

ORIGINAL ARTICLE

Prognosis and segment-specific nodal spread of primary lung cancer in the right lower lobe

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Keywords

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Abstract

Background: Although lobe-specific nodal spread of primary lung cancer has been recently described, segment-specific nodal spread remains unclear. We investigated the frequency of hilar and mediastinal lymph node involvement and survival in patients with tumors located in the superior segment (SS) and basal segment (BS) in the right lower lobe.

Methods: Two hundred and sixty-three patients with primary lung cancer originating in the right lower lobe underwent lobectomy with systematic mediastinal lymph node dissection. Patients were categorized into two groups: SS (n = 114) or BS (n = 149).

Results: Frequencies of metastasis to station 11s and 11i were significantly higher in the SS ($P < 0.0001$) and BS groups ($P = 0.022$), respectively. Both the SS and BS groups showed a high frequency of subcarinal mediastinal zone (station 7) metastasis (96.9% and 90.6%, respectively; $P = 0.271$). The frequencies of superior mediastinal zone (station 2R and 4R) metastasis were 37.5% in the SS and 35.8% in the BS group ($P = 0.878$). In patients with pN2 disease, three-year disease-free survival was significantly shorter in the SS (22.6%) than the BS group (42.1%; $P = 0.020$). In the BS group, the independent predictive factors of a poor or good prognosis were metastasis to station 11i or skip metastasis, respectively; however, we did not detect an independent prognostic factor in the SS group. In the right lower lung lobe, there was no segment-specific nodal spread.

Conclusion: When segmentectomy is undertaken, mediastinal lymph node dissection should be performed in proportion to lobectomy.

Introduction

A pulmonary lobectomy and systematic mediastinal lymph node dissection (SMLND) are performed as a standard procedure independently of tumor location. Cahan *et al.* first reported SMLND in 1951.¹ Clinical studies have provided consistent information regarding lobe-specific nodal spread dependent on tumor location.^{2,3} Lobe-specific nodal spread from the upper and lower lung lobes involves the superior mediastinal and subcarinal lymph nodes, respectively, whereas spread from the middle lobe involves both the superior mediastinal and subcarinal lymph nodes.^{4,5}

Anatomically, the cranial end of the right lower lobe extends above the pulmonary hilum, while the base is located on the diaphragm. The right lower lobe contains the largest volume of lung parenchyma in the thoracic cavity and is made up of five segments (6–10th). The five segments are divided into two parts: the 6th and 7–10th segments are termed the superior and basal segments, respectively. Segment-specific nodal spread may exist in the right lower lobe in the same manner as lobe-specific nodal spread.

Recently, advances in radiography have increased the early detection of non-small cell lung cancer (NSCLC). Previous retrospective studies have shown that there is no difference in

Table 1 Clinicopathological characteristics of patients in the SS and BS groups

Variable	All patients n = 263	SS group n = 114	BS group n = 149	P
Median age (range)	65 (31–82)	64 (31–79)	65 (38–82)	0.814
Gender (male/female)	163/100	73/41	90/59	0.548
Smoking status (never/ever)	105/158	43/71	62/87	0.523
cT (T1/T2/T3/T4)	111/137/14/1	47/60/7/0	64/77/7/1	0.783
cN (N0/N1/N2)	210/28/25	87/16/11	123/12/14	0.288
Surgical procedure				
Pneumonectomy/lobectomy	8/225	7/107	1/148	0.023
Histological type (AD/SCC/others)	177/67/19	73/29/12	104/38/7	0.187
pT (T1/T2/T3/T4)	54/175/30/4	18/82/13/1	36/93/17/3	0.164
pN (N0/N1/N2)	153/25/85	69/13/32	84/12/53	0.354
Adjuvant chemotherapy (all regimens; yes/no)	61/202	21/93	40/109	0.109
Adjuvant chemotherapy (platinum doublet; yes/no)	34/229	13/101	21/128	0.519

AD, adenocarcinoma; BS, basal segment; SCC, squamous cell carcinoma; SS, superior segment.

survival between patients treated with segmentectomy and lobectomy for small peripheral NSCLC.^{6–8} In Japan, a phase III randomized trial involving a comparative evaluation of lobectomy and segmentectomy for small peripheral NSCLC is now in progress (JCOG0802/WJOG4607L). In the near future, segmentectomy for small peripheral NSCLC may be performed as a standard procedure. Consequently, it is important to examine segment-specific nodal spread.

The aim of the present study was to retrospectively review the records of patients with completely resected primary lung cancer located in the right lower lobe, and to investigate the frequency of mediastinal lymph node involvement and patient survival according to tumor location.

Methods

Patients

A total of 263 patients with primary lung cancer located in the right lower lobe underwent lobectomy with SMLND. One hundred and ninety-three patients were treated at the Aichi Cancer Center Hospital from 1996 through 2008, and 70 patients were treated at the Kinki University Hospital from 2007 through 2012. We excluded patients who only underwent sampling or selective mediastinal lymph nodal dissection, and those who harbored a tumor that had invaded multiple lobes. An appropriate and comprehensive approval, including permission for the application of personal data in clinical studies, was obtained in advance from each institutional review board. All patients provided written informed consent at each of the two institutes on admission. Disease staging for all patients was determined according to the tumor node metastasis (TNM) Classification of Malignant Tumors, 7th Edition.⁹ On chest computed tomography (CT) scan, the clinical criteria of lymph node metastasis was a short axis length >1.0 cm. Mediastinoscopy or positron emission

tomography scans were not routinely used pre-operatively. After pulmonary resection, the patients were examined at three to six month intervals for five years and thereafter at one-year intervals. Evaluations included physical examinations, chest radiography or CT scan, and detection of tumor markers. When recurrence was suspected, brain magnetic resonance imaging, bone scintigraphy or positron emission tomography was undertaken.

Among the total patient population, there were 163 men and 100 women. One hundred and five patients had never smoked and 158 were current or former smokers. A non-smoker was defined as a patient who smoked <5 packs per year. Tumor diagnoses were: 177 adenocarcinomas, 67 squamous cell carcinomas, and 19 other histopathological types. Eight patients required pneumonectomy. Thirty-four patients received adjuvant platinum doublet chemotherapy (Table 1). The patients were divided into two groups according to tumor origin: the superior segment (SS) group and the basal segment (BS) group. We defined the SS and BS as the 6th and 7–10th segments, respectively. Tumor location was identified using pre-operative chest CT scans. The V6b and V6c branches of the pulmonary vein formed the border interface between the SS and BS. When the tumor involved both the SS and BS, the segment with the greater tumor localization was considered.

Hilar and mediastinal lymph node dissection and analyses

Hilar and mediastinal lymph node dissection was performed after right lower lobectomy. In the hilar nodes, station 10 was adjacent to the inferior portion of the main bronchus and was classified as N1 using the TNM Classification of Malignant Tumors, 6th Edition.¹⁰ However, this node is included in the subcarinal zone according to the TNM Classification of Malignant Tumors, 7th Edition.⁹ In the present study, station

Table 2 Frequency of lymph node metastases in the SS and BS groups

Lymph node metastasis	No. (%)			No. (%)		
	Patients with pN1 or pN2 disease		<i>P</i>	Patients with pN2 disease		<i>P</i>
	SS group (n = 45)	BS group (n = 65)		SS group (n = 32)	BS group (n = 53)	
Station 11 s	19 (42.2)	5 (7.7)	<0.0001	–	–	–
Station 11i	7 (15.6)	23 (35.4)	0.022	–	–	–
Intralobar	19 (42.2)	29 (44.6)	0.804	–	–	–
Superior mediastinal zone	–	–	–	12 (37.5)	19 (35.8)	0.878
Subcarinal zone	–	–	–	31 (96.9)	48 (90.6)	0.271
Inferior mediastinal zone	–	–	–	1 (3.2)	7 (13.2)	0.249
Multiple metastasis	–	–	–	11 (34.4)	19 (35.8)	0.890
Skip metastasis	–	–	–	10 (31.3)	19 (35.8)	0.665

BS, basal segment; SS, superior segment.

10 was considered to be station 7. Mediastinal lymph nodes were classified into superior mediastinal (stations 2R and 4R), subcarinal (station 7), and inferior mediastinal zones (stations 8 and 9). Stations 12, 13, and 14 were defined as intralobar lymph nodes. If any of the mediastinal lymph nodes were involved without hilar or intralobar lymph node involvement (N1 lymph nodes), they were considered to be a skip metastasis. Lymph nodes were dissected from the adipose connective tissue of the corresponding anatomic regions by the surgeon immediately after surgery. These lymph nodes were then sent for histopathological examination after hematoxylin and eosin staining. The lymph node stations were recorded according to the defined anatomic region.

Statistical analysis

Differences in the various variables between the SS and BS groups were evaluated using Student's *t*-test, the Chi-square test or Fisher's exact test. Disease-free survival (DFS) was defined as the time from the date of surgery until the first event (recurrence of lung cancer or death) or the date of last follow-up. The Kaplan–Meier method was used to plot survival curves and the log-rank test was used to evaluate differences among the groups. The Cox proportional hazard model was used to assess differences in DFS. The two-sided significance level was set at $P < 0.05$. Statistical calculations were performed using a statistical software package (StatView version 5.0, SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics

Of the 263 patients, 114 were classified into the SS group and 149 into the BS group (Table 1). Seven patients in the SS group and one patient in the BS group underwent

pneumonectomy ($P = 0.023$). There were 69, 13, and 32 patients with pN0, N1, and N2 disease, respectively, in the SS group and 84, 12, and 53 patients with pN0, N1, and N2 disease, respectively, in the BS group ($P = 0.354$). In the SS and BS groups, 13 and 21 patients, respectively, received adjuvant platinum doublet chemotherapy ($P = 0.519$). No other significant differences in clinical characteristics were detected between the two groups (Table 1).

Status of hilar and mediastinal lymph node metastasis

The frequencies of hilar and mediastinal lymph node metastasis are presented in Table 2. In patients with pN1 or N2 disease, the frequency of metastasis to station 11s was significantly higher in the SS than in the BS group (19/45; 42.2% vs. 5/65; 7.7%, respectively; $P < 0.0001$). However, the frequency of metastasis to station 11i was higher in the BS than in the SS group (23/65; 35.4% vs. 7/45; 15.6%, respectively; $P = 0.022$). There was no significant difference in the frequency of metastases to the intralobar lymph nodes. In patients with N2 disease, both the SS and BS groups showed a high frequency of subcarinal mediastinal zone metastasis (31/32; 96.9% and 48/53; 90.6%, respectively; $P = 0.271$). The frequencies of superior mediastinal zone metastasis were 37.5% (12/32) in the SS and 35.8% (19/53) in the BS group, respectively ($P = 0.878$). One of 32 patients in the SS group and seven of the 53 patients in the BS group had metastasis to the inferior mediastinal zone ($P = 0.249$). Furthermore, there were no significant differences in the frequencies of multiple zone metastasis ($P = 0.890$) or skip metastasis ($P = 0.665$) between the two groups.

Prognosis regarding the superior and basal segment groups

The median follow-up time for all patients was 38.8 months. There was no significant difference in the DFS rate of all

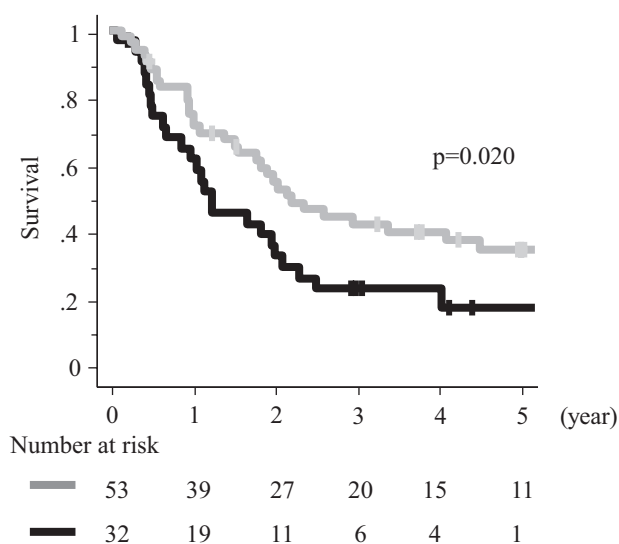


Figure 1 Comparison of the disease-free survival (DFS) rate of patients with pN2 disease between the superior segment (SS) and basal segment (BS) groups. DFS was significantly shorter for patients in the SS group (black line) than for patients in the BS (gray line; $P = 0.020$). —, BS group; —, SS group.

patients and of patients with pN0 and pN1 disease between the SS and BS groups ($P = 0.113$, $P = 0.715$ and 0.129 , respectively). In patients with pN2 disease, DFS in the SS group was significantly lower (3 year DFS, 22.6%) compared with patients in the BS group (3 year DFS, 42.1%, $P = 0.020$; Fig 1). The clinicopathological characteristics of 85 patients with

Table 3 Clinicopathological characteristics of patients with pN2 disease in the SS and BS groups

	SS group (n = 32)	BS group (n = 53)	P
Median age (range)	64 (44–78)	63 (38–77)	0.622
Gender (male/female)	23/9	39/14	0.864
Smoking status (never/ever)	11/21	21/32	0.629
c-T (T1/T2/T3/T4)	12/17/3/0	17/36/0/0	0.262
c-N (N0/N1/N2)	16/9/7	33/8/12	0.162
Surgical procedure			
Pneumonectomy/lobectomy	3/29	1/52	0.148
Histological type (AD/SCC/others)	15/11/6	34/14/5	0.182
p-T (T1/T2/T3/T4)	4/20/8/0	6/39/8/0	0.129
Adjuvant chemotherapy (platinum doublet; yes/no)	11/21	19/34	0.891

AD, adenocarcinoma; BS, basal segment; SCC, squamous cell carcinoma; SS, superior segment.

pN2 disease are presented in Table 3. There were 32 patients in the SS and 52 in the BS group. There were no significant differences between the two groups (Table 3). We analyzed independent prognostic factors for DFS in patients with pN2 disease among the SS and BS groups (Tables 4, 5). In this study, skip metastasis was defined as mediastinal lymph node metastasis without hilar (stations 11s and 11i) and intralobar lymph node metastases. Two separate models were used for multivariate analyses, because metastases to stations 11s and 11i and skip metastases were closely connected (Table 5). In the BS group, an independent predictive factor of a poor

Table 4 Univariate analysis regarding the disease-free survival of patients with pN2 disease among the SS and BS groups

Variables		SS group			BS group		
		HR	95% CI	P	HR	95% CI	P
Age	65≥/ <65	1.318	0.599–2.898	0.492	1.007	0.506–2.004	0.985
Gender	male/female	0.736	0.314–1.724	0.480	0.546	0.266–1.123	0.112
Smoking status	never/ever	1.891	0.783–4.567	0.156	0.648	0.326–1.288	0.216
Histological type	AD/others	1.084	0.490–2.398	0.843	2.339	1.049–5.213	0.038
	SCC/others	1.128	0.495–2.568	0.775	0.480	0.196–1.174	0.108
Surgical procedure							
Pneumonectomy/lobectomy		0.611	0.143–2.620	0.507	1.609	0.217–11.93	0.642
pT	pT2–4/pT1	1.427	0.426–4.784	0.564	2.343	0.558–9.836	0.245
Adjuvant chemotherapy	yes/no	0.635	0.263–1.525	0.314	0.733	0.346–1.551	0.416
Platinum doublet							
Station 11 s	yes/no	0.812	0.366–1.802	0.608	2.716	0.939–7.853	0.065
Station 11i	yes/no	0.831	0.309–2.233	0.714	2.057	1.032–4.102	0.041
Intralobar lymph nodes	yes/no	1.08	0.476–2.451	0.854	1.248	0.626–2.487	0.529
Superior mediastinal zone	yes/no	0.856	0.376–1.949	0.711	0.784	0.379–1.622	0.512
Subcarinal zone	yes/no	1.330	0.178–9.940	0.781	0.928	0.282–3.054	0.902
Inferior mediastinal zone	yes/no	–	–	–	1.805	0.689–4.727	0.229
Multiple metastasis	yes/no	0.897	0.384–2.094	0.802	0.875	0.423–1.809	0.719
Skip metastasis	yes/no	0.986	0.424–2.297	0.975	0.379	0.163–0.879	0.024

AD, adenocarcinoma; BS, basal segment; CI, confidence interval; HR, hazard ratio; SCC, squamous cell carcinoma; SS, superior segment.

Table 5 Multivariate analysis regarding the disease-free survival of patients with pN2 disease in the BS group

Variables		HR	95% CI	P
Model 1				
Histological type	AD/others	2.071	0.912–4.701	0.817
Station 11s	yes/no	1.767	0.869–3.592	0.116
Station 11i	yes/no	3.065	1.046–8.984	0.041
Model 2				
Histological type	AD/others	2.068	0.922–4.637	0.078
Skip metastasis	yes/no	0.421	0.180–0.986	0.046

AD, adenocarcinoma; BS, basal segment; CI, confidence interval; HR, hazard ratio; SCC, squamous cell carcinoma.

prognosis was metastasis to station 11i ($P = 0.041$; Model 1 in Table 5), and an independent predictive factor of a good prognosis was skip metastasis ($P = 0.046$; Model 2 in Table 5). There were no independent prognostic factors in the SS group (Table 4).

Discussion

In the present study, we evaluated the frequencies of mediastinal and hilar lymph node metastases in patients with primary lung cancer of the right lower lobe according to tumor location. There were no differences in the frequencies of superior mediastinal and subcarinal zone metastasis between the SS and BS groups (Table 2), and segment-specific patterns of mediastinal lymph node spread were not detected (Table 2). Previously, Watanabe *et al.* reported on the differences in the metastatic pathway to the mediastinum, and in the prognosis of patients with pN2 disease harboring primary lung cancer locating between the superior and basal segment of the lower lobe.¹¹ Among the BS group, patients without superior mediastinal zone metastases showed a significantly better prognosis than those with. In addition, there were no significant differences in survival between patients with and without superior mediastinal zone metastases in the SS group.¹¹ These authors reported that tumors located in the basal segment tended to metastasize through the subcarinal lymph nodes to the superior mediastinal lymph nodes, whereas tumors located in the superior segment tended to metastasize directly to the superior mediastinal lymph nodes.¹¹ In our study, no significant

differences in survival were detected between patients with and without superior mediastinal zone metastases in the SS and BS groups (Table 4). Our results support the conclusion of Watanabe *et al.* regarding tumors in the SS, but not in the BS.¹¹

In both the SS and BS groups, most of the tumors metastasized to the subcarinal mediastinal zone (31/32; 97% and 48/53; 91%, respectively). We have summarized previous reports regarding the frequency of mediastinal lymph node metastases from right lower lobe tumors in Table 6. Okada *et al.* reported a high frequency of subcarinal lymph node metastasis (41/44; 93.2%), similar to that in the current study (79/85; 92.9%).¹² However, the frequencies of subcarinal lymph node metastasis in the reports by Asamura *et al.* and Watanabe *et al.* were lower than that in our study.^{5,11} Further examination is required to resolve such differences.

We analyzed DFS rather than overall survival in our study because the influence of chemotherapy or targeted molecular therapy after recurrence could not be ignored. The DFS rate of patients with pN2 disease was significantly longer in the BS than in the SS group (Fig 1), similar to the findings of a previous study.¹¹ It has been reported that patients with skip metastasis have a better prognosis than those without it.^{13,14} In this study, the independent predictive factor of a good prognosis was skip metastasis in the BS group (Table 5). In the SS group, we did not detect an independent prognostic factor, and there were no differences in survival among patients with and without skip metastases (Table 4). There were no differences in the frequency of administration of adjuvant platinum doublet chemotherapy in the SS and BS groups ($P = 0.891$; Table 3). The survival of patients with pN0 and pN1 disease in the SS group was similar to that in the BS ($P = 0.715$ and 0.129 , respectively). In patients with pN2 disease, there was no distinct conclusion for poor prognosis in the SS compared with the BS group.

The present study was retrospective and exclusively involved patients with tumors located in the right lower lobe of the lung. Shapiro *et al.* categorized station 5 and 6 as superior mediastinal lymph nodes located on the left side and did not make reference to station 4L.¹⁵ In practice, superior mediastinal lymph node dissection was generally performed for station 5 and 6, but not sufficiently for station 4L. Because it

Table 6 Frequency of mediastinal lymph node metastasis in patients with primary right lower lobe lung cancer

Report	Patients with pN2 disease	Subcarinal lymph node metastasis No. (%)	Superior mediastinal lymph node metastasis No. (%)
This study	85	79 (92.9%)	31 (36.5%)
Okada <i>et al.</i> ¹²	44	41 (93.2%)	15 (34.1%)
Watanabe <i>et al.</i> ¹¹	86	65 (75.6%)	40 (46.5%)
Asamura <i>et al.</i> ⁵	41	24 (58.5%)	31 (75.6%)

was difficult to accurately assess metastases to the superior mediastinal lymph nodes in the left side, patients with tumors located in the left lower lobe of the lung were excluded.

Conclusion

In conclusion, patients with pN2 primary lung cancer in the right lower lobe mostly harbored subcarinal zone metastasis and there were no segment-specific patterns of mediastinal lymph node spread. Among patients with pN2 disease in the BS group, the independent predictive factor of a poor or good prognosis was metastasis to station 11i or skip metastasis, respectively, whereas we did not find an independent prognostic factor in the SS group. When segmentectomy is carried out, mediastinal lymph node dissection should be performed in proportion to the lobectomy.

Disclosure

No authors report any conflict of interest.

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