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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An increase in the percentage of HLA-DR-positive peripheral leukocytes predicts a poor prognosis in patients with squamous cell carcinoma of the lung

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Abstract. Immunologic factors that predict survival in patients with lung cancer have not been established. We examined the relationship between the percentage of HLA-DR-positive peripheral leukocytes [HLA-DR$^+$ (%)] and survival of patients with squamous cell carcinoma of the lung. Before initiating therapy, peripheral blood was taken from 105 patients with squamous cell carcinoma of the lung. HLA-DR positivity was determined by flow cytometry. Patients were divided into 2 groups; a high and a low percentage group. The significance of the intergroup difference in the Kaplan-Meier survival curves was determined by the log rank test. Multivariate analysis was performed using the Cox proportional hazards model. The average HLA-DR$^+$ (%) was 25.9±10.6% (mean ± SD). Survival in the high percentage group (HLA-DR$^+$ (%) ≥25.9%, n=44) was much worse than that in the low percentage group (HLA-DR$^+$ (%) <25.9%, n=61; p=0.0002). The 5-year survival rate in the high percentage group was only 7.4%, while that in the low group was 54.3%. Multivariate analysis identified a significant association between survival and lymph node metastasis (p=0.0028) and HLA-DR$^+$ (%) (p=0.0004). Survival of patients with stages I, II, and IIIA was worse in the high percentage group (n=32) than that in the low percentage group (n=43; p<0.0001). However, survival of patients with more advanced disease, stages IIIB and IV, was similar in the high percentage (n=12) and low percentage groups (n=18; p=0.7610). The peripheral HLA-DR$^+$ (%) predicts survival of patients with resectable squamous cell carcinoma of the lung.

Introduction

Immunologic interactions between host and tumor are an important determinant of survival in cancer patients. However, the immunologic factors that predict survival in lung cancer have not been well characterized. We previously investigated several cell surface markers, NK activity, and lymphoblastogenesis in peripheral blood leukocytes taken from lung cancer patients looking for factors that correlate with a prognosis (1,2). Although other investigators have reported some of these cellular immunologic factors predicted survival (3-7), we found that the percentage of HLA-DR-positive peripheral leukocytes [HLA-DR$^+$ (%)] was the most reliable prognostic factor in lung cancer. The present study analyzed clinical data from 105 patients with squamous cell carcinoma of the lung during a longer follow-up period than the previous study to determine whether or not HLA-DR$^+$ (%) predicts survival.

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Key words: tumor immunity, lung cancer, squamous cell carcinoma, HLA-DR, leukocyte, survival

Patients and methods

One hundred and five patients with squamous cell carcinoma of the lung, treated from April 1995 to November 1998 in our institute, were enrolled in this study. These 98 men and 7 women had an average age of 67.7 years (range, 40-90 years). The diagnosis of squamous cell carcinoma was based upon cytologic or histologic examinations. American Joint Committee on Cancer criteria were used for TNM staging of lung cancer (8). Stages IA and IB patients were grouped together as stage I, and stages IIA and IIB patients were grouped as stage II. Pathologic staging was used when resection was performed, and clinical staging when it was not. When surgery was not performed, the presence of lymph node metastasis was determined by chest computed tomography (CT). The presence of distant metastases was determined by brain CT, chest CT, abdominal CT, and bone scintigraphy. Thirty-nine patients had stage I disease, 10 had stage II, 26 had stage IIIA, 24 had stage IIIB, and 6 had stage IV. Fifty-eight patients underwent surgery and 47 patients did not undergo surgery. Photodynamic therapy (9) was performed for centrally located early squamous cell carcinoma. The mean follow-up period for patients alive was 45.6 months.

Before initiation of therapy, peripheral blood samples were obtained. The HLA-DR$^+$ (%) was determined as described previously (1). In short, the HLA-DR$^+$ cells were stained using a lysed whole blood method: 50 ml of blood from each patient was stained with 50 ml of diluted fluorescein isothiocyanate (FITC)-labeled anti-HLA-DR monoclonal antibody, Leu HLA-DR (Becton-Dickinson, Franklin Lakes, NJ), for 30 min at 4°C in the dark. Then the red blood cells were lysed in lysing buffer. After 15 min, the samples were analyzed by flow cytometry using the FCM-1 (Nihon-bunko, Tokyo,

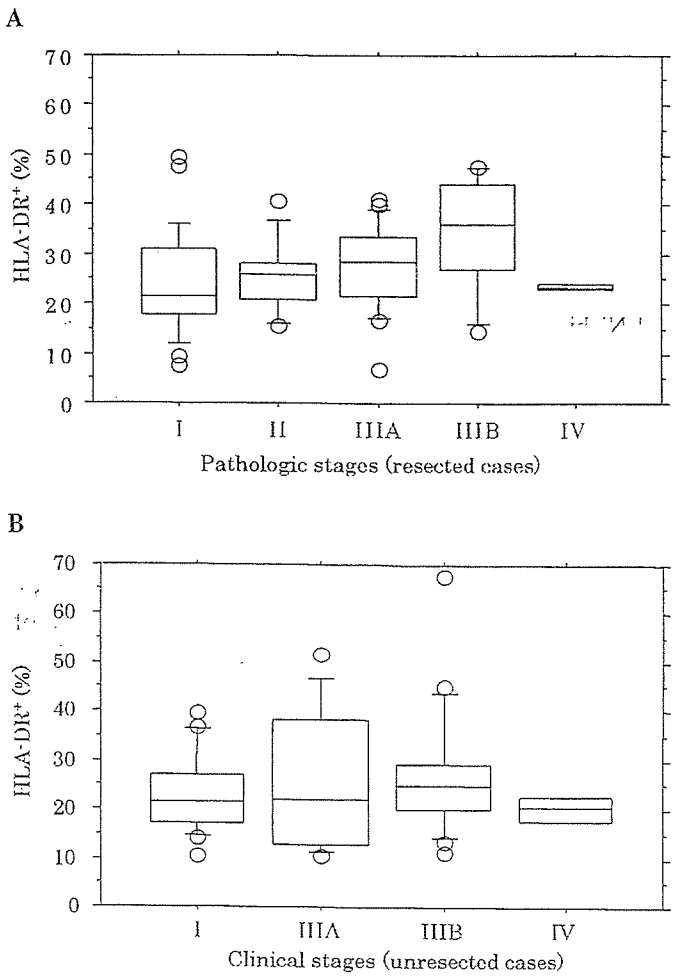

Figure 1. A, Comparison of the percentages of HLA-DR-positive peripheral leukocytes as a function of the pathologic stage in patients who underwent resection of squamous cell carcinoma of the lung. Differences between stages were not significant by the Kruskal-Wallis test (p=0.2976). B, Comparison of the percentages of HLA-DR-positive peripheral leukocytes as a function of the clinical stage in patients who did not undergo resection of squamous cell carcinoma of the lung. Differences between stages were not significant by the Kruskal-Wallis test (p=0.5406).

Japan). Results are expressed as percentages of the total leukocyte count.

The significance of differences in the HLA-DR+ (%) between groups were compared using the Mann-Whitney U test for 2 groups and the Kruskal-Wallis test for ≥3 groups. The patients were divided into a high percentage group, greater than or equal to the average percentage and a low percentage group, less than the average, to determine the correlation between HLA-DR+ (%) and survival. The survival rate was calculated by the Kaplan-Meier method. Survival differences were compared using the log rank test. A multivariate survival analysis was evaluated according to the Cox proportional hazards model in order to detect independent risk factors adjusting for the confounding factors. P<0.05 was considered significant.

Results

The average HLA-DR+ (%) in all 105 patients was 25.9±10.6% (mean ± SD). The HLA-DR+ (%) was similar in patients who did and did not undergo resection (p=0.3179). Additionally,

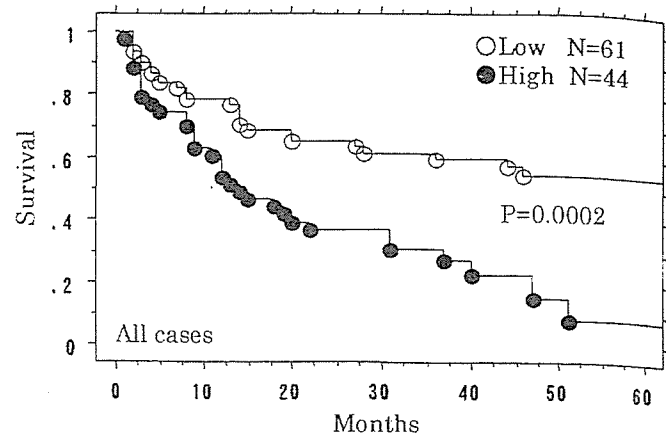

Figure 2. Kaplan-Meier overall survival curves comparing the HLA-DR positive peripheral leukocytes high percentage group and the low percentag group in 105 patients. The difference was significant by the log rank te (p=0.0002).

Table I. Survival analysis of 105 patients with squamous cel carcinoma of the lung in a Cox proportional hazards model.

Prognostic factor	Multivariate analysis P-value (HR: 95% CI)
Age	
≥67.7 vs. <67.7	0.3934 (1.015: 0.981-1.051
Gender	
Men vs. women	0.1399 (4.622: 0.606-35.1C
T-factor	
T_{2-4} vs. T_1	0.2555 (1.499: 0.746-3.012
N-factor	
N_{1-3} vs. N_0	0.0028 (2.728: 1.414-5.263
M-factor	
M_1 vs. M_0	0.2925 (1.715: 0.628-4.695
HLA-DR+ (%)	
≥25.9 vs. <25.9	0.0004 (2.743: 1.565-4.808

HR, hazard ratio; CI, confidence interval.

HLA-DR+ (%) between stages was similar overall and i patients who did and did not undergo resection (Fig. 1).

Survival in the high percentage group [HLA-DR+ (% ≥25.9 %; n=44] was significantly worse than in the lo percentage group [HLA-DR+ (%) <25.9%; n=61] with 5-ye survival rates of 7.4 and 54.3%, respectively (Fig. 2). Mult variate analysis including age, gender, T-factor, N-facto M-factor, and HLA-DR+ (%) as co-variables indicated significant association between survival and lymph nod metastasis (p=0.0028) and HLA-DR+ (%) (p=0.0004) (Table I

Among the 58 patients who underwent resection, survivi in the high percentage group (n=29) was worse than that i the low group (n=29), with 5-year survival rates of 9.3 an 67.6%, respectively (Fig. 3). Among the 47 patients who di

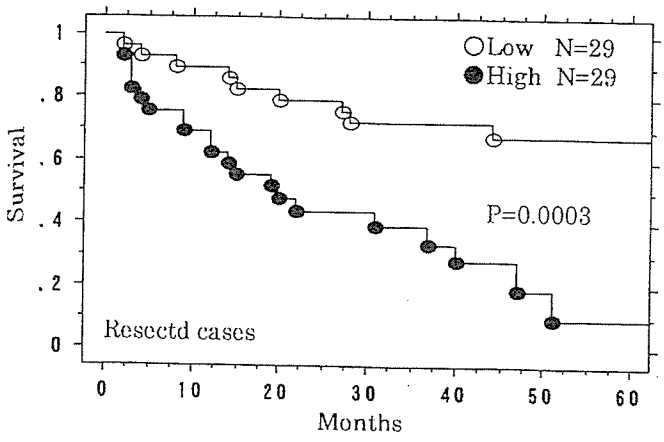

Figure 3. Kaplan-Meier survival curves comparing the HLA-DR-positive peripheral leukocytes in high and low percentage group in 58 patients who underwent resection of squamous cell carcinoma of the lung. The difference was significant by the log rank test (p=0.0003).

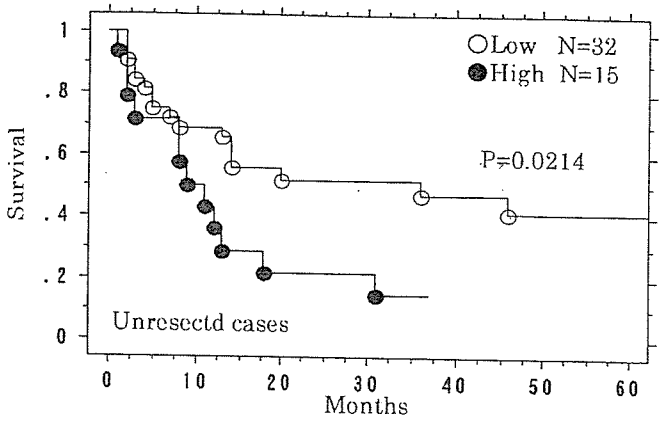

Figure 4. Kaplan-Meier survival curves comparing the HLA-DR-positive peripheral leukocytes in high and low percentage group in 47 patients who did not undergo resection of squamous cell carcinoma of the lung. The difference was significant by the log rank test (p=0.0214).

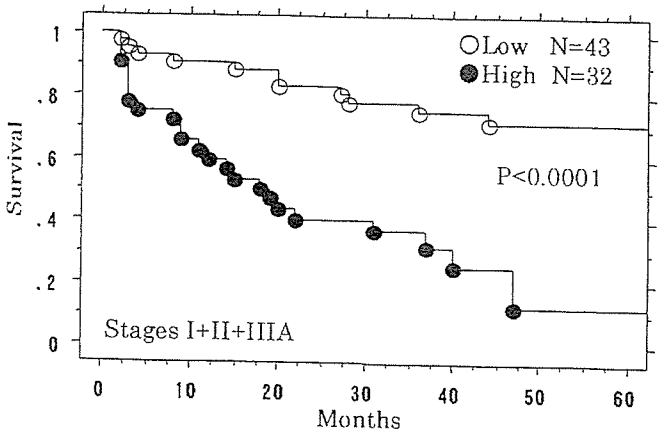

Figure 5. Kaplan-Meier survival curves comparing the HLA-DR-positive peripheral leukocytes in high and low percentage group in stages I, II, and IIA of patients with squamous cell carcinoma of the lung. The difference was significant by the log rank test (p<0.0001).

not undergo resection, survival in the high percentage group (n=15) was worse than in the low percentage group (n=32), with no 5-year survivors in the high percentage group and a 41.5% survival rate in the low percentage group (Fig. 4).

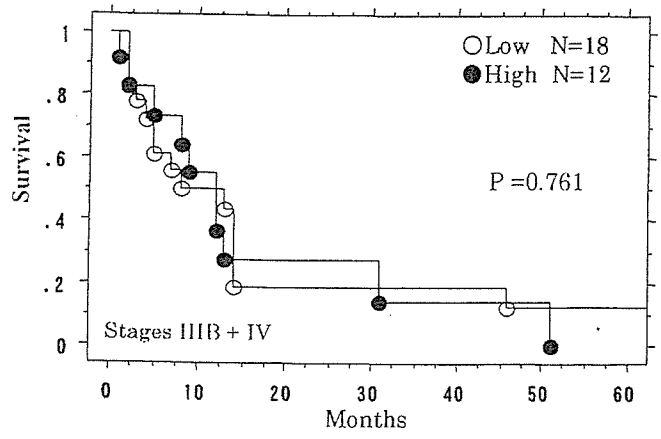

Figure 6. Kaplan-Meier survival curves comparing the HLA-DR-positive peripheral leukocytes in high and low percentage group in stages IIIB and IV of patients with squamous cell carcinoma of the lung. The difference was not significant by the log rank test (p=0.7610).

Among patients with stages I, II, or IIIA disease, survival in the high percentage group (n=32) also was worse than in the low percentage group (n=43), with 5-year survival rates of 12.5 and 71.5%, respectively (Fig. 5). However, survival in the high (n=12) and the low (n=18) percentage groups were similar in patients with more advanced disease, stages IIIB and IV (Fig. 6).

Discussion

HLA-DR antigens are shared by activated T cells, activated NK cells, B cells, monocytes, macrophages, dendritic cells, and hematopoietic progenitor cells (10). A decrease in peripheral blood monocyte HLA-DR expression has been correlated with a poor prognosis in patients with severe injury or sepsis (11-13). Conversely, our study of patients with lung cancer revealed that an increase in HLA-DR$^+$ (%) strongly correlates with a poor outcome. We performed additional flow cytometric analyses to determine the HLA-DR$^+$ subset more precisely using double-staining with combinations of HLA-DR/CD4 and HLA-DR/CD8 in another series of patients with lung cancer. In that study, the subset that best predicted poor survival was HLA-DR$^+$ CD8$^-$ leukocytes (14).

We believe the following facts are relevant: i) HLA-DR$^+$ (%) does not increase with stage progression. Since the HLA-DR$^+$ (%) does not rise to maintain a correlation with the pathologic or clinical stages, some immunologic reactions probably are induced by only some tumor cells through an increase in the number of HLA-DR$^+$ cells. ii) HLA-DR$^+$ (%) predicts survival in patients with squamous cell carcinoma, but not in patients with adenocarcinoma (2). This finding implies that tumor immunogenicity plays an important role in determining survival. For example, spontaneous regression of squamous cell carcinoma of the lung has been the subject of several reports (15-19), but this phenomenon has not been documented in adenocarcinoma of the lung, probably due to lower immunogenicity of this histologic type. iii) Survival differences related to the HLA-DR$^+$ (%) disappear in stages IIIB and IV. This may be because the host immune response is weakened in advanced disease.

The status of HLA-DR expression by peripheral leukocytes and prognosis in cancer patients has received little attention. Tisch *et al* (20) studied peripheral leukocytes in patients with head and neck squamous cell carcinoma and found a negative correlation between survival and HLA-DR6 positivity. Yacyshyn *et al* (21) reported that patients with breast cancer who showed a greater than median decrease in peripheral $CD20^-HLA\text{-}DR^+$ cells following cyclophosphamide treatment had a survival advantage over patients who had less than the median decrease in the percent of the same subset. Kikuchi *et al* (22) reported that the percentage of peripheral $CD3^+HLA\text{-}DR^+$ cells in patients with ovarian cancer with minimal residual tumors after surgery was higher than it was pre-operatively, while the value in patients with a large residual tumor volume was lower. Arista *et al* (23) reported greater numbers of peripheral $HLA\text{-}DR^+$ T lymphocytes in patients with colorectal cancer than in healthy volunteers. These reports on breast, ovarian, and colorectal cancer suggested that certain subsets of $HLA\text{-}DR^+$ cells are induced by the presence of cancer cells. We do not believe that the stimulation of leukocytes by cancer cells is always advantageous in cancer patients. Although we did not analyze cytokines in the present study, a Th1/Th2 imbalance in cancer patients (24-26) may play an important role in killing cancer cells in the host's immune response. Ito *et al* (27) reported that the Th1/Th2 ratio in infiltrative lymphocytes is elevated in patients with squamous cell carcinoma of the lung. In addition, Gerrard *et al* (28) reported that a Th2-type cytokine, interleukin 4, increases HLA-DR expression in normal human monocytes. Thus, an increase in the $HLA\text{-}DR^+$ (%) in patients may reflect a Th2-dominant state that makes the prognosis in these patients worse. Further studies are needed on this point.

In conclusion, $HLA\text{-}DR^+$ (%) can be a useful immunologic marker to predict survival in potentially respectable, stages IA to IIIA squamous cell carcinoma of the lung.

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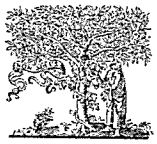

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A randomized trial comparing adjuvant chemotherapy versus surgery alone for completely resected pN2 non-small cell lung cancer (JCOG9304)

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KEYWORDS
Non-small cell lung cancer;
Adjuvant chemotherapy;
CDDP;
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: $\times$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

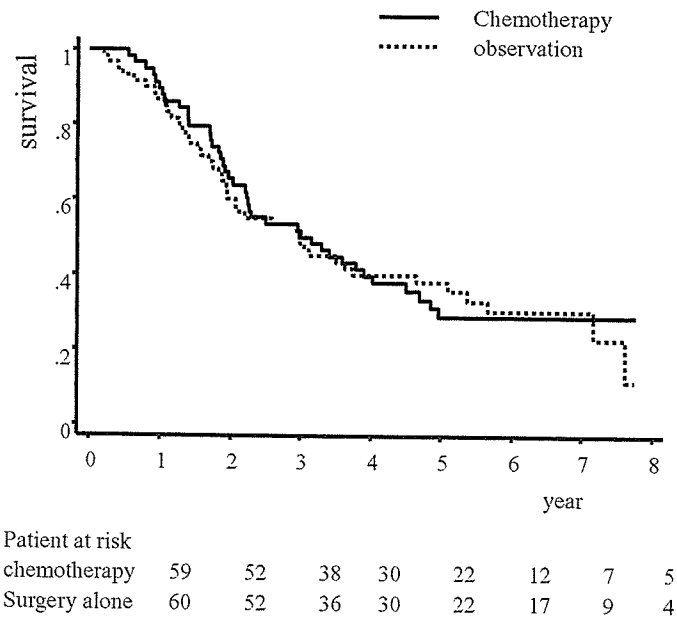

Fig. 1 Actual survival. The solid line indicates the adjuvant group and dotted line indicates the observation group ($P = 0.89$).

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

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KEYWORDS
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Limited resection;
Ground-glass opacity;
Computed tomography

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%,

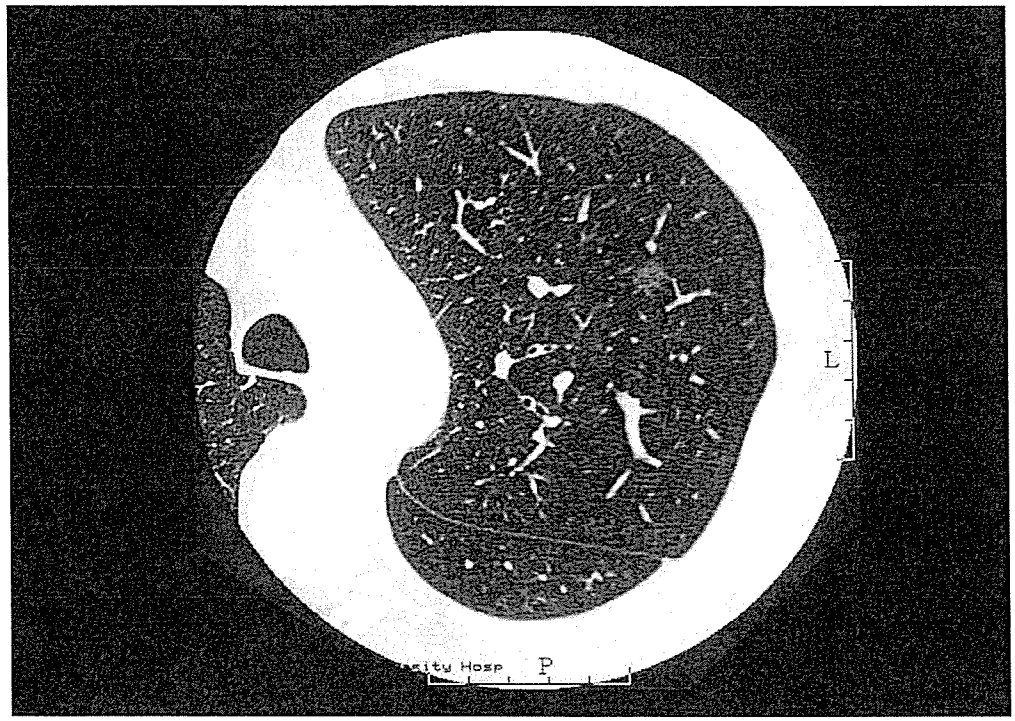

Fig. 1 Representative findings of high-resolution computed tomography (CT) showing a tumor with pure ground-glass opacity (PGGO). The pathologic diagnosis of this tumor was bronchioloalveolar carcinoma.

$P = 0.0003$; 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).

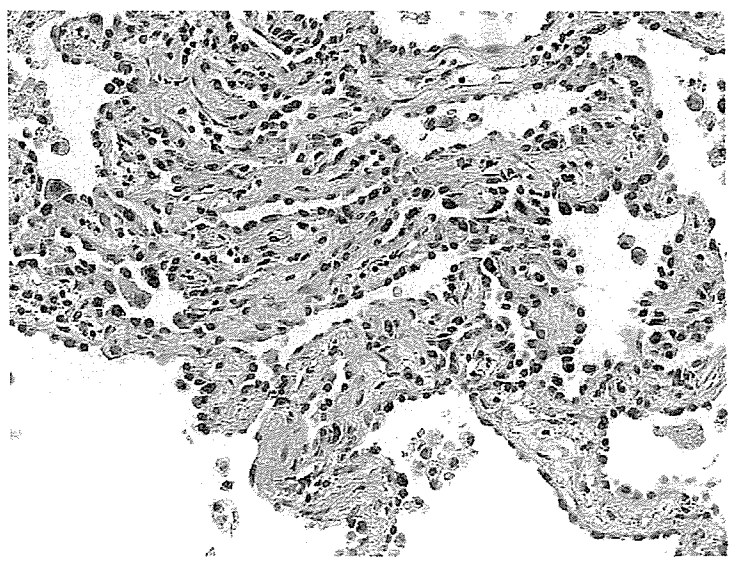

Fig. 2 As in the lesion shown here, the pathologic diagnosis in resection specimens of all pure ground-glass opacity (PGGO) tumors in this study was bronchioloalveolar carcinoma without microscopic blood vessel or lymph vessel invasion (hematoxylin and eosin; 200×).

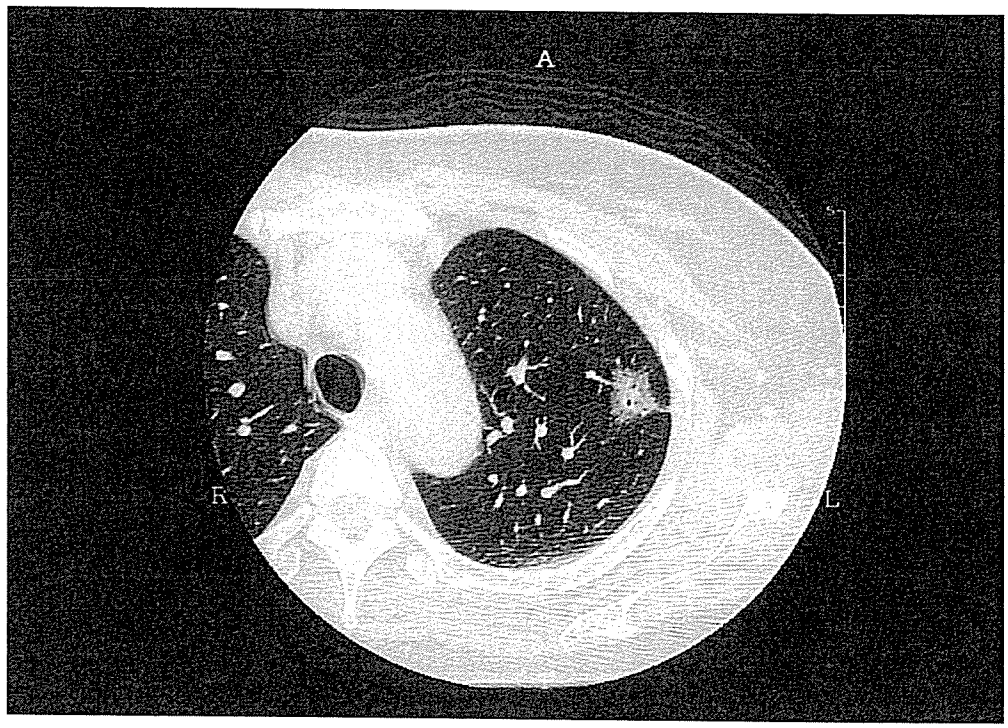

Fig. 3 Representative findings of high-resolution computed tomography (CT) showing a non-pure ground-glass opacity (non-PGGO) tumors. A solid component can be seen at the center of the tumor.

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

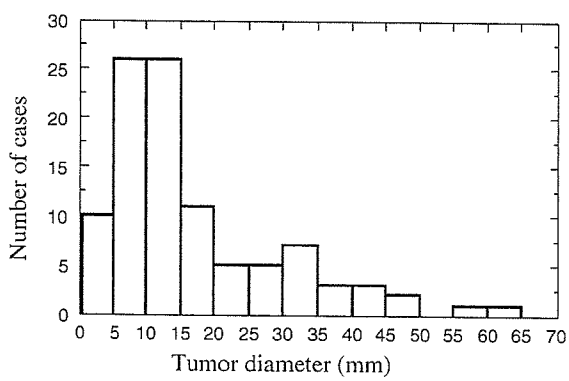

Fig. 4 Distribution of the longest dimension of the resected tumor.

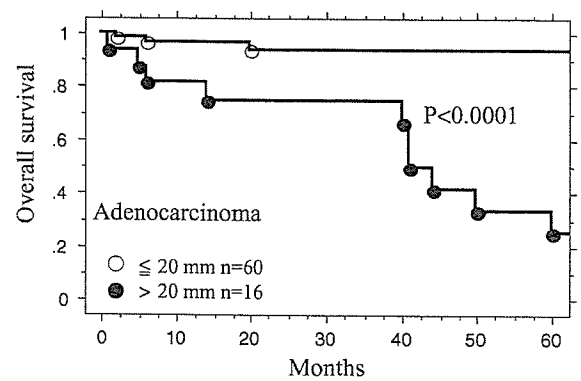

Fig. 5 An overall survival difference ($P < 0.0001$) was found between smaller adenocarcinomas (≤20 mm; $n = 60$; open circles) and larger adenocarcinomas (>20 mm; $n = 16$; filled circles).

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

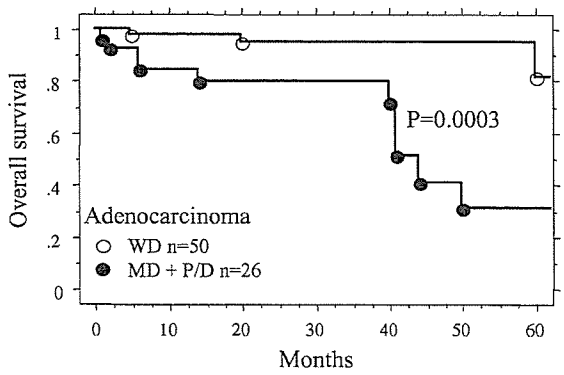

Fig. 6 An overall survival difference ($P = 0.0003$) was found between well-differentiated (WD) adenocarcinomas ($n = 50$; open circles) and a group including moderately–plus poorly–differentiated (MD + PD) adenocarcinomas ($n = 26$; filled circles).

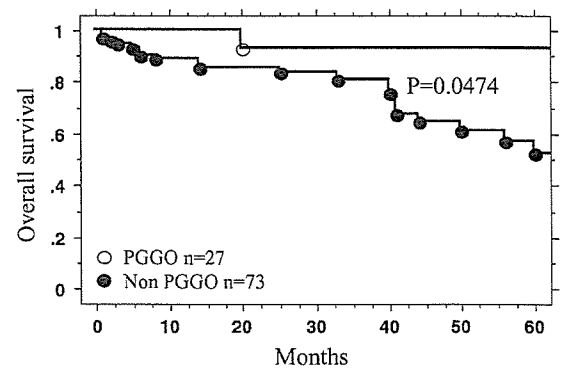

Fig. 7 An overall survival difference ($P = 0.0474$) was found between pure ground-glass opacity (PGGO) tumors ($n = 27$; open circles) and non-PGGO tumors ($n = 73$; filled circles).

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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