A Clinicopathological Study of Resected Adenocarcinoma 2 cm or Less in Diameter

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Background. The biological behavior of small adenocarcinoma is different in each patient and these are especially enormous differences when evaluating solid tumors and nonsolid tumors.

Methods. A total of 159 adenocarcinomas 2 cm or less in diameter were studied. Several clinicopathological factors were retrospectively analyzed.

Results. The diameter of the primary tumors was less than 1 cm in 47 patients, 1–1.5 cm in 49 patients, and 1.5–2 cm in 63 patients, respectively. Almost all patients (147) were pathologic N0 and there were 12 node-positive patients (7.5%). Lymph-node involvement was observed in 1 patient with a tumor diameter measuring less than 1 cm and in 11 patients with a tumor diameter measuring 1–2 cm. According to Noguchi' s classification, 33 patients belonged to class A or B, 71 patients belonged to class C, and 55 patients belonged to class D, E, or F. The ratio of ground-glass opacity (GGO) area in the main tumor in high resolution computed tomography was classified into two groups with a threshold of 50%. There were 44 patients with a GGO ratio of equal to or greater than 50%, none of which indicated lymph-node metastasis or tumor recurrence during follow-up (5-year survival = 100%). On the contrary among 115 patients with a GGO ratio less than 50%, lymph-node involvement was indicated in 12 patients (10.4%) and the 5-year survival rate was 83.9%.

Conclusions. The biological malignancy of small adenocarcinomas might be accurately evaluated by the proportion of GGO area as well as the Noguchi classification.

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Lung cancer is the greatest cause of cancer-related death in the world because most lung cancers are detected at a late stage and curative treatment is not an option. Nevertheless a cure rate of greater than 70% was obtained in completely resected patients of stage I cancer [1]. Prevention and early detection are thus essential with regard to the reduction of lung cancer mortality. Adenocarcinoma is the most common type of lung cancer arising from the peripheral lung parenchyma. Chest x-ray surveys have been considered useful for early detection. However if the lesions are located in a "dead angle" on the chest roentgenogram film, such as behind the aorta or heart, abnormalities may be overlooked. Bronchioloalveolar carcinoma (BAC) seldom reveals abnormalities on chest roentgenogram because it grows without destroying alveolar structure [2]. Helical computed tomography (CT) screening has greatly increased the sensitivity of cancer detection compared with that of conventional chest roentgenogram screening [3–7]. A prospective randomized trial comparing the lung cancer mortality rate of a CT screening group with that of a conventional chest roentgenogram screening group has been conducted by the National Cancer Institute [8]. In this respect, the biggest issue facing thoracic surgeons is the treatment strategy for small cancers detected by CT screening, including the possibility of limited resection. BAC is known to exhibit a relatively nonaggressive nature, therefore a favorable outcome can be expected after curative operation [2, 9–12]. However patients with solid images on chest CT tend to have invasive adenocarcinomas and their survival is definitely worse than that of BAC [9–11]. Pathologic classification of the tumor is essential regarding the evaluation of the aggressiveness of each patient [2] but postoperative pathologic findings cannot exhibit a strong impact on the choice of treatment.

There are several reports indicating that the ratio of the size of ground-glass opacity (GGO) and that of consolidation on high resolution CT (HRCT) is strongly related to the stage and prognosis of the cancer [10, 13–15]. Lung cancers with a large GGO component tend to be BAC or minimally invasive adenocarcinomas that exhibit favorable prognoses [10, 13–15]. If a definition of peripheral early cancer could be established, it would be useful with regard to selecting optimal treatment for individual patients. For this purpose we retrospectively analyzed clinicopathological features of adenocarcinomas with a diameter of 2 cm or less resected in our hospital between 1997–2002.

Patients and Methods

Patients

A total of 983 lung cancer operations were performed from January 1997 to December 2002 at the Department

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Table 1. Patient Characteristics

Character	
Age	
Average	63
Minimum	40
Maximum	84
Sex	
Male	67
Female	92
Smoking habit	
Non-smoker	89
Smoker	70
Operative procedure	
Lobectomy	112
Segmantectomy	20
Wedge resection	27

of Thoracic Surgery, Tokyo Medical University Hospital (Tokyo, Japan). Among these, there were 168 patients with peripheral adenocarcinomas less than 2 cm in diameter as well as a total of 159 patients who had undergone high-resolution computed tomography (HRCT) and in whom complete records were available for study (Table 1). There were 67 men and 92 women ranging in age from 40–84. There were 89 nonsmokers and 70 smokers. The primary lesions were detected by chest x-ray in 115 patients: detection was determined by mass survey or private general check-up in 81 patients, follow-up for other diseases in 18 patients, and respiratory symptoms in 16 patients. The other 44 patient's lesions were detected by chest CT performed by mass survey program or private general check-up.

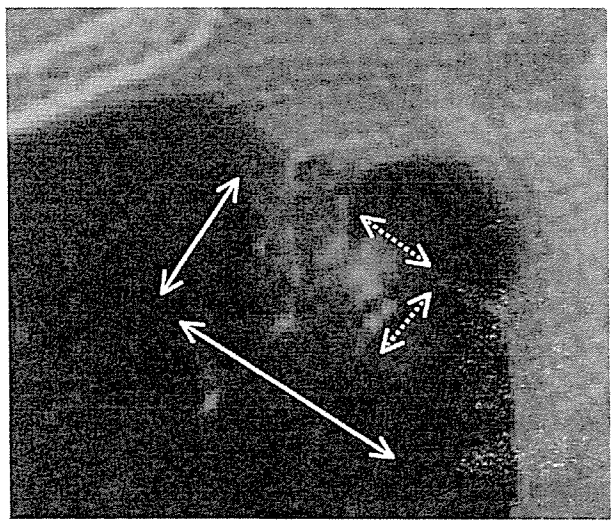

Fig 1. Thin section computed tomographic scan of lung cancer depicting solid attenuation and ground-glass opacity (GGO). The largest area of tumor (solid line) *and solid attenuation* (dotted line) *were decided based on this film. The proportion of GGO area to the entire tumor was defined; GGO ratio = (maximum GGO − maximum consolidation)/maximum GGO. Max GGO* (solid arrow)*; Max consolidation* (dotted arrow).

All patients underwent a physical examination and blood examination, respiratory function test, electrocardiogram, and chest radiography. Also, all patients received helical CT of the chest preoperatively with 10-mm thick continuous sections. HRCT images with 1–2 mm slices of the primary tumors were then performed to obtain the precise findings of GGO and consolidation of the tumors. Histologic typing was diagnosed based upon the classification of the World Health Organization (WHO) and we also classified all of the patients into six subtypes using the Noguchi classification. The staging of patients was determined by the thoracic wall, node involvement, and metastases (TNM) classification of the International Union Against Cancer (UICC).

Lobectomy combined with systemic mediastinal lymph-node dissection was performed in 112 patients and limited surgery was performed in 47 patients. Of these 47 patients, 37 received intentionally limited operation because of the nonaggressive appearance on HRCT and the remaining 10 patients because of impaired condition. Segmentectomy with mediastinal sampling was performed in 27 patients and wedge resection without nodal dissection was performed in 20 patients. All patients that underwent wedge resection indicated pure GGO or enormously GGO-dominant findings on HRCT as well as being clinically node negative.

CT Findings

In this study the ratio of the size of solid attenuation to that of GGO was extensively analyzed. GGO was defined as a hazy increase in lung attenuation without obscuration of the underlying vascular marking. At least two experienced chest surgeons and radiologists reviewed the hard-copy films of HRCT and determined the maximal area of GGO and tumor. Discrepancies between reviewers were resolved by consensus. The ratio area of GGO to the area of primary tumor was calculated as illustrated in Figure 1. Patients were divided into two groups: those with a GGO ratio greater than 50% and those with a GGO ratio less than 50%.

Pathology

Resected lungs were fixed in formalin and stained by hematoxylin and eosin staining in a routine manner and also stained with elastica van Gieson. Experienced pathologists diagnosed the subtypes of primary tumors according to the Noguchi classification as well as the nodal status. The Noguchi classification is presented in Table 2. Types A and B are considered to be noninvasive cancers and types D, E, and F are considered to be invasive cancer.

Statistics

We examined the relation of the proportion of GGO area to maximal tumor size, stage, Noguchi classification, and other prognostic factors. The χ^2 test using StatView 5.0 (SAS Institute Inc., Cary, NC) was performed and the differences were considered to be statistically significant

Table 2. Tumor Size and Nodal Status

Tumor Size	N0	N1	N2
1.0 cm or less (n = 47)	46	0	1
1.0–1.5 cm (n = 49)	46	1	2
1.5–2.0 cm (n = 63)	55	2	6

when the p value was less than 0.05. All patients were periodically examined and the average length of follow-up was 40 months. The 5-year survival curve was obtained using the Kaplan–Meier method.

Results

A total of 159 patients were studied. The size was classified into three categories: 1 cm or less, 1–1.5 cm, and 1.5–2 cm. There were 47, 49, and 63 patients, respectively. There were 147 pathologic N0 patients and lymph-node metastasis was recognized in 12 patients (7.5%); N1 in 3 patients and N2 in 9 patients. Table 3 lists the rate of lymph-node involvement according to tumor size. Lymph-node involvement was not indicated in 98% of patients who had a tumor size of 1 cm or less, however even in patients with tiny tumors, 2% indicated N2 disease. In patients who had a tumor size of 1 and 1.5 cm, 94% indicated no metastasis but 6% were either N1 or N2. In patients who had a tumor size of 1.5 and 2 cm, lymph-node involvement was recognized in 13%.

In this study the proportion of the size of GGO to that of the tumor was extensively analyzed. We divided patients into two categories according to how much of the lesion consisted of GGO findings. According to these criteria, 44 tumors consisted of greater than 50% of GGO and 115 tumors consisted of less than 50% of GGO. Patients with a GGO ratio of greater than 50% indicated no lymph-node metastases. On the contrary all node-positive patients indicated a GGO ratio of less than 50% (Table 3). The relationship between the proportion of GGO area on HRCT and the Noguchi classification is indicated in Table 4.

Twenty-five out of 44 patients (76%) of types A and B indicated a GGO component of greater than 50% on HRCT. Seventeen out of 71 patients (24%) of type C indicated greater than 50% GGO and the remaining 54 patients (76%) indicated less than 50% GGO. Fifty three out of 55 patients (96%) of types D, E, and F tumors indicated less than 50% GGO. A favorable correlation between CT findings and the Noguchi classification was recognized.

Table 3. GGO Area and T,N Status

GGO%	$T \leqq 1$	$1 < T \leqq 5$	$1.5 < T \leqq 2$	
50 ↑	18	16	10	44
50 ↓	29 (1)[a]	33 (3)[a]	53 (8)[a]	115 (12)[a]

[a] The number in parentheses corresponds to the number of node-positive cases.

GGO = ground-glass opacity.

Table 4. GGO Area and Noguchi Classification

GGO%	A, B	C	D, E, F	
50 ↑	25	17	2	44
50 ↓	8	54	53	115

GGO = ground-glass opacity.

The relationship between representative clinicopathological factors and the proportion of GGO area is indicated in Table 5. According to the χ^2 test, the ratio of GGO area to that of the tumor is related to the tumor size ($p = 0.0135$) and pathologic stage ($p = 0.04$). In particular a significant relationship was obtained regarding the pathologic features including Noguchi classification ($p = 0.0001$), vascular invasion, and lymphatic invasion .

Patients were followed-up in the outpatient clinic and periodically received blood examinations, chest roentgenogram, and chest CT. The median follow-up period for all patients was 40 months. The overall 5-year survival rate of patients studied was 88.0% (Fig 2), but it was 96.7% in patients with tumors less than 1 cm in diameter, 81.6% in patients with tumors between 1 and 1.5 cm, and 84.4% in patients with tumors between 1.5 and 2 cm (Fig 3).

The 5-year survival rate according to how much of the lesion consisted of GGO findings was also analyzed. In patients with tumors greater than 50% GGO, a 100% 5-year survival rate was obtained, but in patients with tumors less than 50% GGO an 83.9% 5-year survival rate was obtained (Fig 4)

The survival rate according to the Noguchi classification is illustrated in Figure 5. A 100% 5-year survival rate was obtained in types A and B, 97.4% in type C, and 67.1% in types D, E, and F, respectively, which was statistically lower than the results of types A, B, and C.

Comment

Because of the increasing widespread application of helical CT, the detected number of small lung peripheral nodules has enormously increased [3–7]. In addition the size of peripheral type adenocarcinomas has been smaller on average when they were detected. This has raised several issues: discerning how to discriminate

Table 5. Relationship Between Prognostic Factors and GGO Ratio on HRCT

Prognostic Factor	χ^2	p Value
Gender	0.162	0.687
Tumor size	8.616	0.0135
p stage		
I or II–IV	4.168	0.0412
Noguchi classification		
A, B, C or DEF	14.442	0.0001
Vascular invasion	6.76	0.0093
Lymphatic invasion	5.326	0.0206

GGO = ground-glass opacity; HRCT = high resolution computed tomography.

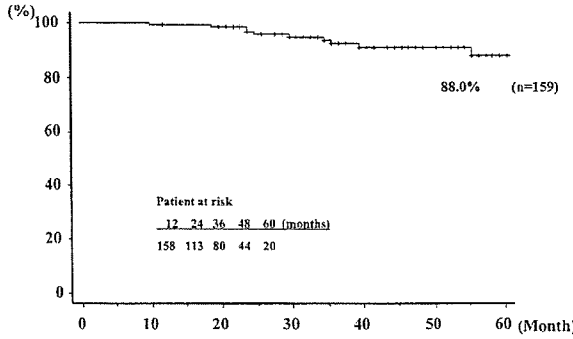

Fig 2. Five-year survival rate of adenocarcinoma less than or equal to 2 cm was 88.0%.

malignant from benign nodules, the usefulness of CT screening in diminishing lung cancer mortality, the optimal intervention in patients who have small nodules, and so on [16, 17]. The management of small cancers is a particular concern of thoracic surgeons, because some of these small cancers might be managed appropriately by limited resection. As previously reported adenocarcinoma tends to metastasize to the regional lymph nodes even if small in size. Nearly 20% of adenocarcinomas less than 2 cm in diameter were reported to be node positive and 5% of adenocarcinomas less than 1 cm were also considered as N1 or N2 disease [18–20]. The Lung Cancer Study Group failed to demonstrate positive results with regard to limited resection for clinical T1 lung cancers. The limited surgery group indicated a local recurrence rate of 5–6 times higher than the lobectomy group [21]. Thus lobectomy and locoregional lymph-node dissection have been recommended as standard lung cancer procedures. However if peripheral early cancer is properly defined, such patients could be managed by lesser resection, which would be useful with regard to decreasing the operative mortality and morbidity as well as enhancing the performance status of the patients.

In our study 12 out of 159 patients (7.5%) exhibited lymph-node metastasis and even tumors measuring 1 cm or less indicated lymph-node metastasis in 2% of patients. The 5-year survival rate did not indicate a statistically significant difference between the three groups

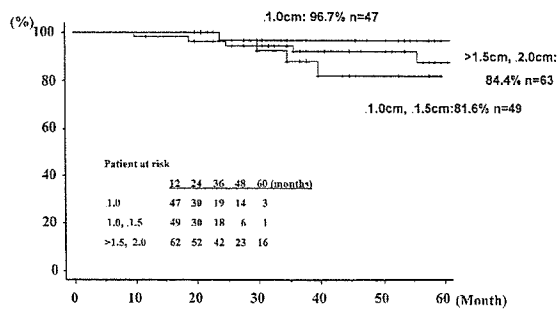

Fig 3. Five-year survival rate according to tumor size. Less than or equal to 1 cm = 96.7%, 1.0–1.5 cm = 81.6%, 1.5–2.0 cm = 84.4%.

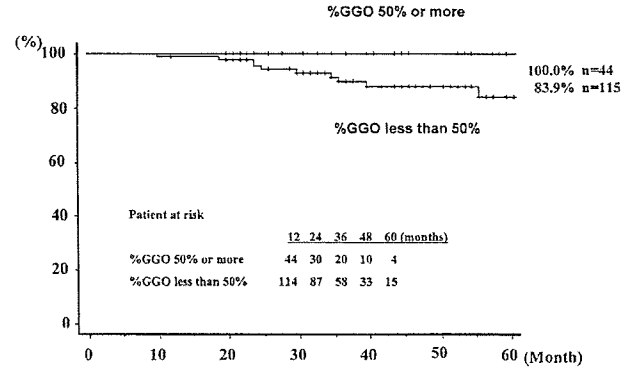

Fig 4. Five-year survival rate according to the proportion of ground-glass opacity (GGO) area. A GGO dominant patient indicated a 100% 5-year survival, whereas patients exhibiting a GGO area less than 50% indicated an 83.9% 5-year survival.

according to tumor size in this study. There are reports that 5%–8% of such tiny adenocarcinomas indicated lymph-node metastasis [18, 22]. Kondo reported 57 adenocarcinomas measuring 1 cm or less, none of which indicated lymph-node metastasis, and 49 revealed BAC without destructive growth that were categorized as nonaggressive tumors [23]. This demonstrates that the indications of limited surgery cannot be determined by size alone. In our study, 47 patients received limited resection. Out of these, mediastinal lymph node or sampling were performed in 20 patients and the rest of 27 patients received wedge resection without nodal dissection. Of these 27 patients stage migration may occur because nodal status was not evaluated pathologically. However these patients indicated pure GGO or overwhelmingly dominant GGO findings on chest CT as well as being clinically node negative. Such patients have been reported to be free from lymph-node metastasis [10, 12–15, 20] and recurrence was not observed in any of these patients by chest CT examination during follow-up.

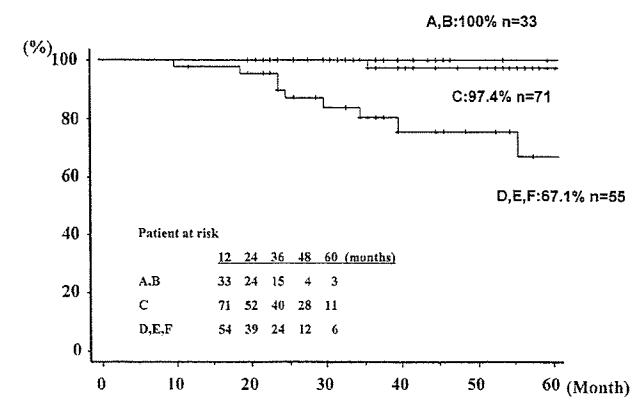

Fig 5. Five-year survival rate according to the Noguchi classification. Noguchi A, B indicated a 100% 5-year survival, type C indicated a 97.4% 5-year survival, and types D, E, and F, indicated a 67.1% 5-year survival, respectively.

Therefore we classified these patients as N0 in this study. Noguchi classified small adenocarcinomas into six categories (types A–F) and this classification indicated a favorable correlation with the biologically aggressive nature of the tumor [2]. Types A and B are localized BAC with or without foci indicating a collapse of alveolar structures that are recognized to be noninvasive. Types D, E, and F are poorly differentiated, tubular, papillary type, respectively, and are invasive. Pathologic analysis revealed that all type A and B patients were N0, however 25%–56% of type D, E, and F patients indicated lymph-node metastasis [2]. Many thoracic surgeons postulated that certain types of adenocarcinomas might be candidates for limited resection and have sought for criteria of "peripheral early cancer." The Noguchi classification is useful with regard to evaluating the aggressive nature in individual patients, but this criteria is based on postoperative pathologic findings and could not have a strong impact on the choice of treatment. Therefore we require criteria that are available preoperatively to define early minimally invasive cancers.

Increased amounts of collagenization or hyalinization microscopically detected in the central fibrotic focus in adenocarcinoma have been reported to influence the prognosis and the smaller the central fibrosis, the more favorable the prognosis [24, 25]. Suzuki reported that central fibrosis in a tumor corresponds to consolidation on HRCT. Thus the ratio of the area of GGO and that of consolidation seems to be strongly related to nodal status and stage [25].

In our study there were 12 N1 or N2 out of 159 patients, in all of whom the proportion of the area of GGO to the entire tumor was less than 50%. All patients with a ratio of GGO greater than 50% survived without recurrence during the follow-up period, although patients with GGO less than 50% indicated an 83.9% 5-year survival rate. The proportion of the GGO area correlates well with the Noguchi classification [26]. There were 33 Noguchi type A and B patients, 25 of which indicated a GGO area of greater than 50% and 8, of which indicated a GGO area of less than 50%. As for type D, E, and F patients, 53 out of 55 indicated a low GGO% and only 2 patients belonged to the high GGO ratio group. A statistically significant correlation was obtained between GGO% and Noguchi classification but types A and B could be completely diagnosed by HRCT findings as they should be the suitable indication of limited surgery. The 5-year survival rate of the high GGO group was 100% and the 5-year survival rate of the low GGO group was 83.9%. Similar results were obtained by Matsuguma who compared the preoperative HRCT findings with pathologic results in 96 patients who underwent surgical resection because of stage Ia cancers [14]. They determined that patients in whom the proportion of GGO to the whole tumor on CT was equal to or greater than 50% exhibited no nodal metastasis or postoperative recurrence. Small cancers with a high GGO ratio might be candidates for limited resection and a large multicenter study is necessary to confirm this postulate.

Limited resection has mostly been performed on patients with poor pulmonary reserve. Intentional limited surgery has not been common, particularly because lobectomy has been considered to be the standard treatment, which was confirmed by a randomized trial of the Lung Cancer Study Group [21]. However some successful results regarding limited surgery for T1 N0 tumors were published by Yamato who proposed limited resection for BAC by employing intraoperative pathological examination to confirm the absence of nodal metastasis [27]. They planned to convert limited resection to lobectomy if some invasive signs were recognized by frozen section. Tsubota performed extended segmentectomy for 55 patients with peripheral cancers measuring less than 2 cm in diameter and only 1 patient locally recurred in whom N2 disease was not indicated during operation [28]. Nakata performed thoracoscopic wedge resection for 33 pure GGO patients with tumors measuring less than 1 cm and no recurrence or metastasis was indicated during the follow-up period [12]. However well-differentiated adenocarcinomas or GGO-dominant tumors are considered to be indolent and slow-growing, therefore a long-term observation period is necessary to evaluate whether limited surgery could be an alternative to lobectomy.

In this study the ratio of GGO and consolidation on chest CT allows for the evaluation of the aggressive nature of small adenocarcinomas. However further investigation is required in this area, especially to characterize GGO on HRCT. Also genomic or proteomic studies are necessary to provide the clues to discriminate tumors with an indolent nature from those with an aggressive nature. Comprehensive research including pathology and molecular analysis will alter the conventional method of management regarding tiny cancers, which will be of great importance in daily practice.

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Outcome of Surgery for Small Cell Lung Cancer – Response to Induction Chemotherapy Predicts Survival

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Abstract

Background: The role of surgery for local control of small cell lung cancer (SCLC) is controversial. **Methods:** Sixty-nine consecutive patients who underwent complete resection of SCLC in our hospital were reviewed. The patients included 62 men and 7 women. Clinical stage at the time of diagnosis was c-stages IA and B in 29, c-stages IIA and B in 12, c-stage IIIA in 21, and c-stage IIIB in 7. **Results:** Thirty-two patients received induction chemotherapy, and 37 patients underwent initial surgery. The overall response rate to induction chemotherapy was 71.9%. The survival rate stratified by clinical stage at the time of diagnosis was 48.9% for c-stage I, 33.3% for c-stage II, 20.2% for c-stage IIIA, and 0% for c-stage IIIB. Downstaging after induction chemotherapy conferred a survival benefit. Survival after lobectomy or bilobectomy was better than after pneumonectomy. Patients who received adjuvant chemotherapy survived longer than patients who did not. **Conclusions:** Surgery combined with chemotherapy is a therapeutic option in selected patients with SCLC. Pathologic nodal status and response to induction chemotherapy are predictors of survival.

Key words
Chemotherapy · lung cancer · surgery · survival · small cell lung cancer

Introduction

Small cell lung cancer (SCLC) is considered a systemic disease, because the potential for hematogenous and lymphogenic metastases is high. At present, concurrent chemoradiotherapy for limited disease (LD) and chemotherapy for extensive disease (ED) are standard practice. About 30 years ago, a randomized study by the British Medical Research Council [1] concluded that radiotherapy alone for LD was superior to surgery. However, the local recurrence rate after radiation therapy alone subsequently was reported to be 18% to 69% [2]. The Veteran's Administration Surgery Oncology Group [3] reviewed data on 148 resected SCLCs to evaluate the role of adjuvant chemotherapy in non-small cell lung cancers (NSCLCs) and reported a 59.5% 5-year survival rate for stage IA disease. Since then, several series looking at the role of surgery for SCLC have been reported from different institutions. The University of Toronto Lung Oncology Group [4] treated 119 SCLCs with surgery and multi-modality therapy. The overall 5-year survival rate in that study was 39%, and the rates stratified by pathologic stage were 51% in stage I, 28% in stage II, and 19% in stage III. These survival rates were relatively good and represent an acceptable outcome.

To define the role of surgery for SCLC, the Lung Cancer Study Group [5] randomized cases of LD excluding stage I, to undergo resection or not after 5 cycles of chemotherapy with CAV (cyclophosphamide [CPA] + adriamycin [ADR] + vincristine [VCR]) followed by radiation. In that study, surgery did not improve survival.

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At present, the role of surgery combined with chemotherapy or radiotherapy for local control of SCLC is still controversial. Even when a radiographic complete response is obtained, up to 75% of patients have residual viable cancer cells in the surgical specimen [6]. Also, residual chemoresistant NSCLC coexist with SCLC in 10% to 25% of specimens resected after administration of chemotherapy [7]. Therefore we believe that complete resection of the primary tumor is indicated in some circumstances. In Germany, a phase II multicenter trial [8] to treat patients with advanced SCLC, stages IIB/IIIA, using combined modality therapy including surgery, proved effective in achieving local control and in increasing survival after complete resection. This is an encouraging outcome and validates the role of surgery for SCLC in combination with chemotherapy or radiotherapy. We retrospectively analyzed consecutive patients who underwent surgery for SCLC in our hospital to better define the role of surgery in this disease.

Patients and Methods

From January 1977 through December 2002, 79 patients underwent resection of an SCLC in our hospital. The 69 patients in whom complete resection was achieved were the subjects of this study. Table **1** shows the clinicopathologic characteristics of the study group. The patients included 62 men and 7 women, age range 39 to 79 years (mean, 62.2). Disease stage was determined based on the American Joint Committee on Cancer criteria [9]. Clinical stages at the time of diagnosis were c-stages IA and B in 29, c-stages IIA and B in 12, c-stage IIIA in 21, and c-stage IIIB in 7. Thirty-two patients received induction chemotherapy followed by surgery, and 37 patients underwent initial surgery. Forty-eight patients received adjuvant chemotherapy. In the induction chemotherapy group, 62.5% (20/32) patients had c-stage IIIA disease or higher stages. Conversely, only 22.6% (8/37) patients in the initial surgery group had c-stage IIIA disease or higher. Median follow-up of patients alive was 65 months.

The survival rate was calculated by the Kaplan-Meier method. Significance of the survival differences between groups was evaluated by the log rank test. A multivariate analysis was carried out according to the Cox proportional hazards model to identify independent risk factors. $p < 0.05$ was considered significant.

Results

Table **2** shows the therapy administered to the patients in this study. Most patients (59/69, 85.5%) received chemotherapy before and/or after surgery. We used CPA-based chemotherapy (CPA 800 mg/m^2 on day 1, ADR 50 mg/m^2 on day 1, and VCR 1.4 mg/m^2 on day 1) until the mid-1980s, and platinum-analog-based chemotherapy (cisplatin [CDDP] 80 mg/m^2 on day 1 and etoposide [VP-16] 100 mg/m^2 on day 1, 3 and 5, or carboplatin [CBDCA] 400 mg/m^2 and VP-16 100 mg/m^2 on day 1, 3 and 5) after the mid-1980s as the standard regimen. The numbers of cycles ranged from 1 to 6.

The overall radiographic response rate to induction chemotherapy was 71.9% (23/32): there was complete response in 4 (12.5%), partial response in 19 (59.4%), and stable disease in 9 (28.1%). Pathologic complete response was obtained in 3 cases (9.4%). The surgical specimens contained small cell carcinoma and another type of cancer, so-called combined small cell carcinoma [10], in 7.2% (5/69); combined small cell and adenocarcinomas were found in 3 and combined small cell and squamous cell carcinomas in 2 cases.

Table **1** Demographics and clinical characteristics of patients who underwent surgery for small cell lung cancer

	Total (n = 69)	*Induction chemotherapy (n = 32)*	*Initial surgery (n = 37)*
Gender			
Male	62	28	34
Female	7	4	3
Age			
Mean ± SD	62.2 ± 9.1	59.5 ± 7.8	64.5 ± 9.5
Clinical stage			
IA	15	1	14
IB	14	4	10
IIA	1	1	0
IIB	11	6	5
IIIA	21	15	6
IIIB	7	5	2
IV	0	0	0
Pathologic stage			
IA	21	9	12
IB	9	4	5
IIA	4	2	2
IIB	8	3	5
IIIA	16	9	7
IIIB	10	4	6
IV	1	1	0

Table **2** Combination chemotherapy regimens and surgery for small cell lung cancer

	Induction therapy (n = 32)		*Adjuvant therapy (n = 48)*[a]	
	Chemo.	*Chemo. + Rad.*	*Chemo.*	*Chemo. + Rad.*
CDDP or CBDCA based				
CDDP + VP-16	20	1	17	1
CBDCA + VP-16	3	1	13	0
CPA based				
CAV	5	2	11	6
Total	28	4	41	7

Chemo. = chemotherapy; Rad. = radiotherapy
CDDP = cisplatin; CBDCA = carboplatin; VP-16 = etoposide;
CPA = cyclophosphamide; CAV = CPA + ADR (adriamycin) + VCR (vincristine)
[a] Both induction and adjuvant therapy were performed in 21 patients.

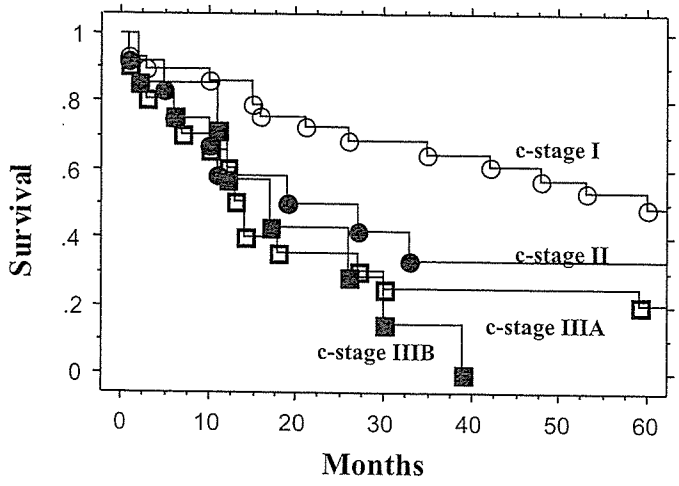

Fig. 1 Comparison of Kaplan-Meier survival curves of patients with small cell lung cancer stratified by clinical stage. The projected 5-year survival rates were 48.9% for c-stage I (n = 29, open circle), 33.3% for c-stage II (n = 12, closed circle), 20.2% for c-stage IIIA (n = 21, open square), and 0% for c-stage IIIB (n = 7, closed square). Survival difference between c-stage I and c-stage IIIA was significant ($p = 0.0349$).

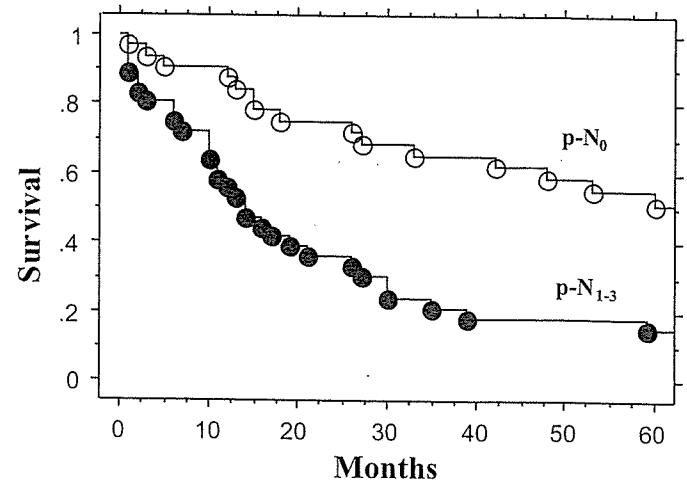

Fig. 2 Comparison of Kaplan-Meier survival curves of patients with small cell lung cancer with and without pathologically proven lymph node metastases. Survival of p-N0 patients (n = 36, open circle) was significantly better than node-positive (p-N1 – 3) patients (n = 33, closed circle; $p = 0.0001$).

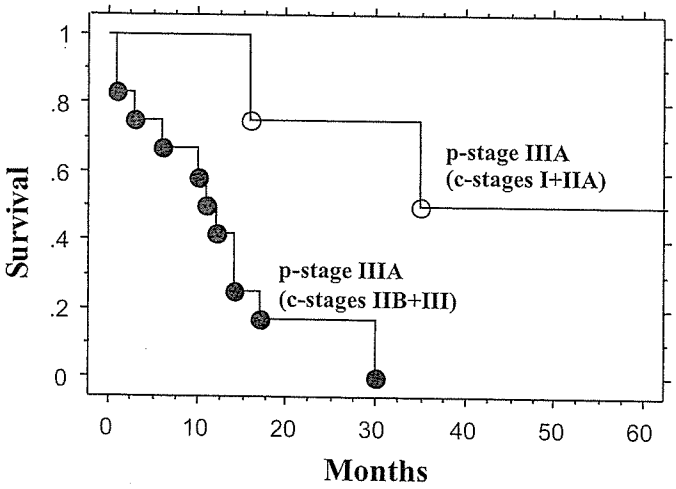

Fig. 3 Comparison of Kaplan-Meier survival curves of patients with p-stage IIIA small cell lung cancer stratified by clinical stage. Survival of patients whose stage was underestimated preoperatively (c-stage I and IIA, n = 5; open circle) was better than the rest of patients with p-stage IIIA disease (c-stage IIB or higher, n = 11; closed circle; $p = 0.0087$).

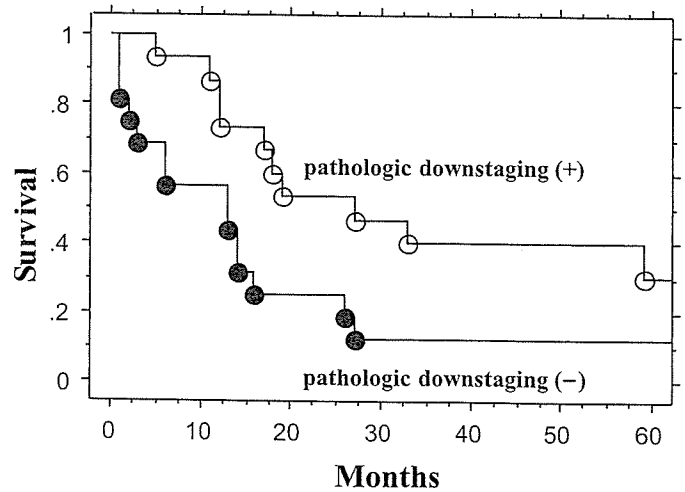

Fig. 4 Comparison of Kaplan-Meier survival curves of patients with small cell lung cancer who did and did not achieve pathologic downstaging with induction chemotherapy. Survival with downstaging (n = 16, open circle) was better than without it (n = 16, closed circle; $p = 0.0312$).

The surgical procedure was a lobectomy in 49 cases (71.0%), bilobectomy in 9 cases (13.0%), and pneumonectomy in 11 cases (15.9%). The overall 5-year survival rate was 32.2%. The 5-year survival rate stratified by clinical stage at the time of diagnosis was 48.9% in c-stage I, 33.3% in c-stage II, 20.2% in c-stage IIIA, and 0% in c-stage IIIB. Survival differences existed between c-stage I and c-stage IIIA, and between c-stage I and c-stage IIIB ($p = 0.0349$ and $p = 0.0018$, respectively; Fig. **1**). The overall 5-year survival rate was 49.5% in p-stage I, 40.0% in p-stage II, 12.5% in p-stage IIIA, 10.0% in p-stage IIIB, and 0% in p-stage IV. A survival difference existed between p-stage I and p-stage IIIA, and between p-stage I and p-stage IIIB ($p = 0.0004$ and $p = 0.0007$, respectively).

Survival of patients with postsurgical pathologic node-negative (p-N0) disease (n = 36) was significantly better than of patients with node-positive (p-N1 – 3) disease (n = 33, $p = 0.0001$; Fig. **2**). Also survival of patients with clinical node-negative (c-N0) disease (n = 32) was better than of patients with clinical node-positive (c-N1 – 3) disease (n = 37, $p = 0.0261$). Survival of patients with p-stage IIIA disease whose mediastinal lymph node metastases were underestimated preoperatively (c-stage I and IIA, n = 5) was better than that of the other patients with p-stage IIIA disease (c-stage IIB or higher, n = 11) ($p = 0.0087$) (Fig. **3**).

Pathologic downstaging occurred in 50% (16/32) of patients who underwent induction chemotherapy, and a survival benefit was observed in the downstaging group ($p = 0.0312$; Fig. **4**). Survival after lobectomy or bilobectomy (n = 58) was significantly better

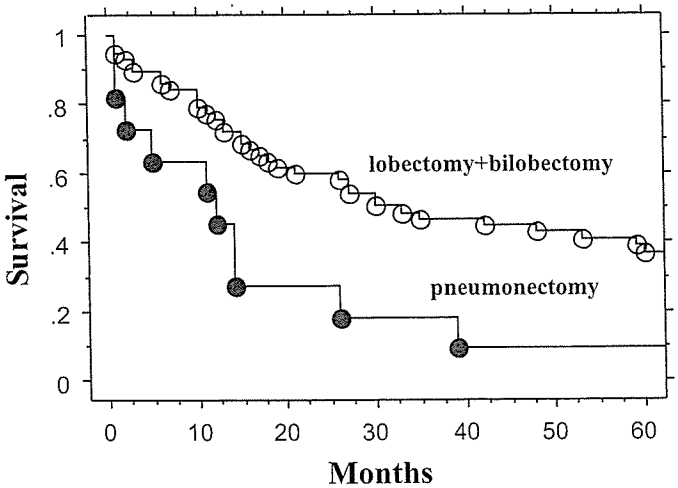

Fig. 5 Comparison of Kaplan-Meier survival curves of patients with small cell lung cancer stratified by the surgical procedure. Survival after lobectomy or bilobectomy (n = 58, open circle) was significantly better than after pneumonectomy (n = 11, closed circle; $p = 0.0163$).

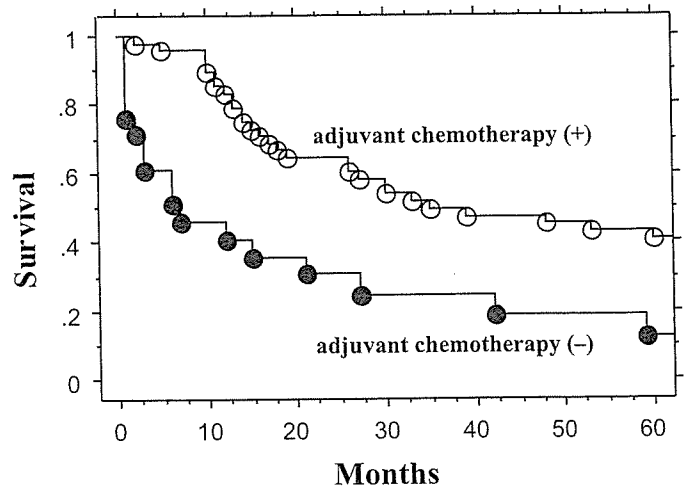

Fig. 6 Comparison of Kaplan-Meier survival curves of patients with small cell lung cancer who did (n = 48, open circle) and did not (n = 21, closed circle) receive adjuvant chemotherapy ($p = 0.0025$).

Table 3 Site of first relapse after surgery for small cell lung cancer as a function of pathologic disease stage

	Pathologic stage							
	IA (n = 21)	*IB* (n = 9)	*IIA* (n = 4)	*IIB* (n = 8)	*IIIA* (n = 16)	*IIIB* (n = 10)	*IV* (n = 1)	*Total*
Brain	1	1	1	2	5	2	1	13
Intrathoracic	1	0	1	1	6	3	0	12
Bone	1	1	0	2	1	0	0	5
Liver	1	2	0	0	0	0	0	3
Axillary lymph node	0	0	0	0	1	0	0	1
Total	4	4	2	5	13	5	1	34

than after pneumonectomy (n = 11, $p = 0.0163$; Fig. **5**). Survival of patients who received adjuvant chemotherapy (n = 48) was better than of patients who did not receive adjuvant chemotherapy (n = 21, $p = 0.0025$, Fig. **6**).

The surgical mortality was 5.8% (4/69), with 2 deaths due to bronchogenic fistula and 2 due to pneumonia.

The first relapse site is shown in Table **3**. In patients with p-stage I disease, relapse after surgery occurred in 8/30 patients (26.7%). The first relapse site was liver in 3, brain in 2, bone in 2, and intrathoracic in 1. The frequency of intrathoracic relapse was 3.3% (1/30). In more advanced p-stages, II to IV, relapse occurred in 27/39 patients (69.2%). The first relapse site in these patients was brain in 12, intrathoracic in 11, bone in 3, and axillary lymph node in 1. Thus, intrathoracic relapses were frequent (11/39, 28.2%) in advanced stages.

Multivariate analysis of prognostic factors revealed that pathologic nodal status ($p = 0.0102$), administration of adjuvant chemotherapy ($p = 0.0039$), and surgical procedure ($p = 0.0432$) were significant predictors of survival (Table **4**).

Discussion

Evaluating the role of surgery for SCLC is difficult for a number of reasons. First, only a small number of patients present in relatively early stages that can be treated by surgery. Second, a comparison between surgery and nonsurgical treatment in the same disease stage is difficult because staging for most patients treated without surgery is based only on the LD/ED classification. LD usually includes a very heterogeneous group of patients, stages IA to IIIB. Third, it is difficult to conduct prospective studies because a multi-institutional randomized controlled study would take a long time to enroll an adequate number of surgical candidates to achieve statistical significance. Thus, retrospective analyses are still essential to advance our understanding of the role of surgery in SCLC.

The main advantage of surgery for SCLC is complete local control of the disease [11]. Even when a complete response is obtained by chemoradiotherapy for LD, the local relapse rate is still 20% to 70% [12–14]. In our study, local relapse after surgery depended on the postsurgical p-stage. In p-stage I, we found that the incidence of intrathoracic recurrence was only 3.3%, whereas it was 28.2% in higher stages. Thus, lymphogenic spread in ad-

Table 4 Multivariate analysis of prognostic factors in patients with small cell lung cancer

Prognostic factors	*P value*	*Hazard ratio*	*95% CI*
Gender (male vs. female)	0.94	1.855	0.620 – 5.556
Age (≥ 62 vs. < 62)	0.1104	1.741	0.881 – 3.438
Pathologic N factor (N1 – 3 vs. N0)	0.0102	2.409	1.232 – 4.711
Adjuvant chemotherapy (done vs. not done)	0.0039	0.404	0.218 – 0.748
Surgical procedure (pneumonectomy vs. lobectomy or bilobectomy)	0.0432	2.528	1.028 – 6.215

CI = confidence interval

vanced stages makes complete local elimination of cancer cells by surgery unlikely. In addition, survival after pneumonectomy was significantly worse than after lobectomy or bilobectomy, and survival of patients with clinical or pathologic lymph node involvement was significantly worse than without lymph node involvement.

The 5-year survival rate after surgery for p-stage I disease ranges from 22% to 67%, and that for p-stage II ranges from 17% to 50% [15 – 17]. Reported survival in p-stage IIIA or higher varies greatly, from 0% to 55.5% [15,18 – 20]. The randomized study by the Lung Cancer Study Group [5] showed that surgery does not prolong survival in c-stage IIIA SCLC even in patients who undergo induction therapy. Although 19% of resected tumors showed complete pathologic response, this good response to chemotherapy did not improve the survival. However, in our study, pathologic downstaging did predict improved survival. Thus, we believe pathologic downstaging may be a selection criterion for identifying surgical candidates. Evaluation of the residual tumor cells by positron emission tomography (PET) or by lymph node sampling by mediastinoscopy after induction chemotherapy are alternate strategies.

In conclusion, a 32% overall 5-year survival was obtained in selected patients with SCLC who underwent surgery. Survival after surgery clearly depended on disease stage. Nodal status and pathologic downstaging after induction therapy predict survival. A randomized study is needed to identify surgical candidates.

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Home Monitoring of Patients after Prosthetic Valve Surgery – Experimental Background and First Clinical Attempts

Abstract

Purpose: The purpose of this study was to investigate whether: 1. sound phenomena may be used to detect prosthetic valve dysfunction; 2. clinical and experimental data permit conclusions about alterations in the functional state of mechanical valves; 3. patients can record and pass on signals via Internet. **Methods:** 1. We implanted bi-leaflet valves in pigs. By gradually influencing the motion of the tilting discs prosthetic dysfunction could be generated. 2. Thrombosis and lysis of bi-leaflet valves was studied in sheep. This process was documented using echocardiography and acoustically by the Fast Fourier Transformation. 3. Thirty devices were set up and handed out to patients following mechanical valve replacement. All patients regularly sent data to the hospital via Internet, regardless of their location at the time. The data were evaluated by comparing them with the reference file. **Results:** Animal experiments proved that changes in prosthetic function led to a significant change in sound phenomena. In contrast to echocardiography alterations at an early stage (onset of thrombosis) could be reliably verified. The sensitivity was greater than in echo-control analysis. All patients regularly recorded and passed on their signals. Surveys revealed high acceptance and easy handling of the devices. **Conclusions:** Online registration of sound phenomena seems to be suitable for the detection of changes in prosthetic function. This led to the development of the first hand-held device for home monitoring of valve function. Registration of flow, frequency spectrum, and ECG envisaged at the next level opens up potential applications for Internet-based, remote monitoring of cardiac patients.

Key words
Valve prosthesis · follow-up · prosthetic valve sound · valve replacement

Introduction

Despite enormous advances in the surgical treatment of pathological heart valves, a complication rate of 3 – 6%/patient/year is still present [1]. Unfortunately, cases like the one reported by Kucukaksu et al. are the exception rather than the rule [2]. Considering that approximately 100 000 heart valve operations are performed worldwide every year, the number of serious complications due to thrombosis, tissue ingrowth, leaflet tears, calcification, leakage, etc. amounts to 5000/year.

A prosthetic valve non-structural dysfunction which is consistent with a disturbed motion of the leaflets caused by complications like thrombus formation or tissue ingrowth, apart from very rare technical defects, mostly develops over a period of several weeks. This means that they usually occur within the diagnostic window between two medical consultations, i.e. echocardiography or other physical examinations. Usually heart valve dysfunction is discovered when serious, potentially irreversible events, such as thromboembolic complications etc. have already

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Microwave Coagulation Therapy in Canine Peripheral Lung Tissue[1]

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Background. **New modalities for local treatments that destroy tumor effectively but which are less invasive and less damaging to normal lung tissue must be developed for patients who are unable to undergo even video-assisted thoracic surgery (VATS) due to poor cardiopulmonary function, severe adhesion, or advanced age, etc. We evaluated the use of microwave coagulation therapy (MCT), which has been used successfully for coagulation of hepatic tumors, in normal canine lung tissue to evaluate its efficacy and safety.**

Materials and methods. **Measurements of thermal response and coagulation area and histological examinations after microwave coagulation were performed in normal canine lung tissue.**

Results. **The temperature in normal canine lung tissue increased to 90–100°C at 5 mm from the electrode after 60 s and 70–80°C at 10 mm after 90 s at 40 or 60 W. The coagulation area was approximately 20 mm in diameter at 40 W and 60 W. Histological analysis demonstrated thickening of collagen fiber shortly after coagulation, stromal edema and granulation tissue after 3 months, and, finally, scar tissue was seen after 6 months.**

Conclusions. **Microwave coagulation therapy (MCT) is a useful modality for minimally invasive therapy in peripheral lung tumors.**

Key Words: **microwave coagulation; MCT, PMCT, ablation; lung tumor; peripheral lung cancer.**

INTRODUCTION

Recently, the problem of population aging on a global scale is calling for minimally invasive therapies providing good quality of life (QOL) and activity of daily living (ADL). Many investigators are looking into the problems of poor cardiopulmonary function as a result of advanced age, previous surgery, and/or synchronous or metachronous carcinoma. Meanwhile, the detection rate of early-stage carcinoma or precancerous lesions has increased due to recent advances in medical technology. In the field of chest diseases, the detection rate of tiny tumors in the peripheral lung, such as early-stage lung cancer, small metastases, or atypical adenomatous hyperplasia (AAH) has increased with the increasing use of high-resolution CT scans. Video-assisted thoracic surgery (VATS) usually is used for many of these cases. However, we believe that less-invasive therapy is necessary for patients who are inoperable due to poor cardiopulmonary function, severe adhesion, or advanced age.

There is, therefore, a need for local treatment that effectively destroys tumor but is minimally invasive and less damaging to normal tissue than surgery. In the present study, we focused on microwave coagulation therapy (MCT), which has successfully been used to coagulate hepatic tumors [1–4]. The mechanism of coagulation is dielectric heating, *i.e.*, frictional heat of water molecules. Since the dielectric heat energy cannot be generated in the presence of air, selective tumor damage may be achieved and damage to the surrounding normal air-filled lung tissue may be limited. To assess the application of PMCT for lung tumors, we evaluated its efficacy and safety in experimental studies.

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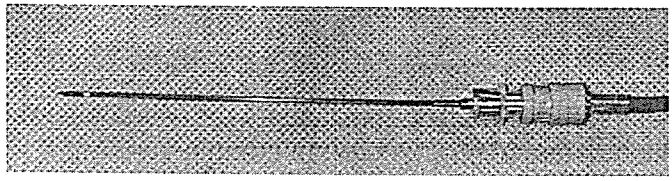


FIG. 1. A specially designed single-needle electrode, 150 mm in length and 1.6 mm in diameter, was inserted 20 mm into the normal lung.

MATERIALS AND METHODS

Measurements of Thermal Response

Animal studies were performed with the approval of the Institutional Committee for Ethical Research Animal Care. Adult beagles (10-15 kg) were given artificial respiration under general anesthesia with 30 mg/kg of phentobarbital sodium intravenously and placed in the left lateral recumbent position. Using an aseptic technique, thoracotomy was performed through the 5th intercostal space. A specially designed single-needle electrode (MD-16CBT-10/150, Azwell, Osaka, Japan, Fig. 1) that is 150 mm in length and 1.6 mm in diameter was inserted 20 mm into the normal lung. Then, tissue coagulation was performed using a microwave generator (Microtaze HSD-20W, Azwell, Fig. 2) that emitted 2450 MHz microwaves of 12 cm wavelength at a power output of 20, 40, and 60 W for 4 min. Temperature change was continuously monitored for 4 min using a K-type electric thermometer at 5 mm and 10 mm from the electrode with a sensor inserted 10 mm into the normal lung. The data of temperature were plotted for every 15 s. Measurements of temperature change were performed three times in each condition. Three beagles were used for this study.

Measurements of Coagulation Area

Microwave electrodes were inserted into normal lung tissue of beagles using the same procedure as mentioned above. Microwave coagulation was performed three times under each condition at power outputs of 20, 40, and 60 W for 1, 2, 3, and 4 min. Three beagles were used for this study. Shortly after microwave coagulation, the beagles were euthanized with an intravenous phentobarbital sodium overdose and pneumonectomy was performed. The resected canine lungs were inflated with bubbling air and 10% buffered formalin from the bronchial stump using an enema syringe pump and preserved in 10% buffered formalin for tissue fixation.

Under the same conditions, microwave coagulation was performed for normal human fresh lung tissue after resection of central type lung carcinoma, inflated with bubbling air using an enema syringe pump from the bronchial stump. Coagulation was performed once under each condition using two fresh lung lobes after resections. Informed consent was obtained in all cases. Tissue fixation was performed in the same manner as in the animal experiment.

The fixed lung tissue was transected perpendicular to the direction of the inserted electrode. The longest dimension of the maximum coagulation area of fixed lung tissue was measured.

Histological Examinations after Microwave Coagulation

Microwave coagulations were performed in three beagles at a power output of 40 W for 3 min. One beagle was euthanized with an intravenous phentobarbital sodium overdose immediately, and the other two beagles were followed up to assess histological change of the coagulated tissue. The normal activity and condition of each beagle was monitored daily. These beagles were euthanized at 3 and 6 months after the procedure. Histological changes of normal lung tissue immediately, 3 and 6 months after microwave coagulation were investigated by H-E staining and Elastica von Gieson staining.

Statistical Analysis

Data were expressed as means ± standard deviations (SD), and statistical analyses were done using Student's t test with computer software (Microsoft Excel, version 2002). A P value of less than 0.05 was considered to indicate a statistically significant difference.

RESULTS

Measurements of Thermal Response

The data of thermal response of normal canine lung tissue to microwave coagulation is shown in Fig. 3. At 5 mm from the electrode (Fig. 3A), the temperature rose rapidly over 80°C (15 s for 60 W: 83.1 ± 13.0°C; 30 s for 40 W: 83.9 ± 3.4°C), and thereafter the temperature reached a plateau around 90-100°C at both 40 and 60 W. There was no significant difference between the two groups for each time point. At 20 W, the temperature rose gradually to only 65°C and reached a plateau. At 10 mm from the electrode (Fig. 3B), the temperature rose gradually to 70°C (45 s for 60 W: 70.6 ± 11.6°C; 90 s for 40 W: 70.9 ± 13.0°C), and thereafter the temperature reached a plateau around 80°C at 40 and 60 W. There was no significant difference between the two groups for each time point. At 20 W, the temperature rose to only 50°C after 90 s and reached a plateau. It appeared that 20 W was not enough for coagulation. The same thermal re-

FIG. 2. Microwave coagulation was performed using a microwave generator that emitted 2450 MHz microwaves of 12 cm wavelength at a power output of 20, 40, and 60 W.

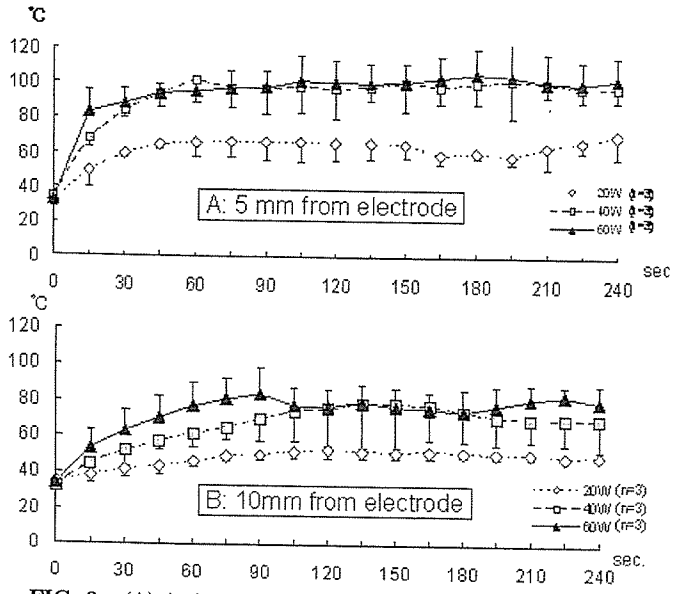


FIG. 3. (A) At 5 mm from the electrode, the temperature rose rapidly to 85°C (for 15 s at 60 W and 30 s at 40 W). The temperature reached a plateau around 90-100°C at 40 and 60 W. There was no significant difference between 40 and 60 W for each time point. (B) At 10 mm from the electrode, the temperature rose gradually to 70°C (45 s at 60 W and 90 s at 40 W). The temperature reached a plateau around 80°C at 40 and 60 W. There was no significant difference between 40 and 60 W for each time point.

sponse was obtained in the two groups of 40 W and 60 W at same distances from the electrode.

Measurements of Coagulation Area

The data of the diameter of the maximum coagulation area in the animal model is shown in Fig. 4. The maximum coagulation area increased with increased power and coagulation time. The diameter of the maximum coagulation area was 18.3 ± 10.4 mm at 40 W for 4 min and 21.7 ± 2.9 mm at 60 W for 4 min. There was no significant difference in the coagulation area at each time period when using 40 W and 60 W.

The diameter of the maximum coagulation area in normal human fresh lung tissue after resection of central-type lung cancer is shown in Fig. 5. The maximum coagulation area increased with increased power and coagulation time until 3 min. After 3 min, the diameter of the maximum coagulation area was 25 mm at 40 W and 26 mm at 60 W. At 40 and 60 W for 4 min, the diameter of the maximum coagulation area shrank to 15 mm. There was no difference between 40 and 60 W for each period of coagulation.

Histological Examinations after Microwave Coagulation

All beagles tolerated the procedure well. During 6 months of follow up to assess histological change of the coagulated tissue, the normal activity and condition of each beagle was monitored daily. There was no death due to serious complications such as hemoptysis or pneumothorax during the period.

The histological changes after microwave coagulation are shown in Fig. 6. Histological findings shortly after microwave coagulation showed degeneration and thickening of collagen fiber and exfoliation and ulceration of bronchial epithelium surrounding the electrode. No surrounding bronchioli or veins were destroyed. No blood clots or debris were observed in surrounding veins (Fig. 6A). After 3 months, histological findings showed stromal edema and loose collagen fiber, immature neoangiogenesis, progression of bronchial epithelial hyperplasia, infiltration of inflammatory cells at the boundary zone (lymphocyte > plasma cell > neutrophil) between the central coagulation area and normal tissue (Fig. 6B). After 6 months, coagulated tissue became scar tissue that showed disappearance of stromal edema, tight collagen fiber, mature capillaries, disappearance of inflammatory cells, and completion of epithelial hyperplasia (Fig. 6C).

DISCUSSION

With the increasing use of high-resolution CT scans, the rate detection of small nodules in the peripheral lung, such as early-stage lung cancer, small metastases, or AAH has increased. Kaneko *et al.* demonstrated that the detection rate of peripheral lung carcinoma by mass screening using CT scan was 0.45% (15 of 3457 examinations), 73% of which were detected by low-dose spiral CT but were not visible on standard chest radiography [5]. Noguchi *et al.* investigated 236 surgically resected small-size peripheral adenocarcinomas measuring 2.0 cm or less in greatest dimension and demonstrated that type A (localized bronchioloalveolar carcinoma: LBAC) and type B (LBAC with foci of structural collapse of alveoli) that showed ground glass opacity (GGO) on CT scanning images demonstrated

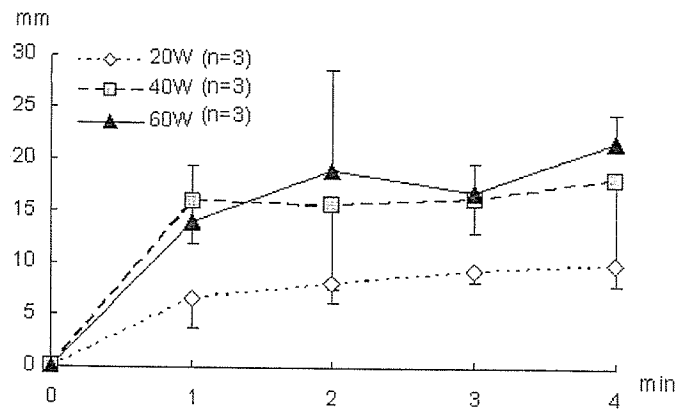
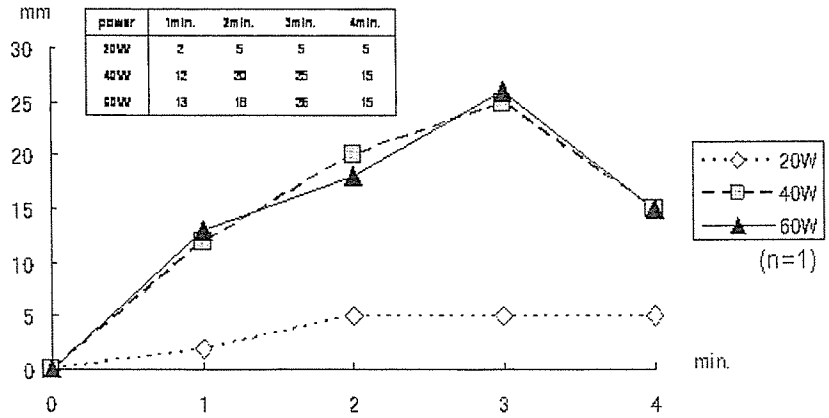


FIG. 4. The diameter of the maximum coagulation area was 18 mm at 40 W for 4 min and 22 mm at 60 W for 4 min. There was no significant difference between 40 W and 60 W for each coagulation time.



power	1min.	2min.	3min.	4min.
20W	2	5	5	5
40W	12	20	25	15
60W	13	18	25	15

FIG. 5. The diameter of the maximum coagulation area was 25 mm at 40 W and 60 W for 3 min. There was no difference between 40 and 60 W for each time. The diameter of the maximum coagulation area shrank to 15 mm at 40 and 60 W for 4 min.

no lymph node metastasis and had the best 5-year survival rate (100%) [6]. Meanwhile, according to a pathological study on lymph node metastasis of primary lung carcinoma after surgery, the rate of metastasis (N1 and N2) was 0% with a tumor 1.0 cm or less, 17% with a tumor 1.1 to 2.0 cm, and 37% with a tumor 2.1 to 3.0 cm in diameter [7]. As a result, it seems to be possible to control 83% of lung carcinomas smaller than 2.0 cm in size by local treatment. Also, the rate of local lymph node metastasis of metastatic lung tumor is known to be low.

We usually perform surgery for such patients as a possible cure, but this may lead to considerable lung damage with significant loss of function. Although VATS has widened the indication of surgery recently, some patients are unable to undergo even VATS due to poor cardiopulmonary function, severe adhesion, or advanced age, etc. Radical radiotherapy or chemotherapy or both may be offered with curative intent to such patients, but the prospect of cure is substantially worse than with surgical options, while it may also lead to considerable lung damage with significant loss of function caused by radiation fibrosis, systemic toxicity due to the anticancer agent. Therefore, new modalities for local treatment that effectively destroy tumor but are less invasive and less damaging to normal lung tissue are required. Recently, several investigators tried to use radiofrequency ablation (RFA) [8–10] or photodynamic therapy (PDT) for peripheral lung tumors [11, 12].

We are interested in microwave coagulation therapy (MCT), which has been successfully used to perform coagulation of hepatic tumors. In 1978, hepatic surgery with MCT was introduced by Tabuse [1], and recently the effectiveness of percutaneous microwave coagulation therapy (PMCT) under ultrasonography or CT scan guidance for small hepatocellular carcinoma was demonstrated [3, 4]. We considered this modality to be applicable for patients with lung tumors who are poor surgical candidates, as well as patients with hepatic tumors, and evaluated the efficacy and safety of MCT for lung tissue experimentally.

The microwave generator emits a higher frequency wavelength than electrocautery and generates dielectric heat energy due to friction of water molecules when irradiating living tissue. MCT applies this mechanism to achieve tumor necrosis. Because the dielectric heat energy cannot be generated in the presence of air, selective tumor damage may be achieved, with limited damage to the surrounding normal air-filled lung tissue. We considered it essential to know how MCT affects normal lung tissue before performing PMCT clinically for peripheral lung malignancies. An experimental study was deemed necessary to evaluate the thermal response, coagulation extent, and histological changes in the air-filled normal lung.

With regard to thermal response, the temperatures of normal canine lung tissue rose with increased microwave power and coagulation time. The temperatures in normal lung tissue rose to 90-100°C at 5 mm from the electrode after 60 s and 70-80°C at 10 mm after 90 s, thereafter reaching a plateau. A power of 20 W was not sufficient to coagulate lung tissue. These data suggested that the same thermal response could be obtained at 40 and 60 W. The coagulation area in normal canine lung tissue increased to 18 mm and 22 mm at 40 W and 60 W for 4 min, respectively. Therefore, it may be possible to coagulate a diameter of approximately 20 mm. In solid tumors, there is a possibility to achieve more extensive coagulation. In human resected normal lung with central-type lung carcinoma, the coagulation area increased to 25 mm at 40 and 60 W for 3 min and shrank to 15 mm for 4 min. This phenomenon may be explained by shrinking of lung tissue due to rapid elevation of the temperature in the tissue, because there is no radiator effect in the resected lung due to the lack of blood supply. From the current study, we concluded the optimal condition in clinical PMCT to be 40-60 W for 3–4 min of coagulation.

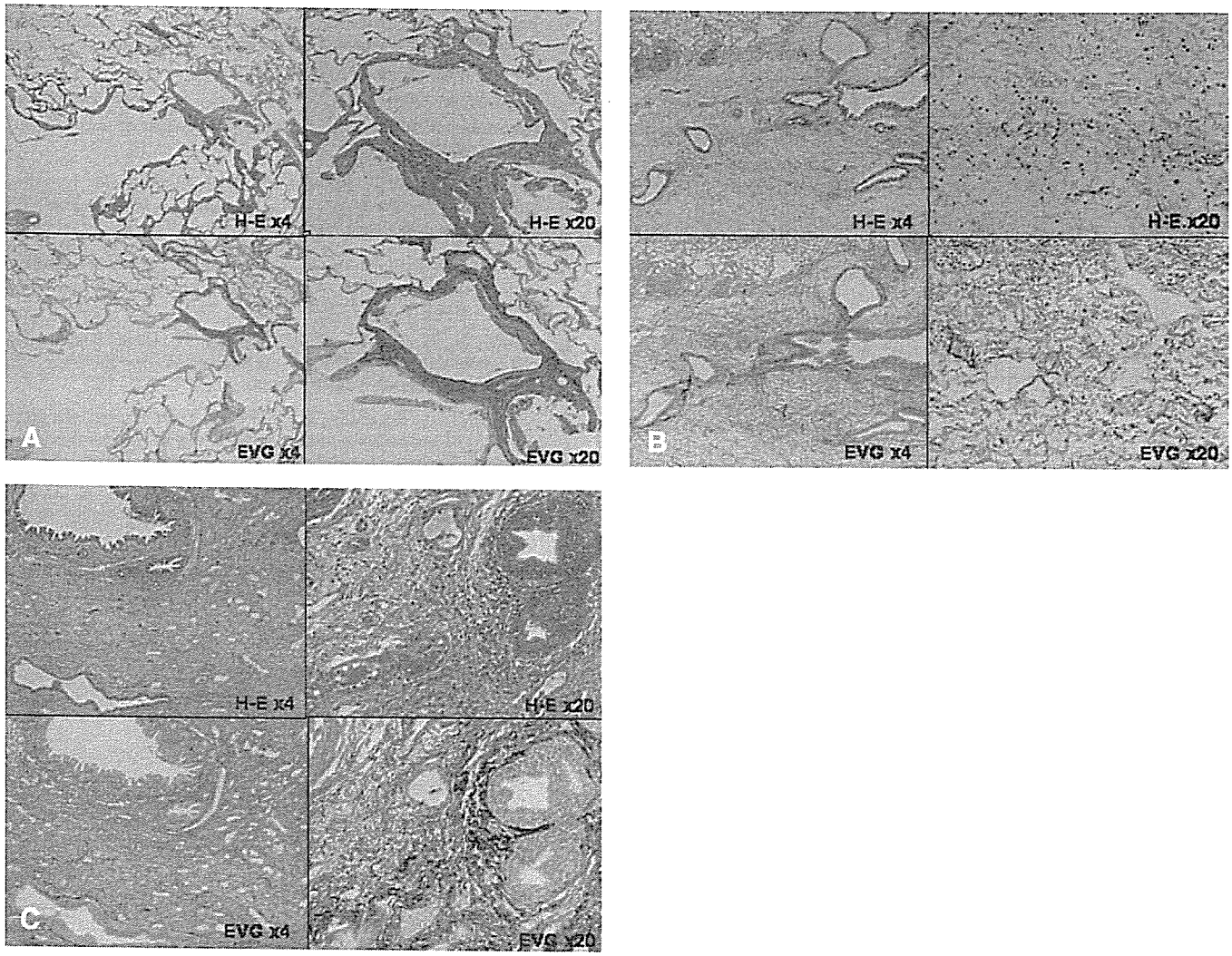


FIG. 6. (A) Histological findings shortly after microwave coagulation showed degeneration and thickening of collagen fiber and exfoliation and ulceration of bronchial epithelium surrounding the electrode. Surrounding bronchial and veins were not destroyed. (B) After 3 months, histological findings showed stromal edema and loose collagen fiber, immature neoangiogenesis, progression of bronchiolus epithelial hyperplasia, infiltration of inflammatory cells at the boundary zone between the central coagulation area and normal tissue. (C) After 6 months, coagulated tissue became scar tissue that showed disappearance of stromal edema, tight collagen fiber, mature capillaries, disappearance of inflammatory cells and completion of epithelial hyperplasia. (Color version of figure is available online.)

Histological analysis following MCT for normal canine lung tissue demonstrated exfoliation and ulcer formation of the epithelium in the bronchioli and degeneration and thickening of collagen fiber in the parenchyma by heat coagulation shortly after MCT. The coagulated lesions were gradually repaired by progression of epithelial hyperplasia and infiltration of inflammatory cells, showing stromal edema and granulation tissue after 3 months and finally becoming scar tissue after 6 months. We concluded MCT to be a safe modality for lung tissue because no destruction of bronchioles or veins was seen in the specimens during 6 months.

The present studies of MCT for peripheral lung tissue demonstrated that this new modality had no serious adverse effects and could be performed safely. However, the incidence of pneumothorax by CT-guided RFA was demonstrated to be 38.5% (3/8) in a rabbit model [8] and 33.3% (1/3) and 53.8% (7/13) in clinical cases [9, 10], which seems to be relatively high. Therefore, the development of a fine electrode with a cooling system will be necessary to prevent complications such as pneumothorax and heat sensation for clinical use.

From our experimental studies, the advantages of PMCT are the fact that this modality is minimally invasive, may be performed by local anesthesia, and is applicable for patients with poor cardiopulmonary function. In addition, the microwave generator is a very simple device, maintenance free, easy to handle, and portable, and the procedure is easy compared with RFA and PDT. The possibility of pneumothorax, heat

sensation or pain, or both during treatment and the limited coagulation area are considered the disadvantages for clinical use at present. Nevertheless, our results demonstrated the possibility of MCT for patients with small peripheral lung tumors with the intent of curative treatment. Although MCT is considered to be a useful modality as minimally invasive therapy for small peripheral lung tumors, further comparative research is necessary with other modalities such as RFA and PDT for peripheral lung tumors.

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Frequent loss of E-cadherin and/or catenins in intrabronchial lesions during carcinogenesis of the bronchial epithelium

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Plakoglobin;
Intrabronchial lesions;
Early-stage bronchial squamous cell carcinoma;
Immunohistochemistry

Summary Inactivation of the cadherin-mediated cell–cell adhesion system is believed to play a role in the initial steps of cancer invasion and metastasis. Expression of E-cadherin and its intracytoplasmic binding molecules (α-catenin, β-catenin, and plakoglobin) was examined immunohistochemically in 84 cases of intrabronchial precancerous lesions (bronchial squamous metaplasia (BSM) without atypia, BSM with atypia, dysplasia), and 21 cases of carcinoma in situ, and 4 cases of microinvasion to the bronchial wall, and 32 cases of stage I well differentiated squamous cell carcinoma (squamous cell carcinoma) to investigate the association between expression of E-cadherin and/or catenins and cancer progression. Reduced expression of E-cadherin and/or catenins was closely correlated with an atypical grade of dysplasia in the basal layer ($p < 0.05$). In particular, downregulation of E-cadherin and/or catenins was associated with an atypical grade of BSM with atypia in intrabronchial lesions ($p < 0.01$). We conclude that downregulation of α-catenin and/or β-catenin, which may reflect dysfunction of the cadherin-mediated cell–cell adhesion system, is an important marker for atypical grade during carcinogenesis of the bronchial epithelium.

1. Introduction

Cadherins are a family of cell–cell adhesion molecules that are essential for tight junctions

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between cells [1,2], and E-cadherin is the form most strongly expressed in epithelial cells. Cadherins form a complex with cytoplasmic proteins, known collectively as catenins. This molecular complex, together with other cytoskeletal components such as actin, constitutes the intercellular adherence junction [2–4]. The catenins are classified into two groups, α-catenins and β-catenins, and the latter group includes plakoglobin and *Drosophila* Armadillo protein as well as β-catenin itself [5,6]. Plakoglobin is isolated from the desmosomal fraction [7] and is present in both desmosomes and adherence junctions [8], and may therefore be a common regulatory molecule in cell junctions.

Cadherin-mediated cell adhesion acts as a suppressor of the invasion of cancer cells in vitro [9–11], and dysfunction of the E-cadherin system correlates with cancer cell invasion in human cancers [12,13]. The role of α-catenin in the cadherin adhesion system has been revealed by studies with cancer cells. The human lung cancer cell line PC9 expresses an aberrant α-catenin mRNA and shows very loose cell–cell association [14,15]. PC9 cells become much more closely associated and acquire an epithelioid arrangement after transfection with cDNA for a subtype of α-catenin and αN-catenin [16]. These results suggest that α-catenin is indispensable for cadherin-mediated cell–cell adhesion.

Previous immunohistochemical studies have revealed many examples of reduced and/or heterogeneous expression of E-cadherin [17–19] and α-catenin [20] in undifferentiated invasive cancers, and impaired expression of E-cadherin or α-catenin has been reported to be associated with high incidences of lymph node metastasis of human breast [21], esophageal [22], and head and neck [23] cancers. However, there have been few studies on the relationship between reduced E-cadherin expression and the prognosis of cancer patients [24–28].

The role of β-catenin and plakoglobin in determining the fate of cells has been suggested by work on a *Drosophila* homologue of this protein, Armadillo [29,30]. Moreover, it has been revealed that the association between E-cadherin and α-catenin is mediated by β-catenin [31], and that β-catenin in turn mediates the interactions of the cadherin–catenin complex with the c-erbB-2 gene product and epidermal growth factor receptor (EGF-R) [32–34]. A tumor suppressor gene product, APC protein, has been shown to interact with β-catenin and plakoglobin and to play important roles in the E-cadherin-mediated cell adhesion system and to participate in tumor invasion and metastasis.

In a previous study, we divided primary lung cancers into two groups on the basis of their expression of E-cadherin and catenins, as detected by immunohistochemistry [35]. In addition, we demonstrated a close relationship between E-cadherin-associated cell–cell adhesion, catenins, and cytologic features, in particular the formation of cellular clusters and the frequency of solitary cells. Preoperative evaluation of both cytologic features and E-cadherin-associated cell–cell adhesion may be useful for predicting the malignant characteristics of lung cancer [36].

E-cadherin and α-catenin, and also β-catenin and plakoglobin, play important roles in the cadherin-mediated cell adhesion system in various cancers. However, in the context of carcinogenesis of the bronchial epithelium, expression of E-cadherin, α-catenin, β-catenin, and plakoglobin in intrabronchial precancerous lesions has not yet been reported. In order to investigate a possible dysfunction of the E-cadherin-mediated cell adhesion system in intrabronchial lesions, we used immunohistochemistry to examine the expression of E-cadherin, α-catenin, β-catenin, and plakoglobin in biopsy specimens.

2. Materials and methods

2.1. Biopsy specimens

The biopsy samples were obtained from 109 patients with intrabronchial lesions resected between 1991 and 2000 at the Department of Surgery of Tokyo Medical University Hospital. These lesions were diagnosed pathologically as BSM without atypia in 32 cases, BSM with atypia in 25 cases, dysplasia in 5 cases, carcinoma in situ in 21 cases, microinvasion to the bronchial wall in 4 cases, and stage I well differentiated squamous cell carcinoma in 32 cases. The specimens were fixed with 10% formalin and embedded in paraffin.

2.2. Immunohistochemistry

Mouse monoclonal antibodies against human E-cadherin (HECD-1; Takara, Kyoto, Japan), α-catenin and β-catenin (anti-α-catenin and anti-β-catenin; Transduction Laboratories, Lexington, KY), and plakoglobin (CBL175; Cymbus Bioscience, Southampton, UK) were used for immunohistochemical staining. Four-micrometer-thick tissue sections were prepared from all paraffin-embedded specimens and collected on silane-coated glass slides. After deparaffinization, the formalin-fixed paraffin-embedded sections were treated with