Future Surgical Procedures for Peripheral Early Stage Lung Cancer

Tumors with 100% GGO findings on CT images could indicate the suitability of surgical limited resection by VATS. Lesions consisting of between 50% and 100% of GGO in area may also be indication for limited resection in cases less than 2 cm in diameter, and also perhaps in cases consisting of between 10% and 50% GGO finding with a tumor size less than 1 cm in diameter.

The evaluation of limited resection for the small peripheral nodules were reported previously by several researchers,[6,7,9] however different opinions concerning these modalities have been reported.[10,11] There are still controversies concerning limited resection of peripheral small lung cancers. A randomized clinical trial by the Lung Cancer Study Group (LCSG) demonstrated disadvantages of limited resection for T1N0 tumors in relation to lobectomy.[11] Therefore clinical evidence of the usefulness of limited resection for peripheral early stage lung cancers should be proven. The features of peripheral lung cancers suitable for limited resection without lymph node dissection should be clarified. That will make it possible to determine the optimal CT findings for limited resection.

In our experience, even if the primary lesion was less than 1 cm in size, nodal involvement was confirmed histologically in some cases. Prognostic factors may not solely depend on tumor size but also on the percentage of the area of GGO. It is necessary to clarify the findings of CT images of non-invasive cancer by a clinical multicenter study.

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A randomized trial comparing adjuvant chemotherapy versus surgery alone for completely resected pN2 non-small cell lung cancer (JCOG9304)

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Adjuvant chemotherapy;
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Vindesine;
N2 disease;
Complete resection

Summary The purpose of this study was to evaluate the efficacy of adjuvant chemotherapy with three courses of cisplatin and vindesine, in comparison to observation only, for N2 non-small cell lung cancer that had been completely resected. Patients with pathologically demonstrated mediastinal lymph node metastasis (N2), who had undergone complete resection, were randomized to observation or adjuvant chemotherapy (cisplatin 80 mg/m^2 on day 1; vindesine 3 mg/m^2 on days 1 and 8: ×3 courses). Cycles started within 6 weeks after complete resection and were repeated every 4 weeks. This trial was terminated before accumulation of the planned numbers for registration because of a slow accrual rate. A total of 119 patients were randomized (59 patients in the adjuvant arm and 60 with surgery alone). The median survival

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was 36 months for both groups. Postoperative cisplatin with vindesine chemotherapy was not shown to be efficacious in cases of completely resected N2 non-small cell lung cancer in this setting of timing, dose and agents studied.

1. Introduction

Even completely resected non-small cell lung cancer (NSCLC) usually relapses with distant metastases. Many adjuvant chemotherapy trials have been conducted to reduce the incidence of postoperative distant metastases. Holmes et al. reported that adjuvant cyclophosphamide, doxorubicin, and cisplatin (CAP) therapy improved disease-free survival for stage II-III adenocarcinomas [1]. Since then, many cisplatin based adjuvant chemotherapy trials have been conducted around the world. Most trials for adjuvant chemotherapy have neither reduced distant metastases nor local recurrence.

Mountain and Dresler reported that some patients with stage I (70-80%) and II (50%) disease can be cured by surgery alone [2]. For these patients, adjuvant chemotherapy would be unnecessary. Postoperative stage IIIA disease relapses in more than two-thirds of cases treated surgically. There are very few stage IIIA patients who could be cured with surgery alone, in whom adjuvant chemotherapy would be unnecessary. The Japanese Clinical Oncology Group (JCOG) conducted a randomized study of postoperative adjuvant chemotherapy focusing only on stage IIIA NSCLC [3], but showed no survival benefit of adjuvant chemotherapy compared with observation alone. There were more cases of N2 disease enrolled in the adjuvant chemotherapy group than in the surgery alone group. In Ohta's report, chemotherapy had to be administered for two or three courses, and many patients received only two cycles of chemotherapy, only 41% of the patients received three cycles of chemotherapy. In the present protocol, cycles of chemotherapy should be administered three times because the low compliance of drug delivery might have contributed to the negative result of the study of Ohta et. al. Also, the present protocol included only N2 patients so as to make the population more uniform.

2. Patients and methods

The protocol was reviewed by JCOG Clinical Trial Review Committee and approved by the Institutional Review Board of each participating hospital. Patient eligibility was dependent on the following criteria: to have undergone complete resection with systematic mediastinal dissection (as described in "General rule for clinical and pathological record of lung cancer" [4]), histologically documented non-small cell lung cancer, including squamous cell carcinoma, adenocarcinoma, large cell carcinoma or adeno-squamous cell carcinoma; age less than 75 years and World Health Organization (WHO) performance status 0-1; normal hematological data (WBC $\geq$ *4000*/mm^3, platelet count $\geq$100,000/mm^3); normal hepatic function (bilirubin $\leq$1.5 mg/dl, SGOT and SGPT within twice the normal range); and normal renal function (blood urea nitrogen $\leq$25 mg/dl, serum creatinine $\leq$1.5 mg/dl, creatinine clearance $\geq$50 ml/min). Furthermore, to be eligible, the absence of no distant metastasis prior to surgery had to be established by full staging procedures including brain computed tomography (CT) or magnetic resonance imaging (MRI), chest CT, bone scans, and abdominal CT or abdominal ultrasonography revealed. Mediastinoscopy was not mandatory before surgery. All patients had ipsilateral mediastinal lymph node metastasis. Finally, patients could not have been previously treated with chemotherapy or radiation therapy for any malignancy and could not have active secondary cancers. Written informed consent, signed by patients, was mandatory before registration.

The following were excluded.: low-grade malignant lung cancers such as carcinoid tumor, adenoid cystic carcinoma or mucoepidermoid carcinoma, N3 lymph node metastases (contralateral mediastinal, contralateral hilar, supraclavicular nodes, or scalene nodes) and cases with malignant pleural effusion or pleural dissemination, T4 disease, i.e. direct invasion to the mediastinal lymph nodes, esophagus, vertebral bodies, heart or carina. Patients with Pancoast type tumor; superior vena cava syndrome or pretracheal or paratracheal lymph node metastases from cancers in which the primary lesion was located in the left lung were also excluded.

At post-operative registration, patients were randomly assigned to either observation or adjuvant chemotherapy. Neither group was allowed to receive any other treatments for cancer other than the planned adjuvant chemotherapy until relapse.

The adjuvant chemotherapy regimen was as follows: intravenous cisplatin (CDDP) 80 mg/m^2 on day 1 and vindesine (VDS) 3 mg/m^2 on days 1 and 8, every 4 weeks for 3 cycles. Chemotherapy started within 6 weeks after surgery.

3. Statistical considerations

Randomization was carried out by a blocked arrangement that balanced the treatment assignments within each institution. All patient data, including clinical, pathological, and outcome measures were entered into a computerized database using a Stat view version 5.0 (SAS Institute Inc. Cary, NC, USA.). The chi-square test and Fischer's test were used to examine the deviation of each patient's characteristics. The Kaplan-Meier method was used to calculate survival analyses. The log-rank test and the generalized Wilcoxon test were used to determine survival differences.

We planned to enter 100 cases into each group. The benefit of adjuvant chemotherapy was assumed to be a 20% increase in the 3-year survival rate (60% in the adjuvant group and 40% in the observation group) [5,6]. Given these assumptions, 154 patients were required, assuming a type 1 error of 0.05 and a type 2 error of 0.20. The primary endpoint was overall survival. The secondary endpoints was disease-free survival. However, the accrual rate was very slow. We abandoned this study in July 1998 after acquiring permission to do so from the JCOG clinical trial review committee. The endpoint was changed to overall survival only. Follow up was done every 6 months by the JCOG data center. The final outcome was confirmed in August 2001.

4. Results

From January 1994 to July 1998, 119 cases were entered from 26 institutes. Of the 119 patients, 59 were randomized to the CDDP + VDS arm and 60 to the surgery alone arm. Only one patient was lost to follow-up.

Forty men and 19 women were included in the adjuvant chemotherapy arm, and 37 men and 23 women were included in the control arm. The median age was 62 in both groups. Pneumonectomy was performed in only six patients in each group. The two groups were well balanced in regard to sex, age, operation performed, preoperative stage, pathological T factors, pattern of combined resection and number of N2 stations (Table 1).

There were no ineligible cases. There were no toxic deaths during adjuvant chemotherapy. Thirty-five of the 59 patients assigned to the chemotherapy arm received three courses of chemotherapy, 55 patients received one or more courses of chemotherapy, and 44 patients received two or more courses. The major cause of

Table 1 Patient characteristics

	Adjuvant chemotherapy	Observation	
Gender (male/female)	40 (68%)/19	37 (62%)/23	0.48
Median age	62 (41–75)	62 (43–74)	0.93
Operation			
Pneumonectomy	6 (10%)	6 (10%)	0.97
Lobectomy	53	54	
Clinical stage			
Stage I–II	44 (75%)	41 (68%)	0.45
Stage III	15 (25%)	19 (32%)	
Pathological T			
T1–/T3	50	55	0.24
Histology			
Adenocarcinoma/squamous cell carcinoma/others	47 (80%)/9/3	40 (67%)/15/5	0.28
Combined resection			
Chest wall	6	3	0.28
Diaphragm	1	1	
Others	9	4	
None	43 (73%)	52 (87%)	
Number of N2 stations			
1	31 (52%)	28 (47%)	0.75
2	24	25	
Unknown	4	6	

Table 2 Compliance of chemotherapy and causes for discontimuation

Chemotherapy	Case no.	Cycles performed			
		0	1	2	3
Fully administered	59	4	11	10	34 (58%)
	34	0	0	0	34
Cause of discontinuation					
Adverse effect	5	0	3	2	–
Patient refusal	18	3	7	8	–
Others	2	1	1	1	–

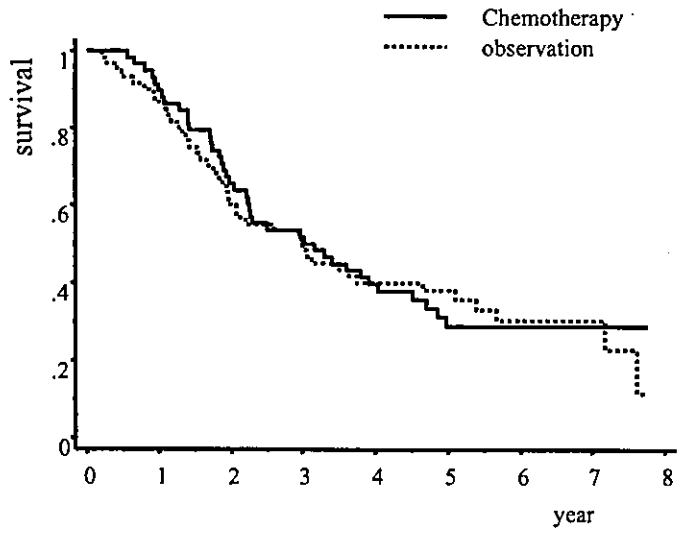
discontinuation of the chemotherapy was patient withdrawal, which accounted for 17 cases (Table 2). There were no grade four adverse effects on hematological data during chemotherapy. The major toxicity was grade 3 neutropenia, which 50% of patients experienced. Only two patients had grade 3 bilirubinemia, and one had grade 3 creatinine elevation.

The 5-year survival was 28.2% in the chemotherapy arm and 36.1% in the control group ($P = 0.89$). The median disease-free survival was 18.3 months in the chemotherapy group and 16.1 months in the control group ($P = 0.66$). There were no statistical differences between the two groups in overall survival by either the log-rank test or the generalized Wilcoxon test (Fig. 1). Almost all deaths were from the original cancer, especially distant metastasis (46%). Lung, bone and brain were frequent sites of relapse in both groups. Lymph node relapses were more frequently seen in the observation group than the adjuvant chemotherapy group ($P = 0.049$) (Tables 3 and 4). Univariate analysis was performed to examine the following factors: treatment arm, age, gender, tumor histology, extent of surgery, existence of combined resection, and number of N2 stations (Table 5). Only an age of 61 or younger was found to be a significant favorable prognostic factor ($P = 0.042$).

5. Discussion

We set out to clarify whether adjuvant chemotherapy is effective in cases of completely resected N2 non-small cell lung cancer.

The first report of adjuvant chemotherapy for completely resected non-small cell lung cancer



Patient at risk								
chemotherapy	59	52	38	30	22	12	7	5
Surgery alone	60	52	36	30	22	17	9	4

Fig. 1 Actual survival. The solid line indicates the adjuvant group and dotted line indicates the observation group ($P = 0.89$).

Table 3 Treatment-related adverse effects (WHO grade) by chemotherapy

Adverse effect	Grade 1–2 (%)	Grade 3 (%)	Grade 4 (%)
WBC	44	51	0
Hb	85	7	0
Plt	11	2	0
Bilirubin	11	4	0
SGOT	22	0	0
SGPT	24	0	0
Creatinine	25	1	0
Nausea/vomit	73	9	0
Diarrhea	16	0	0
Infection	5	2	0
Alopecia	78	–	–

Four patients who did not have chemotherapy were excluded from this analysis. $n = 55$.

Table 4 Relapse patterns for each group

Relapse site	Adjuvant chemotherapy	Observation	*P*-value
Bone	10 (2)	8 (1)	0.77
Brain	13 (1)	8	0.31
Lung	13 (2)	10 (4)	0.60
Mediastinal or cervical LN	7	18 (3)	0.049
Others	4 (1)	5	0.99

Data in parentheses represent metastasis found synchronously at another site. All data reflect absolute numbers of patients.

Table 5 Univariate analyses according to prognostic factors

Factors		*P*-value
Study arm	Adjuvant vs. obsevation	0.840
Age	≤61 vs. >61	0.042
Gender	Female vs. male	0.505
Histology	Adenocarcinoma (ad) vs. non-ad	0.220
Operation	Pneumonectomy vs. lobectomy	0.614
Combined resection	With vs. without	0.116
Number of N2 station	1 vs. 2	0.333

There is no significant difference between any factors.

using a CDDP-based regimen, reported by Holmes et al. [1], included stages II and III, and demonstrated slight effectiveness of adjuvant chemotherapy for large cell and adenocarcinoma cases. LCSG801 [7] also included T2N0 and T2N1 patients, but revealed no effectiveness of adjuvant chemotherapy for non-small cell lung cancer at all. Niiranen et al. reported another randomized trial for completely resected non-small cell lung cancers [8]. Although they demonstrated the efficacy of adjuvant chemotherapy for T1-3N0 patients, the higher number of pneumonectomies included in the observation group might have caused the difference. A meta-analysis of adjuvant chemotherapy by the Non-Small Cell Lung Cancer Collaborative Group reported that the hazards ratio in most trials slightly favored adjuvant chemotherapy but the *P*-value was not significant [9]. The 5-year survival rate for adjuvant chemotherapy patients was 5% better than for surgery alone. A BLT study (ASCO 2003, abstract#2543), which enrolled 381 patients from 56 institutes and included all stages, also could not show the effectiveness of chemotherapy. An 8% 2-year survival advantage was seen with chemotherapy in another meta-analysis for node positive patients [10]. Therefore, the selection of particular stages for perioperative chemotherapy may have been the key to the success seen in that adjuvant chemotherapy trial.

Dautzenberg reported a randomized trial that compared adjuvant radiation versus adjuvant radiation plus chemotherapy [11]. They found no significant difference in overall survival. However, in the subset analyses, patients with N2 disease treated with chemoradiation had a significantly better survival than radiation alone. Keller also reported no difference between survival rates for adjuvant chemo-radiotherapy and adjuvant radiotherapy for stage II and IIIa cancers [12]. Although there have been many clinical trials for non small cell lung cancer, there have been almost no reports on clinical trials of adjuvant chemotherapy for n2 disease. Only Pisters et al. [13] made a report on comparing adjuvant chemo-radiotherapy and adjuvant radiotherapy limited to 71 cases of T1-2 N2 disease including incompletely resected patients. They also did not demonstrate any therapeutic effectiveness. There are several large-scale randomized control studies of adjuvant chemotherapy for patients with completely resected lung cancers. An ALPI study (ASCO 2002, abstract#1157) reported ineffective results, while an IALT study (ASCO 2003, abstract#6) showed slight efficacy of adjuvant chemotherapy. Those two trails included radiation therapy frequently for patients with nodal metastasis. Those reports, mentioned above, aimed to

determine the efficacy of adding chemotherapy to radiation therapy after surgery for patients with nodal metastasis. PORT meta analysis reported that post operative radiation therapy was not useful even in nodal metastasis patients [14], so we aimed to determine the efficacy of adding chemotherapy after surgery for patients with mediastinal nodal metastasis without radiation therapy.

Ohta et al. reported an adjuvant trial for stage IIIa disease conducted by JCOG [3], which also revealed no effectiveness of adjuvant chemotherapy. Although the patients were randomly assigned to each group, the surgery alone group included a higher number of N2 disease patients than the adjuvant chemotherapy group, which may have been related to the negative result. We enrolled only completely resected N2 disease to reduce the heterogeneity of diseases.

Compliance is important in adjuvant chemotherapy. LCSG801 [7] was criticized for low compliance, which was seen as one possible reason for negative data. In our series, 58% of patients received the targeted dose and 75% received two or more courses without serious adverse effects. This appeared sufficient for adjuvant chemotherapy. Although the number of patients accrued was small, the two survival curves were almost identical. Thus, in pathological N2 disease, adjuvant chemotherapy using CDDP and VDS does not improve survival.

The initial target of neoadjuvant chemotherapy was only locally advanced cancer. A few small-sample trials have shown some efficacy of perioperative chemotherapy [15,16]. Recently, a Bimodality Lung Oncology Trial (BLOT) study focused on earlier stages as a target for chemotherapy [13]. The French trial for neoadjuvant chemotherapy also included stages I-IIIa [17]. These two groups hold great expectations for perioperative chemotherapy in earlier stages. Considering these studies, adjuvant chemotherapy is also warranted with new agents for earlier stages of cancer.

6. Conclusion

Patients with N2, NCSLC who had undergone complete resection, were randomized to surgery only or adjuvant chemotherapy (cisplatin 80 mg/m^2 on day 1; vindesine 3 mg/m^2 on days 1 and 8; ×3 courses). This trial was terminated before accumulation of the planned numbers for registration because of a slow accrual rate. A total of 119 patients were randomized (59 patients in the adjuvant arm and 60 with surgery alone). The median survival was 36 months for both groups. There was no significant difference in survival between the adjuvant chemotherapy group and the observation group. The efficacy of adjuvant chemotherapy for completely resected NSCLC with N2 disease might be so small that the number of patients in this study was insufficient to detect the efficacy of this classic regimen.

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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.

(Ann Thorac Surg 2004;78:1011–6)

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.

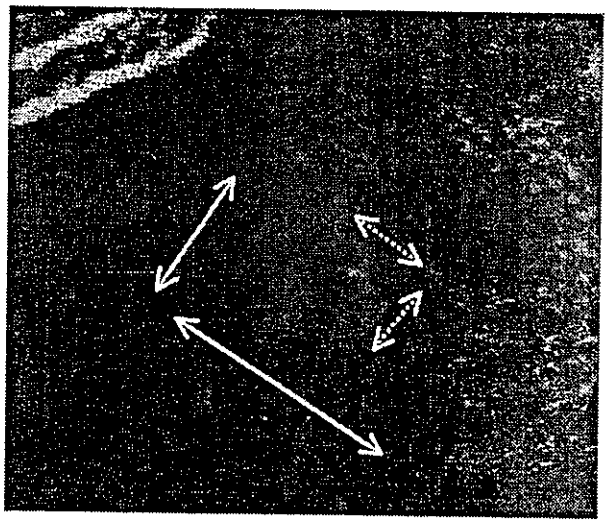

Fig 1. Thin section computed tomographic scan of lung cancer depicting solid attenuation and ground-glass opacity (GGO). The largest area of tumor (solid line) *and solid attenuation* (dotted line) *were decided based on this film. The proportion of GGO area to the entire tumor was defined; GGO ratio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

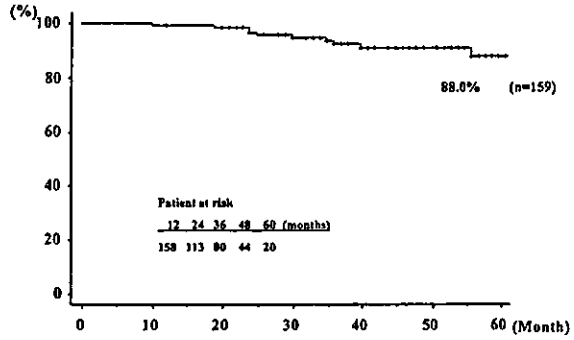

Fig 2. Five-year survival rate of adenocarcinoma less than or equal to 2 cm was 88.0%.

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

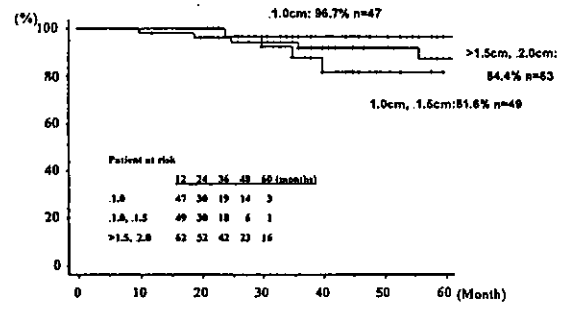

Fig 3. Five-year survival rate according to tumor size. Less than or equal to 1 cm = 96.7%, 1.0–1.5 cm = 81.6%, 1.5–2.0 cm = 84.4%.

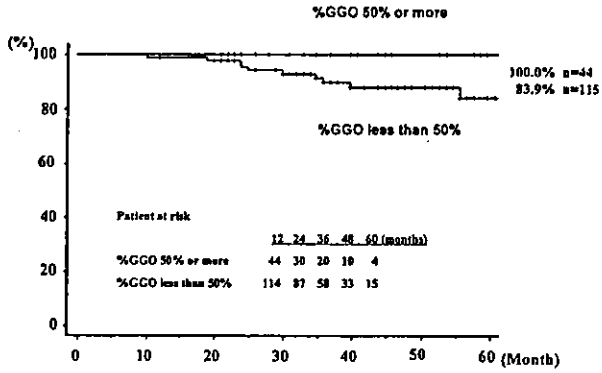

Fig 4. Five-year survival rate according to the proportion of ground-glass opacity (GGO) area. A GGO dominant patient indicated a 100% 5-year survival, whereas patients exhibiting a GGO area less than 50% indicated an 83.9% 5-year survival.

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.

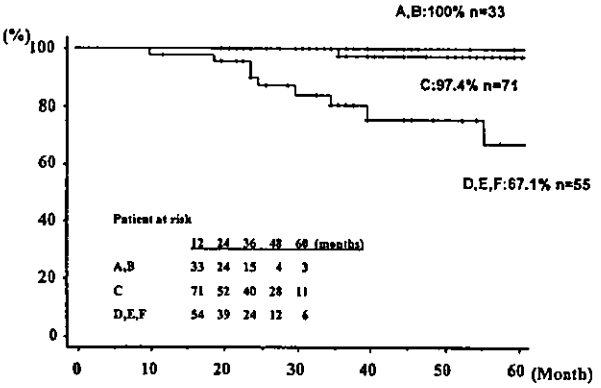

Fig 5. Five-year survival rate according to the Noguchi classification. Noguchi A, B indicated a 100% 5-year survival, type C indicated a 97.4% 5-year survival, and types D, E, and F, indicated a 67.1% 5-year survival, respectively.

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.

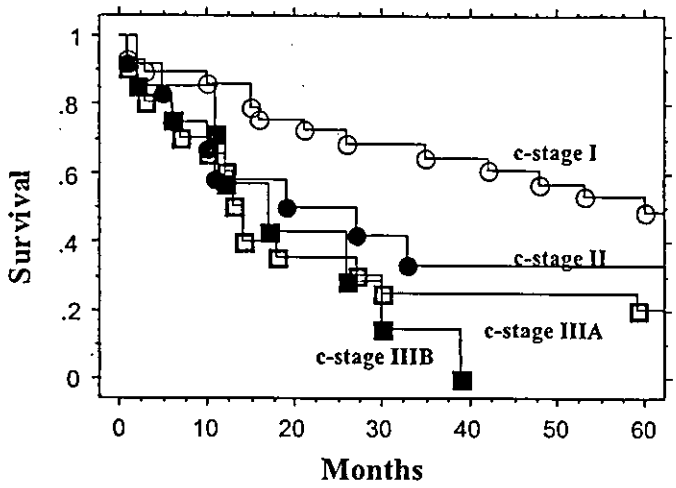

Fig. 1 Comparison of Kaplan-Meier survival curves of patients with small cell lung cancer stratified by clinical stage. The projected 5-year survival rates were 48.9% for c-stage I (n = 29, open circle), 33.3% for c-stage II (n = 12, closed circle), 20.2% for c-stage IIIA (n = 21, open square), and 0%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

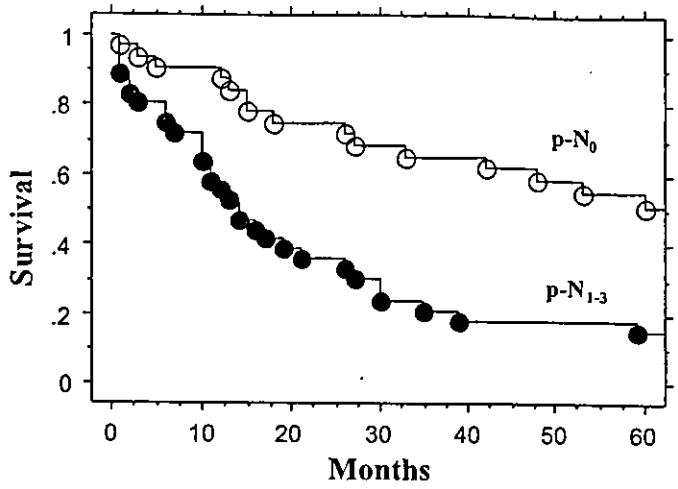

Fig. 2 Comparison of Kaplan-Meier survival curves of patients with small cell lung cancer with and without pathologically proven lymph node metastases. Survival of p-N0 patients (n = 36, open circle) was significantly better than node-positive (p-N1–3) patients (n = 33, closed circle; $p = 0.0001$).

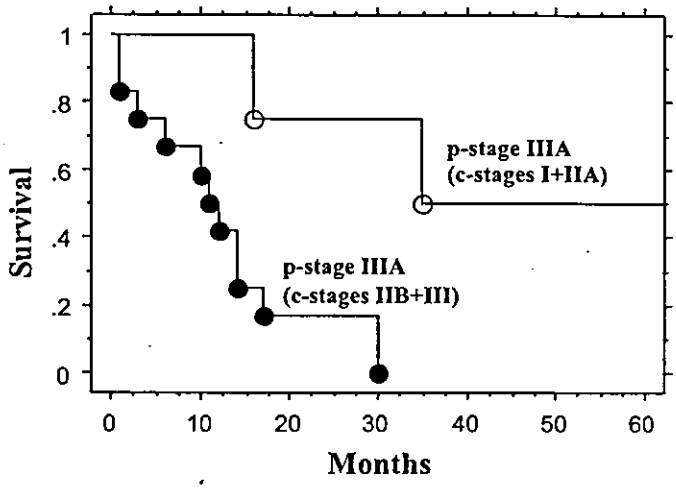

Fig. 3 Comparison of Kaplan-Meier survival curves of patients with p-stage IIIA small cell lung cancer stratified by clinical stage. Survival of patients whose stage was underestimated preoperatively (c-stage I and IIA, n = 5; open circle) was better than the rest of patients with p-stage IIIA disease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

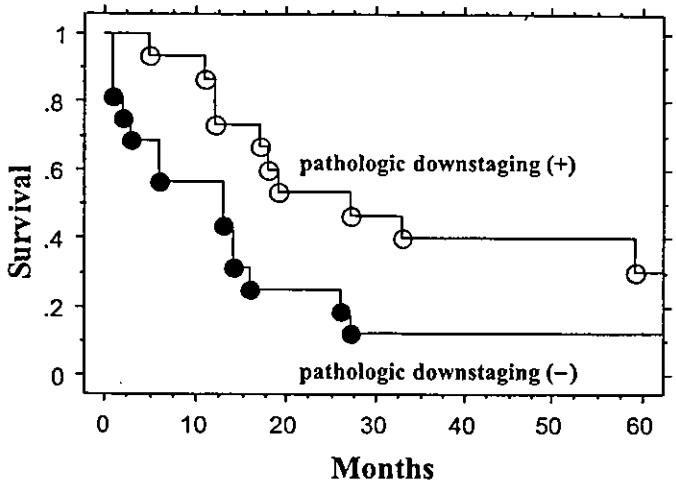

Fig. 4 Comparison of Kaplan-Meier survival curves of patients with small cell lung cancer who did and did not achieve pathologic downstaging with induction chemotherapy. Survival with downstaging (n = 16, open circle) was better than without it (n = 16, closed circle; $p = 0.0312$).

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

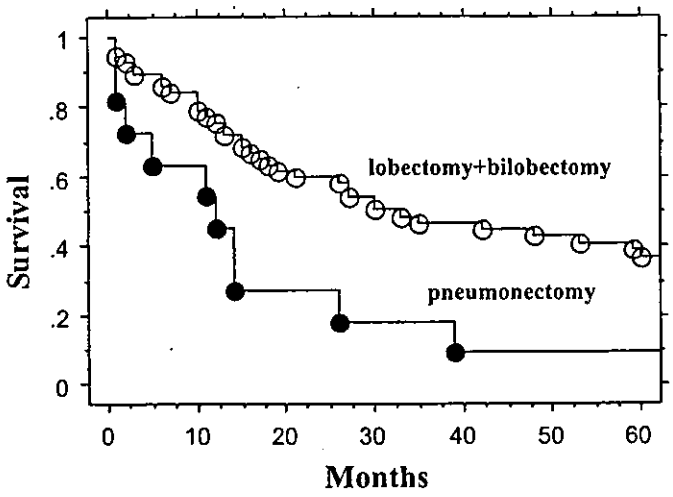

Fig. 5 Comparison of Kaplan-Meier survival curves of patients with small cell lung cancer stratified by the surgical procedure. Survival after lobectomy or bilobectomy (n = 58, open circle) was significantly better than after pneumonectomy (n = 11, closed circle; $p = 0.0163$).

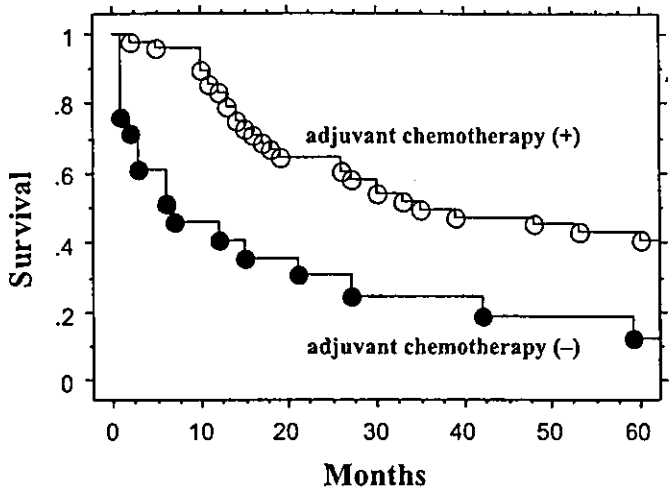

Fig. 6 Comparison of Kaplan-Meier survival curves of patients with small cell lung cancer who did (n = 48, open circle) and did not (n = 21, closed circle) receive adjuvant chemotherapy ($p = 0.0025$).

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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