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Prognostic factors in pathological stage IB non-small cell lung cancer greater than 3 cm

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ABSTRACT

Significant heterogenity of stage IB (sixth edition of the TNM staging system) non-small cell lung cancer (NSCLC) has been identified, and further subclassification according to tumor size has been proposed. The aim of this study is to evaluate the prognostic factors in patients with resected stage IB NSCLC greater than 3 cm.

From January 1980 to December 2000, 525 patients underwent surgical resection for stage IB NSCLC greater than 3 cm at Taipei Veterans General Hospital. The clinicopathologic characteristics of these patients were retrospectively reviewed.

The 5- and 10-year overall survival rates were 44.9% and 27.3%, respectively. Age ($P < 0.001$), tumor size ($P = 0.002$), extent of pulmonary resection ($P = 0.002$), histological type ($P = 0.005$) and number of mediastinal lymph nodes dissected/sampled ($P = 0.004$) were significant predictors for overall survival in multivariate analysis. Patients with tumor size > 7 cm, or > 5 to ≤ 7 cm, had a worse survival than those with tumor size > 3 to ≤ 5 cm. However, visceral pleural invasion did not influence overall survival.

Stage IB NSCLC with a diameter greater than 3 cm may be subclassified according to tumor size with regardless of visceral pleural invasion.

Key words: Non-small cell lung cancer, stage IB, survival, tumor size, visceral pleural invasion

Introduction

Lung cancer is the leading cause of cancer-related death worldwide. Histological identification and tumor staging play a critical role for the optimal management of lung cancer. The Union Internationale Contre le Cancer was the first organization to classify lung cancer by tumor, node, metastasis (TNM) staging system in 1968. The TNM staging system for lung cancer was first applied by the American Joint Committee on Cancer in 1974 [1]. The fifth edition of the TNM staging system for lung cancer was published in 1997, and stage I non-small cell lung cancer (NSCLC) was subdivided into IA (T1N0M0, tumor size ≤ 3 cm) and IB (T2N0M0, tumor size > 3 cm) [2]. In addition to tumor size greater than 3 cm, the current T2 descriptor also includes tumors that invade the visceral pleura regardless of size, tumors that involve the main bronchus □ 2 cm distal to the carina, and tumors that result in associated atelectasis and obstructive pneumonitis that extends to the hilar region but does not involve the entire lung radiographically [2]. The current (sixth) edition of the TNM staging system for lung cancer was published in 2002 [3], without changes to the previous edition [2]. Significant heterogenity of stage IB patients has been identified in several studies, and further subclassification according to tumor size has been proposed [4-7]. The seventh edition of the TNM classification of lung cancer has been published in 2009. The changes to the sixth edition of the TNM staging system for lung cancer were based upon the proposals from the International Association for the Study of Lung Cancer (IASLC). The IASLC lung cancer

staging project committee has recommended that T2 tumors be classified into T2a (> 3 to ≤ 5 cm), T2b (> 5 to ≤ 7 cm), and T3 (> 7 cm) [8-10].

Among the three non–size-based T2 descriptors, visceral pleural invasion (VPI) is the main criteria [4, 11, 12]. Hammar suggested a classification of pleural invasion as follows: Px and P0, lack of pleural invasion beyond the elastic layer; P1, invasion beyond the elastic layer; P2, invasion to the surface of the visceral pleura; and P3, invasion of the parietal pleura and/or chest wall [13, 14]. According to his proposal, P0 is not a T descriptor and the T category in such cases should be assigned by other criteria. P1 or P2 correspond to T2, and P3 corresponds to T3. The International Staging Committee of the IASLC has proposed the definition of VPI as invasion beyond the elastic layer (PL1) including invasion to the visceral pleural surface (PL2) [15]. They also recommend that elastic stains be used in cases when the distinction between PL0 and PL1 is not clear based on evaluation of hematoxylin and eosin sections [15]. Although VPI has generally been reported as a poor prognostic factor [16-21], some studies have demonstrated that VPI was not a prognostic factor for survival [4, 6, 7, 11, 22, 23]. The prognostic value of VPI in patients of early stage NSCLC with larger tumor size has remained to be demonstrated.

In our previous study [24], we have demonstrated that VPI did not influence overall survival in resected stage I NSCLC with a diameter of 3 cm or less. Therefore, we recommend that patients with tumor size ≤ 3 cm but are staged as stage IB (T2N0M0) due to VPI to be

treated as stage IA (T1N0M0). According to our proposal, the category of stage IB NSCLC only consists of patients with stage I NSCLC with a diameter greater than 3 cm. In this regard, we analyzed the prognostic factors of survival in stage IB NSCLC with a diameter greater than 3 cm and evaluate the validity of the new staging system of T descriptors proposed by the IASLC. Furthermore, we investigated the prognostic value of VPI and its relationship with tumor size in these patients.

Materials and methods

From January 1980 to December 2000, a total of 597 patients underwent surgical resection for pathologic stage IB (T2N0M0) NSCLC at Taipei Veterans General Hospital. Of these, 525 (87.9%) patients who had tumors with a diameter greater than 3 cm were identified and included in this retrospective study. The preoperative staging workup, including chest and upper abdomen computed tomographic scans, bronchoscopic examination and nuclear medicine survey (bone and brain), was done as previous described [24, 25]. Mediastinoscopy was not a routine preoperative staging procedure, and was performed only when enlarged mediastinal lymph nodes (diameter over 1.0 cm) were shown by computed tomographic scan. Among the 194 patients with available data on whether pre-operative mediastinoscopy was performed for staging, 12 (6.2%) underwent mediastinoscopy before operation. In the study period, positron emission tomography scan was not available as a staging modality. Patients with suspected distant metastasis were excluded from consideration of operation. Complete

resection of lung cancer with mediastinal lymph node dissection/sampling was performed in all patients as previously described [24, 25]. No patient received adjuvant chemotherapy after surgical resection. Histological typing was determined according to the World Health Organization classification [26]. Determination of disease stages was based on the TNM classification of the International Union Against Cancer [3].

VPI was examined in tumor sections with hematoxylin and eosin stain. VPI was classified according to Hammar's suggestion [13, 14]: Px and P0, lack of pleural invasion beyond the elastic layer; P1, invasion beyond the elastic layer; P2, invasion to the surface of the visceral pleura; and P3, invasion of the parietal pleura and/or chest wall. Presence of VPI was defined as tumors with P1 and P2, whereas absence of VPI was defined as tumors with Px and P0. Elastic stains were performed in tumor sections when the status of VPI was indeterminate by hematoxylin and eosin stains.

The hospital charts of all patients, including pathologic and surgical reports, were reviewed to collect data of clinicopathologic characteristics and survival. Patient demographics, pack years, tumor location, histological type of the tumor, histologic grade, tumor size (> 3 to ≤ 5 vs. > 5 to ≤ 7 vs. > 7 cm), extent of pulmonary resection, presence of VPI and number of mediastinal lymph nodes dissected/sampled were documented. The number of mediastinal lymph nodes dissected/sampled, including N1 and N2 nodes, was recorded from pathologic reports. All patients were followed up at our outpatient department quarterly in the first two

years after resection and semi-annually thereafter. 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 overall survival rate was calculated by the Kaplan-Meier method [27]. The $\chi 2$ test, the independent-sample *t* test, or the one-way analysis of variance test was used to compare between groups with respect to categorical and continuous variables as appropriate. Univariate and multivariate analyses were performed by means of the Cox proportional hazards model using SPSS software (version 16.0; SPSS, Chicago, Illinois, USA). Variables with *P* value less than 0.05 after the univariate analysis were entered into multivariate analysis. Statistical analysis was considered to be significant when the probability value was < 0.05.

Results

The median follow-up time for these 525 patients with surgically resected stage IB NSCLC with a diameter greater than 3 cm was 50.3 months (95% confidence interval [CI], 43.8 to 58.0 months). The characteristics of these patients are listed in Table 1. There were 16 patients lost to follow-up. At the last follow-up session, 119 patients were alive (including 5 patients alive with recurrent cancers), 210 patients died of other causes without evidence of tumor recurrence, and 180 patients (16.2%) died of cancer. Twenty-three postoperative deaths (4.4%) occurred, ten patients with pneumonectomy, four with bilobectomy, five with

lobectomy and four with wedge resection. The 5- and 10-year overall survival rates were 44.9% and 27.3%, respectively (Figure 1).

The relationship between clinicopathologic characteristics and tumor size is listed in Table 2. The tumor size of > 3 to ≤ 5 cm group consisted with more female patients than > 5 to ≤ 7 cm ($P = 0.001$) and > 7 cm ($P = 0.023$) groups. The group of > 5 to ≤ 7 cm consisted of higher number of pack years than that of > 3 to ≤ 5 cm ($P = 0.001$). The group with tumor size of > 3 to ≤ 5 cm consisted with less squamous cell carcinoma than > 5 to ≤ 7 cm ($P = 0.001$) and > 7 cm ($P = 0.001$) groups. Patients with tumor size > 7 cm had a higher frequency undergoing pneumonectomy or bilobectomy than those of > 5 to ≤ 7 cm ($P = 0.009$) and those of > 3 to ≤ 5 cm ($P < 0.001$). No association between VPI ($P = 0.232$) or other clinicopathologic characteristics and tumor size was detected.

Univariate analysis indicated that age (hazard ratio [HR] = 1.020, 95% CI, 1.008 to 1.033; $P = 0.001$), gender (HR of male = 1.408; 95% CI, 1.057 to 1.880; $P = 0.019$), pack years (HR = 1.004; 95% CI, 1.000 to 1.007; $P = 0.037$), tumor size ($P < 0.001$), and extent of pulmonary resection (HR for bilobectomy and pneumonectomy = 1.374; 95% CI; 1.109 to 1.703; $P = 0.004$) and number of mediastinal lymph node dissected (HR = 0.988, 95% CI, 0.978 to 0.999; $P = 0.035$) had a significant influence on overall survival (Table 3). The median survivals for patients with tumor size > 3 to ≤ 5 cm, > 5 to ≤ 7 cm, and > 7 cm were 59.6 months (95% CI, 48.762 to 70.505 months), 43.9 months (95% CI, 31.318 to 56.415 months), and 23.7 months

(95% CI, 11.837 to 35.629 months), respectively (Figure 2). The median survivals for patients with and without VPI were 54.4 months (95% CI, 41.705 to 67.162 months) and 49.0 months (95% CI, 41.705 to 67.162 months), respectively (Figure 3). VPI was not associated with an increased hazard of death in this population of patients ($P = 0.424$).

Variables with P value less than 0.05 after the univariate analysis were entered into multivariate analysis. Histological type was also entered for mutual adjustment. Only age (HR = 1.028, 95% CI, 1.014 to 1.043; $P < 0.001$), tumor size ($P = 0.002$), extent of pulmonary resection (HR for bilobectomy and pneumonectomy = 1.456; 95% CI; 1.149 to 1.846; $P = 0.002$), histological type ($P = 0.005$), and number of mediastinal lymph nodes dissected/sampled (HR = 0.983, 95% CI, 0.971 to 0.994; $P = 0.004$) were still significant prognostic indicators in multivariate analysis (Table 4). Patients with tumor size > 7 cm (HR = 1.724; 95% CI, 1.231 to 2.415) and > 5 to ≤ 7 cm (HR = 1.377; 95% CI, 1.059 to 1.790) had a worse survival than those with tumor size > 3 to ≤ 5 cm ($P = 0.002$). Patients with adenocarcinoma (HR = 1.377; 95% CI, 1.059 to 1.790) had a worse survival than those with squamous cell carcinoma ($P = 0.005$).

Discussion

This study investigated the prognostic role of conventional clinicopathologic factors in patients with resected stage I NSCLC of diameter greater than 3cm. The 5- and 10-year overall survival rates were 44.9% and 27.3%, respectively. Age, tumor size, extent of pulmonary

resection, histological type and number of mediastinal lymph nodes dissected/sampled were significant predictors for overall survival in multivariate analysis. VPI did not influence overall survival.

The number of mediastinal lymph nodes dissected/sampled alternatively represents the quality of lymphadenectomy and affects the survival rate for patients with resected stage I NSCLC [24, 25]. In our previous study [24], we have demonstrated that number of mediastinal lymph nodes dissected/sampled was a prognostic factor for overall survival in resected stage I NSCLC with a diameter of 3 cm or less. For resected stage I NSCLC with a diameter of 3 cm or less, patients with 15 or less mediastinal lymph nodes dissected/sampled had worse survival outcome than those with that more than 15 [24]. In the current study, number of mediastinal lymph nodes dissected/sampled was entered into univariate and multivariate analyses as a continuous variable. Patients with more mediastinal lymph nodes dissected/sampled had better survival. Number of mediastinal lymph nodes dissected/sampled could be used as a marker of adequate mediastinal lymph node dissection/sampling and a prognostic predictor in early stage NSCLC with larger tumor size.

The prognostic factors subcommittee of the International Staging Committee of the IASLC has published a paper regarding the impact of additional prognostic factors in NSCLC [28]. Histologic cell type was a significant prognostic factor in stage IIIA NSCLC, with squamous cell carcinoma having a better prognosis in comparison to other cell type [28]. For early-stage

(stage I-II) NSCLC in their study, histologic cell type was not a prognostic factor for survival in their study [28]. In our report, squamous cell carcinoma is a better prognostic factor for stage IB NSCLC greater than 3 cm.

Tumor size is a significant prognostic factor for stage I NSCLC [11, 16, 22]. The use of 3 cm as a cut-off value has been applied to divide patients with T1N0M0 as stage IA from those with T2N0M0 as stage IB since 1997 [2]. Further categorization of tumor size in stage I NSCLC has been proposed in many studies [5-7, 22, 29-31]. Padilla and colleagues [5] reported that tumor size was the only predictor for worse survival in stage IB patients. Jones and associates [4] reported that increased tumor size and histologic grade were significant independent predictors of a worse overall survival in stage IB NSCLC. Carbone and coworkers [6] demonstrated that a tumor size of greater than 5 cm was a poor prognostic factor in T2 NSCLC. For the revision of the seventh edition of TNM staging system, the IASLC lung cancer staging project committee has recommended that T2 tumors be classified into T2a (> 3 to ≤ 5 cm), T2b (> 5 to ≤ 7 cm), and T3 (> 7 cm) [8-10]. In our study, tumor size was a significant predictor for overall survival in resected stage IB NSCLC with a diameter greater than 3 cm. Patients with tumor size > 7 cm and > 5 to ≤ 7 cm survived shorter than those with tumor size > 3 to ≤ 5 cm. Our results support the IASLC proposals for the revision of the T2 tumors in the seventh edition of the TNM Classification for lung cancer. We further showed that patients with tumor size > 5 cm consisted with more squamous cell carcinoma than those

with tumor size > 3 to ≤ 5 cm. Patients with larger tumor size also had a higher frequency undergoing more extensive pulmonary resection (pneumonectomy or bilobectomy).

The reported frequency of VPI in stage I NSCLC patients ranged between 18 to 21% [17, 21]. Jones and coworkers [4] reported that the frequency of VPI in patients with stage IB NSCLC was 36.4%, while Kang and associates [18] reported only 23%. In our study, the frequency of VPI in stage IB NSCLC with a diameter greater than 3 cm was 25.6% (121 of 472 patients). The relationship between frequency of VPI and tumor size has not been well demonstrated. In Manac'h and colleagues' report [17], the frequency of VPI significantly increased as tumor size increased (10% in tumor size 3 cm or less, 19.6% in > 3 to ≤ 5 cm and 33% in > 5 cm). Shimizu and coworkers [21] also demonstrated that tumors with a diameter greater than 3 cm had higher frequency of VPI. However, no correlation between tumor size and VPI was found in Kang and associates' report [18]. Our results showed that there was no association between VPI and tumor size in stage IB NSCLC with a diameter greater than 3 cm.

Although VPI is the most common criteria of the three non–size-based T2 descriptors [4, 11, 12], its prognostic value for survival has remained controversial [4, 6, 7, 11, 16, 21-23]. VPI was shown to correlate with a higher frequency of mediastinal lymph node involvement, and thus a poor survival [17, 18, 21]. However, the impact of VPI in stage I NSCLC is less clear. The effect of tumor size on the impact of VPI is remained unclear. Only a few reports regarding this issue, and the results were inconsistent [20, 22]. Some studies have demonstrated VPI as a

poor prognostic factor in stage I or stage IB NSCLC [16-18, 21]. Ou and colleagues [12] reported that presence of VPI, hilar atelectasis or obstructive pneumonitis in T2 tumors > 3 cm is an independent poor prognostic factor for survival. However, VPI could not be separated from hilar atelectasis and obstructive pneumonitis in their database [12, 32]. Therefore, the specific effect of VPI in stage IB NSCLC could not be analyzed in their study [12]. Lopez-Encuentra and coworkers [11] reported that VPI was not a prognostic factor in stage I NSCLC. Jones and colleagues [4] demonstrated that VPI did not influence overall survival in stage IB NSCLC. In Martini and coworkers' study [22], they showed that VPI, although a contributing adverse factor in patients with larger tumors, did not influence overall survival in stage I NSCLC with a diameter greater than 3 cm (P = 0.18). The International Staging Committee of the IASLC has published proposals for the definition of VPI as invasion beyond the elastic layer (PL1) including invasion to the visceral pleural surface (PL2) [15]. They also recommend the use of elastic stains in cases when the status of VPI is indeterminate [15]. In the current study, we used elastic stains in documenting VPI in sections where the status of invasion is indeterminate by hematoxylin and eosin stains. VPI was not a prognostic factor of overall survival in resected stage IB NSCLC with a diameter greater than 3 cm. Our previous study has demonstrated that VPI was not a prognostic factor for overall survival in stage I NSCLC with a diameter of 3 cm or less [24]. Compared to the patients of stage I NSCLC with a diameter greater than 3 cm, the overall survival was significantly better in patients of stage I

NSCLC 3 cm or less in diameter with VPI ($P = 0.012$). In the current study, we further showed that tumor size is the most determined factor of survival in stage IB NSCLC with a diameter greater than 3 cm. Therefore, small tumors (≤ 3 cm) of stage IB NSCLC with VPI should be treated as T1 disease (stage IA) but not T2 disease. VPI did not influence overall survival in larger tumor (> 3 cm) of stage IB NSCLC.

There are some limitations of this study that should be mentioned. This is a retrospective study with long study period. Data are lacking in some patients for some variables. The information of whether pre-operative mediastinoscopy was done was only available in 37% of patients in the study. Not all patients had received radical mediastinal lymph nodes dissection in our cohort. However, we provided the number of mediastinal lymph nodes dissected/sampled in nearly all patients to alternatively represent the quality of lymphadenectomy. Furthermore, the lack of data on the frequency of other T2 descriptors (tumors that involve the main bronchus □ 2 cm distal to the carina and tumors that result in associated atelectasis and obstructive pneumonitis that extends to the hilar region but does not involve the entire lung radiographically) in the study population was another weakness of our study. However, the main criterion of non–size-based T2 descriptors is VPI [4, 11, 12]. NSCLC is rarely staged as stage IB only according to hilar atelectasis and obstructive pneumonitis [4, 11, 12, 32].

In conclusion, age, tumor size, extent of pulmonary resection, histological type and number of mediastinal lymph nodes dissected/sampled were prognostic factors for overall survival in resected stage IB NSCLC with a diameter greater than 3 cm. We suggest subclassification of stage IB NSCLC with a diameter greater than 3 cm according to tumor size, with regardless of VPI.

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Table 1. Characteristics of 525 patients of resected stage IB non-small cell lung cancer with a diameter greater than 3 cm

Variables	No. of patients (%)
Age, years (mean ± SD)	65.7 ± 8.8
Sex	
Male	437 (83.2)
Female	88 (16.8)
Pack years (mean ± SD)	27.2 ± 25.2
Tumor location	
Right lung	385 (73.3)
Left lung	140 (26.7)
Tumor size, cm (mean ± SD)	5.2 ± 2.0
> 3 to ≤ 5	362 (69.0)
> 5 to ≤ 7	111 (21.1)
> 7	52 (9.9)
Histological type	
Squamous cell carcinoma	272 (51.8)
Adenocarcinoma	188 (35.8)
Bronchioalveolar carcinoma	30 (5.7)
Large cell carcinoma	29 (5.5)
Adenosquamous carcinoma	6 (1.1)
Histologic grade	
Well differentiated	46 (8.8)
Moderately differentiated	174 (33.1)

Poorly differentiated	63 (12.0)
Unknown	242 (46.1)
Extent of pulmonary resection	
Lobectomy or wedge resection	381 (72.6)
Pneumonectomy or bilobectomy	144 (27.4)
Visceral pleural invasion	
Absent	351 (66.9)
Present	121 (23.0)
Unknown	53 (10.1)
Number of LNs dissected/sampled (mean ± SD)	15.4 ± 10.1
LN ≤ 15	298 (56.7)
LN > 15	222 (42.3)
Unknown	5 (1.0)

SD, Standard deviation; LN, lymph node.

Table 2. Relationship between tumor size and clinicopathologic variables in patients of resected stage IB non-small cell lung cancer with a diameter greater than 3 cm

Variables	> 3 to ≤ 5 cm (n=362) No. (%)	> 5 to ≤ 7 cm (n=111) No. (%)	> 7 cm (n=52) No. (%)	*P* value
Age, years (mean ± SD)	65.7 ± 9.3	65.4 ± 7.6	65.8 ± 8.0	0.947
Sex				
Male	286 (79.0)	103 (92.8)	48 (92.3)	0.001
Female	76 (21.0)	8 (7.2)	4 (7.7)	
Pack years (mean ± SD)	24.2 ± 25.2	34.6 ± 23.9	31.4 ± 24.0	< 0.001
Tumor location				
Right lung	274 (75.7)	77 (69.4)	34 (65.4)	0.165
Left lung	88 (24.3)	34 (30.6)	18 (34.6)	
Histological type				
Squamous cell carcinoma	165 (45.6)	71 (64.0)	36 (69.2)	< 0.001
Others	197 (54.4)	40 (36.0)	16 (30.8)	
Histologic grade*				
Well to moderately differentiated	154 (79.4)	44 (71.0)	22 (81.5)	0.339
Poorly differentiated	40 (20.6)	18 (29.0)	5 (18.5)	
Extent of pulmonary resection				
Lobectomy or wedge resection	279 (77.1)	77 (69.4)	25 (48.1)	< 0.001
Pneumonectomy or bilobectomy	83 (22.9)	34 (30.6)	27 (51.9)	
Visceral pleural invasion*				

Absent	238 (72.1)	76 (79.2)	37 (80.4)	0.232
Present	92 (27.9)	20 (20.8)	9 (19.6)	
Number of LNs dissected/sampled*				
≤ 15	200 (55.7)	68 (61.8)	30 (58.8)	0.512
> 15	159 (44.3)	42 (38.2)	21 (41.2)	

SD, Standard deviation; LN, lymph node. *Data are lacking in some patients for these variables.

Table 3. Univariate analysis for overall survival in patients with resected stage IB non-small cell lung cancer with a diameter greater than 3 cm

Variables	Hazard ratio (95% CI)	*P* value
Age, years*	1.020 (1.008-1.033)	0.001
Gender		
Female	1	0.019
Male	1.408 (1.057-1.880)	
Pack years†	1.004 (1.000-1.007)	0.037
Location		
Left	1	0.378
Right	0.907 (0.730-1.127)	
Tumor size (continuous variable, cm)	1.115 (1.067-1.165)	< 0.001
Tumor size, cm		
> 3 to ≤ 5	1	< 0.001
> 5 to ≤ 7	1.282 (1.006-1.632)	
> 7	1.831 (1.340-2.502)	
Histological type		
Squamous cell carcinoma	1	0.226
Adenocarcinoma	1.053 (0.855-1.298)	
Others	1.410 (0.953-2.105)	
Histologic grade		
Well to moderately differentiated	1	0.237
Poorly differentiated	1.213 (0.880-1.672)	
Extent of pulmonary resection		

Sublobar resection or lobectomy	1	0.004
Bilobectomy or pneumonectomy	1.374 (1.109-1.703)	
Visceral pleural invasion		
Absent	1	0.424
Present	0.902 (0.700-1.162)	
Number of LNs dissected/sampled#	0.988 (0.978-0.999)	0.035

CI, confidence interval; LN, lymph node. *The hazard ratio associated with age is that the increase in hazard is associated with a 1-year increase in age. †The hazard ratio associated with pack years is an increased hazard per 1 pack-year of additional smoking. #The hazard ratio associated with number of LNs dissected/sampled is an increased hazard per 1 LN of additional LN dissection/sampling.

Table 4. Multivariate analysis for overall survival in patients with resected stage IB non-small cell lung cancer with a diameter greater than 3 cm

Variables	Hazard ratio (95% CI)	*P* value
Age, years*	1.028 (1.014-1.043)	< 0.001
Gender		
Female	1	0.582
Male	1.100 (0.784-1.543)	
Pack years	1.003 (0.999-1.007)	0.131
Tumor size, cm		
> 3 to ≤ 5	1	0.002
> 5 to ≤ 7	1.377 (1.059-1.790)	
> 7	1.724 (1.231-2.415)	
Extent of pulmonary resection		
Sublobar resection or lobectomy	1	0.002
Bilobectomy or pneumonectomy	1.456 (1.149-1.846)	
Histological type		
Squamous cell carcinoma	1	0.005
Adenocarcinoma	1.377 (1.059-1.790)	
Others	1.724 (1.231-2.415)	
Number of LNs dissected/sampled†	0.983 (0.971-0.994)	0.004

CI, confidence interval; LN, lymph node. *The hazard ratio associated with age is that the increase in hazard is associated with a 1-year increase in age. †The hazard ratio associated with

number of LNs dissected/sampled is an increased hazard per 1 LN of additional LN dissection/sampling.

Figure legends

Figure 1. Cumulative probability of overall survival in patients with surgically resected stage IB non-small cell lung cancer with a diameter greater than 3 cm.

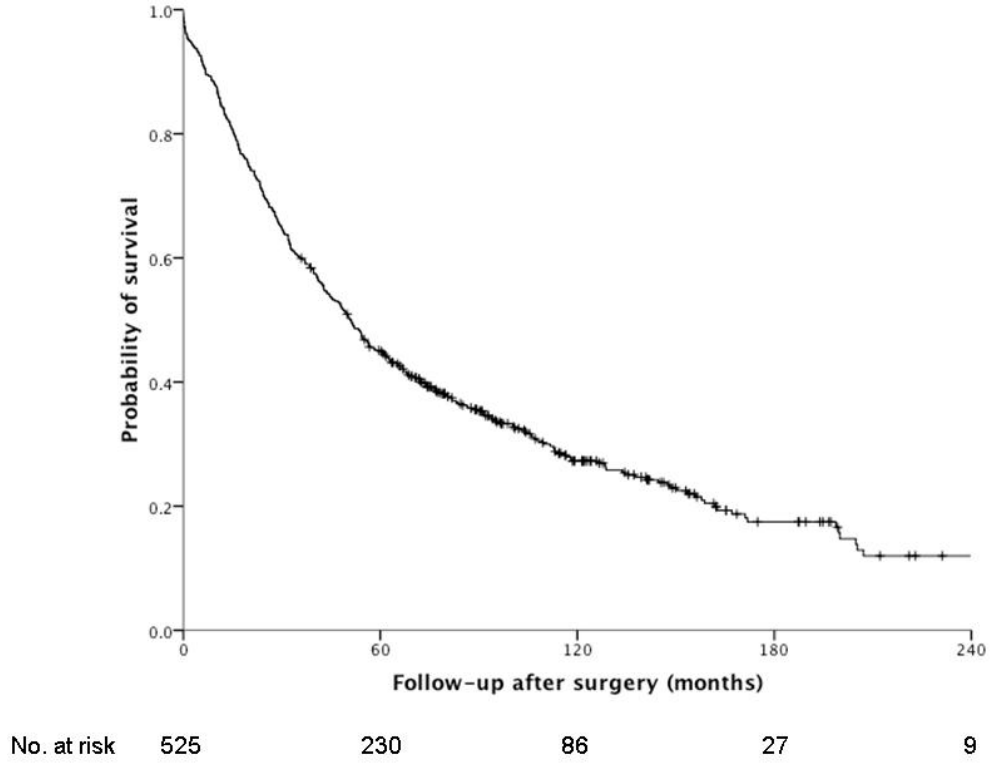
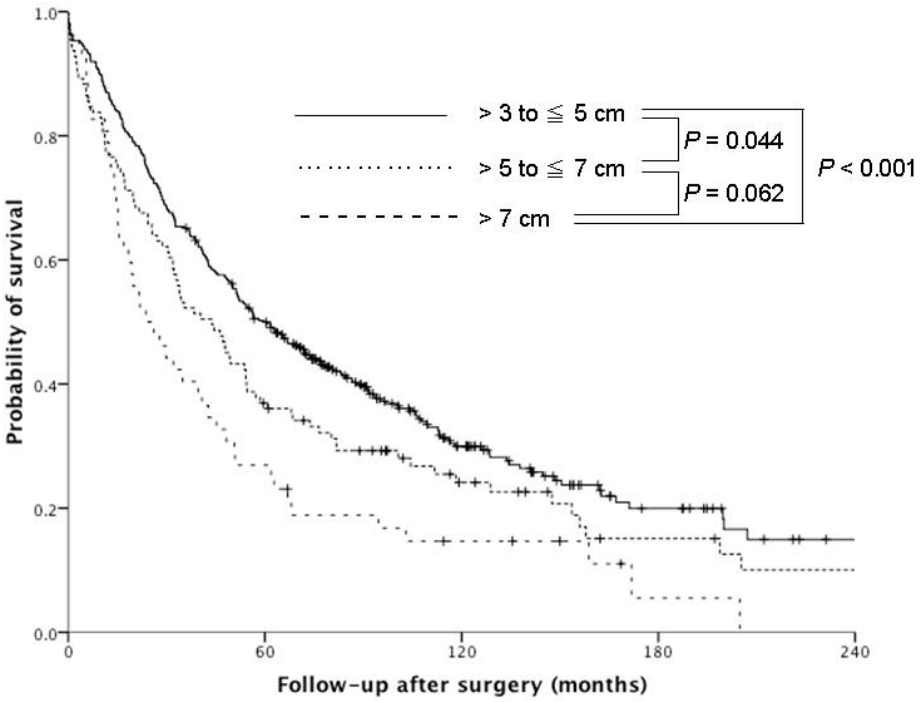
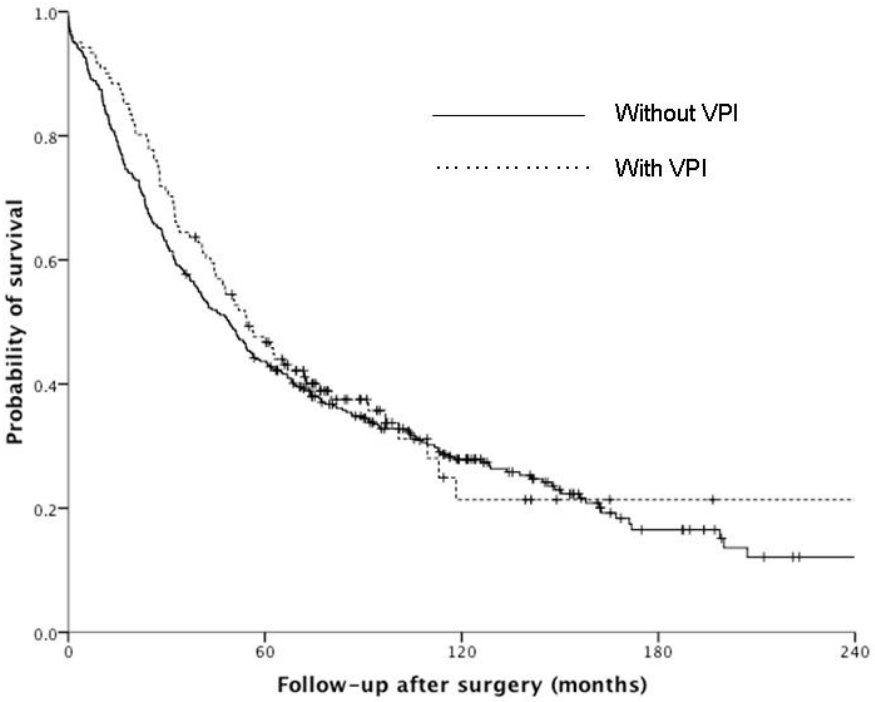


Figure 2. Overall survival in patients with resected stage I NSCLC with a diameter greater than 3 cm grouped according to tumor size (> 3 to ≤ 5, > 5 to ≤ 7 cm, and > 7cm). The log-rank test was used to compare between groups.



No. at risk					
> 3 to ≦ 5 cm	362	176	63	19	5
> 5 to ≦ 7 cm	111	40	17	7	4
> 7 cm	52	14	6	1	0

Figure 3. Overall survival in patients with resected stage I NSCLC with a diameter greater than 3 cm with or without visceral pleural invasion (VPI). $P = 0.424$ (log-rank test).



No. at risk					
Without VPI	351	151	66	17	5
With VPI	121	54	6	2	1