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Lung cancer patients showing pure ground-glass opacity on computed tomography are good candidates for wedge resection

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Summary Small lung cancers frequently have been detected in mass screening by computed tomography (CT) in recent years. Suitability of limited resection for these small lung cancers remains controversial. One hundred patients who underwent sublobular limited resection (wedge resection or segmentectomy) for lung cancer in our hospital from 1981 to 2002 were analyzed retrospectively. From CT findings, tumors were classified into two groups; pure ground-glass opacity (PGGO) and non-PGGO. Patients included 44 women and 56 men, and ages ranged from 40 to 92 years (mean, 71.0). Histologic types included 76 adenocarcinomas, 21 squamous cell carcinomas, and 3 large cell carcinomas. Clinical stages included 83 stage IA and 17 stage IB. By high-resolution CT, 27 tumors (27%) showed PGGO; at postoperative histopathologic examination, all of these were localized bronchioloalveolar carcinomas. Diameter of tumors showing PGGO was 9.3 ± 3.5 mm (mean $\pm$ S.D.); that of non-PGGO tumors was 21.2 ± 13.7 mm. Overall and lung cancer-specific 5-year survival rates in all patients were 58.0 and 64.8%, respectively. Overall 5-year survival rate with small adenocarcinomas ($\leq$20 mm) was 93.7%, significantly better than 24.8% with larger adenocarcinomas ($P < 0.0001$). No intrathoracic recurrence or distant metastasis has been observed in PGGO tumors. For peripheral localized bronchioloalveolar carcinoma showing PGGO, wedge resection appears to be the best operation. Definitive study of more patients with longer follow-up is needed.

1. Introduction

The present standard operation for primary lung cancer is considered to be lobectomy with systematic lymphadenectomy. However, suitability of limited resection has been examined by several investigators. Outcome of segmentectomy first was reported in a large number of patients by Jensik et al. [1] in the 1970s. They performed segmentectomy for 168 stage I peripheral lung cancers, obtaining a survival rate of 53% at 5 years after surgery; this survival rate was comparable to that with

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lobectomy. However, a later study [2] from the same institution demonstrated a higher recurrence rate with segmentectomy than with lobectomy in stage I lung cancer. In that study, the rate of locoregional recurrence was 22.7% (15/66) after segmentectomy versus 4.9% (5/103) after lobectomy. A randomized controlled trial comparing limited resection (segment or wedge) with lobectomy for T1N0 non-small cell lung cancer (NSCLC) was carried out by the Lung Cancer Study Group [3] beginning in the 1980s.That study clearly found outcome with limited resection to be inferior to that with lobectomy, in terms of both survival and locoregional recurrence. Since then, limited resection for stage IA lung cancer generally has been avoided, except for patients with impaired cardiopulmonary function.

On the other hand, small cancers with diameters less than 1 cm frequently have been found in the periphery of the lung since introduction of mass screening by computed tomography (CT) in recent years [4–6]. Most such small cancers are not detectable in chest radiopraphs; by CT, they show ground-glass opacity (GGO) [7]. Most of them are diagnosed pathologically as localized bronchioloalveolar carcinoma or as atypical adenomatous hyperplasia (AAH) [8,9], a precancerous lesion. Further, development of video-assisted thoracoscopic surgery (VATS) can permit relatively noninvasive wedge resection of small lung nodules in a short operating time, which is particularly important for poor-risk patients [10–12]. However, indications for sublobular resection and curability of these small lung cancers by such procedures still are controversial. Avoidance of excessive surgery for small lung cancers detected by increasingly wide spread mass CT screening will become an important issue. We therefore sought to identify the clinicopathologic characteristics of lung cancers suitable for wedge resection by retrospectively analyzing outcomes of patients with primary NSCLC removed by sublobular resection without systematic dissection of lymph nodes.

2. Patients and methods

2.1. Patients

We analyzed consecutive 100 patients with primary NSCLC initially treated at our hospital from January 1981 to December 2002 by wedge resection or segmentectomy without systematic dissection of lymph nodes. Patients who underwent lobectomy for primary lung cancer prior sublobular resection or who underwent sublobular resection as a palliative operation for advanced disease were excluded from the present analyses. As 2051 patients with NSCLC underwent surgery during this period, those undergoing sublobular resection represented 100/2051 of cases (4.8%). Patients included 44 women and 56 men, and their ages ranged from 40 to 92 years (mean, 71.0). The final histologic diagnosis was determined from the resection specimen. Histologic types included 76 adenocarcinomas, 21 squamous cell carcinomas, and 3 large cell carcinomas. All patients were staged according to UICC (Union Internationale Centre le Cancer) criteria [13]. Cases included 83 representing clinical stage IA and 17, stage IB. By high-resolution CT, 27 tumors (27%) showed pure GGO (PGGO). PGGO was defined as lesions with no solid component in the tumor detected by high-resolution CT [14,15]; this type of lesion has been referred to as "G type" in another report [16]. The mean follow-up period of all patients after surgery was 32.2 months.

2.2. Operation

Wedge resection or segmentectomy was performed as a sublobular limited resection. Systematic dissection of lymph nodes was not performed in any case. Wedge resection was performed for 97 patients and segmentectomy was performed for three patients, considering both size and anatomic location of the tumor. Informed consent regarding possible elevated risk of locoregional recurrence and inferior survival rate after limited resection was obtained from all patients whose cardiopulmonary function was adequate to permit lobectomy. VATS was performed in 62 patients, and open thoracotomy was performed in 38 patients. For patients with severe pleural adhesions or large tumors, open thoracotomy was performed. Mortality in the postoperative period was 2%.

2.3. Statistical tests

Significance of differences between groups was evaluated using the nonparametric Mann–Whitney U-test or the χ^2-test as appropriate. The survival rate was calculated by the Kaplan–Meier method. Survival differences were compared using the log rank test as a univariate analysis. A multivariate analysis also was carried out according to the Cox proportional hazards model in order to detect independent risk factors. $P < 0.05$ was considered significant.

Table 1 Clinicopathologic features of patients undergoing sublobular limited resection for non-small cell lung cancer

	All cases ($N = 100$)	PGGO ($N = 27$)	Non-PGGO ($N = 73$)	Difference between PGGO and non-PGGO: P value
Age (mean ± S.D.)	71.0 ± 9.7	66.4 ± 10.4	72.6 ± 9.0	0.0064
Gender				
Women	44	15	29	0.1568
Men	56	12	44	
Histology				
Ad	76	27	49	0.0029
WD	50	27	23	
MD	15	0	15	
PD	11	0	11	
Sq	21	0	21	
WD	2	0	2	
MD	15	0	15	
PD	4	0	4	
La	3	0	3	
Mean diameter (mm)	18.0 ± 13.0	9.3 ± 3.5	21.2 ± 13.7	< 0.0001

PGGO: pure ground-glass opacity; S.D.: standard deviation; Ad: adenocarcinoma; Sq: squamous cell carcinoma; La: large cell carcinoma; WD: well-differentiated; MD: moderately differentiated; PD: poorly differentiated.

3. Results

Clinicopathologic features of the patients are shown in Table 1. Twenty-seven tumors (27%) showed PGGO by high-resolution CT (Fig. 1). These all were diagnosed histologically as localized bronchioloalveolar carcinoma in resection specimens, and none of these showed microscopic blood vessel or lymph vessel invasion (Fig. 2). Seventy-three tumors (73%) that included solid components of varying extent by CT were defined as non-PGGO tumors (Fig. 3). Patients with PGGO tumors were significantly younger than those with non-PGGO tumors. Although no statistical significance was obtained, PGGO tumors were somewhat more common in women than in men. Non-PGGO tumors showed various histologic types and different differentiation grades. In contrast, all PGGO tumors were bronchioloalveolar carcinomas. Diameter of tumors showing PGGO was 9.3 ± 3.5 mm (mean ± S.D.), while that of non-PGGO tumors was 21.2 ± 13.7 mm, a significant difference ($P < 0.0001$).

The distribution of the longest dimension of resected tumors is plotted in Fig. 4. Seventy-three tumors (73%) were 20 mm or less, while 36 (36%) were 10 mm or less.

Reasons to perform sublobular resection instead of standard lobectomy were small tumor size in 36 patients, poor pulmonary function in 35, advanced age in 18, heart disease in 8, and simultaneous multiple lung cancers in three. The surgical margin was positive for tumor upon postoperative histologic examination in nine cases. Overall and lung cancer-specific 5-year survival rates in all patients were 58.0 and 64.8%, respectively.

Survival rates in groups classified according to various possible prognostic factors are shown in Table 2. No survival differences were noted in relation to gender or age. Overall survival with squamous cell carcinoma was significantly worse than with adenocarcinoma ($P = 0.0382$). Significant overall survival differences were obtained for size of tumor (≤10 mm versus >10 mm, ≤20 mm versus >20 mm, and ≤30 mm versus >30 mm; $P = 0.0384$, $P = 0.0002$ and $P = 0.0047$, respectively) and degree of differentiation (well differentiated [WD] versus moderately differentiated [MD] and poorly differentiated [PD]; $P = 0.0007$). Survival rates in adenocarcinoma are shown in Table 3. Overall 5-year survival rate with small adenocarcinomas (≤20 mm) was 93.7%, which was significantly better than 24.8% with larger adenocarcinomas ($P < 0.0001$, Fig. 5). The overall 5-year survival rate with WD adenocarcinoma (81.2%) also was significantly better than in a group combining MD + PD adenocarcinomas (30.7%,

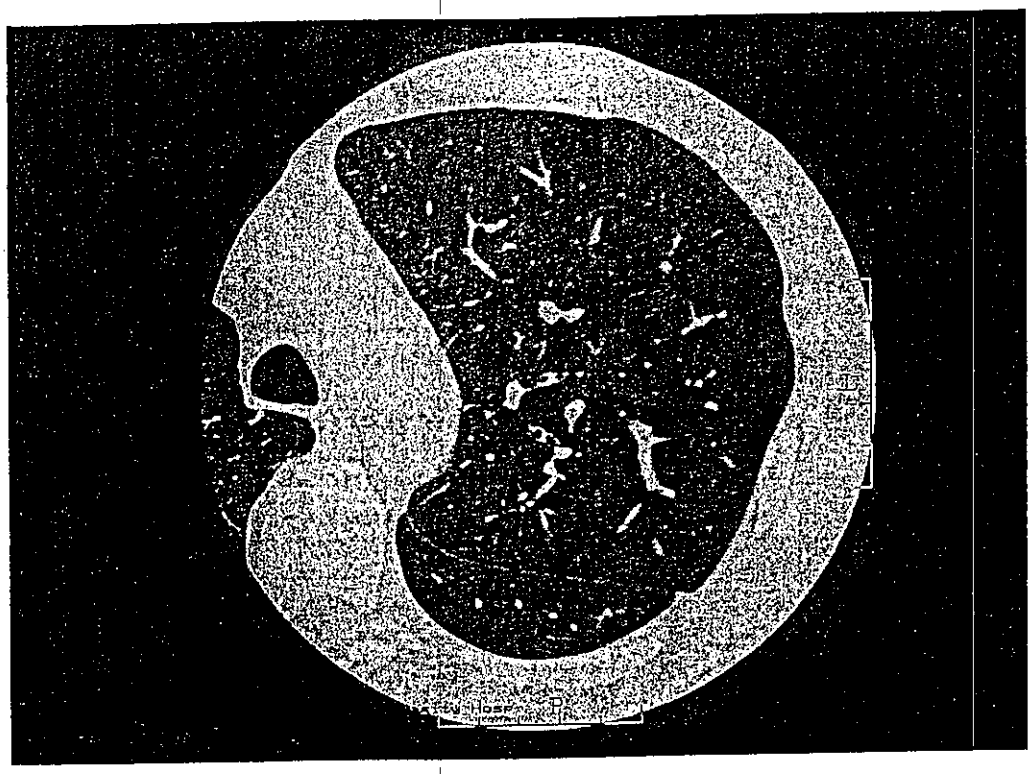

Fig. 1 Representative findings of high-resolution computed tomography (CT) showing a tumor with pure ground-glass opacity (PGGO). The pathologic diagnosis of this tumor was bronchioloalveolar carcinoma.

$P = 0.0003$; Fig. 6). When all patients were analyzed together by multivariate analysis including tumor size (≤20 mm versus >20 mm) and degree of differentiation (WD versus MD + PD), both factors were independent significant predictors for survival ($P = 0.0338$ and 0.0364, respectively).

The observation period after surgery for patients with PGGO ranged from 1 to 64 months (mean, 25.4). Neither locoregional recurrences nor lung cancer-specific deaths have been observed in this group so far, though one patient died from other disease, specifically rupture of an aortic aneurysm (Fig. 7).

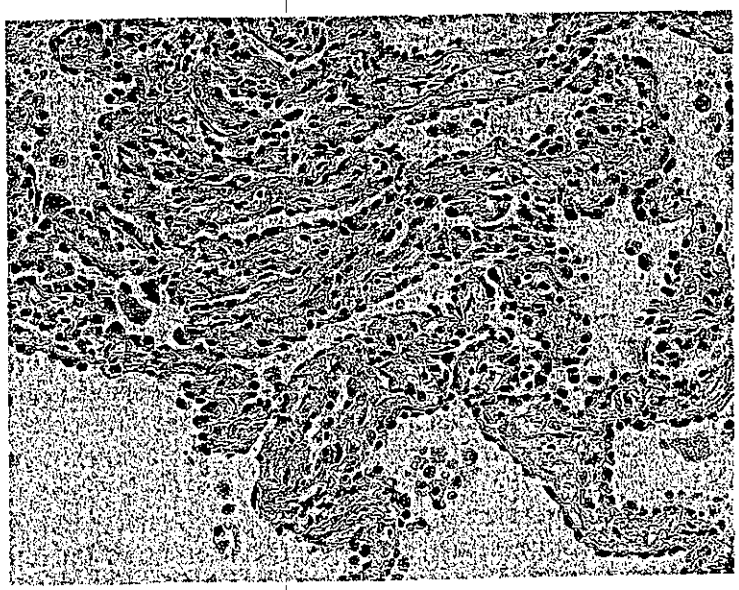

Fig. 2 As in the lesion shown here, the pathologic diagnosis in resection specimens of all pure ground-glass opacity (PGGO) tumors in this study was bronchioloalveolar carcinoma without microscopic blood vessel or lymph vessel invasion (hematoxylin and eosin; 200×).

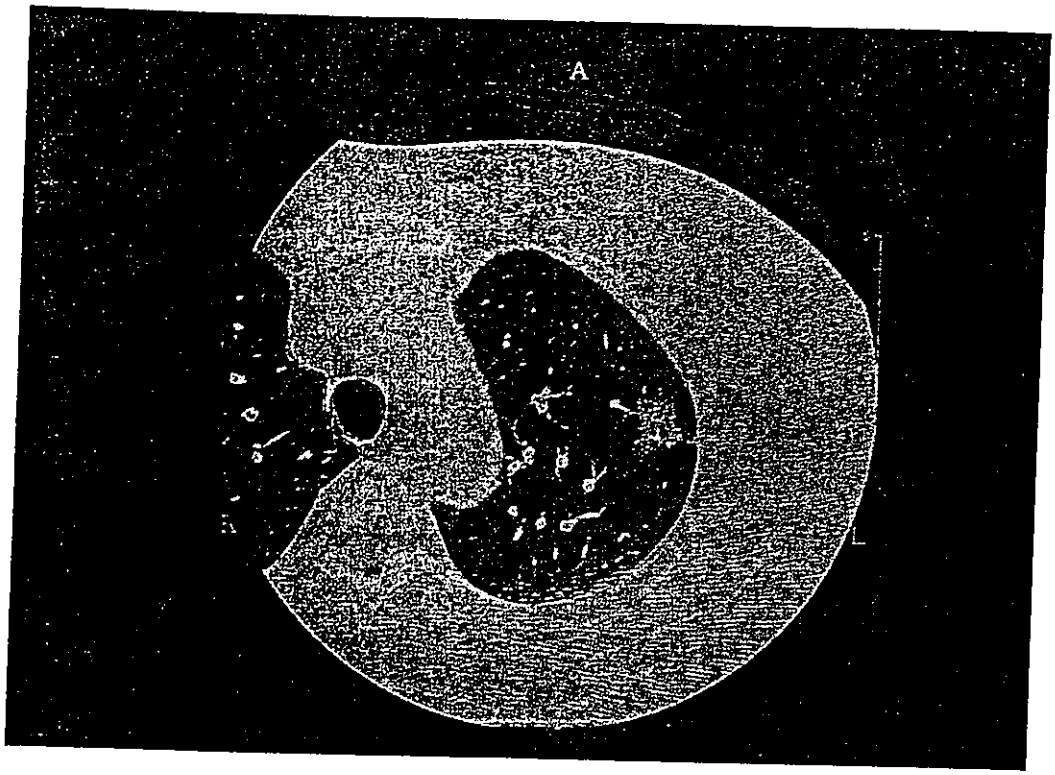

Fig. 3 Representative findings of high-resolution computed tomography (CT) showing a non-pure ground-glass opacity (non-PGGO) tumors. A solid component can be seen at the center of the tumor.

4. Discussion

Screening for lung cancer using chest CT is becoming more prevalent, and small peripheral lung cancers are being detected more frequently. Most of these lung cancers detected by chest CT but not by radiography are approximately 10 mm or less in diameter; histologically, they are well differentiated, bronchioloalveolar-type adenocarcinomas. The typical appearance of these lesions by high-resolution CT is so-called GGO, which resembles focal fibrosis or inflammatory change. In contrast, small lung cancers detected in chest radiographs include squamous cell carcinomas and poorly differentiated adenocarcinomas, which form solid nodules.

Because of a high incidence of intrathoracic recurrences after wedge resection [2,17], this surgical method has been used mainly for patients who could not tolerate lobectomy. However, we need to re-evaluate the role of wedge resection in the present era when many tiny peripheral lung cancers are detected and relatively noninvasive VATS techniques are commonly available [10,12]. In doing

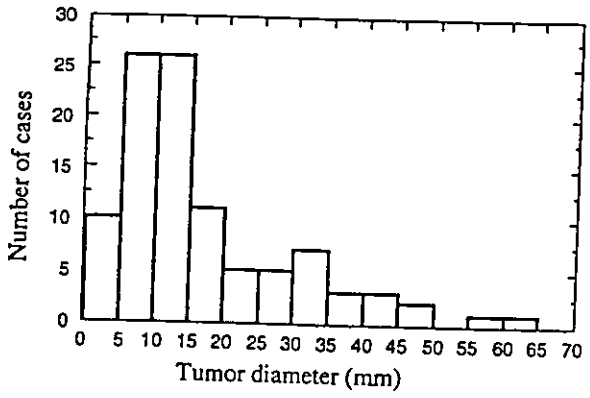

Fig. 4 Distribution of the longest dimension of the resected tumor.

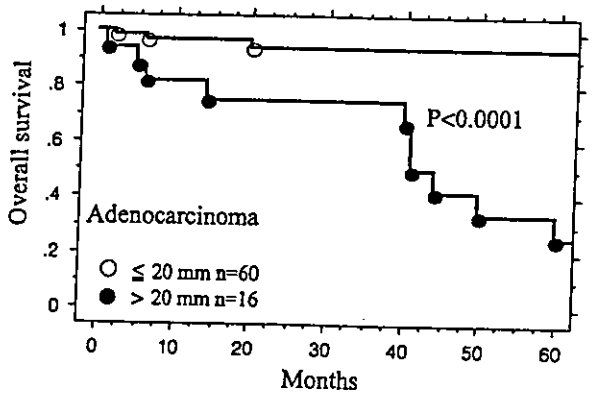

Fig. 5 An overall survival difference ($P < 0.0001$) was found between smaller adenocarcinomas (≤20 mm; $n = 60$; open circles) and larger adenocarcinomas (>20 mm; $n = 16$; filled circles).

Table 2 Univariate analysis for 100 patients with non-small cell lung cancer undergoing sublobular limited resection

Prognostic factor	Overall		Lung cancer specific	
	Five-year survival rate (%)	P value	Five-year survival rate (%)	P value
Gender				
Women ($n=44$)	57.7	0.6463	61.9	0.8782
Men ($n=56$)	56.8		65.3	
Age				
≥73 ($n=48$)	55.8	0.7185	64.2	0.8728
<73 ($n=52$)	62.8		67.8	
Histologic type				
Ad ($n=76$)	63.2	0.0382	66.4	0.7567
Sq ($n=21$)	42.1		58.7	
Tumor size (1 cm)				
≤1 cm ($n=36$)	65.6	0.0384	75.0	0.0403
>1 cm ($n=64$)	52.4		58.2	
Tumor size (2 cm)				
≤2 cm ($n=73$)	78.2	0.0002	87.6	0.0001
>2 cm ($n=27$)	33.2		37.6	
Tumor size (3 cm)				
≤3 cm ($n=83$)	64.6	0.0047	72.5	0.0057
>3 cm ($n=17$)	37.2		42.1	
Differentiation				
WD ($n=52$)	79.7	0.0007	83.9	0.0041
MD + PD ($n=45$)	38.0		45.7	

Ad: adenocarcinoma; Sq: squamous cell carcinoma; WD: well differentiated; MD: moderately differentiated; PD: poorly differentiated.

so, the group of patients for whom wedge resection is sufficient for cure must be identified. Miller et al. [18] compared outcomes of 25 sublobular resections (13 wedge resections and 12 segmentectomies) with those of 71 lobectomies for lung cancer less than 1 cm, and found that patients who underwent lobectomy had significantly better survival and fewer recurrences than patients who had wedge resection or segmentectomy. Landreneau

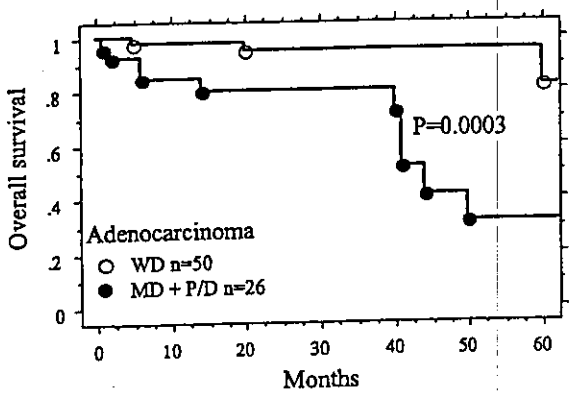

Fig. 6 An overall survival difference ($P = 0.0003$) was found between well-differentiated (WD) adenocarcinomas ($n = 50$; open circles) and a group including moderately–plus poorly–differentiated (MD + PD) adenocarcinomas ($n = 26$; filled circles).

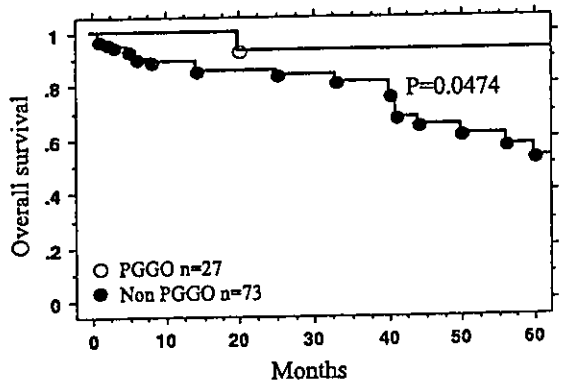

Fig. 7 An overall survival difference ($P = 0.0474$) was found between pure ground-glass opacity (PGGO) tumors ($n = 27$; open circles) and non-PGGO tumors ($n = 73$; filled circles).

Table 3 Univariate analysis for 76 patients with adenocarcinoma undergoing sublobular limited resection

Prognostic factor	Overall		Lung cancer-specific	
	Five-year survival rate (%)	*P*-value	Five-year survival rate (%)	*P*-value
Gender				
Women ($n = 35$)	78.3	0.5821	83.0	0.2765
Men ($n = 41$)	57.1		59.3	
Age				
≥71 ($n = 39$)	65.5	0.5235	67.2	0.7318
<71 ($n = 37$)	60.9		65.9	
Tumor size (1 cm)				
≤1 cm ($n = 29$)	94.4	0.0321	100.0	NC
>1 cm ($n = 47$)	51.6		53.9	
Tumor size (2 cm)				
≤2 cm ($n = 60$)	93.7	<0.0001	98.2	<0.0001
>2 cm ($n = 16$)	24.8		26.5	
Tumor size (3 cm)				
≤3 cm ($n = 66$)	71.5	0.0101	74.6	0.0180
>3 cm ($n = 10$)	35.0		38.9	
Differentiation				
WD ($n = 50$)	81.2	0.0003	83.9	0.0006
MD + PD ($n = 26$)	30.7		33.3	

Ad: adenocarcinoma; Sq: squamous cell carcinoma; WD: well differentiated; MD: moderately differentiated; PD: poorly differentiated; NC: not calculated.

et al. [19] analyzed pathologic stage IA NSCLC for which the patient underwent open wedge resection ($n = 42$), video-assisted wedge resection ($n = 60$), or lobectomy ($n = 117$). At 5 years survival was 58% for patients with open wedge resection, 65% for those with video-assisted wedge resection, and 70% for those with lobectomy. They concluded that this difference resulted from a significantly greater rate of deaths unrelated to cancer in the 5 years following wedge resection. These two studies failed to find clinicopathologic characteristics that might define tumors suitable for limited resection. In our present study, 93.7% 5-year survival was obtained following wedge resection in patients with WD adenocarcinomas less than 20 mm. Histopathologic differentiation also is a significant prognostic factor. Kodama et al. [20] performed limited resection for selected T1N0 patients despite sufficient pulmonary function to tolerate more extensive surgery, and reported a 5-year survival rate of 93%.

Small tumor size alone probably is inadequate as an indication for limited surgery. Ohta et al. [21] found nodal micrometastasis in 21.7% (23/106) of patients with adenocarcinomas with diameters of 2 cm or less. However, when Noguchi et al. [22] analyzed cases by histopathologic type, localized bronchioloalveolar carcinoma showed no lymph node metastasis. In our 27 bronchioloalveolar carcinomas showing PGGO, we have not yet encountered a locoregional recurrence or a distant metastasis after wedge resection. These PGGO tumors included 18 type A, 6 type B and 3 type C in Noguchi's classification [22]. Watanabe et al. [15] also reported absence of cancer death or relapse during median follow-up time of 32 months after wedge resection of 17 bronchioloalveolar carcinomas showing PGGO. In addition, Nakata et al. [8] found that none of 34 adenocarcinomas showing focal GGO and measuring 2 cm or less in diameter had lymph node involvement. Thus, we believe that this group of adenocarcinomas is slow-growing and relatively noninvasive. For instance, Hasegawa et al. [16] reported a mean volume doubling time in PGGO tumors of 813 days, which was significantly longer than in partly GGO tumors with a solid central component (457 days) or in entirely solid nodules (149 days). The higher growth rate presumably reflects an increase in malignant biologic characteristics during development of adenocarcinoma. Accordingly, we believe that wholly PGGO tumors are good candidates for VATS wedge resection

without lymphadenectomy. To obtain definitive evidence, a multi-institutional trial now is underway with the sponsorship of the Japan Clinical Oncology Group (JCOG 0201). In that study, nodal status in clinical stage IA adenocarcinoma including PGGO is being examined by standard lobectomy and systematic lymphadenectomy. If absence of lymph node metastasis is proven in PGGO tumors in this trial, wedge resection for these lesions should become accepted as standard surgery.

In conclusion, relatively good outcome was obtained by wedge resection for small (≤20 mm), peripheral WD adenocarcinomas. VATS wedge resection for these tumors is an important option for patients with impaired cardiopulmonary function. However, since locoregional recurrence developed in 4/60 (6.7%) of these patients in our study, we still consider lobectomy to be the "gold standard". For peripheral localized bronchioloalveolar carcinoma showing PGGO, however, wedge resection appears to be the best option. Study over a longer follow-up period is needed, and larger numbers of cases should be examined with respect to histologic nodal status.

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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.

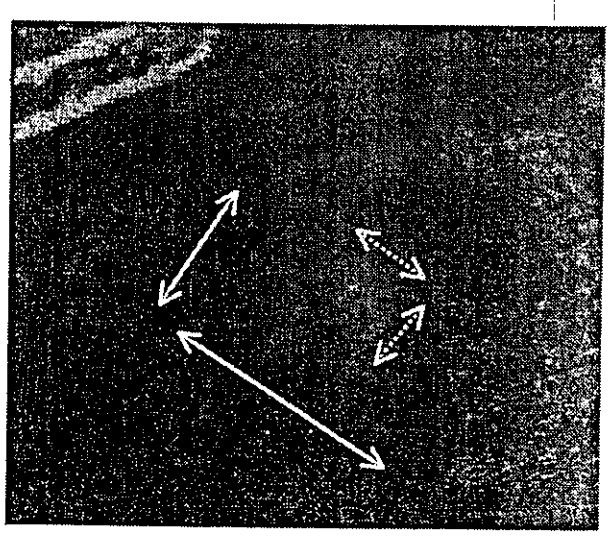

Fig 1. Thin section computed tomographic scan of lung cancer depicting solid attenuation and ground-glass opacity (GGO). The largest area of tumor (solid line) *and solid attenuation* (dotted line) *were decided based on this film. The proportion of GGO area to the entire tumor was defined; GGO ratio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

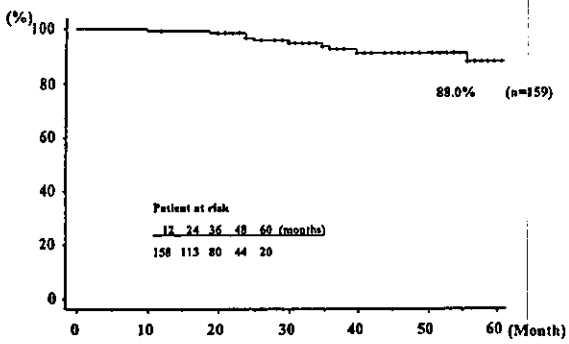

Fig 2. Five-year survival rate of adenocarcinoma less than or equal to 2 cm was 88.0%.

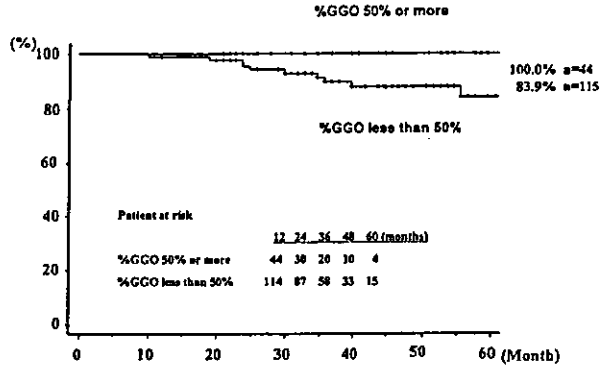

Fig 4. Five-year survival rate according to the proportion of ground-glass opacity (GGO) area. A GGO dominant patient indicated a 100% 5-year survival, whereas patients exhibiting a GGO area less than 50% indicated an 83.9% 5-year survival.

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 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.

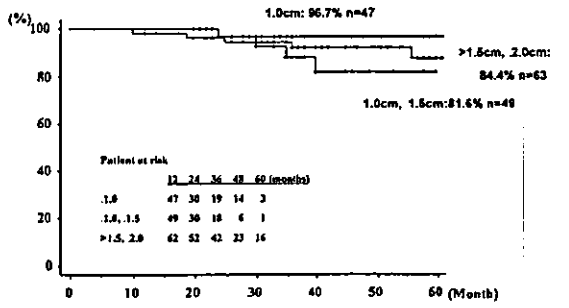

Fig 3. Five-year survival rate according to tumor size. Less than or equal to 1 cm = 96.7%, 1.0–1.5 cm = 81.6%, 1.5–2.0 cm = 84.4%.

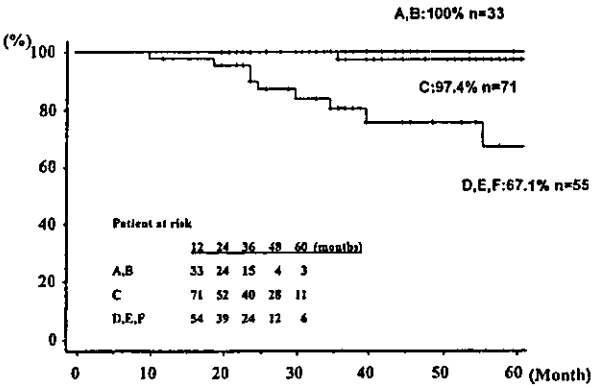

Fig 5. Five-year survival rate according to the Noguchi classification. Noguchi A, B indicated a 100% 5-year survival, type C indicated a 97.4% 5-year survival, and types D, E, and F, indicated a 67.1% 5-year survival, respectively.

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.

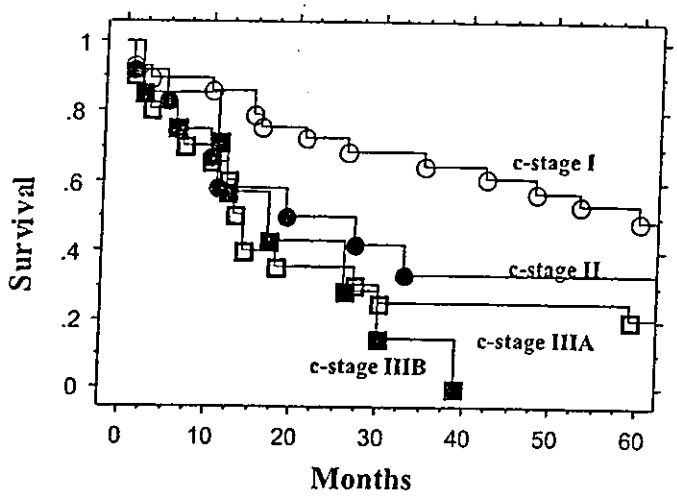

Fig. 1 Comparison of Kaplan-Meier survival curves of patients with small cell lung cancer stratified by clinical stage. The projected 5-year survival rates were 48.9% for c-stage I (n = 29, open circle), 33.3% for c-stage II (n = 12, closed circle), 20.2% for c-stage IIIA (n = 21, open square), and 0%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

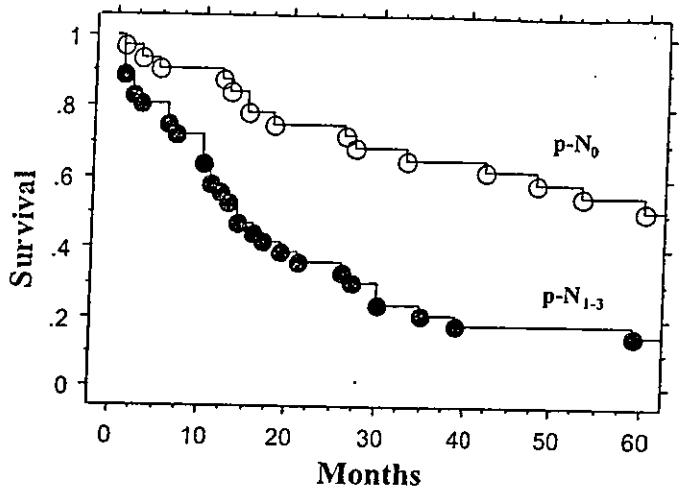

Fig. 2 Comparison of Kaplan-Meier survival curves of patients with small cell lung cancer with and without pathologically proven lymph node metastases. Survival of p-N0 patients (n = 36, open circle) was significantly better than node-positive (p-N1–3) patients (n = 33, closed circle; $p = 0.0001$).

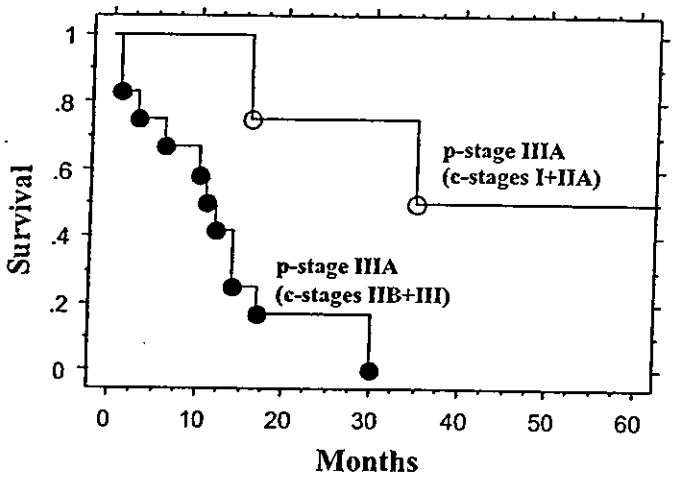

Fig. 3 Comparison of Kaplan-Meier survival curves of patients with p-stage IIIA small cell lung cancer stratified by clinical stage. Survival of patients whose stage was underestimated preoperatively (c-stage I and IIA, n = 5; open circle) was better than the rest of patients with p-stage IIIA disease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

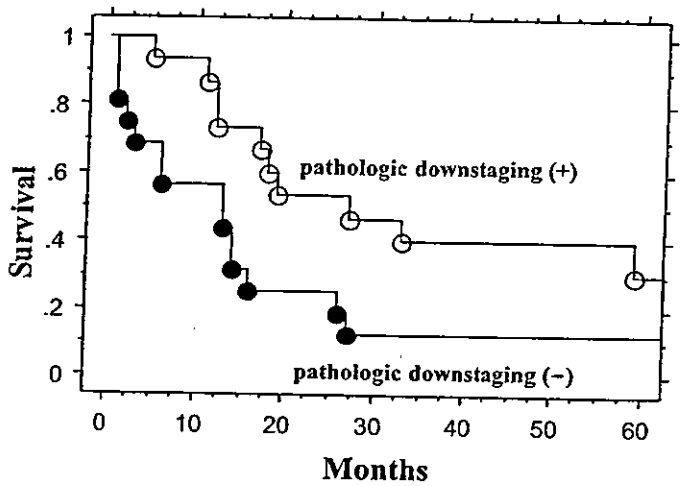

Fig. 4 Comparison of Kaplan-Meier survival curves of patients with small cell lung cancer who did and did not achieve pathologic downstaging with induction chemotherapy. Survival with downstaging (n = 16, open circle) was better than without it (n = 16, closed circle; $p = 0.0312$).

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

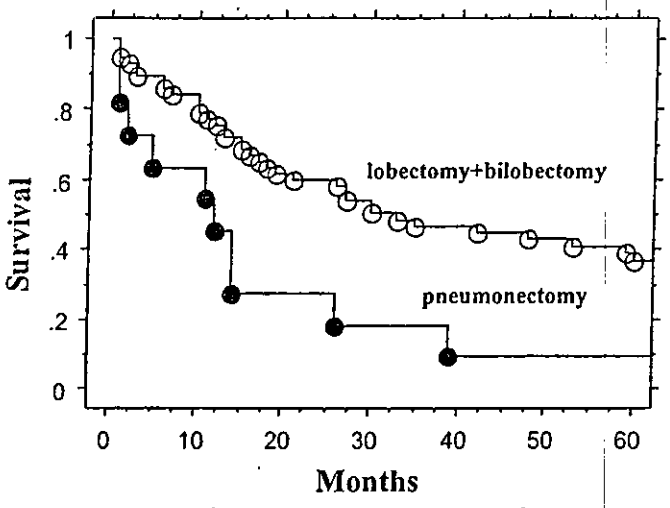

Fig. 5 Comparison of Kaplan-Meier survival curves of patients with small cell lung cancer stratified by the surgical procedure. Survival after lobectomy or bilobectomy (n = 58, open circle) was significantly better than after pneumonectomy (n = 11, closed circle; $p = 0.0163$).

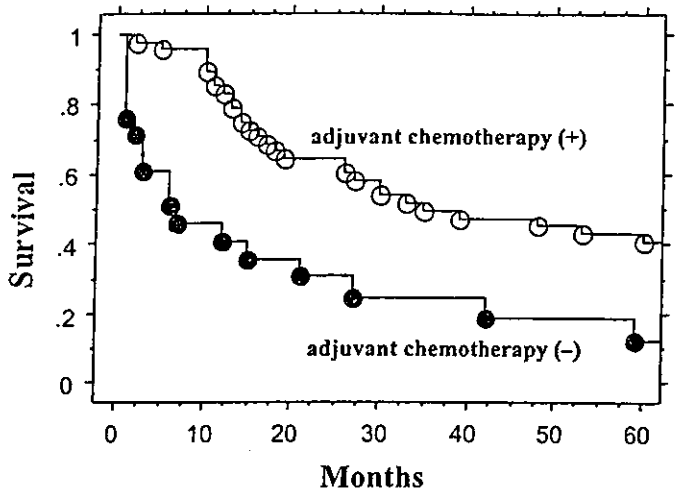

Fig. 6 Comparison of Kaplan-Meier survival curves of patients with small cell lung cancer who did (n = 48, open circle) and did not (n = 21, closed circle) receive adjuvant chemotherapy ($p = 0.0025$).

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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