ORIGINAL ARTICLE

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

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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.⁸-¹⁰ Watanabe et al. reported that superior and basal segment lung cancers in the lower lobe have different lymph node metastatic pathways to the mediastinum.⁸ 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. 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.

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.

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.

The modalities and protocols used during follow-up have also been previously described. 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. 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. 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 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 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
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 or 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, 1.242–4.845; $P = 0.010$), 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 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.

**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, 1.242–4.845; $P = 0.010$), 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|
| Angiolympathic 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 dominant | 1    |             |      |
| Micropapillary/solid dominant  | 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|
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. 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. 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. 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. Our study showed that basal segment tumors had a significantly higher possibility of developing N2 lymph node metastasis than superior segment tumors in patients...
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.

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         | 1     |              |        |
| predominant                      |       |              |        |
| Micropapillary/solid             | 1.000 | 0.438–2.281  | 0.999  |
| predominant                      |       |              |        |
| 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         | 1     |              |        |
| predominant                      |       |              |        |
| Micropapillary/solid             | 2.611 | 1.446–4.712  | 0.001  |
| predominant                      |       |              |        |
| 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.

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), angio-lymphatic 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.

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Disclosure

No authors report any conflict of interest.

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