FIGURE 2. Schematic drawing (A) and microphotograph of grade 0 invasion (B, C). The tumor shows a bronchioloalveolar growth pattern with no stromal invasion. Hematoxylin and eosin staining (B) and Elastica staining (C): original magnification ×200. N, normal alveolar cells; T, tumor cells; EF, elastic fiber framework.

FIGURE 3. Schematic drawing (A) and microphotograph (B, C) of grade 1 invasion. The tumor shows features of histologic invasion in the area of bronchioloalveolar growth (arrows). Hematoxylin and eosin staining (B): original magnification ×40. Elastica staining (C): original magnification ×200. CF, collagen fiber (collagenization).

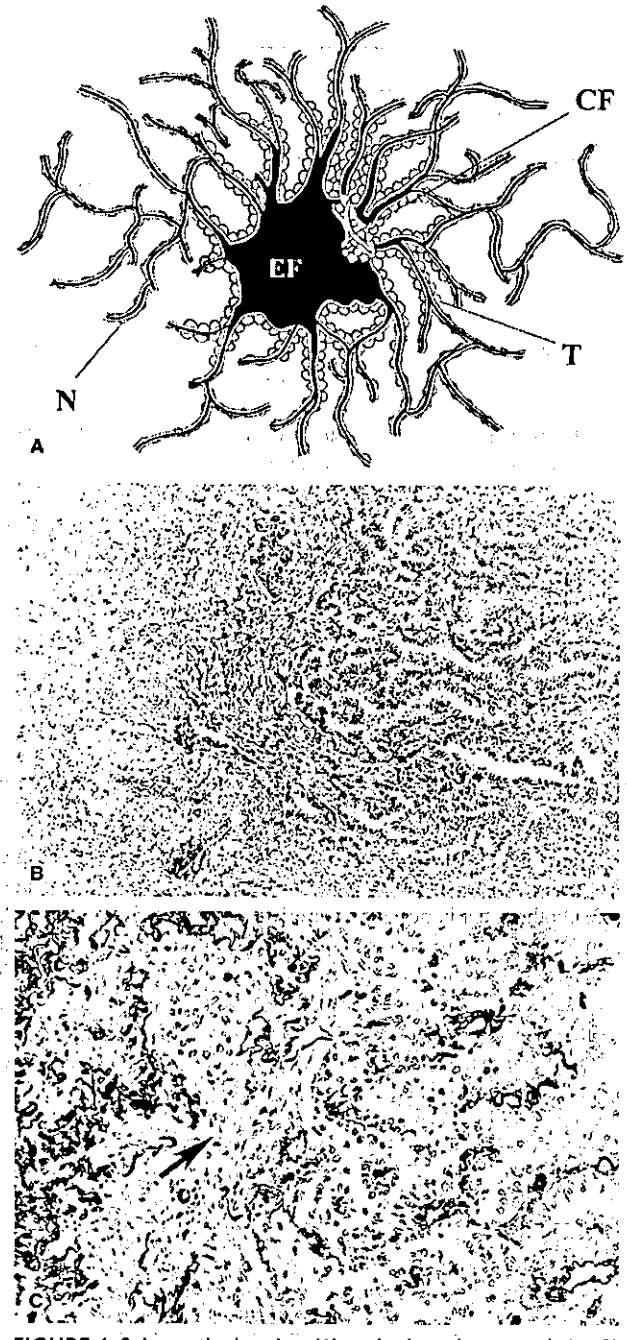

FIGURE 4. Schematic drawing (A) and microphotograph (B, C) of grade 2 invasion. The tumor shows features of histologic invasion localized on the periphery of a central fibrosis (arrow). The invasive foci are seen at the boundary between the central collapsed fibrosis and the surrounding tumor cells showing bronchioloalveolar growth. Hematoxylin and eosin staining (B): original magnification ×40. Elastica staining (C): original magnification ×200. EF is the black area.

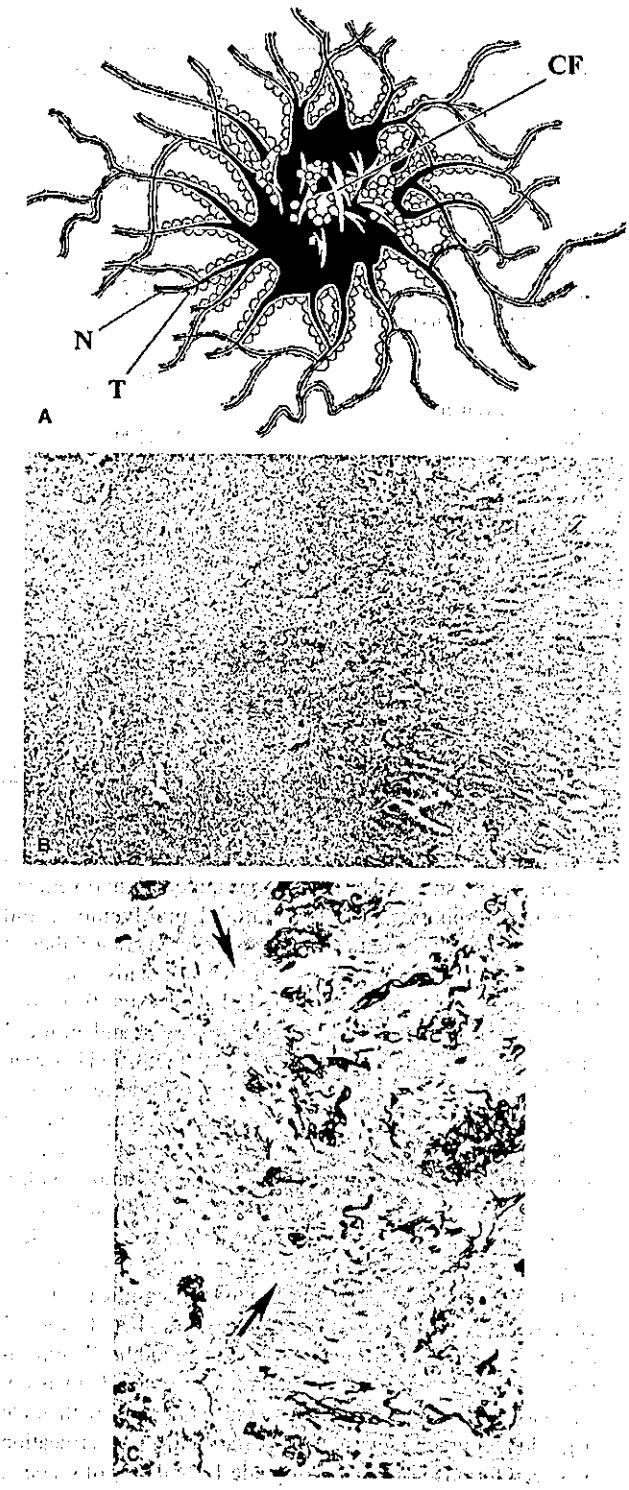

FIGURE 5. Schematic drawing (A) and microphotograph (B, C) of grade 3 invasion. The tumor shows features of histologic invasion into the center of a fibrotic focus (arrows). Hematoxylin and eosin staining (B): original magnification ×40. Elastica staining (C): original magnification ×200.

TABLE 3. Grade of Invasion and Pathologic Characteristics

	Grade of Invasion			
	Grade 0 (n = 85)	Grade 1 (n = 37)	Grade 2 (n = 46)	Grade 3 (n = 212)
Tumor size (cm)				
Mean	1.2	1.6	1.5	1.6
Range	0.4–2.0	0.7–2.0	0.7–2.0	0.8–2.0
Size of fibrotic focus (mm)				
Mean	2.0	3.8	6.7	7.9
Range	0–11	0–17	2–16	1–19
Pleural involvement				
Negative	85 (100%)	32 (100%)	46 (100%)	194 (92%)
Positive	0 (0%)	0 (0%)	0 (0%)	18 (8%)
Vascular/lymphatic permeation				
Negative	85 (100%)	36 (97%)	45 (98%)	68 (32%)
Positive	0 (0%)	1 (3%)	1 (2%)	144 (68%)
Nodal involvement				
N0	85 (100%)	37 (100%)	46 (100%)	155 (73%)
N1–N3	0 (0%)	0 (0%)	0 (0%)	57 (27%)
Pathologic stage				
I	85 (100%)	37 (100%)	46 (100%)	150 (71%)
II	0 (0%)	0 (0%)	0 (0%)	26 (12%)
III–IV	0 (0%)	0 (0%)	0 (0%)	36 (17%)

related to the progression of adenocarcinoma, as represented by tumor size, size of the fibrotic focus, pleural involvement, vascular/lymphatic permeation, nodal involvement, and pathologic stage. The tumor size was smaller in grade 0 than in other grades of invasion. This difference was statistically significant between grade 0 and grade 1 (Tukey's significant difference test, $P < 0.0001$), between grade 0 and grade 2 (Tukey's significant difference test, $P = 0.0005$), and between grade 0 and grade 3 (Tukey's significant difference test, $P < 0.0001$), but there were no significant differences among grades of invasion other than grade 0. The size of the fibrotic focus within the lesion tended to increase in tumors with a more advanced grade of invasion. Although this difference was only marginally significant between grade 2 and grade 3 (Tukey's significant difference test, $P = 0.056$), it was significant between grade 0 and grade 1 (Tukey's significant difference test, $P = 0.0009$) and between grade 1 and grade 2 (Tukey's significant difference test, $P = 0.0009$). Pleural involvement was only seen in tumors with grade 3 invasion, whereas no pleural involvement was seen in tumors with grade 0, grade 1, or grade 2 invasion. Vascular/lymphatic permeation was seen for one lesion (3%) of grade 1, one (2%) of grade 2, and 144 (68%) of grade 3, but not for grade 0. Lymph node involvement was seen for 57 tumors (27%) with grade 3 invasion: 24 in N1 stations, 32 in N2 stations, and one in N3 stations. However, there was no lymph node involvement for tumors with grade 0, grade 1, or grade 2 invasion. The pathologic stage was IA in all of the lesions in grade 0, grade 1, and grade 2. On the other hand, there were 144 lesions (68%) of stage IA in grade 3. The relationship between the grade of invasion and the histologic subtype as adenocarcinoma defined by the WHO classification is shown in Table 4. All of the acinar, papillary, and solid adenocarcinomas had grade 3 invasion. On the other hand, adenocarcinomas with mixed subtypes (n = 257) had various grades of invasion: 37 lesions (14%) with grade 1 invasion, 46 (18%) with grade 2 invasion, and 174 (68%) with grade 3 invasion.

TABLE 4. Relationship Between Grade of Invasion and WHO Classification

	WHO Classification (n = 380)				
Grade	BAC	Acinar	Papillary	Solid	Mixed Subtypes
0	85	0	0	0	0
1	0	0	0	0	37
2	0	0	0	0	46
3	0	4	7	27	174
Total	85	4	7	27	257

WHO, World Health Organization; BAC, bronchioloalveolar carcinoma.

Prognosis

The postoperative median follow-up period was 4.5 years. There were no operative deaths. The 3- and 5-year disease-free survival rates of all 380 patients with adenocarcinoma ≤2.0 cm in diameter were 82.3% and 76.4%, respectively (Fig. 6). The disease-free survival curves, according to the histologic subtype by the WHO classification, are shown in Figure 7. The 5-year disease-free survival rates were 100% (BAC), 72.4% (mixed subtypes), 55.6% (solid), and 42.9% (papillary), respectively. No significant difference in disease-free survival was found among these histologic subtypes. The disease-free survival curves according to the histologic grade of invasion (grade 0-3) are shown in Figure 8. The 5-year disease-free survival rates were 100%, 100%, 100%, and 59.6% for grade 0, grade 1, grade 2, and grade 3, respectively. Tumors with grade 0, grade 1, or grade 2 invasion all had a very excellent prognosis, which indicated that tumors with grade 1 and grade 2 invasion could be considered minimally invasive lesions.

DISCUSSION

In 1999, the WHO histologic classification of lung and pleural tumors was revised. With regard to adenocarcinoma, BAC is described as a form of adenocarcinoma with a pure bronchioloalveolar growth pattern and no evidence of stromal, vascular, or pleural invasion. If there is histologic evidence of invasive growth, it was considered "adenocarcinoma with mixed subtypes." In recent reports, the pattern of recurrence and survival in patients with resected stage I BAC were investigated.[4,9,24,30] The 5-year disease-free survival rate was reported to be 73% by Volpino et al,[30] 74% by Breathnach et al,[4] and 81% by Rena et al.[24] Despite the clear definition of a "non-invasive" morphology for BACs, these reports included BACs

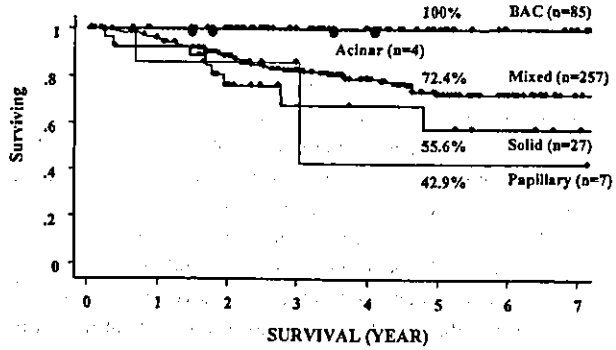

FIGURE 7. Survival curves according to the WHO classification. The 5-year disease-free survival rates are 100% (BAC), 72.4% (mixed subtypes), 55.6% (solid), and 42.9% (papillary), respectively.

with both local and distant recurrence. These results suggested that tumors with postoperative recurrence must have had invasive features and therefore should not be diagnosed as BAC without invasive growth. The difficulties of unequivocally recognizing invasive features by morphology must be addressed.

Several studies have examined the morphologic features related to "tumor development or invasion" in adenocarcinoma.[10,19–21,25,27,28,31,32] Shimosato et al focused on "scar" formation, which is a characteristic histologic feature in adenocarcinoma of peripheral lung, and demonstrated that the degree of collagenization in the fibrotic focus was closely correlated with tumor growth and prognosis.[25] They proposed that tumors with little or no collagenization could be considered to be in an "early stage" of development. Yamashiro et al reported that histologic invasion could be suggested by tumor cells accompanied by a stromal desmoplastic reaction in ad-

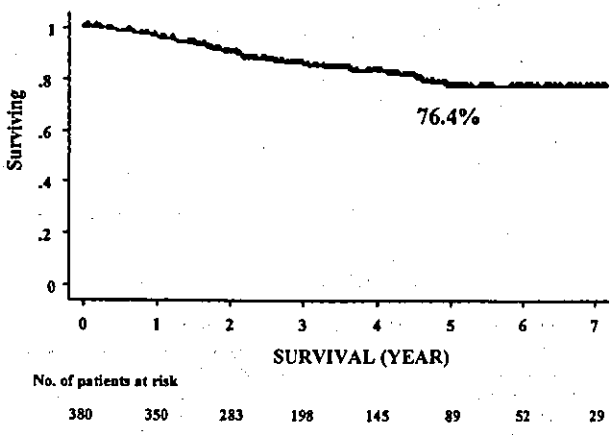

FIGURE 6. Survival curve for all 380 patients with pulmonary adenocarcinoma ≤2.0 cm in diameter. The 3- and 5-year disease-free survival rates are 82.3% and 76.4%, respectively.

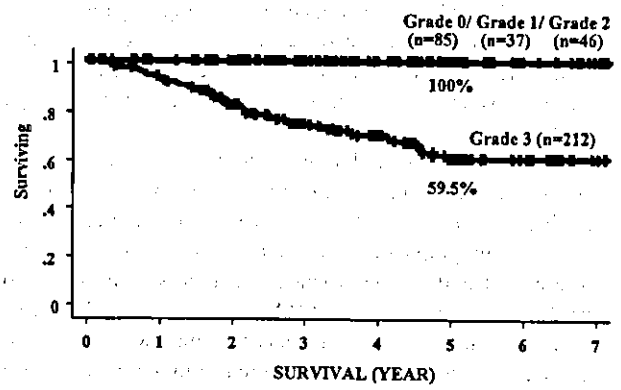

FIGURE 8. Survival curves according to histologic grade of invasion (grade 0–3). The 5-year disease-free survival rates are 100% (grade 0), 100% (grade 1), 100% (grade 2), and 59.6% (grade 3), respectively.

enocarcinoma, and a greater proportion of invasion to the fibrotic focus was correlated with a worse prognosis.[31] Noguchi et al suggested that active fibroblast proliferation in adenocarcinoma was related to the invasive growth of tumors.[21] They thought that localized bronchioloalveolar carcinomas without active fibroblastic proliferation could be considered in situ adenocarcinomas with an excellent prognosis (5-year survival rate, 100%). Eto et al analyzed the change in the stromal elastic framework in adenocarcinoma and concluded that the elastic framework was preserved in the early development of the tumor but was disrupted as the tumor grew, indicating stromal invasion.[10] Suzuki et al reported that adenocarcinomas with a fibrotic focus of ≤5 mm in size had an excellent prognosis (5-year survival rate, 100%), and the size of the fibrotic focus within the tumor was shown to be a significant prognostic factor.[27] In the present study, among 91 patients of adenocarcinoma with fibrotic focus ≤5 mm in size, there were 3 (3.3%) patients with recurrence. Terasaki et al measured the size of invasive foci, which were considered by fibroblastic proliferation and architectural distortion of tumor cells, and adenocarcinoma with invasive foci of ≤5 mm in size showed low prevalence of vascular, lymphatic, and pleural involvement.[28] Indeed, these histologic features were likely to be closely related to the tumor invasion and development. However, practically, a diagnosis of "invasion" often relies on the discretion of the pathologist because the definition of morphologic "invasion" is equivocal.

In the present study, histologic "invasion" was considered cellular arrangement in acinic/papillotubular structures or solid nests in a fibroblastic stroma accompanied by collagenization, as in the 1999 WHO classification. In addition, the structural deformity of the stromal elastic fiber framework was also evaluated. By highlighting the elastic fiber framework using elastic stain, we were able to more precisely analyze the morphologic details. Indeed, vascular/pleural involvement could not be demonstrated in any of the 85 patients without disruption of the stromal framework. As a result, a histologic diagnosis of BAC could be established precisely, and no postoperative recurrence was observed in these patients.

According to our definitions for the grade of invasion in adenocarcinoma, tumors with grade 1 or grade 2 invasion had neither lymph node metastasis nor postoperative recurrence, even though lymphatic permeation was seen in one case each in grades 1 and 2. The prognosis of tumors with grade 1 or grade 2 invasion, like that of BAC, was excellent. Therefore, despite stromal invasion, adenocarcinomas with grade 1 or grade 2 invasion should be considered "minimally invasive lesion" with the same prognosis as BAC.

In summary, the prognosis of BACs was excellent and the 5-year disease-free survival rate was 100%. In addition, adenocarcinomas with grade 1 or grade 2 invasion, ie, "stromal invasion in the area of bronchioloalveolar growth" and "stromal invasion localized on the periphery of a fibrotic focus," also had an excellent prognosis. Adenocarcinomas with grade 1 or grade 2 invasion can be considered "minimally invasive adenocarcinomas" or "early adenocarcinomas."

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Clinicopathologic Features of Peripheral Squamous Cell Carcinoma of the Lung

Hiroyuki Sakurai, MD, Hisao Asamura, MD, Shun-ichi Watanabe, MD, Kenji Suzuki, MD, and Ryosuke Tsuchiya, MD

Division of Thoracic Surgery, National Cancer Center Hospital, Tokyo, Japan

Background. The clinicopathologic features are still unknown in peripheral squamous cell carcinoma of the lung, unlike centrally located carcinomas. In this retrospective study, we investigated the clinicopathologic characteristics of patients with peripheral squamous cell carcinomas.

Methods. Of 1,381 primary lung carcinomas surgically resected at the National Cancer Center Hospital, Tokyo, from 1995 through 2001, 70 (5.1%) peripheral squamous cell carcinomas of 3.0 cm or less in diameter were studied retrospectively in terms of clinicopathologic characteristics such as age, sex, past history, smoking, tumor size, mode of operation, extent of lymph node dissection, pathologic lymph node status, mode of recurrence, and cause of death.

Results. These patients ranged in age from 49 to 82 years, with a mean age of 69.2 years. Thirty-nine patients (56%) were at increased risk preoperatively. The incidence of lymph node metastasis was 25%, and larger tumors tended to be associated with a higher prevalence, although this difference was not significant ($p = 0.12$). None of the patients with N2 disease had skipping metastasis. Recurrence was observed in 13 patients (19%). There was no significant correlation between recurrence and the extent of lymphadenectomy or the mode of operation. The 5-year overall and disease-specific survival rates were 73.4% and 85.9%, respectively. The cause of death was recurrence in 53% and other disease in 47%.

Conclusions. We propose that mediastinal hilar lymphadenectomy should be routinely conducted as a curative operation for low-risk patients with small peripheral squamous cell carcinoma. We further propose that for patients who may have difficulty tolerating this procedure, pathologic examination of intraoperative frozen sections from the hilar node could be useful for planning a surgical strategy.

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Many squamous cell carcinomas of the lung arise in central airways, where the tumor shows both endobronchial and invasive growth into the peribronchial tissue, lung parenchyma, and nearby lymph nodes, sometimes compressing the pulmonary artery and vein. The clinicopathologic features such as carcinoma in situ and extension along the bronchus are well known in centrally located squamous cell carcinoma [1–5]. On the other hand, in peripheral squamous cell carcinoma, a smaller tumor is supposedly associated with the "early stage" of tumor development. Several reports have indicated that peripheral squamous cell carcinoma is accompanied by a quite low prevalence of lymph node metastasis, especially in tumors 2 cm or less in diameter [6–12]. This might reflect its tendency to remain localized and slow in tumor growth [11, 13]. However, few, if any, studies have specifically examined the clinical and histopathologic features of peripheral squamous cell carcinoma because of its relative infrequency.

So far a causal relationship between cigarette smoking and squamous cell carcinoma of the lung has been established from many epidemiologic and laboratory studies [3, 14, 15]. Smoking is an important risk factor for cardiovascular disease and impaired pulmonary function with chronic obstructive pulmonary disease [16]. With regard to surgical treatment, we sometimes are obliged to performed lesser resection, irrespective of surgical curability, for patients with peripheral squamous cell carcinoma because of their risk factor, although major lung resection has been the standard operation of choice for non–small cell lung cancer [17]. However, if peripheral squamous cell carcinomas actually tend to remain localized, even lesser resection may be considered curative resection.

In this retrospective study, we sought to clarify the clinicopathologic features of patients with surgically resected peripheral squamous cell carcinoma and to work out the surgical strategy.

Patients and Methods

For the 7-year period from January 1995 through December 2001, a total of 1,381 patients underwent surgical resection for primary lung carcinoma at the National Cancer Center Hospital, Tokyo. Among these, 70 patients (5.1%) with peripheral squamous cell carcinomas of 3.0 cm or less in diameter were considered for this analysis. These patients accounted for 22% of all 317 patients with

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Address reprint requests to Dr Sakurai, Division of Thoracic Surgery, National Cancer Center Hospital, 1-1, Tsukiji 5-chome, Chuo-ku, Tokyo 104-0045, Japan; e-mail: sakuraihm@ybb.ne.jp.

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primary squamous cell carcinomas that were resected during the same period. Their TNM stages were determined according to the Union Internationale Contre le Cancer (International Union Against Cancer) staging system [18]. Peripheral squamous cell carcinoma was defined as that arising from subsegmental or other distal bronchi and bronchioli, based on a previous report by Shimosato and colleagues [19]. The medical record of each patient was reviewed for age, sex, past history, smoking, tumor size, mode of operation, extent of lymph node dissection, curability, pathologic lymph node status, mode of recurrence, and cause of death. The following patients were considered preoperatively as being at increased risk as previously reported [20, 21]: (1) patients older than 75 years of age; (2) patients with pulmonary dysfunction, defined as forced expiratory volume in 1 second of less than 800 mL; (3) patients with a past history of myocardial infarction or angina pectoris; (4) patients with a past history of cerebral infarction; and (5) patients with insulin-dependent diabetes mellitus. Patients were considered as being at increased risk when they had diabetes based on history and need of insulin. Smoking status (never, former, or current) was recorded at the time of admission. Smoking history was categorized as negative for "never" cigarette smoker and as positive for "former" or "current" smoker. The extent of lymph node dissection or sampling was based on the lymph node map for lung cancer proposed by Naruke and colleagues [22]. In addition, we performed selective mediastinal lymph node dissection according to the report by Asamura and associates [23]. This report demonstrated that single-station lymph node metastasis to the subcarinal station without superior mediastinal involvement occurred rarely, less than 2%, for tumors of the right upper lobe and the left upper segment. In this procedure, for tumors of the upper lobes, subcarinal and lower mediastinal lymph node dissection could be omitted unless involvement of the pretracheal lymph nodes was noted by a frozen-section examination during the operation. Mediastinal metastasis was considered "skipping" if any of the mediastinal lymph nodes was involved by the tumor, without hilar or intrapulmonary node metastasis. Operative death was defined as any death within 30 days of the operation or during hospitalization. Cancer recurrence was carefully divided into three categories according to the site of the initial relapse: locoregional, distant, and at both sites simultaneously. Locoregional recurrence was defined as any recurrent disease within the ipsilateral hemithorax, mediastinum, or supraclavicular lymph nodes. All other sites of recurrence were considered distant metastases.

After discharge from the hospital, patients were followed at 3- to 4-month intervals for the first 2 years, 6-month intervals for the subsequent 3 years, and yearly thereafter. Follow-up evaluation included physical examination and routine hematologic and biochemical analyses, and chest roentgenograms were monitored for evidence of recurrent or other disease. Computed tomography was selectively used as a follow-up screening study when the screening roentgenographic studies suggested a new abnormality. In some patients who were lost from this postoperative follow-up schedule, follow-up was obtained by direct patient contact by telephone interviews, and also obtained from the referring physicians if direct patient contact was not possible. Postoperative follow-up was complete with regard to survival and the time and location of any recurrent disease in all patients.

Table 1. Characteristics of Patients

Characteristic	Number
Sex	
Male	65 (93%)
Female	5 (7%)
Age (y)	
Range	49–82
Mean	69.2
Smoking	
Positive	69 (99%)
Negative	1 (1%)
Tumor size (cm)	
Range	1.0–3.0
Mean	2.2
Lymph node dissection	
Mediastinohilar	23 (33%)
Hilar only/ none	47 (67%)
Curability of surgery	
Complete	69 (99%)
Incomplete	1 (1%)

Survival rates were calculated by the Kaplan-Meier method using the date of operation as the starting point and the date of death or last follow-up as the end point. Disease-specific survival was defined as the time between operation and cancer-related death, where deaths by causes other than lung cancer were considered censored. Overall survival was defined as the time between operation and overall deaths. A χ^2 test was used to compare the various rates. Significance was defined as a p value of less than 0.05.

Results

Clinicopathologic Findings

The clinical characteristics of the 70 patients are presented in Table 1. Sixty-five patients (93%) were men and 5 (7%) were women. These patients ranged in age from 49 to 82 years, with a mean age of 69.2 years. Sixty-nine (99%) patients were smokers, whereas only 1 was a

Table 2. Patients at Increased Risk

Factor	Number
High age (≥ 75 y)	17 (24%)
Cardiac disease	10 (14%)
Pulmonary dysfunction	12 (17%)
Cerebral infarction	3 (4%)
Total	39 (56%)

Table 3. Mode of Operation for Patients and Percentage of Patients at Increased Risk

Mode of Operation	Number	Increased Risk
Pneumonectomy	2 (3%)	0 (0%)
Lobectomy	43 (62%)	17 (40%)
Segmentectomy	8 (11%)	7 (87%)
Wedge resection	17 (24%)	15 (88%)
Total	70 (100%)	39 (56%)

nonsmoker. The tumor size ranged from 1.0 to 3.0 cm, with a mean size of 2.2 cm. Curative lung resection was performed in 69 patients (99%). The exception was 1 patient who had a residual tumor because of a perinodal invasion extending from the hilar lymph node to the bronchus. Thirty-nine patients (56%) were preoperatively at increased risk (Table 2). Approximately a quarter of them were older than 75 years of age. With regard to the mode of operation, pneumonectomy was performed in 2 patients (3%), lobectomy in 43 (62%), segmentectomy in 8 (11%), and wedge resection in 17 (24%). No patients received adjuvant chemotherapy or radiotherapy after surgery. The fraction of preoperative increased-risk cases in each mode of operation is shown in Table 3. The prevalence of patients at increased risk was higher in limited resections such as segmentectomy and wedge resection. Intraoperative lymph node dissection or sampling was performed in 55 of 70 patients. It was omitted in the other 15 patients because of their increased risk. Among these 55 patients with lymph node dissection or sampling, the pathologic stage was IA in 39 patients, IB in 2, IIA in 8, IIB in 1, IIIA in 4, and IIIB in 1. The TNM stages for each of the tumor were also recorded (Table 4). Fourteen (25%) of these 55 patients had lymph node metastases. The relationship between tumor size and lymph node metastasis for the 55 patients is shown in Table 5. The incidence of lymph node metastasis tended to be higher in tumors larger than 2.0 cm in diameter (33%) than in those that were 2.0 cm or less in diameter (14%), but this difference was not significant ($p = 0.12$). Cancer recurrence was observed in 13 patients (19%) and was locoregional in 6, distant in 4, and both simultaneously in 3. The time intervals from the initial operation to the discovery of recurrence varied from 0.4 to 2.7 years.

Table 4. Stage by TNM Category

TNM Stage	No. of Patients
Stage I	Total = 41
T1 N0 M0	39 (70%)
T2 N0 M0	2 (4%)
Stage II	Total = 9
T1 N1 M0	8 (15%)
T2 N1 M0	1 (2%)
Stage III	Total = 5
T1 N2 M0	4 (7%)
T4 N2 M0	1 (2%)

Table 5. Lymph Node Involvement According to Tumor Diameter

	Lymph Node Metastasis		
Tumor Diameter (cm)	Negative	Positive	*p* Value
≤ 1.0	1 (100%)	0 (0%)	
> 1.0 and ≤ 2.0	18 (86%)	3 (14%)[a]	0.12
> 2.0 and ≤ 3.0	22 (67%)	11 (33%)[b]	
Total	41 (75%)	14 (25%)	

[a] Two of 3 cases with N2 disease. [b] Three of 11 cases with N2 disease.

Cancer recurrence was analyzed retrospectively by taking into account the mode of operation and the extent of lymph node dissection (Tables 6, 7). First, patients were divided into two groups according to the mode of operation. The lobectomy group included 45 patients who underwent pneumonectomy or lobectomy. The limited group included the remaining 25 patients who underwent segmentectomy or wedge resection. There was no significant difference in cancer recurrence between these two groups (Table 6). Second, patients were divided into two groups according to the extent of lymph node dissection (Table 7). The regional group included 47 patients who underwent node dissection up to the hilum or who received no sampling. The systematic group included 23 patients who underwent systematic mediastinal hilar node dissection. There was no significant correlation between the extent of lymph node dissection and the mode of recurrence. Five (22%) of the 23 patients with mediastinal hilar lymph node dissection had N2 disease. Although the number of patients was limited, none of these patients had skipping metastasis (Table 8).

Prognosis

The median follow-up period was 3.5 years. The overall and disease-specific survival curves for all 70 patients are shown in Figure 1. The overall 3- and 5-year survival rates were 80.4% and 73.4%, respectively. In contrast, the disease-specific 3- and 5-year survival rates were 85.9% and 85.9%, respectively. None of the 15 deaths was considered an operative death. The cause of death was cancer recurrence in 8 patients (53%) and other disease in 7 patients (47%; Table 9).

Table 6. Relationship Between Cancer Recurrence and Mode of Operation

	Mode of Operation		
Mode of Recurrence	Lobectomy (n = 45)	Limited (n = 25)	*p* Value
Locoregional	3 (7%)	3 (12%)	0.65
Distant	3 (7%)	1 (4%)	0.45
Both simultaneously	2 (4%)	1 (4%)	0.93
Total	8 (18%)	5 (20%)	0.81

Table 7. Relationship Between Cancer Recurrence and Extent of Lymph Node Dissection

Mode of Recurrence	Node Dissection: Systematic (n = 23)	Node Dissection: Regional (n = 47)	p Value
Locoregional	1 (4%)	5 (11%)	0.38
Distant	2 (9%)	2 (4%)	0.45
Both simultaneously	1 (4%)	2 (4%)	0.99
Total	4 (17%)	9 (19%)	0.86

Comment

Squamous cell carcinoma of the lung more often arises in the central airway. The prevalence of peripheral squamous cell carcinoma among all squamous cell carcinomas has been reported to range from 15% to 30% [24, 25]. Epidemiologically, cigarette smoking is likely to be a major factor in the causation of squamous cell carcinoma [14, 15]. In this study, peripheral squamous cell carcinoma was also closely associated with cigarette smoking. All of the patients except one woman were smokers. However, this one patient inhaled passive smoke and had worked with smoking colleagues for 25 years. Smoking is closely related to cardiovascular and pulmonary diseases, and the present study had increased risk as cardiovascular and pulmonary diseases in 35% of patients. There was also a marked male predominance in its incidence.

The incidence of nodal involvement in 70 patients with peripheral squamous cell carcinomas that were 3 cm or less in diameter was 25%. When stratified by tumor size, the incidence of nodal involvement was 14% in tumors 2 cm or less in diameter and 33% in those more than 2 cm in diameter. There was a lower tendency for nodal involvement in tumors 2 cm or less in diameter, although this difference was not significant. The rate calculated for tumors 2 cm or less in diameter was greater than those reported previously: 6.3% by Asamura and colleagues [6], 7.4% by Oda and colleagues [10], and 0% by Watanabe and colleagues [12].

In the present study, none of the patients with N2 disease had skipping metastasis, although the total number of patients in this study was limited. So far it has been reported that skipping metastases for peripheral non–small cell lung cancer occur in approximately 25% of N2 disease [26, 27]. On the other hand, Asamura and colleagues [6] reported that skipping metastasis occurred almost exclusively in adenocarcinomas. This rarity of skipping metastasis in squamous cell carcinoma may reflect the relatively slower growth and greater tendency to remain localized than the other cell types. None of the patients in the present study were included in that earlier study. Thus, as Asamura and colleagues [6] proposed, among small peripheral squamous cell carcinomas, mediastinal lymphadenectomy might be dispensable if the hilar lymph node is proven to be tumor-free on pathologic examination of frozen sections during the operation. The findings in the present study are consistent with this strategy for lymphadenectomy in patients with peripheral squamous cell carcinoma, as mediastinal nodal involvement is less common and no skipping metastasis occurred.

Most of the patients were at increased risk preoperatively, and this was the main reason that some were inevitably candidates for limited resection. The preoperative risk level for patients might determine the mode of operation. Moreover, this would account for the relatively high prevalence of noncancerous deaths. In the present study, 4 of the 7 patients who died of noncancerous diseases died of pneumonia. A policy of immunizing postoperative patients with a pneumococcal pneumonia

Table 8. Lymph Node Involvement in Patients With Mediastinal Hilar Node Dissection

Pathologic Node Status	Number
N0	16 (71%)
N1	2 (7%)
N2[a]	5 (22%)
Total	23 (22%)

[a] Zero of 5 cases of N2 disease involved skipping metastasis.

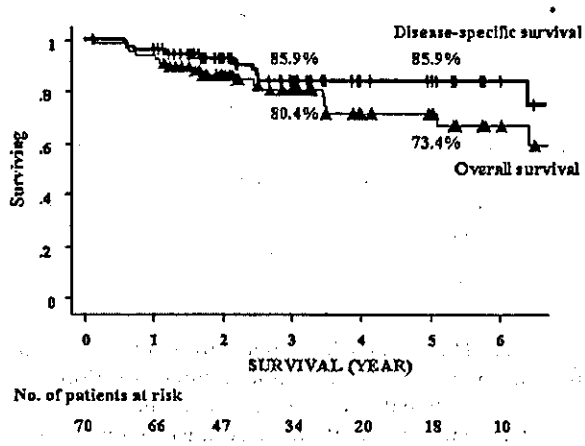

Fig 1. Overall and disease-specific survival curves for all 70 patients with peripheral squamous cell carcinomas 3.0 cm or less in diameter. The 3- and 5-year overall survival rates were 80.4% (95% confidence interval, 68.7% to 93.4%) and 73.4% (95% confidence interval, 52.7% to 89.0%), respectively. The 3- and 5-year disease-specific survival rates were 85.9% (95% confidence interval, 71.3% to 95.1%) and 85.9% (95% confidence interval, 66.8% to 99.2%), respectively.

Table 9. Causes of Death

Cause of Death		Number
Perioperative		0 (0%)
Cancer-specific		8 (53%)
Other disease		7 (47%)
Pneumonia	4	
Cardiac failure	1	
Gastric cancer	1	
Drowning	1	
Total		15 (100%)

vaccine might be effective in preventing pneumonia, although we did not have this policy for any patients.

Lobectomy for T1 peripheral non–small cell lung cancers has been the standard operation of choice since the randomized trial conducted by the Lung Cancer Study Group [17]. This study demonstrated that the limited resection such as wedge or segmentectomy had three times more local recurrence than the lobectomy. In addition, several reports have suggested that complete mediastinal hilar lymph node dissection can improve survival for non–small cell lung cancer [28–30]. In the present study, there was no significant difference in cancer recurrence among the modes of operation. Regarding the extent of lymph node dissection, although the information in Table 7 indicates a slight suggestion that complete mediastinal hilar lymph node dissection improves survival, this difference was not significant. However, the lack of statistical significance might indicate a type II error because the numbers in our study were too small to draw inferences from.

We considered the clinicopathologic features of peripheral squamous cell carcinomas to be as follows:

- These tumors were closely associated with a smoking history.
- Patients with these tumors were frequently at increased risk.
- Larger tumors were associated with a higher prevalence of lymph node involvement.
- Skipping metastasis of N2 disease was rare.
- There was a relatively high prevalence of noncancerous death.

We conclude that mediastinal hilar lymphadenectomy should be performed routinely in peripheral squamous cell carcinomas that are 3 cm or less in diameter, as well as in peripheral non-squamous cell carcinomas if the patient is at good risk. Furthermore, if it is suspected that the patient will not easily tolerate this procedure because of his or her increased risk, pathologic examination of intraoperative frozen sections of the hilar node would be useful for planning a surgical strategy. On the evidence of no hilar lymph node metastasis, limited resection may be curable for peripheral squamous cell carcinomas in oncologic and physical aspects.

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The Society of Thoracic Surgeons: Forty-first Annual Meeting

Please mark your calendars for the Forty-first Annual Meeting of The Society of Thoracic Surgeons, to be held in Tampa, Florida, from Jan. 24–26, 2005. The program will provide in-depth coverage of thoracic surgical topics selected to enhance and broaden the knowledge of cardiothoracic surgeons. Attendees will benefit from traditional Abstract Presentations, as well as Surgical Forums, Breakfast Sessions, Surgical Motion Pictures, and Town Hall Meetings on specific topics.

Advance registration forms, hotel reservation forms, and details regarding transportation arrangements, as well as the complete meeting program, will be mailed to Society members this fall. Also, complete meeting information will be available on the Society's Web site at www.sts.org. Nonmembers who wish to receive information on the Annual Meeting may contact the Society's secretary, Gordon F. Murray.

Abstracts for the meeting must be submitted electronically. The electronic submission form may be accessed at http://www.ctsnet.org/abstracts/sts. There is no charge for submitting your abstract electronically. The electronic submission deadline is August 20, 2004 at 5 pm CDT. The DVD submission deadline is August 9. Please direct any questions to STS headquarters.

Gordon F. Murray, MD
Secretary
The Society of Thoracic Surgeons
633 N. Saint Clair St, Suite 2320
Chicago, IL 60611-3658
Telephone: (312) 202-5800
Fax: (312) 202-5801
e-mail: sts@sts.org
website: www.sts.org

悪性気道狭窄に対するスパイラルZステントの有用性
—多施設共同試験—

多田弘人[1]；宮澤輝臣[2]；細川芳文[3]；滝口裕一[4]；
坪井正博[5]；鈴木道明[6]；古川欣也[7]；桑原正喜[8]；
荒木　潤[9]

索引用語 —— 悪性気道狭窄，スパイラルZステント

（気管支学．2003;25:632-636）

Co-operative Study of Spiral Z Stent for Malignant Airway Stenosis

Hirohito Tada[1]; Teruomi Miyazawa[2]; Yoshifumi Hosokawa[3]; Yuichi Takiguchi[4]; Masahiro Tsuboi[5]; Michiaki Suzuki[6]; Kinya Furukawa[7]; Masayoshi Kuwabara[8]; Jun Araki[9]

ABSTRACT —— ***Purpose.*** To evaluate the feasibility and efficacy of the spiral Z stent in multi-institutional prospective study. ***Patients and Methods.*** Patients who have dyspnea from malignant airway stenosis and are candidate for airway stents insertion were treated with Spiral Z stents, with local anesthesia in 25 cases and with general anesthesia in 16 cases. ***Results.*** Sixty spiral Z stents were placed to trachea to bronchi for 41 patients with few complications. The degree of airway stenosis and the WHO dyspnea index were improved significantly up to 2-3 months after insertion of this stents. ***Conclusion.*** Spiral Z stent is safety and effective for relieve symptoms of the patients with malignant airway stenosis. (*JJSB.* 2003;25:632-636)

KEY WORDS —— Malignant airway stenosis, Spiral Z stent

はじめに

近年肺癌の罹患率は急速に増加しており，そのいずれかの時点で気道狭窄を生じることはしばしば経験される．また，食道癌などの他臓器癌においても気道狭窄を来すことが多い．これら気道狭窄は，著明な呼吸困難を生じQuality of Life（QOL）の低下をもたらす．

最近のビデオ装置の進歩と主に，硬性気管支鏡や軟性気管支鏡の技術が向上してきた．これらを用いて，QOLの改善を目指した様々なステント治療が行われるように

[1]大阪市立総合医療センター呼吸器外科；[2]広島市民病院呼吸器科；[3]日本大学練馬光が丘病院呼吸器科；[4]千葉大学医学部附属病院呼吸器内科；[5]東京医科大学外科第1講座；[6]公立昭和病院呼吸器科；[7]東京医科大学霞ヶ浦病院呼吸器科；[8]京都桂病院呼吸器センター；[9]山口県立中央病院呼吸器科．

著者連絡先：多田弘人，大阪市立総合医療センター呼吸器外科，〒534-0021　大阪市都島区都島本通2-13-22.

[1]Department of Chest Surgery, Osaka City General Hospital, Japan; [2]Department of Respirology, Hiroshima City Hospital, Japan; [3]Department of Internal Medicine, Nihon University Nerima Hikarigaoka Hospital, Japan; [4]Department of Respirology, Chiba University Hospital, Japan; [5]First Department of Surgery, Tokyo Medical University, Japan; [6]Department of Respirology, Showa General Hospital, Japan; [7]Department of Chest Surgery, Tokyo Medical University Kasumigaura Hospital, Japan; [8]Respiratory Division, Kyoto Katsura Hospital, Japan; [9]Department of Respirology, Yamaguchi Prefectural Central Hospital, Japan.

Corresponding author: Hirohito Tada, Department of Chest Surgery, Osaka City General Hospital, 2-13-22 Miyakozimahondori, Miyakozima-ku, Osaka, 534-0021, Japan.

Table 1. Demographics

Age	mean 64 y.o. (42-88 y.o.)
Gender	male : female 29 : 12
Original disease	
lung cancer: 32 (adenocarcinoma: 15, squamous cell carcinoma: 13, small cell carcinma: 3, unclasified: 1)	
esophageal cancer: 5	
others: breast cancer: 1, thyroid cancer: 1, thymoma: 1, gastric cancer: 1	
Previous therapy (treated: 28 *, none: 13)	
chemotherapy	5
radiation therapy	3
chemo-radiation	10
other stent insertion	3
laser/elctrocautery	2
Toal 41 cases (60 stents were inserted)	

* There are some overlaps in the number of cases.

なってきた.

従来は, Dumon stent[1] に代表されるシリコンステントや Ultraflex stent[2] によるステント留置が本邦において中心的位置を占めてきた. しかし, シリコンステントでは硬性気管支鏡を必要とすることから全身麻酔を余儀なくされる. 一方, Ultraflex stent は軟性気管支鏡で挿入できることから, 患者に対する負担は少ないものの, 保険行政的立場から定価の約 1/3 の価格しか材料費を請求できないため各病院における使用には病院サイドからの大きな抵抗があった. 一方, Gianturco Z stent[3] は製品自体がいくつかの問題点を含んでいたため価格的には問題はなかったが, 汎用されることはなかった. 近年スパイラルZステントが上梓され, Gianturco Z stent から多くの点で改善が行われたが, このステントの有用性, 安全性に関しては何ら報告がなされておらず, 気道狭窄に対する治療成績についての調査が必要であると考えられていた. 今回, 日本においてステント治療を多く行っている施設を中心にスパイラルZステントの特別調査が行われたのでその結果を報告する.

目 的

悪性気道狭窄に対する気管用スパイラルZステントの安全性, 有用性を多施設共同で prospective に検討する.

対象ならびに方法

悪性気道狭窄 (狭窄度 50% 以上) により呼吸困難を有する症例を対象とした. ただし, 瘻孔, 食道ステント挿入例は除外するものとした. 肺機能検査, 動脈血ガス分析, 内視鏡による狭窄度判定, WHO dyspnea index, ECOG performance status, 生存予後について調査することとした. 症例集積期間は 2001 年～2002 年で, 参加施設はステント治療を積極的に行っている全国 9 施設である. 目標症例数は 30 例とした. 治療前および治療後 1, 2 週目, その後は 1 ヶ月毎に, 気管支鏡による観察による狭窄度の判定, WHO dyspnea index, ECOG の Performance status, 呼吸機能, 動脈血ガス分析を可能な限り行うこととした. また, 総合判定として, 拡張力, 柔軟性, 留置位置の正確性, 有用性, 安全性について判定した.

結 果

千葉大学医学部付属病院呼吸器内科, 東京医科大学付属病院外科学第一講座, 東京医科大学霞ヶ浦病院呼吸器科, 日本大学医学部付属病院練馬光が丘病院呼吸器科, 公立昭和病院呼吸器科, 京都桂病院呼吸器センター, 大阪市立総合医療センター呼吸器外科, 社会保険広島市民病院呼吸器科, 山口県立中央病院呼吸器科, が本試験に参加した. 同期間中に予定を上回る 41 例が登録され, 計 60 本のスパイラルZステントが挿入された. 症例の内訳は, 平均年齢 64 歳で, 男女比は 29：12 例であった. 肺癌 32 例, 食道癌 5 例, その他 4 例であった. 前治療は, 化学療法のみ 5 例, 放射線療法のみ 3 例, 放射線化学療法が行われていたもの 10 例であった. その他に他のステントがすでに留置されていたもの 3 例, レーザーや高周波凝固が各 1 例に施行されていた (Table 1).

狭窄の様式は内腔への浸潤性狭窄と外圧性の混合型が最も多く 18 例に, 浸潤性 8 例, 外圧性 10 例, 肉芽性 1 例, ポリープ性 3 例であった (Table 2).

ステントの挿入時は, 16 例が全身麻酔科に 25 例が局所麻酔下にステントが留置され, 12 例が硬性気管支鏡下に 29 例が軟性気管支鏡下に留置された. ステント挿入時の前処置としてはバルーン拡張が 9 例に, レーザー/高周

Table 2. Mode of stenosis

		n = 41
1	Mixed stenosis	18
2	Infiltrative stenosis	8
3	Extraluminar stenosis	10
4	Granulation stenosis	1
5	Polypoid stenosis	3

Table 3. Anesthesia and the dilation method before insertion

Genaral anesthesia	16
Local anesthesia	25
Balloon dilatation	9
Laser/electrocautery	5
Debulking with rigid scope	1
Without dialtion	26

Table 4. Mode and size of spiral Z stent (single stent insertion: 26, more than 2 stents insertion: 15) and site of placement

Straight type (diameter × length)	
10 mm × 50 mm	1
12 mm × 30 mm	11
12 mm × 50 mm	7
15 mm × 40 mm	6
15 mm × 60 mm	3
18 mm × 80 mm	3
20 mm × 80 mm	3
Taper type (diameter × length)	
10/8 mm × 30 mm	3
12/10 mm × 40 mm	6
14/12 mm × 40 mm	7
16/12 mm × 60 mm	3
18/12 mm × 100 mm	4
20/14 mm × 100 mm	2
Site of placement	
trachea	8
trachea-main bronchus	13 (rt: 6, lt: 7)
trachea-intermedius	3
main bronchus	8 (rt: 2, lt: 6)
main bronchus-intermedius	12
intermedius	6
right lower lobe bronchus	1

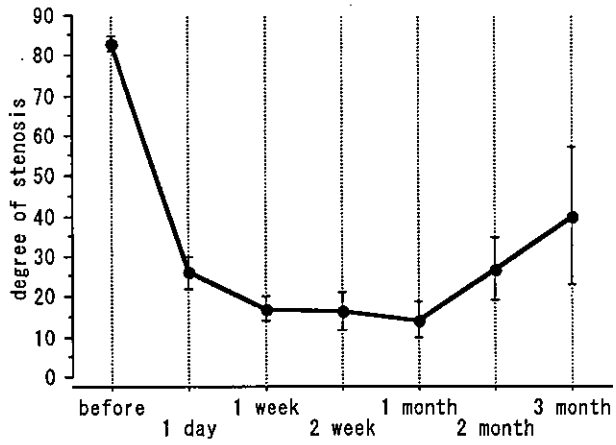

Figure 1. The changes in degree of airway stenosis.

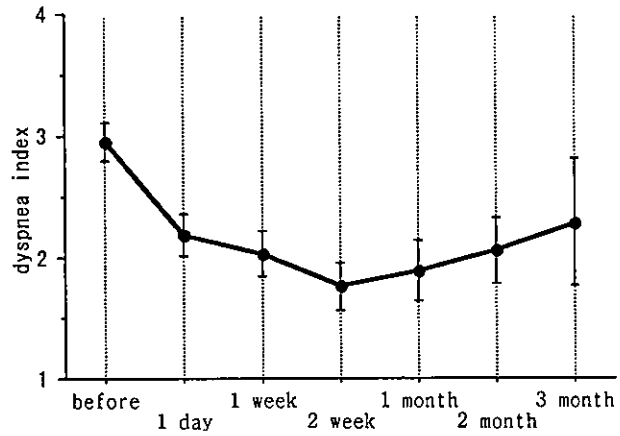

Figure 2. The changes in WHO dyspnea index.

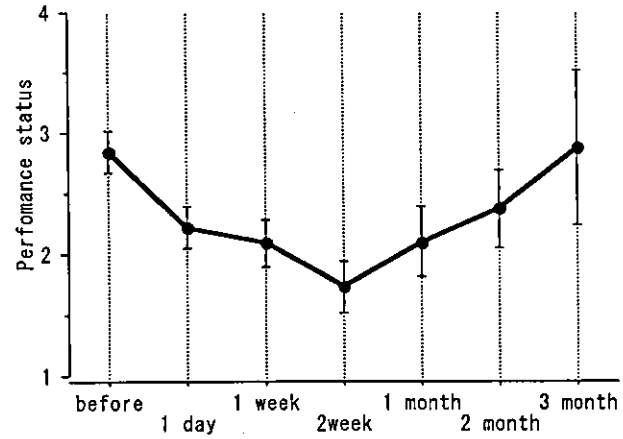

Figure 3. The changes in ECOG performance status.

波による開大が5例に，硬性鏡による debulking が1例に行われたが，その他は無処置のままスパイラルZステントが挿入された（Table 3）．

使用されたスパイラルZステントは，ストレート型のものが34本，テーパー型のものが25本用いられた．挿入部位は気管分岐部をまたがって挿入されたものが最も多く21本，主気管支から中間気管支にわたるものも12

Table 5. Complication

Stent fracture	2 (immediately, immediately)
Stent migration	2 (immediately, after 6 months)
Hemoptysis	1 (after 1.5 months)
Pneumothorax	1 (immediately)
Pneumomediastinum	1 (immediately)
Fever	1 (immediately)
Pain	1 (after 5 days)

本あった．気管のみ，主気管支のみ，中間気管支幹，下葉気管支にそれぞれ8，8，6，1本挿入された(Table 4)．

気道狭窄程度は，全狭窄を100%とし，狭窄ないものを0%と表現すると，留置前はすべての症例で81～90%の狭窄範囲であった．ステント留置直後から1週間では狭窄度は11～20%と改善し，その効果は3ヶ月以上有意に改善していた(Figure 1)．WHOのdyspnea indexの中央値はIII度からII度へと改善した(留置前と比較して2ヶ月目まで有意に改善，Figure 2)．Performance statusは，留置前と比較して1ヶ月目まで有意に改善していた(Figure 3)．

合併症はTable 5にまとめた．ステント破損とステントの位置移動が各々2例にみられた．ステント破損の2例はステントをラムダ型に挿入した症例であり，ラムダ型に挿入する際にステントの目のあいだからステントを挿入する操作の間に損傷したものである．その他に，周辺組織の損傷，気胸，縦隔気腫，発熱がそれぞれ1例みられた．気胸はガイドワイヤーの挿入に起因している．8例に再狭窄を認めたが，閉塞までの気管の中央値は70日(50～140日)と良好であった．予後は，悪性疾患の終末期である症例が多いために，多くは2～3ヶ月で死亡しており MST は3.2ヶ月であった (Figure 4)．

総合判定は40例について判定された．拡張力は強い・良い・弱いとの回答は3, 30, 8例，柔軟性は良い・普通・悪いとの回答は24，16，0例，留置位置の正確性については28，12，1例と回答された．安全性については，非常に安全・安全・安全でないと回答されたものは22，14，4例であり，90%の症例で安全であったと判定された．有用性については，非常に有用・有用・有用でないとの回答は各々20, 17, 3例であり，92.5%が有用であったと判定された．

考　察

近年，多種のステントが開発され使用されている．現在我が国で使用可能なステントは，Dumon stent，Dynamic stent,[4] Ultraflex stent，と spiral Z stent である．

Z stentは，当初いくつかの施設で使用されたが，それらの殆どは自作のステントであった．その後Cook社から気管用Gianturco Z stentが発売されたが内径が35 mmのものまで存在し，migration予防のためフックがついていた．このZ stentを用いたところ，穿孔する症例があったり，ステントの破損がみられたと報告され汎用されることはなかった.[5,6]

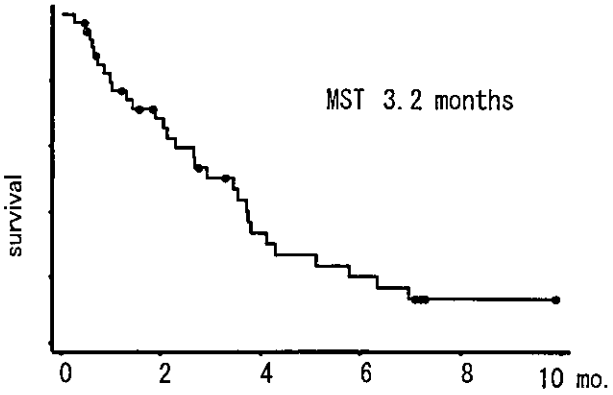

Figure 4. Survival after stent insertion.

Ultrtraflex stentは挿入が簡便である事と，編み目が小さいため気管支壁に対する柔軟性が良好であり，有効なステントであると考えらている.[7,8] しかし，その価格が保険によるカバーを大きく上まわるために，使用に制限がかかっている．シリコンとメタルの合成であるDynamic stentも同様に価格が非常に高く，使用するにはハードルが高い．結果的に，市販のシリコンステントであるDumon stentが多く用いられるようになった．シリコンステントは挿入のためには技術が必要であるため，多くの施設で簡便に用いられる事はなかった．

今回開発されたスパイラルZステントは，従来のCook社のステントについていたフックをなくしたこと，溶接部分をなくして長期しようにおける金属疲労による破損を少なくしたこと，スパイラルにすることでzigzag部分のつなぎ目をなくしたこと，当初作成された径3 cmに及ぶような過大な径のステントを作らなくしたこと，テーパー型のステントを追加したこと，等の工夫をして作成されたものである．腫瘍は気管・気管支の中で一部分のみに限定された狭窄様式を示すのではなく，末梢に行くにつれて，徐々に径が縮小してゆく中で腫瘍浸潤が成立する事が通常である．そのため，気管・気管支狭窄は，"気管だけ"，"主気管支だけ"といった狭窄を呈する事は比較的まれである．しかし，テーパー型のステントはシリコン性の場合にはmigrationを起こしてしまうので，migrationしにくいmetallic stentである事が必要となる．さらに，この報告でもみられるよう気管からか気管支にかけて，もしくは主気管支から中間気管支幹にわたるステント留置においては網の目の大きな

Zステントは，Ultraflexより適していると考えられる．

Metallic stentでは，挿入前の処置として狭窄部位の開大が必要であるとされているが，実際の臨床の場では必ずしも，前処置を行わずにステントが挿入されることが多い．今回の症例でも気道処置を行わないまま留置されている症例が多くみられるが，それによる不具合は報告されなかった．

結　論

スパイラルZステントは強い抗張力を有し，高度の気道狭窄や緊急例に対しても局所麻酔下に留置可能であり，90%以上の症例について安全且つ有用と判定された．

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Optimal Distance of Malignant Negative Margin in Excision of Nonsmall Cell Lung Cancer: A Multicenter Prospective Study

Noriyoshi Sawabata, MD, Mitsunori Ohta, MD, Akihide Matsumura, MD, Katsuhiro Nakagawa, MD, Hiroshi Hirano, MD, Hajime Maeda, MD, and Hikaru Matsuda, MD, PhD, for the Thoracic Surgery Study Group of Osaka University

Division of General Thoracic Surgery, Department of Surgery (E-1), Osaka University, Graduate School of Medicine; Division of Surgery, Suita, Japan; Toneyama National Hospital, Toyonaka, Osaka, Japan; Division of Surgery, National Kinki-Chuo Hospital for Chest Diseases, Sakai, Japan; Division of Surgery, Habikino Hospital, Habikino, Japan; and Department of Pathology, Hyogo College of Medicine, Nishinomiya, Japan

Background. Complete excision of nonsmall cell lung cancer is necessary during a limited resection procedure, as a malignant positive margin can lead to margin relapse. Because there is scant information available regarding the optimal size of a malignant negative margin, we conducted a multicenter, prospective study to more fully elucidate this area of concern.

Methods. Two hundred five pulmonary tumors (22 nonsmall cell lung cancers and 183 undiagnosed lesions) were excised, of which 118 nonsmall cell lung cancer lesions were analyzed. Malignant status was considered positive when either a cytologic or histologic technique revealed the margin to be malignant. Maximum tumor diameter (from 4 to 45 mm with an average of 15.3 mm), margin distance (from 0 to 25 mm with an average of 9.3 mm), tumor location, extent of stapling carried out, and performance of a thoracotomy were the variables.

Results. Seventy-two of the sample tissues (61%) were malignant negative. The negative group had smaller maximum tumor diameter, greater margin distance, lesions in more easily resectable regions, and more often required stapling only. Using a multivariate analysis, maximum tumor diameter and margin distance were found to be independent factors. The number of malignant negative margins was 7/7 (100%) when the margin distance was greater than 20 mm, and the number of malignant negative margins was 21 of 21 (100%) when the resected tumors had a margin distance greater than the maximum tumor diameter.

Conclusions. Malignant positive margins were not found when the margin distance was greater than the maximum tumor diameter, which was considered to be the optimal margin distance for prevention against margin relapse.

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A limited pulmonary resection for nonsmall cell lung cancer (NSCLC) has two indications: (1) an intentional limited resection and (2) a compromised limited resection. In the former, a segmentectomy is an option, which is generally carried out for small peripheral lesions (less than 2 cm maximum diameter) and has a similar survival rate as a lobectomy [1, 2]. A wedge resection can also be used for an intentional, limited resection and is usually carried out for lesions with a diminutive malignant potential (eg, bronchiolo-alveolar cell carcinoma) [3, 4]. As for a compromised limited resection, a wedge resection is one of the most common techniques to remove NSCLC tumors from high-risk patients [5–8].

An NSCLC lesion should be resected appropriately, as a malignant positive margin has the potential to cause surgical margin relapse [5–11]. It has been shown that cytologically malignant positive margins cause margin relapse in 40% to 60% of such cases, even if the resected malignant tumor has a negative histology margin [12–15].

A large amount of distance between the surgical margin and tumor can provide a malignant negative margin; however, it is sometimes very difficult to obtain, because the amount of lung tissue that is removable is limited. We conducted a multicenter, prospective study in order to determine the distance threshold for a malignant negative surgical margin for excision of NSCLC using both compromised patients and good-risk patients who underwent a completion lobectomy.

Material and Methods

Study Design

We recently developed a new technique (the run-across method) that is used to extract tissue samples from the whole of the surgical margin. An explanation of this technique and preliminary results were first published in 1999 [12]. In that study we found that approximately half of the surgical margins contained malignant cells, which

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Address reprint requests to Dr Sawabata, Division of Surgery, Toneyama National Hospital, 5-1-1 Toneyama, Toyonaka, Osaka 560-8552, Japan; e-mail: nsawabata@m5.dion.ne.jp.

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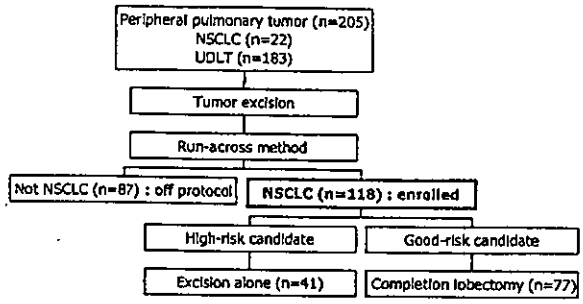

Fig 1. Flow chart of patients. (NSCLC = *nonsmall cell lung cancer;* UDLT = *undiagnosed lung tumor.*)

have a potential to cause relapse. Following that report, we established a protocol for our technique and carried out a multicenter study, which has been reviewed by a local institution review board. The protocol states that the selection criteria for a high-risk patient is clinical stage I, which is diagnosed using a chest computed tomographic scan, brain magnetic resonance image, an abdominal computed tomographic scan, and a bone scintigram. Furthermore, in good-risk patients with an undiagnosed pulmonary nodule, a completion lobectomy is performed when the lesion is a nonadvanced NSCLC. During the excision, the lung is deflated using a single lung ventilation technique in cases undergoing video-assisted thoracic surgery or a thoracotomy.

The end point of the present study was to determine the malignant status of each surgical margin, which was considered malignant positive when either a histologic or cytologic technique revealed a malignant positive status. A malignant negative conclusion required both the histologic and cytologic techniques to reveal malignant negative status. Maximum tumor diameter, margin-distance, tumor location, extent of stapling carried out, and performance of a thoracotomy (video-assisted thoracic surgery or other procedure) were used as variables.

Patient Backgrounds

This study was conducted from September 1999 to September 2002. The ratio of contribution by the individual institutions was 172 regions by Toneyama National Hospital, 29 regions by National Kinki-Chuo Hospital for Chest Diseases, two regions by Osaka University, Graduate School of Medicine, and two regions by Habikino Hospital, and a total of 202 patients with 205 lesions were enrolled after providing informed consent to the study protocol. A flow chart of the patients is shown in Figure 1. Of the 205 excised lesions, 22 (9%) were preoperatively diagnosed as NSCLC and 183 (91%) were preoperatively undiagnosed lung nodules. After surgery, 118 lesions from 115 patients were confirmed to be NSCLC, which were included in the present study. Three of these patients had 2 lesions, of whom 2 had synchronous lesions, and 1 had a metachronous lesion. Seventy-seven of the NSCLC patients underwent a residual lobectomy for a preoperatively undiagnosed lesion that was diagnosed as NSCLC during surgery, and 41 lesions in 38 patients were resected using an excision technique alone. The reasons for not performing completion lobectomy were cardiopulmonary impairment in 33 patients with 35 lesions and age (greater than 80 years old) in 5 patients with six lesions. Of those who had lesions with a malignant positive margin, 37 patients could not undergo further proximal resection because of an anatomical difficulty.

Surgery

All lesions were wedge-resected and three stapling methods were used. In the first method, the complete area of the surgical margin was stapled, which was classified as complete. In the second method, most of the surgical margin area was stapled and the remaining area was resected using a tool other than a stapler, which was classified as partial. In the third method, the whole area was resected using a tool other than a stapler, which was classified as not used. However, staplers were used predominantly, but only partially when the remaining proximal parenchyma of the lung was too thick to be stapled. A laser or an electrosurgical unit was used when a lesion was located deep inside the lung.

Tumor locations were divided into two regions according to the method of Lewis and colleagues [16]. Thus, lesions in the lingual, apex, and lung edge areas were defined as easily resectable, whereas those in the base of the lung, deep in a fissure, or on a large ovoid surface were defined as difficult to resect.

Cytopathological Diagnosis of the Surgical Margin

Cytologic examinations of the surgical margins were carried out using the run-across method and were undertaken before the cross-section was studied, in order to prevent malignant cell contamination by the tumor. To extract the specimen, a glass slide was run across the whole of the stapled area at least three times until a sufficient amount of material was collected. The extracted sample was spread onto another glass slide and immediately fixed with ethanol spray. After the materials for cytologic examination were extracted, the wedge-resected specimen was cut and examined grossly. The distance from the tumor to the margin was measured using a cross-section of the lesion without removing the staples, which provided the maximum diameter of the tumor. The materials from the margin were stained with half-time Papanicolaou stain before being examined. A positive result was defined as at least three malignant cells or clustered malignant cells being observable on the glass slide. Afterward, the specimen was examined by pathologic means. Staples, if any, were removed for pathologic examination.

Statistical Analysis

Statistical analyses were performed using a commercially available software package (Stat View 5.0 [Abacus Computer, Berkeley, CA]). Maximum tumor diameter, margin distance, tumor location, extent of stapling carried out, and performance of a thoracotomy were used as vari-

Table 1. Characteristics of Excised Pulmonary Malignant Tumors

Variables	
No. of lesions	118
No. of patients	115
Maximum diameter (mm)	
(Minimum, Maximum, Average ± Standard deviation)	(5, 45, 15.3 ± 7.0)
0<, < or = 10	32
10<, < or = 20	68
20<, < or = 30	14
30<	4
Margin distance[a] (mm)	
(Minimum, Maximum, Average)	(0, 25, 9.2 ± 5.6)
0<, < or = 10	51
10<, < or = 20	60
20<, < or = 30	7
Location	
Difficult to resect region	29
Easily resectable region	89
Stapler	
Complete	85
Partial	18
Not used	15
Approach	
Open	72
Video-assisted thoracic surgery	46

[a] Margin distance is the distance from the margin to the tumor.

ables. To compare maximum tumor diameter and margin distance in the malignant positive and malignant negative groups, a *t* test was used. To compare the prevalence of tumor location, the extent of stapling carried out, and the performance of a thoracotomy, a χ^2 test and Fischer's exact test were used as appropriate. Univariate logistic regression analyses were carried out using all five variables. A multivariate logistic regression analysis was carried out using variables from the univariate analysis results that were statistically significant. Significance was considered when a p value was less than 0.05.

Results

Characteristics of Pulmonary Malignant Tumors that Underwent Excision

Prevalence rates for the five variables are shown in Table 1. The NSCLC subtype was adenocarcinoma in 104 lesions, squamous cell carcinoma in 12 lesions, and large cell carcinoma in two lesions. Prevalence rates of the histologic and cytologic diagnoses are shown in Table 2. Eighty-four of 118 surgical margins (71%) had matching histologic and cytologic diagnoses. At the time this article was written, there were 6 cases of margin relapse, 2 of which were both histologically and cytologically malignant positive, and 4 that were cytologically malignant positive only.

Table 2. Comparison of Prevalence Between Histology and Cytology Results

	Histology		
Cytology	Malignant Positive	Malignant Negative	Total
Malignant positive	12	28	40
Malignant negative	6	72	80
Total	18	100	118

Histological diagnosis: sensitivity (TP/[TP + FN]) = 0.45, specificity (TN/[TN + FP]) = 1.0. Accuracy ([TP + TN]/total number) = 0.76, negative predictive value (TN/[TN + FN]) = 0.72, positive predictive value (TP/[TP + FP]) = 1.0. Cytological diagnosis: sensitivity = 0.7, specificity = 1.0, accuracy = 0.95, negative predictive value = 0.92, positive predictive value = 1.0.

TP = true positive; FN = false negative; TN = true negative; FP = false positive.

Comparisons of Variables Between Negative and Positive Groups

Statistically significant differences were observed between the negative and positive groups for maximum tumor diameter, margin distance, tumor location, and extent of stapling, but not for performance of a thoracotomy (Table 3).

Logistic Regression Analyses

In univariate analyses, maximum tumor diameter, margin distance, tumor location, and extent of stapling were statistically significant among the five variables (Table 4). A multivariate analysis was then carried out using these four variables, and only maximum tumor diameter and margin distance were found to be independent factors (Table 5).

Table 3. Comparison Between Malignant Positive and Malignant Negative Groups

	Margin Diagnosis		
Variables	Malignant Negative (n = 72)	Malignant Positive (n = 46)	*p* Value
Maximum diameter (mm) (mean ± SD)	14.2 ± 7.1	17.1 ± 6.6	0.02
Margin distance (mm) (mean ± SD)	11.0 ± 5.3	6.5±5.1	< 0.0001
Location			
Difficult to resect region	8	21	< 0.0001
Easily resectable region	64	25	
Stapler			
Complete	61	24	0.001
Partial	9	9	
Not used	2	13	
Approach			
Open	39	33	0.08
Video-assisted thoracic surgery	33	13	