison with lobectomy [13, 14], which may be attributed to one additional lobe resection during the surgery. In this

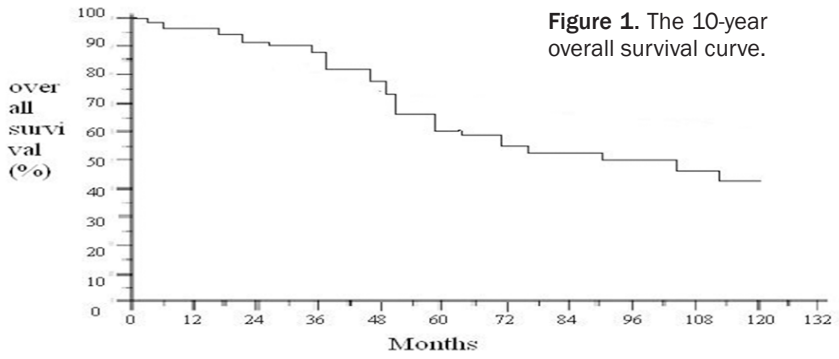

Figure 1. The 10-year overall survival curve.

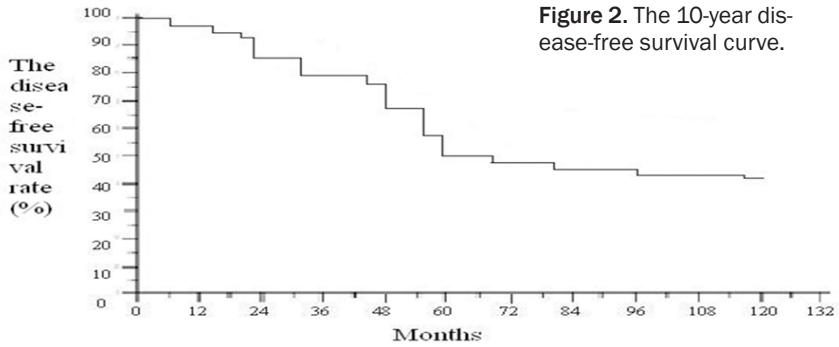

Figure 2. The 10-year disease-free survival curve.

Table 4. Univariate analysis of clinical and pathological characteristics to overall survival and disease-free survival

Characteristics	Overall Survival		Disease-free survival	
	χ^2	*P*	χ^2	*P*
Age (>65 years or ≤65 years)	13.556	0.059	26.243	0.021
Gender	9.343	0.087	10.012	0.078
FEV1	12.198	0.067	13.024	0.063
DLCO	11.436	0.072	13.208	0.061
Comorbidity	15.472	0.052	12.110	0.068
Number of comorbidity	9.016	0.091	9.731	0.082
ASA score	8.324	0.102	7.213	0.153
Neoadjuvant therapy	7.764	0.127	9.526	0.084
Surgical type	13.111	0.062	11.123	0.074
Smoking status	12.249	0.066	13.551	0.059
Histological type	14.836	0.055	9.842	0.079
Mediastinal lymph node metastasis (N2 disease)	25.071	0.023	21.139	0.031
Clinical stage	29.237	0.013	27.984	0.019
Residual tumor	12.004	0.069	13.206	0.061

FEV1: forced expiratory volume in 1 second. DLCO: diffusing capacity of carbon monoxide.

study, the 30-day mortality post operation was 0%. It was inconsistent with the previous report, which showed that mortality post operation ranged between 0.97% and 6.1%. The possible reasons for the lower mortality in our study may be due to the extensive experience of the surgeons (All surgeions in this study had conducted bilobectomy in more than 500 cases with lung cancer), appropriate selection of patients, intensive postoperative care, and early detection and treatment of postoperative complications. The highest mortality rate (6.1%) in the literature was reported by Deneuville et al [2]; however, the surgeries in their report were performed between 1978 and 1988, when the technical conditions, such as the level of intensive care and surgical instruments, were significantly inferior to those nowadays, which may lead to a high mortality.

In this study, the incidence of complications within 30 days postoperation was 30.8%, which is in line with previous studies (between 24.7% and 71 %). Most complications were mild and could be cured by conservative treatment. The highest complication occurrence rate (71%) in the literature was reported by Icard et al [15]. In 2013, although similar to that in our study, the vast majority of complications were mild. The large variations in the incidence rate of complications among the different studies are likely, at least partly, due to variations in the definition of complications.

Table 5. Multivariate Cox regression analysis of clinical and pathological characteristics to overall survival and disease-free survival

	Regression coefficient (β)	Standard error (SE)	Odds ratio	Wald value	95% CI	P
Age	1.079	1.896	2.943	5.214	3.862~6.914	0.084
Gender	0.316	1.154	1.371	0.756	0.371~1.121	0.167
FEV1	-0.014	0.586	0.986	0.937	0.406~1.452	0.075
DLCO	-0.079	0.882	0.924	1.412	0.724~2.112	0.077
Comorbidity	0.252	2.256	1.286	1.137	0.846~1.674	0.131
Number of comorbidity	0.452	3.124	1.572	1.425	0.952~1.939	0.065
ASA score	0.640	2.348	1.896	9.326	8.014~11.241	0.076
Neoadjuvant therapy	0.980	1.076	2.664	10.154	8.106~12.374	0.086
Surgical type	0.927	1.653	2.528	6.576	4.953~8.138	0.089
Smoking status	0.559	0.847	1.749	4.728	2.545~5.923	0.095
Histological type	1.010	1.285	2.746	7.021	3.206~8.954	0.075
Mediastinal lymph node metastasis (N2 disease)	1.271	0.983	3.563	8.412	3.247~13.472	0.026
Clinical stage	1.397	1.689	4.043	9.137	4.846~12.674	0.024
Residual tumor	1.039	1.204	2.827	7.736	5.954~10.245	0.060

Herein, The 5- and 10-year overall survival were 60% and 55.3%, respectively; the 5- and 10-year disease-free survival rates were 50.8% and 43.5%, respectively, indicating there was a high and satisfactory long-term survival in NSCLC after bilobetomy. It was noted that the 5-year overall survival in our study was 60%, which was similar with that reported by Icard et al (57.8%) [15] and Galetta et al (58%) [17], but higher than that reported by Kim et al (42%) [16] and Massard et al (40%) [18].

To identify the risk factors associated with the prognosis, the Cox regression analysis was conducted and indicated that clinical stage III and mediastinal lymph node metastasis were found to be independent predictors of prognosis, and this finding is similar to that in previous studies in European population [19]. Notably, resection of the middle and lower lobes was reported to be an independent predictor of poor prognosis in some previous studies [20], whereas this study showed that the surgical type was not associated with prognosis.

This study presented some limitations. First, selection bias of the study subjects is inevitable because it was a collected retrospectively and not prospectively in a database service, which may reduce the reliablity of the results and increasing the risk of loss of information. Second, the data used in this study covered a long period of 10 years. The adjuvant chemotherapy had achieved remarkable progress during this 10-year period. In another word, the presence or absence of postoperative chemotherapy may have altered survival in these patients. So the changes in the drugs used for adjuvant chemotherapy will likely affect the long-term survival outcomes of the patients. There also was a major difficulty that was to identify the principal anatomic indication of bilobectomy, occasionally rendering distinction very difficult, particularly in larger masses requiring lower-middle bilobectomy, due to a large central mass crossing the fissure and invading the 2 bronchi.

To conclude, conclusion, bilobectomy is effective in the treatment of NSCLC with a satisfactory long-term survival. And clinical stage III and N2 disease are independent predictors of poor prognosis in NSCLC patients after bilobectomy.

Disclosure of conflict of interest

None.

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