TABLE 1. Patient Characteristics According to the Method of Detection

Variables	Group n (%) SCR (n = 1279)	SYM (n = 466)	INC (n = 536)
Age (Median)			
Range	20–89 yr (67)	26–86 yr (65)	38–89 yr (69)
Gender			
Male	712 (55.7)	320 (68.7)	333 (62.1)
Female	567 (44.3)	146 (31.3)	203 (37.9)
Smoking histology			
Never	564 (44.2)	120 (25.9)	202 (38.1)
Ever/current	711 (55.8)	343 (74.1)	328 (61.9)
Tumor diameter			
≥2.0 cm	520 (42.6)	83 (17.8)	209 (39.0)
2.1–3.0 cm	378 (31.0)	88 (18.9)	155 (28.9)
3.1–5.0 cm	266 (21.8)	149 (32.0)	113 (21.1)
5.1–7.0 cm	44 (3.6)	74 (15.9)	25 (4.7)
>7.1 cm	12 (1.0)	29 (6.2)	9 (1.7)
Histologic type			
Adenocarcinoma	1097 (85.8)	273 (58.6)	392 (73.1)
Squamous cell carcinoma	135 (10.6)	165 (35.4)	123 (23.0)
Large cell carcinoma	39 (3.0)	17 (3.6)	17 (3.2)
Adenosquamous carcinoma	8 (0.6)	11 (2.4)	4 (0.7)
Surgical procedure			
Limited resection	132 (10.3)	25 (5.4)	80 (14.9)
Lobectomy	1066 (83.3)	366 (78.5)	428 (79.9)
Pneumonectomy	37 (2.9)	51 (10.9)	13 (2.4)
Exploratory thoracotomy	44 (3.4)	24 (5.2)	15 (2.8)
Clinical stage			
I	1135 (88.7)	266 (57.1)	478 (89.2)
II	83 (6.5)	114 (24.5)	30 (5.6)
III	58 (4.5)	78 (16.7)	26 (4.9)
IV	3 (0.2)	8 (1.7)	2 (0.4)
Pathological stage			
I	905 (70.8)	208 (44.6)	373 (69.6)
II	128 (10.0)	105 (22.6)	72 (13.4)
III	237 (18.5)	146 (31.3)	87 (16.2)
IV	9 (0.7)	7 (1.5)	4 (0.8)

SCR, screen-detected; SYM, symptom-detected; INC, incidental; T, tumor.

The type of screening was roughly divided into three groups; screening sponsored by local government, screening held by company, and screening at patients' expense. The last screening consists of members who pay dues and are entitled to screening. Furthermore, members can choose the modality of screening depending on the price. Thus, many types of screening were enrolled in this study. The SYM group was defined as patients who complained of the kind of respiratory symptom, and the incidentally detected group was defined as patients who were detected during screening for other diseases.

Statistical Analysis

Survival was calculated using the Kaplan-Meier method and differences in survival were determined by log-rank analysis. The median follow-up time for patients was 35.1 months. p values lower than 0.05 were considered statistically significant.

RESULTS

Characteristics of Screen-Detected Lung Cancer

Screen-detected lung cancers were smaller in diameter (<2 cm: 42.6%), less advanced (p-stage I: 70.8%), and showed a higher incidence of adenocarcinoma (85.8%). Incidentally detected lung cancers showed a similar tendency to SCR lung cancers, but SYM lung cancers were larger diameter, more advanced. Several characteristic findings were observed in CT-detected lung cancers: smaller diameter (<2 cm: 76.4%), less advanced (clinical stage I: 97.2%, pathologic stage I: 93.1%), and more frequently adenocarcinoma histologically (92.6%).

Survival According to the Method of Detection

The overall 5-year survival rate for the 2281 patients was 75.4%. The 5-year survival rates for the SCR, SYM, and INC groups were 79.6%, 74.6%, and 64.6%, respectively. The differences between the three groups were statistically significant (SCR versus SYM: $p < 0.0001$, SCR versus INC: $p = 0.0377$). The survival curves according to the method of detection are shown in Figure 1. Of the 2281 total patients, 1486 had pathologic stage I non-small cell lung cancer. In this subgroup, the 5-year survival rates overall and in the SCR, SYM, and INC groups were 89.6%, 92.9%, 84.0%, and 84.6%, respectively (Figure 2). The 30-day mortality was 3 patients in SCR, 5 patients in SYM, and no patients in INC group.

Survival of Screen-Detected Lung Cancer According to Modality

The 5-year survival rates for the CXR, CT, PET, and SC were 77.8%, 91.2%, 90.9%, and 80.9%, respectively. The difference in survival between the detection modalities was significant ($p = 0.0127$). Moreover, 896 patients had pathologic stage I non-small cell lung cancer, and the overall 5-year survival rates for the CXR and CT were 81.4% and 91.7%, respectively ($p < 0.0001$) (Figure 3).

Adenocarcinoma Equal to or Smaller than 2 cm in Diameter

Of 1762 adenocarcinomas, 733 had a maximal diameter of less than 2 cm. Of these, 477 were in the SCR group. Bronchioloalveolar carcinoma (BAC) was observed in 76 patients (6.1%) and invasive adenocarcinoma in 392 patients (31.5%). The distribution of the types is shown in Table 3. No patients with adenocarcinomas were observed in the SC group, and no patients with BACs were detected by PET. The proportion of BAC in the CT group (22.2%) was much higher than that in CXR (3.5%).

TABLE 2. Patient Characteristics According to the Modality of Detection in the Screen-Detected Group

	Subgroup *n* (%)			
Variables	CXR (*n* = 1047)	CT (*n* = 176)	PET (*n* = 20)	SC (*n* = 17)
Age (Median)				
Range	20–89 yr (63)	42–82 yr (63)	44–76 yr (65)	45–82 yr (65)
Gender				
Male	565 (54.0)	104 (59.1)	13 (65.0)	16 (94.1)
Female	482 (46.0)	72 (40.9)	7(35.0)	1 (5.9)
Smoking history				
Never	470 (45.0)	95 (50.0)	14 (70.0)	1 (5.9)
Ever/current	574 (55.0)	80 (50.0)	6 (30.0)	16 (94.1)
Tumor diameter				
≤2.0 cm	359 (36.2)	133 (76.4)	11 (55.0)	12 (70.6)
2.1–3.0 cm	339 (34.2)	24 (13.8)	5 (25.0)	2 (11.8)
3.1–5.0 cm	241 (24.3)	16 (9.2)	4 (20.0)	1 (5.9)
5.1–7.0 cm	40 (4.0)	1 (0.6)	0 (0)	2 (11.8)
>7.1 cm	12 (1.2)	0 (0)	0 (0)	0 (0)
Histologic type				
Adenocarcinoma	898 (85.8)	163 (92.6)	17 (85.0)	6 (35.3)
Squamous cell carcinoma	105 (10.0)	12 (6.8)	2 (10.0)	11 (64.7)
Large cell carcinoma	36 (3.4)	1 (0.6)	1 (5.0)	0 (0)
Adenosquamous carcinoma	8 (0.8)	0 (0)	0 (0)	0 (0)
Surgical procedure				
Limited resection	67 (6.4)	55 (31.3)	5 (25.0)	3 (17.7)
Lobectomy	901 (86.1)	120 (68.2)	15 (75.0)	14 (82.3)
Pneumonectomy	37 (3.5)	0 (0)	0 (0)	0 (0)
Exploratory thoracotomy	42 (4.0)	1 (0.6)	0 (0)	0 (0)
Clinical stage				
I	911 (87.0)	171 (97.2)	19 (95.0)	15 (88.2)
II	78 (7.4)	2 (1.1)	1 (5.0)	0 (0)
III	56 (5.3)	3 (1.7)	0 (0)	1 (5.9)
IV	2 (0.2)	0 (0)	0 (0)	1 (5.9)
Pathological stage				
I	705 (67.3)	163 (92.6)	16 (80.0)	12 (70.6)
II	118 (11.3)	5 (2.8)	2 (10.0)	1 (5.9)
III	216 (20.6)	8 (4.6)	2 (10.0)	3 (196)
IV	8 (0.8)	0 (0)	0 (0)	1 (5.9)

CXR, chest x-ray; CT, computed tomography; PET, positron emission tomography; SC, sputum cytology.

Type of Disease According to Smoking in Screen-Detected Lung Cancer

The relationship between smoking and type of disease is shown in Table 4. In the never-smoking-group, the incidence of noninvasive carcinoma such as bronchioloalveolar carcinoma was higher than that in patients with smoking history. As for advanced diseases, the incidence was more frequent in current or previous smokers.

Comment

The present study provides the latest data on screenings for lung cancers in patients who underwent surgical resection. SCR lung cancers were not only smaller (2 cm or less in diameter: 42.6%) and at a lower stage (stage I: 73.0%), but also more often adenocarcinoma (85.8%) than SYM lung cancers. In particular, such findings were more evident with CT in the SCR group (2 cm or less in diameter: 76.4%, pathologic stage I: 93.1%, and adenocarcinoma: 92.6%). The characteristics of SCR lung cancers in other reports were similar to those in the present study. Sobue et al.[7] reported that 82% of patients with lung cancers had stage I lung cancer. The International Early Lung Cancer Action Project (I-ELCAP) [12] also reported that the incidence of stage I lung cancer was 85.1% (412 of 484). In another report on CT screening for patients with a smoking history by Swensen et al.,[8] the incidence of clinical stage I non-small cell lung cancer was 66.7% (24 of 36) and the percentage of patients with cancer smaller than 2 cm was 91.6% (33 of 36). The high proportion of stage I in the present study is consistent with the results of several recent studies.

Previous studies have included high percentages of patients who were current or ever smokers in lung cancer

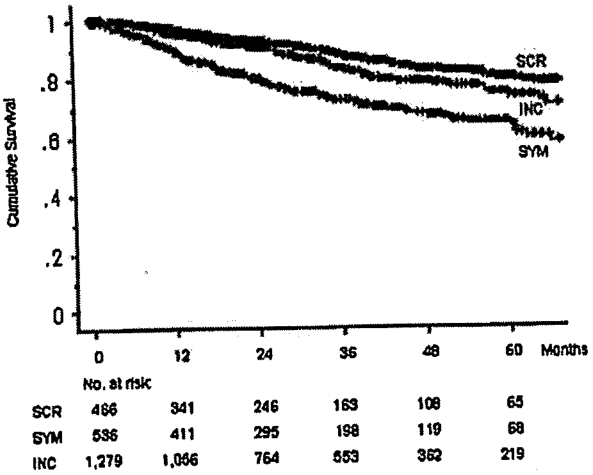

FIGURE 1. Survival curves of groups classified according to the method of detection: screen-detected, symptom-detected, and incidental group. SCR, screen-detected group; SYM, symptom-detected group; INC, incidental group.

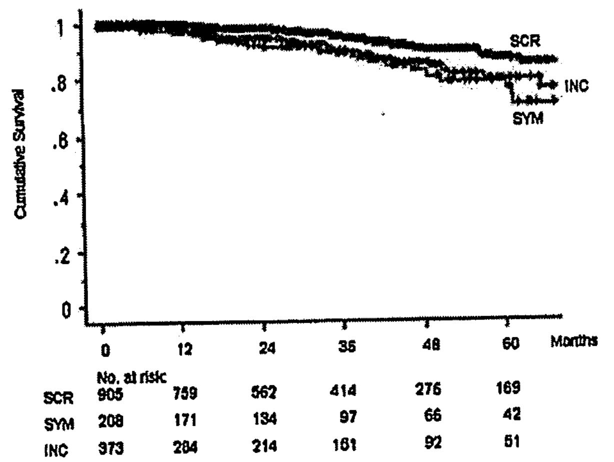

FIGURE 2. Survival curves of groups classified according to the method of detection in pathologic stage I non-small cell lung cancer. SCR, screen-detected group; SYM, symptom-detected group; INC, incidental group.

screening. The present study was not limited to such patients, and the patients had a different background. The percentage of patients with a smoking history in the SCR group was only 55%, which was lower than the rates in the other groups. In the SCR group, the incidence of squamous cell carcinoma histology was 17.7% (126 of 711) in ever or current smokers, and this value was significantly higher than that in never smokers. In the report by Swensen et al.,[8] the percentage of squamous cell carcinoma was 13.8% (4 of 29), which is similar to the result in the present study despite the presence of patients with a smoking history. However, the incidence of adenocarcinoma histology was 97.9% (552 of 564) in never smokers, and screening for all histologic types including adenocarcinoma must not be limited to smokers.

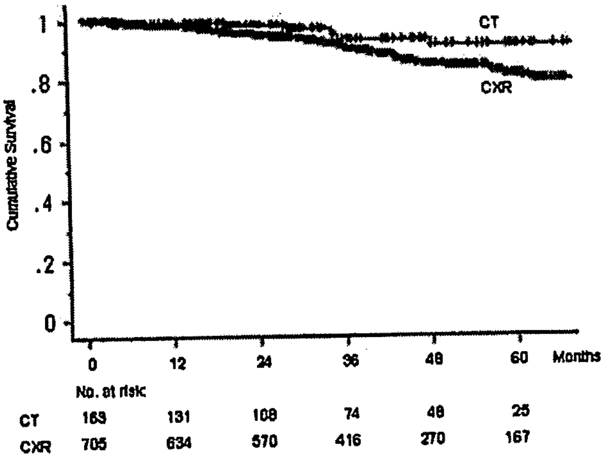

FIGURE 3. Survival curves according to the screening modality in pathologic stage I non-small cell lung cancer. CT, computed tomography; CXR, chest x-ray.

TABLE 3. Classification of Adenocarcinoma Equal to or Smaller than 2 cm in Diameter

	Subgroup *n* (%)			
Type	CXR (n = 1047)	CT (n = 176)	PET (n = 20)	Total (n = 1243)
BAC[a]	37 (3.5)	39 (22.2)	0 (0)	76 (6.1)
Invasive Ad[b]	294 (28.1)	89 (50.6)	9 (45.0)	392 (31.5)

[a] There were no patients with adenocarcinoma that was equal to or smaller than 2 cm in the diameter in sputum cytology group.
[b] Invasive adenocarcinoma includes adenocarcinoma, mixed subtype, acinar adenocarcinoma, papillary adenocarcinoma, and solid adenocarcinoma with mucin production.
CXR, chest x-ray; CT, computed tomography; PET, positron emission tomography; BAC, bronchioloalveolar carcinoma; Ad, adenocarcinoma.

TABLE 4. The Type of Disease According to Smoking History in Screen-Detected Lung Cancer

	Smoking	
Type of Disease	Never	Ever/Current
Early disease[a]	50 (65.8)	26 (34.2)
Advanced diseased[b]	100 (40.7)	146 (59.3)

[a] Noninvasive carcinoma such as Noguchi type A or B, or noninvasive squamous cell carcinoma.
[b] Pathological stage III or IV.

Another characteristic feature of the present study was a high incidence of adenocarcinoma in the SCR group (85.8%), particularly in the CT-detected subgroup (92.6%). Moreover, the incidence of BAC (≤2 cm) in CT-detected lung cancers was 22.2%, which was significantly higher than that in the CXR group (3.5%). In the I-ELCAP report,[12] BAC accounted for 7.1% of adenocarcinoma, which was a much lower incidence than that in the present study, although the present study was focused on adenocarcinoma smaller than 2cm in diameter. Lindell et al.[10] reported similar results, in that the incidence of BAC was 18.8% (9 of 48) by CT-screening. Screening by CT may detect very early lung cancers which could not be detected by CXR or another modality, although these results might reflect a length bias or lead-time bias.

The 5-year survival rate among 1290 patients in the SCR group was 79.6%, and this value was greater than that in patients in SYM and incidentally detected groups. In the SCR group, the 5-year survival rate of 111 patients in the CT subgroup was 91.2%, which was greater than the survival in patients in the conventional CXR and SC groups. Moreover, among these, the 5-year survival rate for patients with pathologic stage I was 91.7%. In previous reports, the 5-year survival rate of radically resected stage I non-small cell lung cancer has ranged from 60 to 80%.[15–19] These reports included CXR screening and the 5-year survival rate was similar to our value of 77.8%. Sobue et al.[7] reported a 5-year survival rate of 100% in their series of 29 patients who underwent resection after pathologic stage I lung cancer was detected on CT. Kaneko et al.[11] showed that detection by CT permitted a 10-fold increase in lung carcinoma detection. A recent report by I-ELCAP[12] demonstrated that the 10-year survival rate of resected clinical stage I lung cancer was 92%, and concluded that annual CT screening could detect lung cancer that was curable. According to these results, screening with low-dose helical CT may be able to improve the efficacy of screening in terms of reducing lung cancer mortality.

Smoking is one of the well-known risk factors for lung cancer, and smoking was related to the increasing prevalence in such natural-history model that carcinoma has been assumed to progress from a few cells to advanced-stage disease. On the contrary, inconsistent findings in other previous studies were also observed in the present study; the incidence of noninvasive cancer was lower in the smoking group, although advanced cancers were observed more frequently in smokers.

The limitations of the present study should also be addressed. First, the present study was retrospective. Detection was performed in various screenings and the screening modality was heterogeneous. Many subjects were enrolled in this study. Furthermore, the number of the people who underwent screening for lung cancer and the number of the lung cancers which were detected by lung cancer screening were not known. Moreover, the patients were limited to those who underwent surgical resection. The present study showed that screening, and particularly CT-screening, could detect lung cancers at an earlier stage and offer better survival. However, this could reflect biases of various types, such as lead-time bias and length bias, and screening did not directly reduce the mortality due to lung cancer. For a direct demonstration of the effectiveness of lung cancer screening, we must wait for the results of ongoing randomized control studies, such as the Nederlands Leuvens Screening Onderzoek trial in Europe and the National Lung Screening Trial in North America. In summary, screening for lung cancer detects early stage lung cancer. Furthermore, CT screening may detect lung cancer at an early stage that would not be detected by screening with CXR. CT screening may be effective for the detection of curable lung cancer.

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The Impact of Residual Tumor Morphology on Prognosis, Recurrence, and Fistula Formation after Lung Cancer Resection

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Introduction: The prognosis and proper management of patients with microscopic residual tumor at the bronchial resection margins (bronchial R1) remain unclear.

Methods: We performed a retrospective analysis of 74 patients who underwent pulmonary resection for lung cancer between 1976 and 2003 and had bronchial R1. The prognosis, pattern of the recurrence, and occurrence of the bronchopleural fistula (BPF) were analyzed according to the types of bronchial R1 morphology: direct extension (DIR, $n = 11$), peribronchial extension (PER, $n = 54$), and carcinoma in situ (CIS, $n = 9$).

Results: Five-year survival rates of patients with DIR, PER, and CIS were 0, 10, and 63%, respectively. The patients with CIS showed significantly better prognosis than those with DIR and PER ($p = 0.0006$, $p = 0.0009$, respectively). No prognostic difference was observed between patients with DIR and PER ($p = 0.1753$). Recurrent disease developed in 43 patients (58%). Only one of nine patients with CIS (11%) had recurrence, whereas 6 of 11 patients with DIR (55%) and 36 of 54 patients with PER (67%) had disease relapse. The recurrence rate in the CIS group was significantly lower than those of the other two groups (CIS versus DIR, $p = 0.036$; CIS versus PER, $p = 0.006$, respectively). BPF formation was not detected in patients with CIS; however, BPF developed in 3 of 11 patients with DIR (27%) and 3 of 54 patients with PER (5.6%).

Conclusions: Residual tumor morphology influenced the prognosis of patients with postresection bronchial R1 disease.

Key Words: Non-small cell lung cancer, Lung resection, Bronchial R1, Bronchopleural fistula.

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Surgical resection is the only potentially curative treatment for non-small cell lung cancer. A gross incomplete resection is associated with poor prognosis and high local recurrence and surgical complication rates.[1–3] Nevertheless, several reports have suggested that microscopic residual disease at the bronchial margin (bronchial R1, according to the tumor, node, metastasis classification of the International Union Against Cancer[4]) does not have the adverse effect on survival that gross residual disease does.[5–12] The prognosis and optimal postoperative management for patients with bronchial R1 disease remain unclear.

To clarify the prognosis, pattern of recurrence, and rate of bronchopleural fistula (BPF) formation in patients with R1 disease, we retrospectively reviewed the records of lung cancer patients who had been treated with pulmonary resection at our hospital, focusing on the relationship between R1 morphology and outcomes.

PATIENTS AND METHODS

Patients

Between June 1976 and June 2003, 4493 patients underwent pulmonary resection for primary lung cancer at the National Cancer Center Hospital, Tokyo. We included all patients ($n = 74$; 1.6%) who received at least lobectomy with mediastinal lymph node dissection and had microscopic residual tumor at the resected end of the bronchus in our retrospective analysis. Histologic typing and disease stage were classified according to World Health Organization classification[13] and tumor, node, metastasis classification of the International Union Against Cancer,[4] respectively. We excluded patients with small cell lung cancer or low-grade malignant histologic types, such as carcinoid or adenoidcystic carcinoma, from this study. Patient characteristics are shown in Table 1. Patients included in this study tended to have advanced (stages III and IV) disease and squamous cell histology.

Intraoperative frozen section examination of the bronchial margins was performed for 28 patients (38%). Although 26 of 28 patients had positive margins detected during surgery they did not undergo further resection because of limited pulmonary reserves or poor risk. Intraoperative examination found the bronchial margins to be tumor-free for two patients, however, postoperative analysis revealed bronchial R1 disease. Forty-six patients did not undergo intraoperative microscopic analysis of the bronchial stump because the bronchial resection line was considered tumor-free according to macroscopic examination.

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TABLE 1. Characteristics of Patients with Bronchial R1 Disease

Characteristics	No. (%)
Sex	
Male	58 (78)
Female	16 (22)
Age	
Range (yr)	39–83
Median (yr)	66
Pathological stage	
0	1 (1)
I	6 (8)
II	10 (14)
III	52 (70)
IV	5 (7)
Histology	
Adenocarcinoma	35 (47)
Squamous cell carcinoma	34 (46)
Large cell carcinoma	3 (5)
Adenosquamous cell carcinoma	1 (1)
Giant cell carcinoma	1 (1)
Pulmonary resection	
Pneumonectomy	17 (23)
With carinal resection	1
Bilobectomy	16 (22)
With bronchial resection	3
Lobectomy	41 (55)
With bronchial resection	15
Type of bronchial R1	
Direct extension	11 (15)
Peribronchial extension	54 (73)
Carcinoma in situ	9 (12)
Postoperative RT	
Yes	21 (28)
No	53 (72)

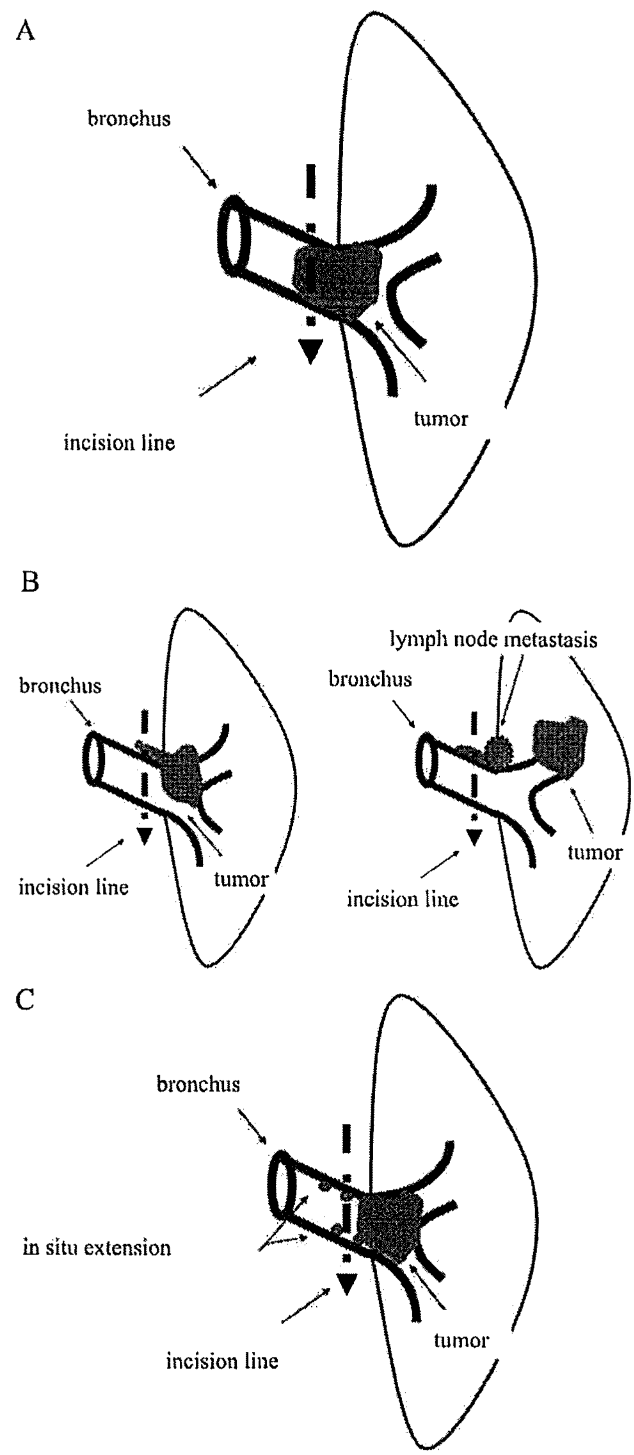


FIGURE 1. Schemas of bronchial R1 (*A*) direct extension, (*B*) peribronchial extension, and (*C*) carcinoma in situ.

Morphology of R1 Disease

Patients with bronchial R1 were classified into the following three categories according to the residual tumor pattern: (1) Direct extension (DIR, $n = 11$, Figure 1*A*), characterized by direct invasive extension of the main tumor proximally in the bronchial wall; (2) Peribronchial extension (PER, $n = 54$, Figure 1*B*), which included tumor infiltration into the peribronchial connective tissues, lymphatic permeation by peribronchial lymphatic vessels, or extracapsular infiltration of the metastatic lymph nodes; (3) Carcinoma in situ (CIS, $n = 9$, Figure 1*C*), characterized by in situ extension of the main tumor, which continued up to the bronchial resection margin. All patients with CIS lesion had squamous cell carcinoma.

Postoperative Therapy

Postoperative radiotherapy was administered for 21 patients (5 with DIR, 11 with PER, and 5 with CIS). Patients in poor physical condition or with advanced disease did not receive radiotherapy. The total radiation dose ranged from 29 to 60 Gy (median, 50 Gy). None of the patients in this study received postoperative chemotherapy.

Prognosis

Tumor recurrence was described as local or distant. Local recurrence was defined as any recurrent disease within the ipsilateral hemithorax or mediastinum. Recurrence was diagnosed by bronchoscopic biopsy or noninvasive diagnostic procedures such as radiography, computerized tomography, magnetic resonance imaging, or bone scan.

Statistical Analysis

Survival curves were estimated by the product limit method of Kaplan and Meier, and the differences in survival were tested with log-rank analysis. The length of survival was defined as the interval between the day of initial operation and the day of death or last follow-up. Observation was censored at the last follow-up when patients were alive, and all deaths, including operative deaths, were considered events. The median follow-up period for the 12 surviving patients was 51 months. The χ^2 test was performed to evaluate the correlation between bronchial R1 morphology and recurrence. Statistical significance was set at $p < 0.05$.

RESULTS

The median survival time for all patients with bronchial R1 was 14 months, with actual survival rates of 57, 26, and 14% at 1, 3, and 5 years, respectively (Figure 2). According to the bronchial R1 morphology, the 5-year survival rates of patients with DIR, PER, and CIS were 0, 10, and 63%, respectively (Figure 3). Patients with CIS fared significantly better than did patients with the other types of bronchial R1 (DIR versus CIS, $p = 0.0006$; PER versus CIS, $p = 0.0009$). On the other hand, we detected no difference in the prognoses of patients with DIR and PER ($p = 0.1753$). Among patients with DIR and PER, histologic classification or pathologic nodal status did not affect the probability of survival (squamous cell carcinoma versus nonsquamous cell carcinoma, $p = 0.4227$; pN0–1 versus pN2, $p = 0.1768$).

During follow-up, progressive disease developed in 43 (58%), 20 patients were free of disease, and details of predeath status were not known for 11 patients. Correlations between the first site of relapse and bronchial R1 morphology are shown in Table 2. In patients with CIS, local recurrence developed in only one patient (11%) and no distant metastasis was observed. On the other hand, recurrence rates of patients with DIR (54%) and PER (66%) were significantly higher than that of patients with CIS ($p = 0.036$, $p = 0.006$, respectively), and 34 of the 42 recurrences (81%) included distant metastases. Among 21 patients treated with postoperative radiotherapy, 12 patients relapsed (Table 3). Despite the radiotherapy, local recurrence developed in 4 patients (19%). Furthermore, in DIR and PER group, half of the patients that received radiotherapy (8 of 16) had recurrences at the distant sites. Prognosis was not affected by postoperative radiotherapy ($p = 0.667$, Figure 4).

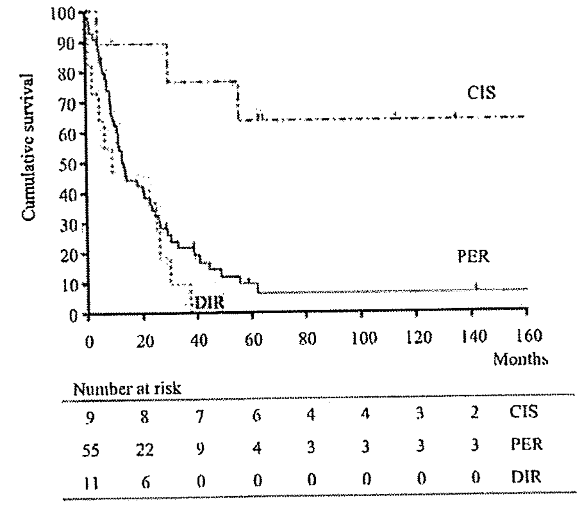


FIGURE 3. Survival by type of bronchial R1 disease. Carcinoma in situ (CIS) versus direct extension (DIR), $p = 0.0006$; CIS versus peribronchial extension (PER), $p = 0.0009$, DIR versus PER, $p = 0.18$.

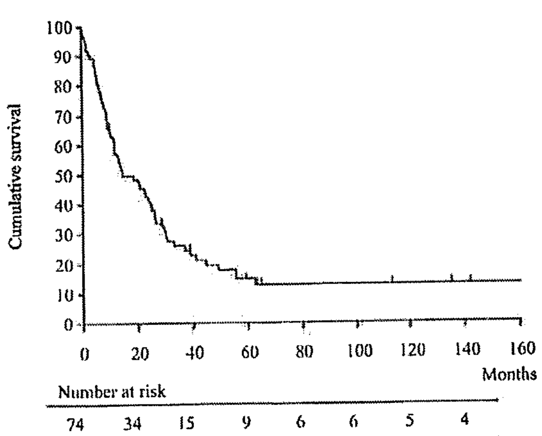


FIGURE 2. Cumulative survival for the entire group.

TABLE 2. First Site of Relapse in Patients with Bronchial R1

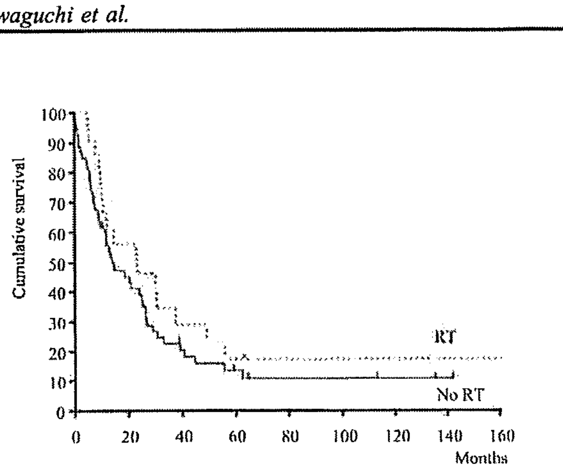
	DIR (n = 11) (%)	PER (n = 54) (%)	CIS (n = 9) (%)
Local	2 (18)	6 (11)	1 (11)
Distant	4 (36)	26 (48)	0 (0)
Local + distant	0 (0)	4 (7)	0 (0)
Total	6 (54)	36 (66)	1 (11)

DIR, direct extension; PER, peribronchial extension; CIS, carcinoma in situ.

TABLE 3. First Site of Relapse in 21 Patients Undergoing Postoperative Radiotherapy

	DIR (n = 5) (%)	PER (n = 11) (%)	CIS (n = 5) (%)
Local	1 (20)	2 (18)	1 (20)
Distant	2 (40)	5 (45)	0 (0)
Local + distant	0 (0)	1 (9)	0 (0)
Total	3 (60)	8 (72)	1 (20)

DIR, direct extension; PER, peribronchial extension; CIS, carcinoma in situ.



Number at risk								
21	12	6	4	3	3	3	3	RT
53	23	10	6	4	4	3	2	No RT

FIGURE 4. Survival in patients with or without postoperative radiotherapy (RT). RT versus non-RT, $p = 0.667$.

BPF developed in six patients (8.1%), 3 of the 11 patients with DIR (27%) and 3 of the 54 patients with PER (5.6%). BPF formation was not detected in patients with CIS. One of the six patients with BPF was treated with postoperative radiotherapy. The mortality rate of patients with BPF was 50% (3 of 6).

DISCUSSION

Gross residual tumors at the resection margin adversely affect the outcome of patients with non-small cell lung cancer; patients with microscopic residual disease at a bronchial resection margin tend to survive longer than do patients with residual gross disease.[3] The incidence of bronchial R1 resection in this study (1.6%) was slightly lower than that reported in the literature (2.6–5.4%).[5,7–11] In our clinical practice, we find that the incidence of cancer arising in the periphery of lung is increasing, therefore the incidence of bronchial R1 disease is less than that reported for this study.

The reported three-year survival rate of patients with bronchial R1 varies from 24 to 40%,[7,10] and the 3-year survival rate detected in this series fell within this range (26%). Because of the heterogeneity of bronchial R1 disease, many authors classify the pattern of bronchial R1 and evaluate prognoses according to these patterns.[5–8,10–12] Soorae and Stevenson[12] analyzed the morphology of microscopic residual tumor at the resected end of bronchus, and classified bronchial R1 disease into four patterns: direct extension of the main tumor mass proximally in the bronchial wall; lymphatic permeation through peribronchial and submucosal lymphatic vessels; extension through parabronchial tissue; and in situ extension. In their study, 15 of 64 patients with bronchial R1 disease survived for more than 5 years. The long-term survivors consisted of seven patients with in situ extension, 7 with DIR, and one with in parabronchial extension. There were no long-term survivors among patients with lymphatic permeation. Therefore, they concluded that bronchial R1 morphology was associated with outcome. Several other studies, including ours, have used the same classification scheme when analyzing patients with bronchial R1.[5–8,10,11]

Among the different morphologies of R1 disease, CIS has been reported to be a favorable indicator of prognosis.[6,8] Snijder et al.[8] analyzed the outcomes of patients with resected stage I disease with bronchial R1 and found no difference in survival between patients with residual CIS and the same-stage R0 patients. Massard et al.[6] reported that cancer-related death was observed in only 5 of 20 patients with CIS (distant metastases in three, combined local recurrence and distant metastases in one, and second primary lung cancer in one). In previous studies, the cause of good prognosis of patients with residual CIS disease was speculated to be: (1) spontaneous regression of residual neoplastic cells caused by smoking cessation; (2) interference with nutrition; (3) local scarring phenomena; or (4) unknown immunologic pathways.[8,12] In our study, the 5-year survival rate of patients with CIS was significantly higher than that of patients with the other two morphologic subtypes (DIR and PER). Cancer-related death occurred in only one of nine patients with CIS. In addition, four of eight patients without recurrence had no postoperative radiotherapy. According to these observations, the prognostic impact of residual CIS disease was different from that of the other types of R1 disease. The role of postoperative radiotherapy for residual CIS disease needs to be further refined. Some patients with CIS disease might be followed up with observation only. Otherwise, the indication for radiotherapy should be determined according to the amount of residual tumor.

We found no difference in the prognoses of patients with either DIR or PER. Among patients with such morphologic subtypes, neither tumor histology nor stage was associated with prognosis. Previous studies have reported prognostic differences related to the pattern of bronchial R1, disease stage, or histology.[5,7,9,10] Liewald et al.[10] reported that the prognosis for patients with extramucosal microscopic residual disease (infiltrating by peribronchial lymphatics or connective tissue) was worse than that for patients with mucosal microscopic residual disease (spreading directly along endobronchial pathway). Others have found prognostic differences associated with disease stage, histology, or presence of lymphangiosis carcinomatosa at the bronchial resection margin.[5,7,9] Nevertheless, according to our analysis, the presence of bronchial R1 disease, except for CIS, was latently associated with disease advancement regardless of tumor histology and stage.

There is no established standard of care for bronchial R1 disease. Several authors have noted that local recurrence develops more often in patients with bronchial R1 than in patients without residual tumor.[6–11] Some of these studies recommended repeated resection for selected cases to prevent local recurrence.[7,8,10,11] Nevertheless, 34 of 42 relapsed patients in our study (81%) with DIR or PER disease had distant metastases, and local therapy such as postoperative radiation did not affect the survival. Therefore, postoperative local therapy might not improve overall survival, since the local therapy does not control distant metastases. The benefit of postoperative local therapy for patients with DIR or PER disease should be considered limited.

In this series, the 8.1% incidence of BPF in patients with R1 disease exceeded that of patients without residual tumor at our hospital (1.5%).[14] Previous studies have reported that the high incidence of BPF was the cause of high mortality rate of patients with bronchial R1 disease.[7,12] Some have speculated that the occurrence of BPF might be related to the presence of residual tumor in the bronchial mucosa.[7,11,12] Based on this study, in which there was no BPF in patients with CIS, in situ extension of tumor cells at the bronchial stump might not be responsible for fistula formation. On the other hand, full thickness invasion to the bronchial partition, which is seen in DIR or PER pattern disease, might promote BPF formation.

We conclude that residual tumor morphology influences the prognosis of patients with bronchial R1 disease after lung cancer resection. The outcomes of patients with CIS are different from those of patients with DIR and PER. The morphology of the residual disease at the resected margin should play an important role in planning postoperative management for patients with bronchial R1.

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Clinical application of costal coaptation pins made of hydroxyapatite and poly-L-lactide composite for posterolateral thoracotomy

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Abstract

Background: Costal coaptation pins made of hydroxyapatite and poly-L-lactide (HA/PLLA) composite are used to prevent slippage of the connected ribs in posterolateral thoracotomy. The objective of this study was to evaluate rib fixation achieved by HA/PLLA costal coaptation pins. **Methods:** Between September 2005 and January 2006, HA/PLLA costal coaptation pins were used in 106 consecutive patients who underwent posterolateral thoracotomy at the National Cancer Center Hospital, Tokyo, Japan. Among these, 96 patients who were followed for one year were analyzed. Fixation was assessed on chest X-ray at one week, two months, and one year after surgery, and classified into four types: no displacement, vertical displacement, lateral displacement, and combined vertical with lateral displacement. **Results:** The incidence of displacement at one week, two months, and one year after surgery was 22%, 19%, and 31%, respectively. No severe adverse events leading to the removal of HA/PLLA pins occurred. At one year, the most frequent type of displacement was vertical displacement (15%), which reflected a delay in bone formation. The use of analgesics among patients with different types of displacement was not significantly different ($p = 0.97$). **Conclusions:** Based on the results of this study, the fixation of cut ribs with HA/PLLA costal coaptation pins may be less advantageous in posterolateral thoracotomy, as displacement and delay of bone formation appear to occur frequently.

Keywords: Chest wall; Lung cancer; Pain; Tissue engineering; Thoracotomy

1. Introduction

A fixation device made of hydroxyapatite and poly-L-lactide (HA/PLLA) composite is a newly developed modality that is being increasingly used in thoracic surgery. Costal coaptation pins made of HA/PLLA are absorbable, easy to handle, and safe to use. Costal coaptation pins are used for rib fixation during posterolateral thoracotomy and to reposition multiple rib fractures [1–5]. There have been few reports on the use of HA/PLLA costal coaptation pins for thoracotomy, and in particular it has not been well documented whether such costal pins are beneficial for rib fixation. The objective of the present study was to evaluate post-thoracotomy rib displacement over time based on radiographic findings.

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2. Materials and methods

2.1. Patients

Between September 2005 and January 2006, 135 lung resections were performed at the National Cancer Center Hospital, in Tokyo, Japan. Costal coaptation pins made of HA/PLLA composite were used in 106 consecutive patients who underwent posterolateral thoracotomy during the same period. Costal pins were not applied for the following reasons: wedge resection without rib resection in 12 patients, and complicated resection, such as chest wall resection, in 17 patients. The patient characteristics are shown in Table 1.

2.2. PLLA costal coaptation pins and the surgical procedure

Two sizes of HA/PLLA costal coaptation pins (Super-FIXSORB®: Ethicon Inc., Somerville, NJ) were used: 2 mm × 2 mm × 27 mm (thin) and 3 mm × 3 mm × 34 mm (thick) (Fig. 1). During posterolateral thoracotomy, the ribs were usually cut at the costal angle. The caliber was measured by a calibrator, and the bone marrow space was dilated using a reamer, if necessary. Small holes were made on both sides of the cut ribs using a drill. An absorbable suture

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Table 1
Patient characteristics

Characteristic	(*n* = 106)
Age (years)	
Median	67
Range	31–84
Gender (%)	
Male	66 (62)
Female	40 (38)
Size of pins (%)	
Thin	56 (53)
Thick	50 (47)
Disease (%)	
Lung cancer	94 (89)
Others	12 (11)
Operative procedure (%)	
Limited resection	12 (11)
Lobectomy	88 (83)
Pneumonectomy	6 (6)

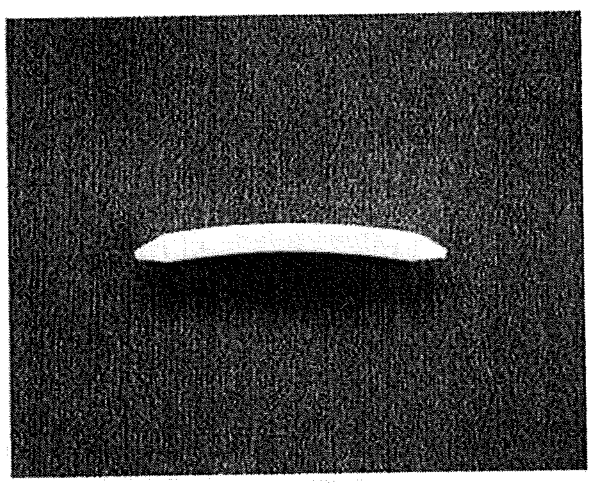

Fig. 1. Costal coaptation pins were used to close the posterolateral thoracotomy. The pin sizes were 2 mm × 2 mm × 27 mm (thin) and 3 mm × 3 mm × 34 mm (thick).

was threaded through the rib holes, and the pins were inserted into the bone marrow of the cut rib. The cut ribs were connected and ligated (Fig. 2).

2.3. *Radiographic evaluation*

Chest X-rays (posteroanterior view) were obtained at one week, two months, and one year after surgery. Based on the degree of fixation, the patients were classified into four groups: no displacement, vertical displacement, lateral displacement, and combined vertical with lateral displacement (Fig. 3). Displacement was defined as being vertical when the shift was more than one third of a rib's width, and as being lateral when the shift was ≥5 mm.

2.4. *Statistical analysis*

Statistical analyses were performed using SPSS software, version 13.0J (SPSS Inc., Chicago, IL). The chi-square test and

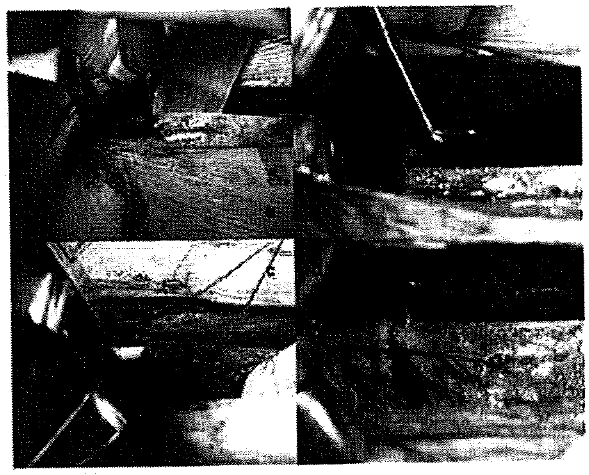

Fig. 2. A hand-drill was used to make holes on both sides of the cut rib (a). The caliber was measured by a calibrator, and a reamer was used to dilate the bone marrow space (b). Costal coaptation pins were inserted into the bone marrow (c). The ribs were ligated with absorbable sutures, and connected (d).

Mann–Whitney's *U*-test were used to determine the relationship between rib displacement and clinical factors. A *p*-value ≤0.05 was considered significant.

3. Results

3.1. *Clinical findings*

Of the 106 patients, 93 were followed for one year. In 13 patients, the follow-up was not complete: 9 patients had recurrence or died, and 4 patients were followed only with computed tomography. Displacement according to the

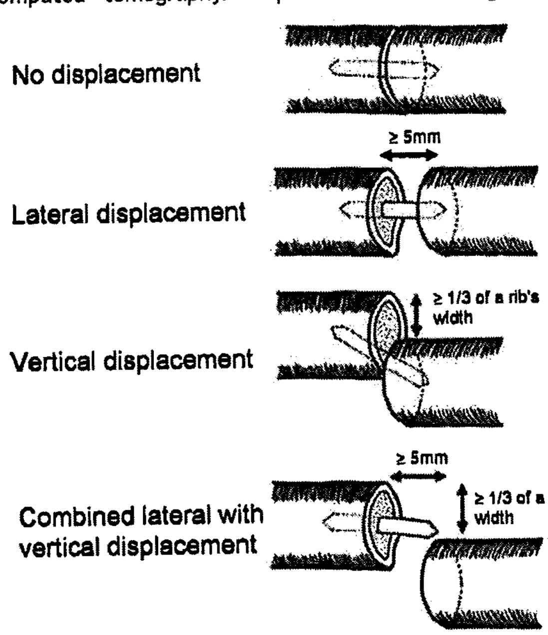

Fig. 3. The degree of fixation was categorized as no displacement, vertical displacement, lateral displacement, or combined vertical with lateral displacement.

Table 2
Displacement according to clinical and surgical factors

Character	Fixation			
	Displacement (−) (*n* = 64)	Displacement (+) (*n* = 29)	Total (*n* = 93)	*p* value
Age (years)				0.32
Median	70	63	67	
Range	31–80	50–84	31–84	
Gender (%)				0.78
Male	41 (71)	17 (29)	58	
Female	23 (66)	12 (34)	35	
Size of pins (%)				0.92
Thin	33 (67)	16 (33)	49	
Thick	31 (71)	13 (29)	44	
Disease (%)				0.99
Lung cancer	59 (69)	26 (31)	85	
Others	5 (63)	3 (37)	8	
Operative procedure (%)				0.45
Limited resection	6 (86)	1 (14)	7	
Lobectomy	56 (68)	27 (32)	82	
Pneumonectomy	2 (50)	2 (50)	4	
Analgesic intake at two months after surgery (%)				0.97
(−)	51 (69)	23 (31)	74	
(+)	13 (68)	6 (32)	19	

clinical and surgical factors of the 106 patients who were followed for one year is shown in Table 2.

3.2. Radiographic findings of displacement

The radiographic findings according to the type of displacement are shown in Table 3. The characteristic features were the incidence of displacement and the variation of displacement over time. Displacement occurred in 20 patients (22%) at one week, 18 patients (19%) at two months, and 29 patients (31%) at one year after surgery. Vertical displacement was more common during the early period after surgery, and lateral displacement was more frequent one year after surgery. Of the 73 patients who did not have displacement one week after surgery, 24 developed some displacement during follow-up; in 15 (63%), displacement was noted between one week and two months. In contrast, displacement improved in 12 patients between one week and two months.

One year after surgery, 12 patients had lateral displacement; in these patients, the chest X-ray showed a lucent zone at the connection of the ribs. In patients who had lateral displacement, computed tomography showed that the ribs were completely separated, and no bone tissue was observed (Fig. 4).

Table 3
Displacement over time

	Time after surgery		
	One week (%)	Two months (%)	One year (%)
No displacement	73 (78)	75 (81)	64 (69)
Vertical displacement	18 (19)	14 (15)	10 (11)
Lateral displacement	1 (1)	2 (2)	14 (15)
Combined displacement	1 (1)	2 (2)	5 (5)

3.3. Clinical findings and displacement

With respect to the results associated with different surgical procedures, 29 patients with rib displacement (32%) had lobectomy or pneumonectomy, and 1 patient had a limited resection (14%); the difference in rib displacement between surgical procedures was not significant ($p = 0.56$).

The effect of rib displacement on pain was assessed. Surgical wounds, which included the rib connection, were considered painful when oral analgesics were required two months after surgery. Nineteen patients were prescribed oral analgesics two months after surgery. Of these 19 patients, 13 had no displacement (20%), and 6 had displacement (21%); 2 patients had vertical displacement, 3 had lateral displace-

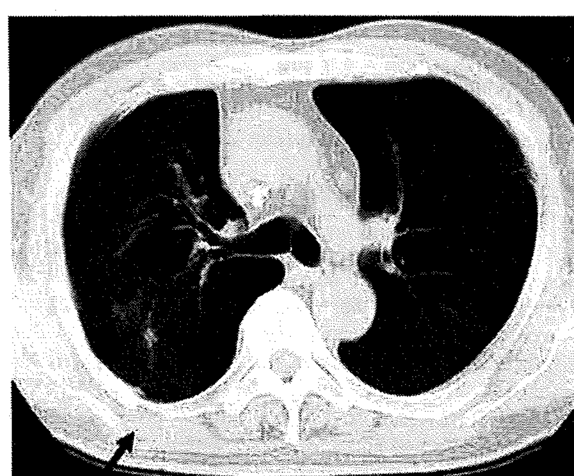

Fig. 4. The arrow shows the rib connection. The edge of the cut rib is clubbed, and the pin is not covered with bone tissue; a bare costal coaptation pin is present.

ment, and 1 had the combined type. Thus, there was no significant difference in analgesic use among the groups ($p = 0.97$). Moreover, complications (parenchymal lung injury and sputum retention with atelectasis) which induced excessive cough and subsequent costal dislocation were not seen in our series.

4. Comment

Absorbable fixation devices made of hydroxyapatite and poly-L-lactide (HA/PLLA) composite are increasingly being used in orthopedic surgery for procedures such as fractured bone fixation and bone grafting. In thoracic surgery, costal pins are used for fixation of the sternum and ribs in procedures for chest deformity, chest trauma, and thoracotomy. However, only a few reports have dealt with the use of costal coaptation pins [1–6]. The trend in thoracic surgery is toward a minimally invasive approach, and rib separation is not routinely performed, even in posterolateral thoracotomy in the present series, despite its widespread indication for intrathoracic diseases. When ribs are separated in thoracotomy, the need for rib coaptation has been controversial among thoracic surgeons, and the advantages of rib coaptation have not yet been defined [1,2]. The efficacy of coaptation pins has also not been adequately described. The present study focused on the use of HA/PLLA pins for the closure of posterolateral thoracotomy with regard to the incidence of displacement after surgery at the immediate, intermediate, and late postoperative periods.

The most remarkable finding of the present study was the high incidence of costal displacement even at the immediate postoperative period (one week after surgery) as high as 21%. Throughout the observation period, the incidence continued to be higher than 20%. In the literature, the incidence of displacement has been reported to be 2% by Tatsumi et al. and 1.3% by Tsunezuka et al. [1,2]. These reports concluded that PLLA costal coaptation pins were effective for the fixation of separated rib. Thus, there are large differences in the incidence of displacement between our study and these previous studies. The timing and method of postoperative evaluation might account for these differences. In the two previous studies, the timing of roentgenological evaluation varied, and chest CT was mainly used to evaluate displacement. For example, in Tatsumi's report, evaluation was performed with chest CT at 1–58 months after surgery [1]. The status of costal adaptation might be greatly influenced by the time after surgery, and the study should have incorporated a uniform timing for evaluation. Furthermore, the images on chest CT scan do not seem to be suitable for the evaluation of displacement in a vertical dimension. In fact, this method cannot detect displacement of less than 1 cm. Our strict criteria in the evaluation of displacement at scheduled time-points could have detected even small displacement which might have been overlooked in previous studies.

Another important observation was the increase in the incidence of displacement during the follow-up period. The incidence varied from 21% at the immediate point to 31% at the late point postoperatively. The 21% incidence at the immediate postoperative period clearly indicated that fixation is not enough to ensure stability of the ribs. The increase in displacement at the late period might be caused by a decrease in the tension of the suture materials (absorbable strings). With regards to the ligation technique, ligation was performed with a single suture in our series. If double ligation had been made for tightening the cut rib, the rate of displacement might have decreased in the early period. The cut ribs were too small and too thin for double ligation, especially in the Japanese female patients. Regardless of the cause, the increased incidence in the late period, when bone coaptation should have been achieved, is a substantial problem in practice.

In this study, the status of rib displacement was classified into four patterns according to the images on postoperative chest X-rays. The most common pattern of displacement was lateral displacement (15%), followed by vertical displacement (11%), and combined lateral and vertical displacement (5%) at one year after surgery. On the other hand, two other reports did not show any differences in the incidence of displacement according to patterns [1,2]. The chest CT images of cases with lateral displacement in this series showed the complete separation of both costal ends and their bony clubbing. These findings suggested that bone formation around the costal pins was impaired. The costal pins could induce the proliferation of connective tissue around the pins, as reported previously, which results in impaired bone formation due to a foreign body reaction [7,8].

In summary, ribs connected with costal coaptation pins appear to deviate in a high percentage of patients, although the effect of such displacement on pain is likely minimal and no adverse events, such as parenchymal lung injury requiring reoperation to remove the pins, were noted. Rib fixation with HA/PLLA costal pins may be considered to be less advantageous in posterolateral thoracotomy.

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Superior and Basal Segment Lung Cancers in the Lower Lobe Have Different Lymph Node Metastatic Pathways and Prognosis

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Background. Although the lower lobe is a large entity that occupies half of the hemithorax, all tumors located within the lower lobe have been treated uniformly regardless of tumor location. The aim of this study was to reveal differences in the metastatic pathway to the mediastinum and in prognosis of N2 disease between lung cancers originating from superior and basal segment of the lower lobe.

Methods. Data on 139 patients who underwent pulmonary resection with systematic nodal dissection for pN2 non-small cell lung cancer (NSCLC) originating from the lower lobe between 1980 and 2001 were retrospectively reviewed. Those lower lobe N2 tumors were divided into two groups by origin: 51 were superior segment, and 88 were basal segment.

Results. The superior segment group showed a significantly higher incidence of superior mediastinal metastasis than the basal segment group (64% vs 36%, p = 0.0012). When superior mediastinal metastasis existed, the basal segment group showed a significantly higher incidence of synchronous subcarinal metastasis than the superior segment group (81% vs 39%, p = 0.0006). Pneumonectomy was required significantly more often in the superior segment group than in the basal segment group (45% vs 17%, p = 0.0003). The basal segment origin tumors with only subcarinal metastasis showed significantly better prognosis than other lower lobe N2 tumors (5-year survival, 43% vs 18%; p = 0.0155).

Conclusions. Basal segment tumor metastasizes to the superior mediastinum mostly through the subcarinal node, whereas superior segment tumors often metastasize directly to the superior mediastinum without concomitant metastasis to the subcarinal node. Superior mediastinal dissection will be mandatory for accurate staging of superior segment tumors even when the subcarinal node is negative on frozen section. As for the prognosis among lower lobe N2 tumors, only in cases with basal segment tumor without superior mediastinal metastasis may long-term survival be expected.

(Ann Thorac Surg 2008;85:1026–31)

The lower lobe is a large entity that occupies half of the hemithorax in each side. Its bottom rests just on the diaphragm and the apex reaches above the hilum. However, all tumors located within the lower lobe have been treated uniformly, regardless of location in the lobe. With respect to the anatomic structure, the lower lobe can be primarily divided into two segments, the superior and the basal. We hypothesized that tumors arising in those two lower lobe segments were not alike owing to differences in lymphatic drainage pathways or other clinical behaviors and thus may require different treatment strategies. We therefore investigated segment-specific patterns of nodal spread and prognosis of pN2 disease in each segment. This report describes the differences in the clinical features and prognosis between superior and basal segment tumor of the lower lobe.

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Patients and Methods

Patients

Approval for this retrospective study was obtained and the need for individual patient consent was waived by the Institutional Review Board. From January 1981 to December 2001, 3638 patients underwent pulmonary resection for primary lung cancer at the National Cancer Center Hospital. Basically, we operate on the lung cancer patient who is considered to be cN0 to 1 on computed tomography (CT) scan. Our criterion for lymph node enlargement is more than 1.0 cm in the short axis of each nodal station on CT. Mediastinoscopy, mediastinotomy, or positron emission tomography scan were not routinely used preoperatively.

We retrospectively reviewed 139 patients (3.8%) who underwent at least lobectomy and systematic nodal dissection (SND) for lower lobe tumor in either the right or left lung and who had histologic evidence of non-small cell lung cancer (NSCLC) with mediastinal lymph node metastasis (pN2). We excluded the patients who underwent only sampling or selective nodal dissection. The study excluded tumors that crossed the fissure and invaded multiple lobes or other organs and huge tumors

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Table 1. Patient Characteristics in Pathologic N2 Non-Small Cell Lung Cancer Originating From the Lower Lobe

Patients, No.	139
Age, mean ± SD year (range)	60 ± 11 (26–85)
Sex, No (%)	
Male	95 (68)
Female	44 (32)
Histological type, No (%)	
Adenocarcinoma	94 (68)
Squamous cell carcinoma	37 (27)
Others	8 (5)
Primary tumor location, No (%)	
Superior segment	51 (37)
Right	35
Left	16
Basal segment	88 (63)
Right	51
Left	37

more than 5 cm in size. All patients underwent at least lobectomy with hilar and mediastinal lymphadenectomy.

Patients were subdivided into two groups according to origin: superior segment (n = 51) and basal segment (n = 88). The correlation between the segment of the tumor location and the involved hilar/mediastinal nodes were investigated in each case. The location of the tumor was identified by the involved bronchus in the resected specimen. When the tumor involved both the superior and the basal segments, the patient was placed in the superior segment group.

Surgical Procedure

Pulmonary resection and systematic nodal dissection were performed through posterolateral thoracotomy. At thoracotomy, the diagnosis was confirmed by frozen-section analysis when histologic confirmation was not available preoperatively. When the hilar nodes involved the upper lobe bronchus or pulmonary artery, or both, pneumonectomy was done. Systematic nodal dissection, including the superior and inferior mediastinum, was then performed after pulmonary resection. In left thoracotomy, superior mediastinal lymph nodes indicated the 5, 6, and 4L nodes. In right thoracotomy, superior mediastinal lymph nodes indicated the 1, 2R, and 4R nodes. Inferior mediastinal lymph nodes indicated the 7, 8, and 9 nodes in both side thoracotomies. Histologic analysis of lymph node metastasis was made by hematoxylin and eosin stain.

Statistical Analysis

Survival was calculated by the Kaplan-Meier method, and differences in survival were determined by the log-rank test. Zero time was the date of surgery, and the terminal events were death due to cancer, noncancer, or unknown causes. A multivariable analysis of independent prognostic factors was done by using Cox's proportional hazards regression model. Relative risk and 95% confidence intervals were calculated. Proportions were compared by means of χ^2 analysis. Values of $p < 0.05$ were considered to be statistically significant.

Results

Patient Characteristics

Patient characteristics are summarized in Table 1. The tumor cell types were adenocarcinoma in 94 (68%), squamous cell carcinoma in 37 (27%), and others in 8 (5%). The segments of origin were the superior segment in 51 (37%), in 35 of whom the tumor was on the right side, and basal segment in 88 (63%), in 51 of whom the tumor was on the right side. The size of the primary tumor was less than 3 cm in 65 patients (47%).

Patterns of Nodal Spread

Significant differences in patterns of lymphatic pathways on both sides were found when the superior and basal segment groups were compared (Table 2). The basal segment group showed significantly higher incidence of subcarinal metastasis than the superior segment group (80% vs 57%, $p = 0.0044$). The superior segment group showed significantly higher incidence of superior mediastinal metastasis than the basal segment group (64% vs 36%, $p = 0.0012$; Table 2). When superior mediastinal metastasis existed, the basal segment group showed a significantly higher incidence of synchronous subcarinal metastasis than did the superior segment group (81% vs 39%, $p = 0.0006$; Table 3).

Table 2. Location of the Primary Tumor in the Lower Lobe and Incidence of Subcarinal and Superior Mediastinal Node Involvement

			Metastasis to the Subcarinal Node		Metastasis to the Superior Mediastinal Node	
Side	Primary Tumor Location	Patients, No.	No. (%)	*p* Value	No. (%)	*p* Value
Right	Superior segment	35	22 (63)	0.0229	22 (63)	0.0118
	Basal segment	51	43 (84)		18 (35)	
Left	Superior segment	16	7 (44)	0.0417	11 (69)	0.0385
	Basal segment	37	27 (73)		14 (38)	
Total	Superior segment	51	29 (57)	0.0044	33 (64)	0.0012
	Basal segment	88	70 (80)		32 (36)	

GENERAL THORACIC

Table 3. Location of the Primary Tumor in the Lower Lobe and Incidence of Synchronous Metastasis to the Superior Mediastinal and Subcarinal Nodes

Side	Primary Tumor Location	Patients With Superior Mediastinal Involvement, No.	Synchronous Metastasis to the Subcarinal Node	
			No. (%)	p Value
Right	Superior segment	22	9 (41)	0.0064
	Basal segment	18	15 (83)	
Left	Superior segment	11	4 (36)	0.0325
	Basal segment	14	11 (79)	
Total	Superior segment	33	13 (39)	0.0006
	Basal segment	32	26 (81)	

Differences in Surgical Procedure

The superior segment group more frequently required pneumonectomy than the basal segment group, with a significant difference (45.1% vs 17.0%, $p = 0.0003$), but there was no significant difference in the ratio of T1/T2 between the groups (24 of 21 vs 41 of 47, $p = 0.9021$; Table 4).

Group Differences in Prognosis of N2 Disease

Overall 5-year survival of patients with lower lobe N2 tumor was 27.9%. The 5-year survival of the basal segment group was better than for the superior segment group (32.9% vs 19.9%); however, the difference was not significant ($p = 0.1308$; Fig 1).

Among the basal segment group, the patients without superior mediastinal metastasis showed significantly better prognosis than did those with it, with a 5-year survival of 42.7% vs 15.6% ($p = 0.0453$; Fig 2A).

In the superior segment group, no significant differences in survival were detected between patients with and without superior mediastinal metastasis: at 5 years, the survival was 25.4% for those without and 16.5% for those with, survival with only superior mediastinal node metastasis was 20.0%; and with superior mediastinal and subcarinal metastasis, 10.3% ($p = 0.1623$; Fig 2B).

Collectively, the basal segment origin tumors with only subcarinal metastasis showed significantly better prognosis than other lower lobe N2 tumors (5-year survival 43% vs 18%, $p = 0.0155$).

Comment

The lower lobe has a large volume of lung parenchyma, including 5 segments in the right and 4 segments in the left, and occupies half of the hemithorax in each side. Despite the extensive size of the lower lobe, all tumors located there have been treated similarly, regardless of whether the tumor originated in the superior or the basal segments. Owing to a lack of information on the variations in clinicopathologic features between tumors located in the superior and basal segments, we conducted the present study to investigate the differences in patterns of lymph node metastasis and prognosis of each segment.

Our results on the metastatic pathway showed a possibility that basal segment tumors metastasizing to the superior mediastinum mostly went through the subcarinal node, whereas SS tumors often metastasized directly to the superior mediastinum without concomitant metastasis to the

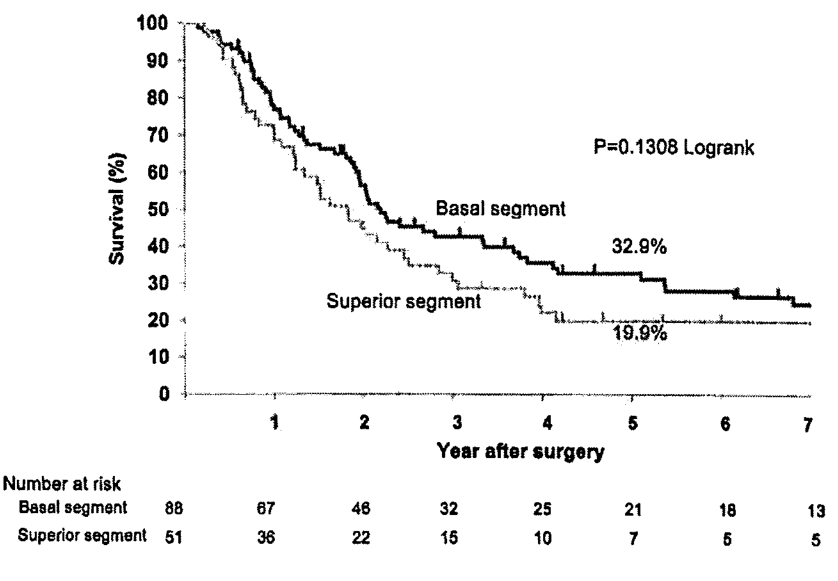

Fig 1. Survival of patients with pN2 tumors located in the basal and superior segment of the lower lobe. The 5-year survival was 32.9% for the basal segment group (black line) and 19.9% for the superior segment group (gray line), but the difference was not significant ($p = 0.1308$).

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Table 4. Types of Surgical Procedure for Lower Lobe pN2 Disease According to the Segment of the Primary Tumor in the Lower Lobe

		Surgical Procedure, No. (%)		
Primary Tumor Location of the	Patients, No.	Pneumonectomy	Lobectomy	T Status (T1/T2)
Superior segment	51	23 (45.1)[a]	28 (54.9)	24/27[b]
Basal segment	88	15 (17.0)[a]	73 (83.0)	41/47[b]
Total	139	38 (27.3)	101 (72.7)	65/74

[a] $p = 0.0003$; [b] $p = 0.9021$.

subcarinal node (Tables 2 and 3). Furthermore, the patterns of metastatic pathway in the right and left side were identical (Tables 2 and 3). The schemes demonstrating a possibility of the main stream of lymphatic spread in each segment on the basis of these results are shown in Figure 3. Perhaps superior segment tumors tend to metastasize directly to the upper mediastinum owing to the anatomically shorter distance between these sites compared with the longer distance between the basal segment and the upper mediastinum. Alternatively, for basal segment tumors, the subcarinal node could be a barrier on its metastatic way to the upper mediastinum.

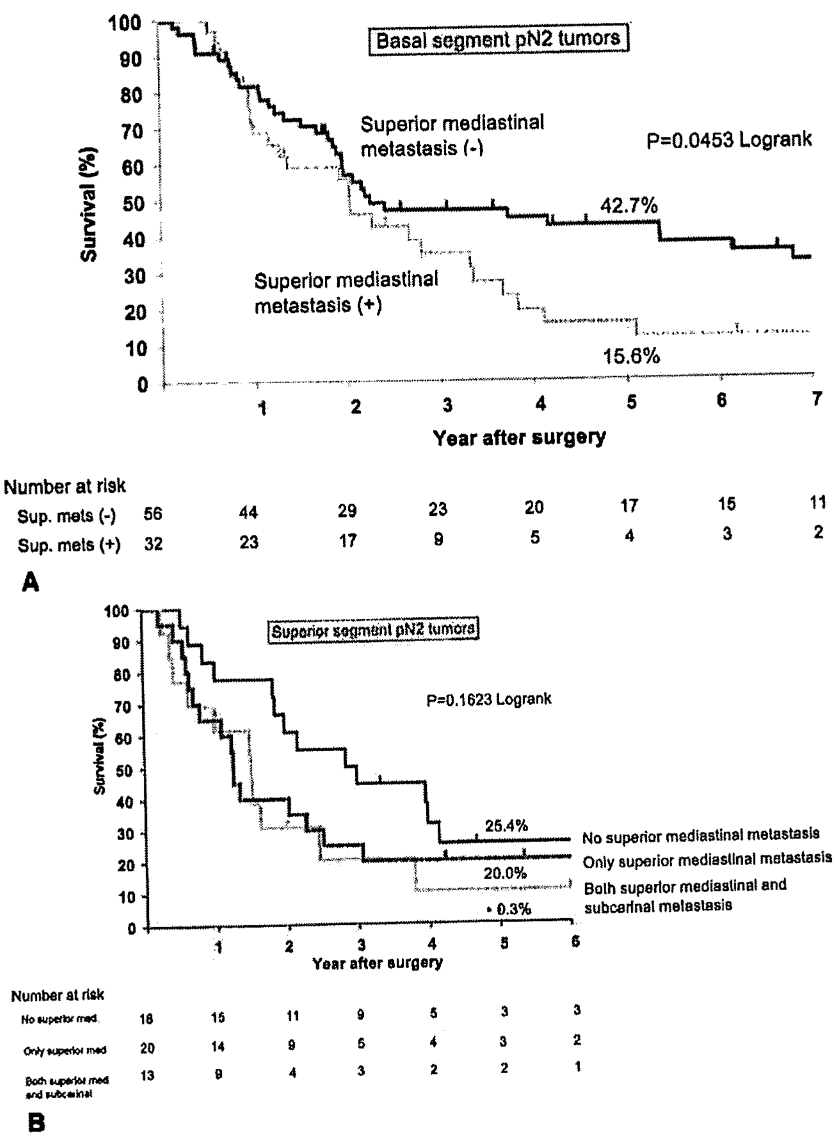

Fig 2. Survival of patients with lower lobe pN2 tumors with and without superior mediastinal metastasis in tumors with (A) basal segment origin and (B) superior segment origin. (A) In the basal segment group, the patients without superior mediastinal metastasis (black line) showed significantly better prognosis than did those with (grey line) superior mediastinal metastasis (5-year survival, 42.7% vs 15.6%, p = 0.0453). (B) Survival of patients with superior segment pN2 tumors grouped by the extent of lymph node metastasis. No significant differences in survival were detected between patients without superior mediastinal metastasis (black line; 5-year survival, 25.4%) and with superior mediastinal metastasis (5-year survival, 16.5%: with only superior mediastinal node metastasis (dark gray line, 20.0%; with superior mediastinal and subcarinal metastasis, light gray line, 10.3%; p = 0.1623).

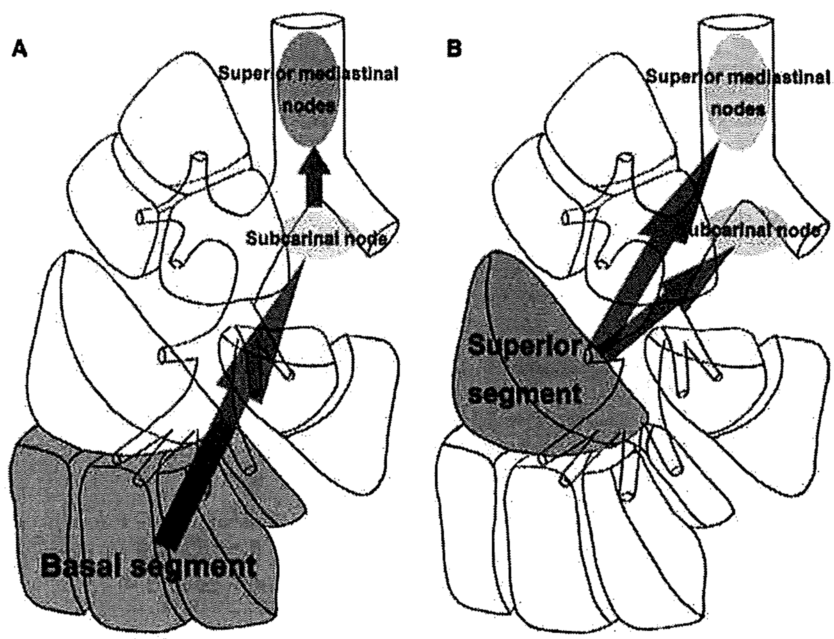

Fig 3. The scheme of the main stream of lymphatic spread of the tumor in each segment. (A) Basal segment tumor metastasizes to the superior mediastinum mostly through the subcarinal node. (B) Superior segment tumor often metastasizes directly to the superior mediastinum, without concomitant metastasis to the subcarinal node.

These factors might contribute to the higher incidence of pneumonectomy in superior segment tumors than that in basal segment tumors. Probably in many patients in the superior segment group, interlobar nodes that were located on the way from the primary site to superior mediastinum were involved. That is, superior segment tumor seems to metastasize to the superior mediastinum by involving the nodes adjacent to the bronchus and pulmonary artery of the upper lobe in consideration of the anatomy of the hilum. Then, this point will lead to the high incidence of pneumonectomy in the superior segment group.

Extensive nodal dissection, including the superior and inferior mediastinum, has been universally performed in lung cancer operations [1, 2]. This technique, termed "systematic nodal dissection" remains an important component of the investigative and therapeutic process in all patients undergoing thoracotomy for lung cancer [3–5]. However, because the number of lung cancers detected early is increasing with the development of CTs scanners, a new therapeutic strategy for selective nodal dissection is required instead of systematic nodal dissection [6, 7]. The extent of nodal dissection could be tailored according to the tumor location–specific patterns of nodal spread [8].

Riquet and associates [9] reported that lung cancer metastasizes so easily to the mediastinum that selection of the patients for limited surgical intervention should be discussed carefully. Some previous reports have described the appropriateness of selective nodal dissection based on the lobe-specific extent of nodal spread [7, 10, 11]. Okada and associates [11] reported that superior mediastinal dissection might be unnecessary for lower lobe tumors when the subcarinal node was negative. Our results support their conclusion for basal segment tumor; however, for the superior segment tumor, our results reveal that superior mediastinal dissection should be mandatory for accurate staging even when the subcarinal node is negative.

The prognosis for patients with superior segment tumors was worse, with a 5-year survival of 20% compared with 33% for patients with basal segment tumors, although this difference was not statistically significant. Poor survival rates may be attributed to the increased incidence of pneumonectomy in superior segment tumors (45%) compared with 17% for basal segment tumors (Table 4). Although the prognoses of patients with superior mediastinal metastasis from superior and basal segment tumors of the lower lobe were dismal, with respective 5-year survivals of 17% and 16%, the patients with basal segment N2 tumors who had only subcarinal metastasis showed significantly better 5-year survival of 43%, an acceptable result, compared with other lower lobe N2 patients. This will be mainly because they have metastasis to a single N2 station with an anatomically shorter distance from the primary site. Only in this small subgroup of lower lobe N2 patients, those with tumors of basal segment origin and having no superior mediastinal metastasis, may long-term survival be expected.

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SHORT COMMUNICATION

Mucoepidermoid carcinoma of the lung: High-resolution CT and histopathologic findings in five cases

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KEYWORDS
Mucoepidermoid carcinoma;
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Summary
Objective: The purpose of this study was to characterize the high-resolution computed tomography (HRCT) findings of mucoepidermoid carcinoma of the lung and correlate them with the histopathological features.
Methods: The study included five patients with pathologically proven mucoepidermoid carcinoma who underwent HRCT before treatment. The HRCT findings were then compared with the histopathological features in all patients.
Results: The HRCT images showed lesions in the central lung in four patients and in the peripheral lung in one. All the lesions were well defined nodules or masses with a smooth margin. The contour of the tumours was oval ($n=3$), round ($n=1$) or lobulated ($n=1$). The contrast-enhanced CT images showed marked heterogeneous enhancement with foci of relatively low attenuation in four of the five lesions and mild heterogeneous enhancement in the other lesion. There was an admixed distribution of areas that are heterogeneous in the densities of blood vessels, as highlighted by immunohistochemical staining of CD31. Most mucin-secreting areas of the tumours showed more densely distributed blood vessels, mostly capillaries, in between tumour cell nests, whereas other areas did less. All five patients in our series underwent lobectomy plus lymph node dissection or sampling. All the patients are alive without evidence of disease an average of 50.4 months after surgery (range, 15–82 months; median, 57 months).

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