Prognostic factors in resected stage I non–small cell lung cancer with a diameter of 3 cm or less: Visceral pleural invasion did not influence overall and disease-free survival

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Objective: Resection is the treatment of choice for patients with stage I non–small cell lung cancer. Stage I non–small cell lung cancer has been further subdivided into IA (T1N0M0, tumor size ≤ 3 cm without visceral pleural invasion) and IB (T2N0M0, tumor size > 3 cm or any size with visceral pleural invasion). The aim of this study was to evaluate the prognostic factors in patients with resected stage I non–small cell lung cancer with a diameter of 3 cm or less.

Methods: We retrospectively reviewed the clinicopathologic characteristics of 445 patients with resected stage I non–small cell lung cancer with a diameter of 3 cm or less who were treated at Taipei Veterans General Hospital between 1980 and 2000. Disease-free survival, overall survival, and their predictors were analyzed.

Results: The 5- and 10-year overall survivals were 61.4% and 40.0%, respectively. The 5- and 10-year disease-free survivals were 74.5% and 73.4%, respectively. Tumor size, smoking index, and number of mediastinal lymph nodes dissected were significant predictors for both disease-free survival ($P = .009$, $P = .002$, and $P = .006$, respectively) and overall survival ($P = .004$, $P < .001$, and $P = .001$, respectively) in multivariate analyses. Visceral pleural invasion did not influence overall survival or disease-free survival.

Conclusions: Tumor size, smoking index, and number of mediastinal lymph nodes dissected were prognostic factors for both overall survival and disease-free survival in resected stage I non–small cell lung cancer with a diameter of 3 cm or less. Small tumors (< 3 cm) of stage IB (T2N0M0) non–small cell lung cancer with visceral pleural invasion should be treated as T1 disease and not T2 disease.

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Lung cancer is a prevalent health problem worldwide. It is the leading cause of cancer death in both men and women in the United States. In Taiwan, it is also the most common cause of death related to malignancy for women and the second most common cause of death for men.¹ Optimal management of lung cancer depends on proper histologic identification and tumor staging. Surgical resection is the treatment of choice for early-stage non–small cell lung cancer (NSCLC).²

The importance of tumor staging on survival for patients with NSCLC has been emphasized. Patients with stage I disease have the most favorable prognosis and are treated with surgical resection. However, survival varies according to reports from different centers.^{2–5} Five-year survival after resection ranges between 55% and 80%. Stage I NSCLC has been further subdivided into IA (T1N0M0, tumor size ≤ 3 cm without visceral pleural invasion [VPI]) and IB (T2N0M0, tumor size > 3 cm or any size with VPI).³ The 5-year survival of patients with resected stage IA NSCLC ranges from 62% to 82%.^{6–9} VPI has been reported as a significant negative indicator of survival in patients who underwent complete resection of NSCLC.^{10–13}

Abbreviations and Acronyms

NSCLC = non-small cell lung cancer
VPI = visceral pleural invasion

The classification of VPI by the Japan Lung Cancer Society is as follows: p0, tumor with no pleural involvement beyond its elastic layer; p1, tumor that extends beyond the elastic layer of the visceral pleura but is not exposed on the pleural surface; p2, tumor that is exposed on the pleural surface but does not involve adjacent anatomic structures; and p3, tumor that involves adjacent anatomic structures.¹⁴ For resected NSCLC with a diameter of 3 cm or less, Shimizu and colleagues¹³ reported that 5-year survivals for patients with p1 or p2 tumors were identical to and significantly worse than survivals of those with p0 tumors. For resected NSCLC with a diameter of 2 cm or less, Inoue and colleagues¹⁵ reported that lymph node metastasis was significantly increased in patients with VPI. However, the prognostic value of VPI in patients with early-stage NSCLC (T₁₋₂N0M0) with a small tumor size has rarely been demonstrated.

Although the prognosis of stage IA NSCLC is relatively good compared with that of more advanced stages,^{6-9,16} the outcome of stage I NSCLC with a diameter of 3 cm or less after surgical resection has rarely been reported. In this report, we analyzed the survival and prognostic factors in stage I NSCLC with a diameter of 3 cm or less after surgical resection.

Materials and Methods

From January 1980 to December 2000, 970 patients underwent surgical resection for pathologic stage I NSCLC (T1N0M0 and T2N0M0) at Taipei Veterans General Hospital. The preoperative staging workup included serum biochemistry tests, chest and upper abdomen computed tomographic scans, bronchoscopic examination, and nuclear medicine survey (bone and brain). Mediastinoscopy was not a routine procedure in the preoperative staging workup unless enlarged lymph nodes (diameter > 1.0 cm) were observed on the contralateral side of the mediastinum from the computed tomography scan. Patients with suspected distant metastasis were excluded from consideration of operation. A complete resection of all disease in the lung with mediastinal lymph node dissection was performed as previously described.¹⁷ Pathologic staging was assessed after examination of the resected specimens had been performed and all regional nodes had been dissected. The surgical and pathologic reports of all patients were reviewed to ensure accurate staging was performed, complete resection was achieved, and no regional nodes (N1 and N2) were involved. Histologic typing was determined according to the World Health Organization classification.¹⁸ Determination of disease stages were based on the TNM classification of the International Union Against Cancer.¹⁹ All patients were followed up at our outpatient department quarterly in the first 2 years after resection and semiannually thereafter.

Of these 970 patients with a final pathologic stage defined as stage I (T1N0M0 and T2N0M0), 445 (45.9%) had tumors with a

TABLE 1. Characteristics of 445 patients with resected stage I non-small cell lung cancer with a diameter of 3 cm or less

Variables	No. of patients (%)
Age, y (mean ± SD)	65.5 ± 9.4
Sex	
Male	348 (78.2)
Female	97 (21.8)
Smoking index (pack-y, mean ± SD)	23.4 ± 25.2
Tumor location	
Right lung	336 (75.5)
Left lung	109 (24.5)
Tumor size, cm (mean ± SD)	2.25 ± 0.6
Histologic type	
Adenocarcinoma	226 (50.8)
Squamous cell carcinoma	145 (32.6)
Bronchioalveolar carcinoma	34 (7.6)
Large cell carcinoma	36 (8.1)
Adenosquamous carcinoma	4 (0.9)
Extent of pulmonary resection	
Lobectomy or wedge resection	375 (84.3)
Pneumonectomy or bilobectomy	70 (15.7)
Visceral pleural invasion	
Absent	368 (82.7)
Present	72 (16.2)
No. of LNs dissected (mean ± SD)	14.4 ± 10.0
LN ≤ 15	262 (58.9)
LN > 15	176 (39.6)
No. of LN stations dissected (mean ± SD)	3.7 ± 1.7
≤ 3	189 (42.5)
> 3	238 (53.5)
Lymphatic invasion	
Absent	142 (31.9)
Present	47 (10.6)
Vascular invasion	
Absent	174 (39.1)
Present	15 (3.4)

SD, Standard deviation; LN, lymph node.

diameter of 3 cm or less, and they formed the samples for this review. The characteristics of these 445 patients are listed in Table 1. To investigate their impact on disease-free survival and overall survival, the following clinicopathologic factors were used in univariate and multivariate analyses: age, gender, smoking index, laterality of tumor (right vs left), histologic type of the tumor (squamous cell carcinoma vs others), tumor size, extent of resection (pneumonectomy or bilobectomy vs lobectomy or wedge resection), VPI (present vs absent), number of mediastinal lymph nodes dissected (>15 vs ≤15), number of mediastinal lymph node stations dissected (>3 vs ≤3), lymphatic invasion (present vs absent), and vascular invasion (present vs absent). The length of 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. The period of disease-free time to recurrence was defined as the interval in months between the date of surgical resection and the date the first site of recurrence was found. For disease-free sur-

Figure 1. Cumulative probability of overall survival in patients with surgically resected stage I NSCLC with a diameter of 3 cm or less.

Figure 2. Cumulative probability of disease-free survival in patients with surgically resected stage I NSCLC with a diameter of 3 cm or less.

vival, an observation was censored at the last follow-up session when the patient was alive or had died of causes other than NSCLC.

The overall survival and disease-free survivals were calculated by the Kaplan–Meier method.²⁰ Univariate and multivariate analyses were performed by means of the Cox proportional hazards model using the Statistical Package for the Social Sciences software (version 12.0; SPSS Inc, Chicago, Ill). Backward stepwise regression procedure was used. Data of lymphatic invasion and vascular invasion were available in only 189 of the 445 patients (42.5%). The 2 variables were only entered into univariate analyses and not multivariate analyses.

Results

The median follow-up time was 70.4 months (mean, 78.4 ± 55.8 months; range, 0.2–298.1 months) for the 445 patients with surgically resected stage I NSCLC with a diameter of 3 cm or less. There were 26 patients lost to follow-up. No patient received adjuvant chemotherapy after surgical resection. At the last follow-up session, 162 patients were alive (including 5 patients alive with recurrent cancers), 144 patients died of other causes without evidence of tumor recurrence, and 103 patients (16.2%) died of cancer. Ten postoperative deaths (2.2%) occurred (lobectomy in 6 patients, pneumonectomy in 3 patients, and wedge resection in 1 patient). Six of these 10 patients died of pneumonia and subsequent acute respiratory distress syndrome. There were no intraoperative deaths. The 5- and 10-year overall survivals were 61.4% and 40.0%, respectively (Figure 1). The 5- and 10-year disease-free survivals were 74.5% and 73.4%, respectively (Figure 2).

Predictors of Disease-free Survival

Univariate analyses showed that smoking index ($P = .005$), tumor size ($P = .003$), and number of mediastinal lymph nodes dissected ($P = .005$) had a significant effect on disease-free survival (Table 2). The hazard of lung cancer recurrence was greater in patients with a higher smoking index, larger tumor size, and smaller number of mediastinal lymph nodes dissected. VPI was not associated with an increased hazard of cancer recurrence in these patients (Figure 3, A).

Smoking index ($P = .002$), tumor size ($P = .009$), and number of mediastinal lymph nodes dissected ($P = .006$) were still found to be significant in multivariate analyses (Table 3).

Predictors of Overall Survival

Univariate analyses indicated that age ($P < .001$), gender ($P < .001$), smoking index ($P < .001$), tumor size ($P = .001$), histologic type ($P = .001$), number of mediastinal lymph nodes dissected ($P = .002$), and number of mediastinal lymph node stations dissected ($P = .002$) had a significant influence on overall survival (Table 2). Survival was significantly better in women and in younger patients. The hazard of death was greater in patients with a higher smoking index, larger tumor size, smaller number of mediastinal lymph nodes dissected, and smaller number of mediastinal lymph node stations dissected. The hazard of death was greater in patients with squamous cell carcinoma versus other histologic types. VPI was not associated with an increased hazard of death in these patients (Figure 3, B).

Only age ($P = .005$), smoking index ($P < .001$), tumor size ($P = .004$), and number of mediastinal lymph nodes

TABLE 2. Univariate analyses for overall and disease-free survivals in patients with resected stage I non-small cell lung cancer with a diameter of 3 cm or less

Variables	Overall survival		Disease-free survival	
	HR (95% CI)	P value	HR (95% CI)	P value
Age, y	1.036 (1.020–1.051)	<.001	1.009 (0.988–1.029)	.410
Gender (male vs female)	1.888 (1.347–2.647)	<.001	1.606 (0.968–2.664)	.067
Smoking index, pack-y*	1.012 (1.008–1.017)	<.001	1.010 (1.003–1.016)	.005
Location (right vs left lung)	0.893 (0.681–1.171)	.411	0.836 (0.549–1.274)	.404
Tumor size†	1.402 (1.146–1.714)	.001	1.632 (1.177–2.264)	.003
Histologic type (squamous cell carcinoma vs others)	1.559 (1.214–2.002)	.001	1.130 (0.757–1.686)	.550
Extent of pulmonary resection (pneumonectomy or bilobectomy vs lobectomy or wedge resection)	0.967 (0.695–1.345)	.841	0.939 (0.544–1.621)	.822
Visceral pleural invasion (present vs absent)	1.016 (0.913–1.130)	.776	0.821 (0.577–1.168)	.274
No. of LNs dissected (> 15 vs ≤ 15)	0.656 (0.504–0.854)	.002	0.553 (0.364–0.840)	.005
No. of LN stations dissected (> 3 vs ≤ 3)	0.671 (0.522–0.864)	.002	0.713 (0.482–1.053)	.089
Lymphatic invasion (present vs absent)	0.811 (0.525–1.252)	.343	1.124 (0.546–2.315)	.751
Vascular invasion (present vs absent)	0.525 (0.214–1.288)	.152	0.616 (0.148–2.561)	.505

NSCLC, Non-small cell lung cancer; HR, hazard ratio; CI, confidence interval; LN, lymph node. *The hazard ratio associated with smoking index is an increased hazard per 1 pack-year of additional smoking. †The hazard ratio associated with tumor size is that the increase in hazard is associated with a 1-cm increase in tumor size.

dissected ($P = .001$) were still significant prognostic indicators in multivariate analyses (Table 3).

Discussion

This study investigated the prognostic role of conventional clinicopathologic factors in patients with resected stage I NSCLC with a diameter of 3 cm or less. The 5-year overall survival and disease-free survivals were 61.4% and 74.5%, respectively. Tumor size, smoking index, and number of mediastinal lymph nodes dissected were significant predictors for both disease-free survival and overall survival. Age was a significant prognostic factor for overall survival only. Gender, extent of pulmonary resection, and VPI did not influence overall survival and disease-free survival. Surgical resection offers a good chance of cure for patients with stage I NSCLC, with the 5-year survival between 55% and 80%.²⁻⁶ Five-year overall survival in resected IA NSCLC has been reported as reaching 62% to 82%.⁶⁻⁹ Five-year disease-free survival in resected stage IA NSCLC has been reported in 75% of cases.⁸ Our study shows similar results of overall survival and disease-free survival in patients with resected stage I NSCLC with a diameter of 3 cm or less.

Tumor size is an important factor in a lung cancer staging system.^{6,21-23} Tumor size is a significant prognostic factor for stage I NSCLC.^{4,6,16} The prognostic significance of tumor size in stage IA NSCLC has been controversial.^{6,8,9,24,25} The use of 2 cm or 3 cm as a cutoff value has been reported. Patz and colleagues⁹ reported that there is no correlation between tumor size and survival. However, Birim and colleagues⁷ and Port and colleagues⁸ reported tumor size as an important predictor of survival in stage IA NSCLC, suggesting 2 cm as a cutoff value. For resected

stage I NSCLC with a diameter of 3 cm or less, our results demonstrated that tumor size was a significant predictor for both disease-free survival and overall survival.

The number of mediastinal lymph nodes dissected affected both disease-free survival and overall survival in multivariate analyses in resected stage I NSCLC with a diameter of 3 cm or less. The number of mediastinal lymph nodes dissected during thoracotomy was used alternatively to represent the quality of lymphadenectomy in patients with resected stage I NSCLC.¹⁷ The quality of lymphadenectomy had an impact on a more accurate tumor staging and significantly affected the survival of patients with stage I NSCLC.¹⁷ Our results show that for resected stage I NSCLC with a diameter of 3 cm or less, patients with 15 or fewer mediastinal lymph nodes dissected had worse survival outcome than those with more than 15. However, the number of mediastinal lymph node stations dissected influenced neither overall survival nor disease-free survival in multivariate analyses.

VPI is an important prognostic factor in patients who underwent complete resection of NSCLC.¹⁰⁻¹³ VPI is also associated with a higher frequency of lymph node involvement.^{10,11,15} The incidence of VPI in resected NSCLC has been reported to be between 19.1% and 26.8%.^{10,11,26} Furthermore, the incidence of VPI has been identified in 18.1% and 21.2% of resected stage I NSCLC cases.^{10,11} The incidence of VPI in T1/2 resected NSCLC with N0 disease was lower than in those with N1/N2 disease.^{10,11} In our study, VPI was observed in 16.2% of the resected stage I NSCLC cases with a diameter of 3 cm or less. Some series demonstrated VPI as a poor prognostic factor in resected stage I and II NSCLC.^{4,12,16} Martini and colleagues⁶ reported that

Figure 3. A, Disease-free survival in patients with resected stage I NSCLC with a diameter of 3 cm or less with or without VPI. B, Overall survival in patients with resected stage I NSCLC with a diameter of 3 cm or less with or without VPI. VPI, Visceral pleural invasion.

VPI did not influence overall survival in resected stage I NSCLC. In Martini and coworkers' study, they also showed that VPI did not influence overall survival in patients with resected stage I NSCLC with a diameter of 3 cm or less. Our present study came to this same conclusion. Further, our study demonstrated that VPI did not influence disease-free survival in patients with resected stage I NSCLC with a diameter of 3 cm or less. There was no significant difference in overall survival and disease-free survival among patients with stage IA and stage IB NSCLC with a tumor size less than 3 cm. Several recently published trials have suggested that adjuvant chemotherapy improves the long-term survival in patients with early-stage NSCLC after a curative

TABLE 3. Multivariate analyses for overall survival and disease-free survival in patients with resected stage I non-small cell lung cancer with a diameter of 3 cm or less

Variables	Hazard ratio (95% CI)	P value
Overall survival		
Age, y	1.024 (1.007–1.041)	.005
Smoking index, pack-y*	1.010 (1.005–1.015)	<.001
Tumor size†	1.348 (1.098–1.655)	.004
No. of LNs dissected (> 15 vs ≤ 15)	0.622 (0.470–0.822)	.001
Disease-free survival		
Smoking index, pack-y*	1.011 (1.004–1.018)	.002
Tumor size†	1.549 (1.116–2.151)	.009
Number of LNs dissected (> 15 vs ≤ 15)	0.544 (0.352–0.840)	.006

NSCLC, Non-small cell lung cancer; CI, confidence interval; LN, lymph node. *The hazard ratio associated with smoking index is an increased hazard per 1 pack-year of additional smoking. †The hazard ratio associated with tumor size is that the increase in hazard is associated with a 1-cm increase in tumor size.

resection.^{27,28} Because patients with resected stage IB NSCLC with a diameter of 3 cm or less have a survival that is indistinguishable from that of patients with stage IA lung cancer, it is likely that the benefit of adjuvant chemotherapy is small or nonexistent in the subset of patients with stage IB NSCLC.

Conclusions

Tumor size, smoking index, and number of mediastinal lymph nodes dissected were prognostic factors for both overall survival and disease-free survival in resected stage I NSCLC with a diameter of 3 cm or less. Small tumors (<3 cm) of stage IB (T2N0M0) NSCLC with VPI should be treated as T1 disease and not T2 disease. Because the current literature suggests that VPI is associated with a high incidence of nodal disease, a full preoperative evaluation to rule out advanced disease is necessary and would alter the therapy offered.

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