

ORIGINAL ARTICLE

Prognostic significance of basal versus superior segment in patients with completely resected lung adenocarcinoma in the lower lobe

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Keywords

Lower lobe; lung adenocarcinoma; recurrence; survival; tumor location.

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Received: 13 October 2018;

Accepted: 6 December 2018.

doi: 10.1111/1759-7714.12957

Thoracic Cancer **10** (2019) 312–320

Abstract

Background: Although the lower lobes of the lungs occupy half of the chest on both sides, the prognostic value of tumor location in lung cancer in the lower lobe has not been well demonstrated. This study investigated the prognostic value of tumor location (basal vs. superior) in patients with resected lung adenocarcinoma in the lower lobe.

Methods: A total of 207 patients undergoing lobectomy for lung adenocarcinoma in the lower lobe were included in the study. The association between tumor location and mediastinal lymph node metastasis was analyzed. Prognostic factors of overall survival and probability of freedom from recurrence (FFR) were also investigated.

Results: During follow-up, 71 (34.3%) patients developed recurrence. Patients with basal segment tumors had a significantly higher possibility of developing N2 lymph node metastasis than those with superior segment tumors ($P = 0.025$). Univariate analysis showed that location in the basal (vs. superior) segment was a significant prognostic factor for a lower probability of FFR ($P = 0.013$). Basal (vs. superior) segment remained a significant prognostic factor for a lower probability of FFR ($P = 0.010$) in multivariate analysis.

Conclusions: Basal segment tumors have a significantly higher possibility of developing N2 lymph node metastasis than superior segment tumors in resected lung adenocarcinoma in the lower lobe. Tumor location at the basal segment was a significant prognostic factor for a lower probability of FFR. This information is useful for patient stratification of risk of postoperative recurrence.

Introduction

Lung cancer is the leading cause of cancer death worldwide.¹ Surgical resection is the treatment of choice for early-stage non-small cell lung cancer (NSCLC).^{2,3} Tumor recurrence is the most common cause of treatment failure after resection.^{4–6} Post-recurrence survival in patients undergoing surgical resection for NSCLC is poor.^{7–9} Therefore, the identification of prognostic factors in patients with resected NSCLC is necessary to stratify high-risk patients for further management.

The lower lobes of the lungs occupy half of the chest on both sides, contain a large volume of lung parenchyma,

and extend from above the pulmonary hilum to the diaphragm. Anatomically, the lower lobe can be divided into two parts, the superior and basal segments. The prognostic factors of tumors located in a specific lobe of the lung, such as the lower lobe, have not been well demonstrated in the literature.^{10–12} Watanabe *et al.* reported that superior and basal segment lung cancers in the lower lobe have different lymph node metastatic pathways to the mediastinum.¹⁰ In the present study, we investigated the relationships between tumor location (basal vs. superior segment) and clinicopathological variables, and the prognostic significance of tumor location in patients with completely resected lung adenocarcinoma in the lower lobe.

Methods

Patients

The Institutional Review Board of Taipei Veterans General Hospital approved this study. The records of all patients who underwent surgical resection for lung adenocarcinomas at Taipei Veterans General Hospital from January 2004 to December 2013 were retrospectively reviewed. Patients undergoing neoadjuvant chemotherapy or radiotherapy were excluded. A total of 876 patients who had undergone resection for lung adenocarcinoma were identified. Among them, 236 patients had tumors located at their lower lobes. Twenty-nine of the 236 patients undergoing sublobar resection were excluded from the analysis. The remaining 207 patients underwent lobectomy for lung adenocarcinoma and were included in the study.

The preoperative staging workup, including chest and upper abdomen computed tomography (CT) scans, brain CT scan or magnetic resonance imaging, and a nuclear medicine survey of the bone, was performed as previously described.^{13,14} A positron emission tomography (PET)-CT scan was available as a staging modality in 90 (43.5%) of the 207 patients. Mediastinoscopy or endobronchial ultrasound was performed when enlarged mediastinal lymph nodes (diameter > 1.0 cm) were shown by CT scan or increased uptake at mediastinal lymph nodes was shown by PET-CT scan. All patients underwent complete resection of the lung cancer with mediastinal lymph node dissection, as previously described.^{13,14}

Clinicopathological characteristics

Patients were subdivided according to tumor location into superior and basal segment groups. The tumor location was identified by the involved bronchus using preoperative chest CT scans. For tumors involving both the superior and basal segments, the segment with the main tumor volume was determined as the tumor location. Correlations between tumor location and clinicopathological variables were analyzed. To investigating their prognostic value, clinicopathological factors, including tumor location (basal vs. superior segment), were examined in univariate and multivariate analyses. Tumor size was defined as the size of the invasive components of the tumor. The determination of disease stage was based on the 8th edition American Joint Committee on Cancer Tumor Node Metastasis (TNM) Classification.¹⁵

Patients follow-up

All patients were followed-up at our outpatient department every three months in the first two years after resection and at six-month intervals thereafter, as previously described.^{13,14}

The modalities and protocols used during follow-up have also been previously described.^{9,13,14} CT scans of chest and upper abdomen were routinely performed at every outpatient department visit for follow-up. A nuclear medicine survey of the bone was taken every six months in the first two years after resection and annually thereafter during follow-up. Brain CT scan or magnetic resonance imaging was performed when neurological symptoms occurred or when clinical suspicions were raised. Secondary primary lung cancer was differentiated from recurrent NSCLC according to suggestions made by Detterbeck *et al.*^{16,17} Overall survival (OS) was defined as the interval between the date of surgical resection and the date of either death or the last follow-up. The period of freedom from recurrence (FFR) was defined as the interval between the date of surgical resection and the date of recurrence or the last follow-up. An observation was censored at the last follow-up session when the patient was alive with recurrence-free status or had died without recurrence.

Statistical analysis

The OS and probability of FFR were calculated using the Kaplan–Meier method.¹⁸ The log-rank test was used to make group comparisons. Univariate and multivariate analyses were performed with the Cox proportional hazards model in SPSS version 20 (IBM Corp., Armonk, NY, USA). All variables with $P < 0.1$ were entered into multivariable analysis, except for T status, N status, and TNM stage, for which only T and N status were entered. Statistical significance was defined as $P < 0.05$.

Results

The median follow-up duration of the 207 patients was 33.9 (range 3.2–110.8) months. Patient characteristics are listed in Table 1. The five-year OS and probability of FFR of all patients were 76.9% and 56.5%, respectively (Fig 1). Of the 207 patients, 73 (35.3%) presented with superior segment tumors, while 134 (64.7%) presented with basal segment tumors (Table 1). Among all patients, 130 (62.8%) were FFR, 71 (34.3%) developed recurrence, and 6 (2.9%) had unknown recurrence status during follow-up. The six patients with unknown recurrence status were excluded from the analysis of FFR probability.

Association between tumor location (basal vs. superior segment) in the lower lobe and clinicopathological variables

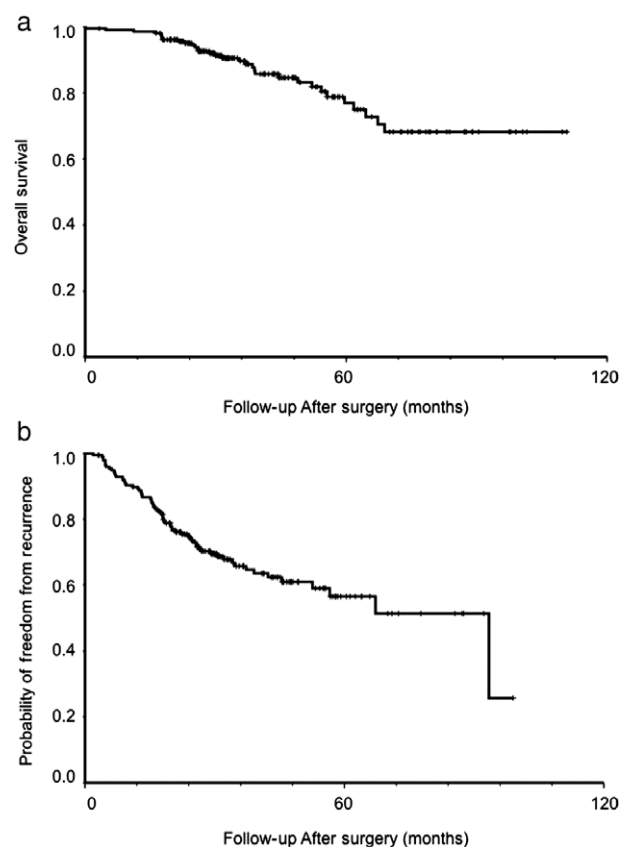
Associations between tumor location (basal vs. superior segment) and clinicopathological variables are presented in

Table 1 Clinicopathological variables in 207 patients with lung adenocarcinoma in the lower lobe

Variables	All patients
Age, years (mean ± SD)	61.6 ± 10.4
Gender, N (%)	
Male	98 (47.3)
Female	109 (52.7)
Tumor location, N (%)	
Superior segment	73 (35.3)
Basal segment	134 (64.7)
Laterality, N (%)	
Left	95 (45.9)
Right	112 (54.1)
Tumor size, cm (mean ± SD)	2.7 ± 1.4
T status, no. (%)	
T1a	16 (7.7)
T1b	28 (13.6)
T1c	16 (7.7)
T2	132 (63.8)
T3	11 (5.3)
T4	4 (1.9)
N status, N (%)	
N0	152 (73.4)
N1	22 (10.7)
N2	33 (15.9)
Stage, N (%)	
I	141 (68.1)
II	25 (12.1)
III	41 (19.8)
Visceral pleural invasion, N (%)	
Absent	75 (36.3)
Present	129 (62.3)
Unknown	3 (1.4)
Angiolymphatic invasion, N (%)	
Absent	139 (67.2)
Present	63 (30.4)
Unknown	5 (2.4)
Histologic grade, N (%)	
Well differentiated	21 (10.2)
Moderately differentiated	118 (57.0)
Poorly differentiated	58 (28.0)
Unknown	10 (4.8)
No. of LNs dissected/sampled (mean ± SD)	20.7 ± 8.8
Predominant pattern, N (%)	
Lepidic predominant	15 (7.2)
Acinar predominant	66 (31.9)
Papillary predominant	62 (30.0)
Micropapillary predominant	42 (20.3)
Solid predominant	22 (10.6)
Adjuvant chemotherapy, N (%)	
No	113 (54.6)
Yes	94 (45.4)

LN, lymph node; SD, standard deviation.

Table 2. Patients with basal segment tumors had a significantly higher possibility of developing N2 lymph node metastasis than those with superior segment tumors ($P = 0.025$). A trend of significantly larger tumor size was

**Figure 1** Cumulative probability of (a) overall survival, and (b) freedom from recurrence in 207 patients with resected lung adenocarcinoma in the lower lobe.

observed in patients with basal segment tumors compared to those with superior segment tumors ($P = 0.052$). No other clinicopathological variables were significantly associated with tumor location.

We further investigated the association between N2 metastasis and clinicopathological variables other than tumor location. The results showed that women ($P = 0.032$), larger tumors ($P = 0.002$), visceral pleural invasion ($P = 0.043$), angiolymphatic invasion ($P < 0.001$), histologic grade (moderately or poorly differentiated vs. well differentiated) ($P = 0.033$), and predominant pattern groups (micropapillary/solid vs. lepidic/acinar/papillary predominant) ($P < 0.001$) were significantly associated with N2 metastasis.

Overall survival in patients with resected lung adenocarcinoma in the lower lobe

Univariate analysis indicated that larger tumor size ($P < 0.001$), T status (T3 or T4 vs. T1 or T2; $P = 0.044$), N status (N2 vs. N0 or N1; $P < 0.001$), TNM stage (II or III vs. I; $P < 0.001$), angiolymphatic invasion ($P = 0.037$), and

Table 2 Association between tumor location (superior vs. basal segment) and clinicopathological variables in 207 patients with lung adenocarcinoma in the lower lobe

Variables	Superior segment (n = 73)	Basal segment (n = 134)	P
Age, years (mean ± SD)	64.0 ± 10.7	60.6 ± 10.1	0.069
Gender, N (%)			
Male	34 (46.6)	64 (47.8)	0.870
Female	39 (53.4)	70 (52.2)	
Laterality, N (%)			
Left	34 (46.6)	61 (45.5)	0.885
Right	39 (53.4)	73 (54.5)	
Tumor size, cm (mean ± SD)	2.3 ± 1.3	2.7 ± 1.7	0.052
T status, N (%)			
T1 or T2	66 (90.4)	126 (94.0)	0.337
T3 or T4	7 (9.6)	8 (6.0)	
N status, N (%)			
N0 or N1	67 (91.8)	107 (79.9)	0.025
N2	6 (8.2)	27 (20.1)	
TNM stage, N (%)			
I	53 (72.6)	88 (65.7)	0.307
II or III	20 (27.4)	46 (34.3)	
Visceral pleural invasion, N (%)†			
Absent	24 (33.8)	51 (38.3)	0.521
Present	47 (66.2)	82 (61.7)	
Angiolymphatic invasion, N (%)†			
Absent	54 (76.1)	85 (64.9)	0.102
Present	17 (23.9)	46 (35.1)	
Histologic grade, N (%)†			
Well differentiated	9 (13.2)	12 (9.3)	0.395
Moderately or poorly differentiated	59 (86.8)	117 (90.7)	
No. of LNs dissected/sampled (mean ± SD)	20.8 ± 8.4 (range 4–39)	20.7 ± 9.0 (range 5–40)	0.976
Predominant pattern group, N (%)			
Lepidic/acinar/papillary predominant	50 (68.5)	93 (69.4)	0.892
Micropapillary/solid predominant	23 (31.5)	41 (30.6)	
Adjuvant chemotherapy, N (%)			
No	43 (58.9)	70 (52.2)	0.357
Yes	30 (41.1)	64 (47.8)	

†Patients with unknown status were excluded from the analysis. LN, lymph node; SD, standard deviation; TNM, tumor node metastasis.

predominant pattern group (micropapillary/solid vs. lepidic/acinar/papillary predominant) ($P = 0.007$) were significant prognostic factors of poor OS (Table 3). The tumor location (basal vs. superior segment; $P = 0.212$) was not a significant prognostic factor of OS (Fig 2a, Table 3). In multivariate analysis, larger tumors (hazard ratio [HR] 1.604, 95% confidence interval [CI] 1.253–2.053; $P < 0.001$), and N status (N2 vs. N0 or N1, HR 4.755, 95% CI, 2.006–11.273; $P < 0.001$) were significant prognostic factors of poor OS (Table 4).

Probability of freedom from recurrence in patients with resected lung adenocarcinoma in the lower lobe

Univariate analysis indicated that tumor location (basal vs. superior segment; $P = 0.013$) was a significant

prognostic factor for a lower probability of FFR (Fig 2b, Table 3). Larger tumor size ($P < 0.001$), N status (N2 vs. N0 or N1 and N1 or N2 vs. N0; both $P < 0.001$), TNM stage (II or III vs. I; $P < 0.001$), visceral pleural invasion ($P = 0.004$), angiolymphatic invasion ($P < 0.001$), histologic grade (moderately or poorly vs. well differentiated; $P = 0.039$), predominant pattern group (micropapillary/solid predominant vs. lepidic/acinar/papillary predominant; $P < 0.001$), and adjuvant chemotherapy ($P < 0.001$) were also significant prognostic factors for a lower probability of FFR (Table 3). In multivariate analysis, tumor location (basal vs. superior segment, HR 2.453, 95% CI, 1.242–4.846; $P = 0.010$), larger tumor size (HR 1.326, 95% CI 1.109–1.585; $P = 0.002$), N status (N2 vs. N0 or N1, HR 3.337, 95% CI, 1.699–6.554; $P < 0.001$), angiolymphatic invasion (HR 2.592, 95% CI 1.387–4.845; $P = 0.003$), and

Table 3 Univariate analyses of overall survival and probability of freedom from recurrence in 207 patients with lung adenocarcinoma in the lower lobe

Variables	HR	95% CI	P
Overall survival			
Age, years†	1.024	0.992–1.057	0.149
Gender			
Male	1		
Female	0.752	0.373–1.513	0.424
Tumor location			
Superior segment	1		
Basal segment	1.606	0.748–3.714	0.212
Laterality			
Left	1		
Right	0.754	0.376–1.511	0.427
Tumor size‡	1.526	1.302–1.789	< 0.001
T status			
T1 or T2	1		
T3 or T4	2.664	1.025–6.925	0.044
N status			
N0 or N1	1		
N2	4.651	2.309–9.368	< 0.001
N status			
N0	1		
N1 or N2	3.586	1.782–7.217	< 0.001
TNM stage			
I	1		
II or III	3.730	1.822–7.634	< 0.001
Visceral pleural invasion			
Absent	1		
Present	1.416	0.652–3.076	0.380
Angiolymphatic invasion			
Absent	1		
Present	2.149	1.048–4.407	0.037
Histologic grade			
Well differentiated	1		
Moderately or poorly differentiated	2.775	0.378–20.382	0.316
No. of LNs dissected/sampled§	1.025	0.986–1.066	0.211
Predominant pattern group			
Lepidic/acinar/papillary predominant	1		
Micropapillary/solid predominant	2.611	1.294–5.271	0.007
Adjuvant chemotherapy			
No	1		
Yes	1.629	0.810–3.278	0.171
Probability of freedom from recurrence			
Age, years†	0.990	0.967–1.012	0.364
Gender			
Male	1		
Female	1.238	0.761–2.013	0.390
Tumor location			
Superior segment	1		
Basal segment	2.042	1.164–3.583	0.013
Laterality			
Left	1		
Right	0.930	0.577–1.498	0.765
Tumor size‡	1.699	1.495–1.932	< 0.001
T status			
T1 or T2	1		
T3 or T4	2.082	0.976–4.439	0.058

Table 3 Continued

Variables	HR	95% CI	P
N status			
N0 or N1	1		
N2	5.946	3.622–9.762	< 0.001
N status			
N0	1		
N1 or N2	6.557	3.985–10.788	< 0.001
TNM stage			
I	1		
II or III	6.664	3.988–11.135	< 0.001
Visceral pleural invasion			
Absent	1		
Present	2.365	1.309–4.274	0.004
Angiolymphatic invasion			
Absent	1		
Present	5.227	3.122–8.753	< 0.001
Histologic grade			
Well differentiated	1		
Moderately or poorly differentiated	8.040	1.114–58.002	0.039
No. of LNs dissected/sampled§	1.003	0.975–1.032	0.844
Predominant pattern group			
Lepidic/acinar/papillary predominant	1		
Micropapillary/solid predominant	3.561	2.195–5.776	< 0.001
Adjuvant chemotherapy			
No	1		
Yes	3.574	2.109–6.058	< 0.001

†The hazard ratio (HR) associated with age is the increase in hazard associated with a one-year increase in age. ‡The HR associated with tumor size is the increase in hazard associated with a 1 cm increase in size. §The HR associated with number of lymph nodes (LNs) dissected/sampled is an increased hazard per LN of additional LN dissection/sampling. CI, confidence interval; TNM, tumor node metastasis.

predominant pattern group (micropapillary/solid vs. lepidic/acinar/papillary predominant, HR 2.611, 95% CI 1.446–4.712; $P = 0.001$) were still significant prognostic factors for a lower probability of FFR (Table 4).

We further examined the prognostic value of tumor location. For multivariate analysis, N status of N1 or N2 vs. N0 was entered instead of N2 vs. N0 or N1. Tumor location (basal vs. superior segment, HR 1.986, 95% CI 1.017–3.879; $P = 0.045$), larger tumor size (HR 1.358, 95% CI 1.124–1.640; $P = 0.001$), N status (N1 or N2 vs. N0, HR 3.151, 95% CI 1.518–6.542; $P = 0.002$), angiolymphatic invasion (HR 2.104, 95% CI 1.085–4.081; $P = 0.028$), and the predominant pattern group (micropapillary/solid vs. lepidic/acinar/papillary predominant, HR 2.084, 95% CI 1.139–3.814; $P = 0.017$) were still significant prognostic factors for a lower probability of FFR.

Discussion

This study investigated the association between tumor location and clinicopathological variables and the prognostic value of tumor location in patients with completely resected lung adenocarcinoma in the lower lobe. Tumor location (basal vs. superior segment) was not a significant

prognostic factor of OS. However, tumor location at the basal (vs. superior) segment was a significant prognostic factor for a lower probability of FFR.

The association between lymphatic drainage pathway and tumor location in the lower lobe has not been well demonstrated. Watanabe *et al.* reported that superior segment tumors showed a significantly higher incidence of superior mediastinal lymph node metastasis than basal segment tumors.¹⁰ They concluded that basal segment tumors metastasize to the superior mediastinum mostly through the subcarinal lymph node, whereas superior segment tumors often metastasize directly to the superior mediastinum without concomitant metastasis to the subcarinal node.¹⁰ Although Handa *et al.* reported that superior segment tumors had a higher incidence of mediastinal lymph node metastasis than basal segment tumors in patients with clinical stage I (clinical N0) lower lobe NSCLC, the difference was not significant.¹¹ Tomizawa *et al.* also reported that no significant difference existed in subcarinal or superior mediastinal lymph node metastasis between superior and basal segment tumors in the right lower lobe.¹² Our study showed that basal segment tumors had a significantly higher possibility of developing N2 lymph node metastasis than superior segment tumors in patients

Table 4 Multivariate analyses of overall survival and probability of freedom from recurrence in 207 patients with lung adenocarcinoma in the lower lobe

Variables	HR	95% CI	P
Overall survival			
Tumor size†	1.604	1.253–2.053	< 0.001
T status			
T1 or T2	1		
T3 or T4	1.220	0.344–4.331	0.758
N status			
N0 or N1	1		
N2	4.755	2.006–11.273	< 0.001
Angiolymphatic invasion			
Absent	1		
Present	0.671	0.294–1.532	0.343
Predominant pattern group			
Lepidic/acinar/papillary predominant	1		
Micropapillary/solid predominant	1.000	0.438–2.281	0.999
Probability of freedom from recurrence			
Tumor location			
Superior segment	1		
Basal segment	2.453	1.242–4.846	0.010
Tumor size†	1.326	1.109–1.585	0.002
T status			
T1 or T2	1		
T3 or T4	1.927	0.745–4.985	0.176
N status			
N0 or N1	1		
N2	3.337	1.699–6.554	< 0.001
Visceral pleural invasion			
Absent	1		
Present	0.985	0.487–1.992	0.966
Angiolymphatic invasion			
Absent	1		
Present	2.592	1.387–4.845	0.003
Histologic grade			
Well differentiated	1		
Moderately or poorly differentiated	2.800	0.363–21.582	0.323
Predominant pattern group			
Lepidic/acinar/papillary predominant	1		
Micropapillary/solid predominant	2.611	1.446–4.712	0.001
Adjuvant chemotherapy			
No	1		
Yes	0.677	0.314–1.458	0.319

†The hazard ratio (HR) associated with tumor size is the increase in hazard associated with a 1 cm increase in size. CI, confidence interval.

undergoing lobectomy for lung adenocarcinoma in the lower lobe. There was a trend for of significantly larger tumors in patients with basal segment tumors than in those with superior segment tumors.

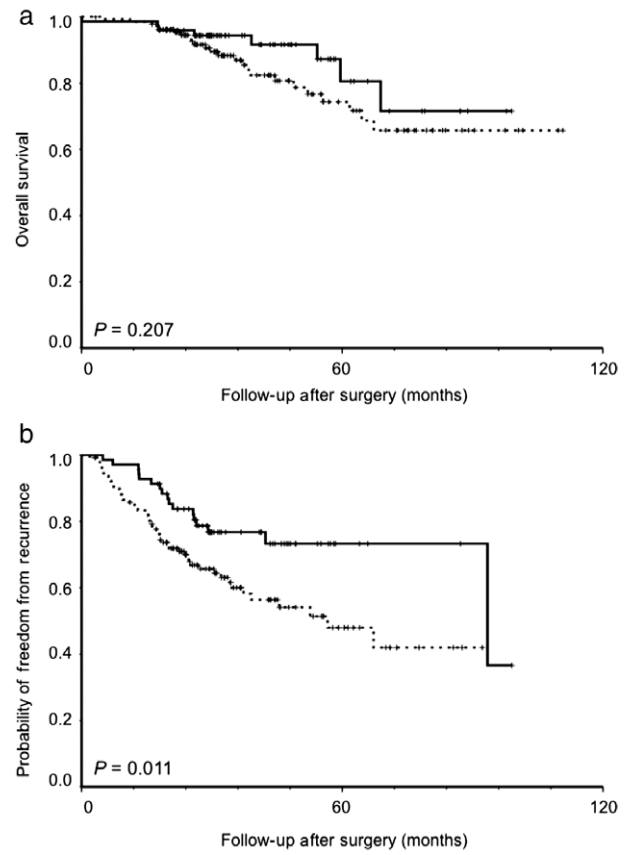


Figure 2 Kaplan–Meier analysis (log-rank test) for (a) overall survival and (b) probability of freedom from recurrence in 207 patients with resected lung adenocarcinoma in the lower lobe according to tumor location (superior vs. basal segment). (—) Superior segment, (.....) Basal segment.

The prognostic factors of lung cancer in a specific lobe, for example, the lower or upper lobe, have not been well demonstrated. Several reports have examined the prognostic value of tumor location (basal vs. superior segment) in lower lobes.^{10–12} In a study of 139 patients with pN2 NSCLC, Watanabe *et al.* reported that there was no significant difference in OS between the basal and superior segment groups.¹⁰ Tomizawa *et al.* reported that there was no significant difference in disease-free survival between basal and superior segment groups in 263 patients with NSCLC in the right lower lobe.¹² In univariate analysis of patients with pN2 disease, they further showed that disease-free survival in the superior segment group was significantly lower than in patients in the basal segment group.¹² However, they did not perform multivariate analysis. Handa *et al.* reported that a superior segment tumor was an independent factor of poor OS and recurrence-free survival in 134 patients with clinical stage I (clinical N0) lower lobe NSCLC.¹¹ However, they mainly examined the preoperative

related factors in multivariate analysis instead of pathological variables. Our results show that tumor location at the basal (vs. the superior) segment is a significant prognostic factor for a lower probability of FFR. Our results also show that larger tumor size, N status (N2 vs. N0 or N1), angiolymphatic invasion, and predominant pattern group (micropapillary/solid vs. lepidic/acinar/papillary predominant) are other significant prognostic factors for a lower probability of FFR in patients with lung adenocarcinoma in the lower lobe.

Some limitations of this study should be mentioned. As a retrospective study, patient selection bias and time trend bias are inevitable. The majority of patients in the study had stage I lung adenocarcinoma. The median follow-up duration (33.9 months) in this study may have been too short to analyze the prognostic factors of OS in these patients. Another limitation is that N status was entered into univariate and multivariate analyses as N2 versus N0 or N1. To solve the problem, we also entered N status as N1 or N2 versus N0 in another multivariate analysis model. Prospective multi-institutional studies and randomized clinical trials are mandatory to further validate the prognostic value of tumor location (basal vs. superior segment) on survival or recurrence in patients with lung cancer in the lower lobe.

In conclusion, basal segment tumors have a significantly higher possibility of developing N2 lymph node metastasis than superior segment tumors in resected lung adenocarcinoma in the lower lobe. Tumor location at the basal (vs. superior) segment is a significant prognostic factor for a lower probability of FFR in patients with resected lung adenocarcinoma in the lower lobe. This information is useful for patient stratification of risk of recurrence after surgery.

Acknowledgments

This work was supported in part by the Ministry of Science and Technology (MOST 107-2314-B-010-062); the Higher Education Sprout Project by the Ministry of Education (MOE) in Taiwan (107AC-D970); Taipei Veterans General Hospital (V107C-149 and V108C-199); the National Yang-Ming University-Far Eastern Memorial Hospital Joint Research Program (107DN10 and 108DN14); the Taipei Veterans General Hospital-National Yang-Ming University-Excellent Physician Scientists Cultivation Program (107-V-B-079); the Yen Tjing Ling Medical Foundation (CI-107-15 and CI-108-20); and the Li-Yang Sheen Medical Education Memorial Foundation. The authors are grateful to Drs Yu-Chung Wu, Han-Shui Hsu, Chih-Cheng Hsieh, Chien-Sheng Huang, and Teh-Ying Chou of Taipei Veterans General Hospital, Taipei, Taiwan for

contributions to this article. We also thank Dr. Ying-Shiun Kao for his assistance with data collection.

Disclosure

No authors report any conflict of interest.

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