Surgical Outcomes in Resected Non-small Cell Lung Cancer ≤ 1 cm in Diameter

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Background: The goal of this study was to investigate the prognostic factors and patterns of recurrence in patients with resected non-small cell lung cancer (NSCLC) ≤ 1 cm in diameter.

Methods: We conducted a retrospective review of the clinicopathological characteristics of 71 patients with NSCLC ≤ 1 cm in diameter in Taipei Veterans General Hospital between 1982 and 2007. Overall survival and its predictors were analyzed.

Results: Median follow-up time of the 71 patients was 33.3 months. Complete resection was performed in 68 patients (95.8%) with stage I disease. The 5- and 10-year overall survival rates of patients who underwent complete resections were 81.7% and 44.9%, respectively. There was tumor recurrence in 6 (8.8%) of these 68 patients. Five (9.3%) of 54 patients who underwent standard resection experienced tumor recurrence, but only 1 (7.1%) of 14 patients who received sublobar resection had recurrent disease. The difference was not statistically significant ($p = 0.569$). Multivariate analysis revealed that sublobar resection (hazard ratio, 5.00; 95% confidence interval, 1.28–20.00; $p = 0.020$) was a significant predictor for worse overall survival.

Conclusion: Survival in patients with NSCLC ≤ 1 cm in diameter is satisfactory. Sublobar resection, performed in patients unfit for standard resection, is a poor prognostic factor for overall survival. [*J Chin Med Assoc* 2010;73(6):308–313]

Key Words: non-small cell lung cancer, predictor, subcentimeter, sublobar resection, survival

Introduction

Lung cancer is the leading cause of cancer death worldwide. It is also the most common cause of cancer death in women and the second most common cause in men in Taiwan.[1] A majority of patients with non-small cell lung cancer (NSCLC) are diagnosed with advanced disease. Surgical resection is the treatment of choice for patients with early-stage NSCLC.[2] The 5-year survival of patients with resected stage I NSCLC ranges from 55% to 80%.[2–5]

Lung cancer screening programs have shown that the stage distribution of lung cancer at diagnosis has shifted to earlier stages, therefore, the possibility of cure has increased.[6,7] Although the risk of death from lung cancer has not significantly reduced,[6,7] these results have led to enthusiasm for early detection of small-size lung cancer. With the wide use of high-resolution computed tomography (CT) for screening in asymptomatic individuals, NSCLC with a diameter of ≤ 1 cm is detected more frequently. Long-term survival rate and patterns of tumor recurrence in these patients have not been well documented in the literature. The optimal extent of pulmonary resection for NSCLC ≤ 1 cm remains controversial.[8–14] Although there is no lung cancer screening program in Taiwan, more lung

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tumors with a diameter of ≤ 1 cm have been detected incidentally due to widespread use of high-resolution CT in recent physical examinations.

In this study, we investigated the surgical outcomes and analyzed the prognostic factors in patients with resected NSCLC ≤ 1 cm in diameter.

Methods

From January 1982 to December 2007, we retrospectively reviewed all patients who underwent surgical resection for NSCLC with a diameter of ≤ 1 cm in Taipei Veterans General Hospital. Patients who had neoadjuvant therapy before surgery were excluded. A total of 71 patients were enrolled. Preoperative staging work-up included complete blood count, serum biochemistry tests, chest CT scan, bronchoscopic examination, and whole body bone scintigraphy. Mediastinoscopy was not a routine procedure in the preoperative staging work-up unless there were enlarged lymph nodes (diameter > 1.0 cm). Mediastinal lymph node dissection or sampling was undertaken in the majority of patients. All resected specimens were examined for pathological staging. Histological typing was determined according to the World Health Organization classification.[15] The disease stages were determined according to the TNM Classification of Malignant Tumours of the American Joint Committee for Cancer Staging and Revised International System for Staging Lung Cancer.[3,16]

To investigate their impact on overall survival, the following clinicopathological factors were used in univariate and multivariate analyses: age (≤ 60 *vs.* > 60 years); sex (female *vs.* male); symptoms (absent *vs.* present); smoking index (≤ 20 *vs.* > 20 pack-years); location (right *vs.* left lung); tumor size (< 1 *vs.* 1 cm); histological type (squamous cell carcinoma *vs.* others); pathological stage (IA *vs.* IB); extent of pulmonary resection (standard *vs.* sublobar resection); and number of lymph nodes dissected (≤ 15 *vs.* > 15). Standard resection was defined as lobectomy or pulmonary resection larger than lobectomy. Operative mortality was defined as death during the same hospitalization or within the first 30 days after the operation. Local recurrence was defined as tumor recurrence in the ipsilateral hemithorax and mediastinum. Distant metastasis was defined as tumor recurrence in the contralateral lung or outside the hemithorax after surgical resection. The length of overall survival was defined as the interval in months between the date of surgical resection and the date of either death or the last follow-up. All the patients were followed up at our outpatient department at intervals of 3 months in the first 2 years after resection, and intervals of 6 months thereafter.

The overall survival was calculated by the Kaplan–Meier method.[17] The χ^2 test was used to compare between groups. Univariate and multivariate analyses were performed by means of the Cox proportional hazards model using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA). Only variables with $p < 0.1$ after univariate analysis were entered into multivariate analysis. A p value < 0.05 was considered significant.

Results

The median follow-up time for the 71 patients was 33.3 months (range, 0.2–254.6 months). The number of patients with NSCLC ≤ 1 cm diameter increased gradually over the study period. The numbers of patients in the first decade, second decade and final 6 years of the study period were 14, 19 and 38, respectively. Sixteen patients (22.5%) were diagnosed before surgical intervention. The clinicopathological characteristics of all patients are listed in Table 1. Pathological stage was IA in 55 patients, IB in 13, IIIA in 1, IIIB in 1, and IV in 1. Sixty-eight patients (95.8%) had stage I disease. Complete resection was performed in these 68 patients. The other 3 patients underwent non-curative resection due to pleural seeding in 2 and encased mediastinal lymph node in 1. There was 1 operative death (1.4%) caused by acute myocardial infarction on postoperative day 5 after complete resection with pneumonectomy for a tumor located in the main bronchus. Postoperative complications occurred in 13 patients (18.3%), and no patient required reoperation during the postoperative period (Table 2). At the last follow-up session, 46 (64.8%) patients were alive (including 1 with recurrent cancer and 2 with non-curative resection). Eighteen patients (25.4%) died of other causes without tumor recurrence, and 6 (8.5%) died of lung cancer.

We excluded the 3 patients who underwent non-curative resection from prognostic analysis of survival. The characteristics of the remaining 68 patients are listed in Table 1. The median follow-up time was 33.8 months (range, 0.2–254.6 months). Only 3 of the 68 patients received adjuvant therapy. The 5- and 10-year overall survival rates were 81.7% and 44.9%, respectively (Figure 1). The pathological stage was IA (80.9%) or IB (19.1%). Sublobar resection was performed in 14 patients (20.6%), with 10 of them due to poor pulmonary reserve and the other 4 due to comorbidity. There were 10 patients who underwent sublobar resection and received lymph node dissection.

Table 1. Clinicopathological characteristics of 71 patients with non-small cell lung cancer with a diameter ≤ 1 cm*

Variables	All patients (n = 71)	Patients with complete resection (n = 68)
Age (yr)	63.9 ± 11.5	63.4 ± 11.4
Sex		
Male	44 (62.0)	43 (63.2)
Female	27 (38.0)	25 (36.8)
Symptoms		
Absent	41 (57.7)	38 (55.9)
Present	30 (42.3)	30 (44.1)
Smoking index (pack-years)	22.8 ± 27.9	23.0 ± 27.9
Tumor location		
Right lung	44 (62.0)	43 (63.2)
Left lung	27 (38.0)	25 (36.8)
Tumor size (cm)	0.9 ± 0.1	0.9 ± 0.1
< 1	25 (35.2)	23 (33.8)
1	46 (64.8)	45 (66.2)
Histological type		
Adenocarcinoma	45 (63.4)	43 (63.2)
Squamous cell carcinoma	20 (28.2)	20 (29.4)
Bronchoalveolar carcinoma	5 (7.0)	4 (5.9)
Large cell carcinoma	1 (1.4)	1 (1.5)
Pathologic stage		
T1N0M0 - IA	55 (77.5)	55 (80.9)
T2N0M0 - IB	13 (18.3)	13 (19.1)
T2N2M0 - IIIA	1 (1.4)	0 (0.0)
T4N0M0 - IIIB	1 (1.4)	0 (0.0)
T4N0M1 - IV	1 (1.4)	0 (0.0)
Extent of pulmonary resection		
Sublobar resection	16 (22.5)	14 (20.6)
Lobectomy	48 (67.6)	47 (69.1)
Bilobectomy	4 (5.6)	4 (5.9)
Pneumonectomy	3 (4.2)	3 (4.4)
No. of LNs dissected	16.5 ± 10.9	17.0 ± 10.8
≤ 15	35 (49.3)	32 (47.1)
> 15	36 (50.7)	36 (52.9)
Residual tumor		
No	68 (95.8)	68 (100.0)
Yes	3 (4.2)	0 (0.0)

**Data presented as mean ± standard deviation or n (%). LN = lymph node.*

The mean number of lymph nodes in the 10 patients was 20.1 ± 10.9.

Six (8.8%) of the 68 patients who underwent complete resection had tumor recurrence during follow-up (Table 3). Three patients had local recurrence, whereas the other 3 developed distant metastases. Five (9.3%) of 54 patients who underwent standard resection developed tumor recurrence, whereas only 1 (7.1%) of 14 patients treated by sublobar resection had recurrent disease. The difference was not statistically significant (p = 0.569).

Table 2. Postoperative complications in 71 patients with non-small cell lung cancer with a diameter ≤ 1 cm

Variables	Patients (n)
Acute myocardial infarction	1
Prolonged air leak > 7 d	4
Persistent pleural drainage > 7 d	3
Empyema	1
Chylothorax	1
Deep vein thrombosis	1
Hoarseness	1
Gastrointestinal bleeding	1

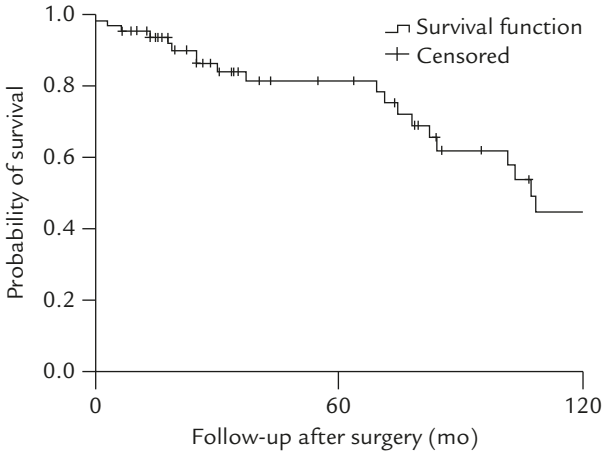

Figure 1. Overall survival of 68 patients who underwent complete resection for non-small cell lung cancer ≤ 1 cm in diameter.

Univariate analysis indicated that sex (p = 0.024), smoking index (p = 0.008), histological type (p = 0.021), extent of pulmonary resection (p = 0.045), and number of lymph nodes dissected (p = 0.038) significantly influenced overall survival (Table 4). The overall survival was significantly worse in male patients, and in those with higher smoking index, squamous cell carcinoma, or who underwent sublobar resection. Sublobar resection was a significant predictor for worse survival (hazard ratio, 5.00; 95% confidence interval, 1.28–20.00; p = 0.020) in multivariate analysis (Table 5).

Discussion

This study investigated the prognostic factors and patterns of recurrence in resected NSCLC ≤ 1 cm in diameter. Most patients (approximately 96%) with

Table 3. Patterns of recurrence in 68 patients after complete resection

No.	Pathological stage	Operation	Recurrence	Sites of recurrence	Disease-free interval (mo)	Post-recurrence survival (mo)	Final status
1	IA	Wedge resection	Local	Margin and mediastinal LNs	3.2	14.6	Dead
2	IA	Lobectomy	Distant	Contralateral lung	20.3	9.2	Alive
3	IA	Lobectomy	Distant	Bone	12.4	42.8	Dead
4	IB	Bilobectomy	Local	Margin	9.9	26.3	Dead
5	IB	Lobectomy	Local	Mediastinal LNs	103.1*	3.5	Dead
6	IB	Lobectomy	Distant	Bone	18.4	6.0	Dead

**This patient was lost to follow-up 1 year after surgery and presented with hoarseness due to mediastinal lymph node recurrence 8 years later. LN = lymph node.*

Table 4. Univariate analysis for overall survival in 68 patients who underwent complete resection for non-small cell lung cancer ≤ 1 cm in diameter

Variables	Hazard ratio* (95% CI)	*p*
Age (≤ 60 *vs.* > 60 yr)	2.19 (0.90–5.35)	0.084
Sex (female *vs.* male)	4.07 (1.20–13.74)	0.024
Symptoms (absent *vs.* present)	1.23 (1.36–3.30)	0.490
Smoking index (≤ 20 *vs.* > 20 pack-years)	3.48 (1.38–8.85)	0.008
Location (right *vs.* left lung)	0.99 (0.44–2.25)	0.993
Tumor size (< 1 *vs.* 1 cm)	1.03 (0.40–2.64)	0.955
Histological type (squamous cell carcinoma *vs.* others)	0.37 (0.16–0.86)	0.021
Pathologic stage (IA *vs.* IB)	0.76 (0.25–2.29)	0.629
Extent of pulmonary resection (standard *vs.* sublobar resection)	3.79 (1.03–13.89)	0.045
No. of LNs dissected (≤ 15 *vs.* > 15)	0.37 (0.14–0.95)	0.038

**Hazard ratio was based on average mortality of the second category of each variable compared with the baseline category. CI = confidence interval; LN = lymph node.*

Table 5. Multivariate analysis for overall survival in 68 patients who underwent complete resection for non-small cell lung cancer ≤ 1 cm in diameter

Variables	Hazard ratio* (95% CI)	*p*
Age (≤ 60 *vs.* > 60 yr)	1.39 (0.54–3.53)	0.492
Sex (female *vs.* male)	1.03 (0.18–5.73)	0.976
Smoking index (≤ 20 *vs.* > 20 pack-years)	2.45 (0.68–8.85)	0.172
Histological type (squamous cell carcinoma *vs.* others)	0.48 (0.18–1.27)	0.138
Extent of pulmonary resection (standard *vs.* sublobar resection)	5.00 (1.28–20.00)	0.020
No. of LNs dissected (≤ 15 *vs.* > 15)	0.75 (0.26–2.16)	0.588

**Hazard ratio was based on average mortality of the second category of each variable compared with the baseline category. CI = confidence interval; LN = lymph node.*

NSCLC ≤ 1 cm in diameter had stage I disease. The 5-year overall survival rate after complete resection was 81.7%. Sublobar resection was a significant prognostic indicator for worse overall survival in multivariate analysis.

Tumor size is a well-established prognostic factor in NSCLC.[3] Some studies have shown improved survival for stage I NSCLC with diameter ≤ 2 cm,[13,18–20] whereas others have not.[21,22] The survival and prognostic factors in NSCLC ≤ 1 cm in diameter have not been well elucidated. The frequency of stage I disease in patients with NSCLC ≤ 1 cm in diameter ranges from 86% to 100%.[8,23,24] Although Lee and colleagues[24] reported a 5-year overall survival rate of 86% in patients with resected NSCLC of diameter ≤ 1 cm, Miller and coworkers[8] found only 64% in their series. Kondo and colleagues[23] showed that the 5-year overall survival rate in patients with peripheral lung adenocarcinoma ≤ 1 cm in diameter was 97.3%. They also indicated that patients with subcentimeter lung adenocarcinomas had significantly better prognosis than those with adenocarcinomas between 1 and 2 cm.[23] In our study, 96% of patients with NSCLC ≤ 1 cm in diameter had stage I disease. The 5-year overall survival rate was 81.7%, which is between those reported in the literature.

The relationship between tumor size and regional lymph node involvement has been reported. The prevalence of pulmonary hilar and mediastinal lymph nodes metastases increases with tumor size.[25,26] Some authors have reported that there is no lymph node metastasis in NSCLC with a diameter of ≤ 1 cm.[23,26–28] Miller and coworkers[8] reported that 7% of patients with NSCLC with a diameter ≤ 1 cm had nodal involvement.

Lee and colleagues[24] reported a similar result of 7.2%. In our study, lymph node metastasis was found in only 1 patient (1.4%). However, pleural spreading was discovered in another 2 patients during surgical exploration. These 3 patients (4.2%) had unexpectedly advanced disease and complete (R0) resection could not be achieved.

There can still be tumor recurrence in subcentimeter lung cancers after complete resection. Miller and coworkers[8] reported that the overall incidence of recurrence in patients with resected stage I NSCLC with a diameter ≤ 1 cm was 18%. They also reported a 55% greater risk of tumor recurrence after sublobar resection compared with lobectomy for NSCLC ≤ 1 cm in size. Lee and colleagues[24] demonstrated that overall incidence of recurrence in patients with resected NSCLC ≤ 1 cm was 6.0%, but no recurrence was found in patients with stage IA disease. Our study showed that tumor recurrence was found in 6 patients (8.8%) after complete surgical resection, including 3 with local recurrence and 3 with distant metastasis. Although complete surgical resection offers a chance to cure the disease, tumor recurrence can take place after surgery. Therefore, regular follow-up is necessary after complete resection in patients with lung cancers < 1 cm in size.

The role of sublobar resection in early-stage NSCLC remains controversial. Complete anatomical resection, including pneumonectomy, bilobectomy and lobectomy, with radical lymph node dissection remains the standard treatment for patients with early-stage NSCLC.[9] Sublobar resection is associated with a significant increase in local recurrence, compared with lobectomy.[10,11] However, there is increasing evidence in the literature to suggest that segmentectomy is an alternative to lobectomy in patients with clinical T1N0M0 tumors ≤ 2 cm in diameter.[12–14] Lee et al[24] reported that there was no difference in overall survival between patients with limited resection and those with complete anatomical resection for NSCLC ≤ 1 cm in diameter. No recurrence was found in either the limited resection or the complete anatomical resection group during follow-up in that study. Miller and colleagues[8] demonstrated that patients who undergo lobectomy for NSCLC that measures ≤ 1 cm have significantly improved survival and less recurrence than those treated with sublobar resection. In our study, the extent of pulmonary resection was a significant predictor for overall survival in multivariate analysis. Patients with standard resection had better overall survival than those with sublobar resection. One patient in the sublobar resection group had local recurrence during follow-up. In the lobectomy group, 1 local recurrence and 3 distant metastases were discovered. Another local recurrence was found in a patient who underwent bilobectomy. However, the difference in recurrence rate was not statistically significant between patients with standard resection and those with sublobar resection in our study. The patients who underwent sublobar resection usually had poor cardiopulmonary function or other comorbidity. These patients might die from diseases other than lung cancer, and this could contribute to a worse outcome. Therefore, unfitness for standard resection might be alternatively used as a predictor for poor overall survival.

The number of mediastinal lymph nodes dissected during thoracotomy could reflect the quality of lymphadenectomy in patients with resected stage I NSCLC. Better quality of lymphadenectomy might lead to more accurate tumor staging and therefore influence survival.[29] In our previous study of prognostic factors for resected stage I NSCLC with diameter ≤ 3 cm, patients with ≤ 15 mediastinal lymph nodes dissected had worse survival outcome than those with > 15.[30] In the current study, univariate analysis revealed a similar outcome in patients with NSCLC with a diameter ≤ 1 cm with regard to the number of mediastinal lymph nodes dissected. However, it was not a significant predictor in multivariate analysis.

There were several limitations in our study. This was a surgical series of patients with NSCLC with a diameter ≤ 1 cm. Some patients with such tumors diagnosed with advanced disease or distant metastasis might not be surgical candidates. Therefore, long-term survival could not be applied to all NSCLC with a diameter ≤ 1 cm at diagnosis. Furthermore, the sample size in our study was not very large. Multicenter, prospective randomized trials are required to compare the benefits and drawbacks between sublobar resection and lobectomy.

In conclusion, most patients with NSCLC ≤ 1 cm in diameter had stage I disease. Long-term survival was good. Sublobar resection, performed in patients unfit for standard resection, is a poor prognostic factor for overall survival.

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