

0.01% trypsin and subjected to microwave antigen retrieval [37].

The immunohistochemical method using the avidin-biotin-peroxidase complex was described previously [35]. The reaction products were visualized with diaminobenzidine and the sections were counterstained with hematoxylin.

Negative control staining, which was performed with the same class of immunoglobulin instead of the first antibody, yielded negative results in all cases. The intensity and pattern of immunostaining with HECD-1, anti- α -catenin, anti- β -catenin, and CBL175 in intrabronchial lesions were compared with those of normal bronchial epithelium, and the immunohistochemical staining results were evaluated as described previously [35]. Levels of immunostaining were evaluated in separate compartments of the bronchial epithelium: the basal layer (the first two-fifths of the distance between the basement membrane and the free surface), the intermediate layer, and the superficial layer (the upper one-fifth of this distance). Expression of E-cadherin, α -catenin, β -catenin, and plakoglobin in each layer was judged to be normal if more than 90%

of the intrabronchial lesion cells were positively stained by the appropriate antibodies. If staining was distinctly weaker than that of normal epithelium, or if less than 90% of the intrabronchial lesion cells were positively stained, the expression was judged to be reduced. Immunohistochemical staining was scored independently by two observers (Y.K., Y.E.).

2.3. Statistical analysis

The data were analyzed using the Cochran–Armitage test [38], which was conducted by a stepwise method excluding E-cadherin, α -catenin, β -catenin, and plakoglobin, since these four variables are the variables of interest. Differences at $p < 0.05$ were considered to be statistically significant.

3. Results

In bronchial epithelium, E-cadherin and all catenins were expressed at a high level. Immunohistochem-

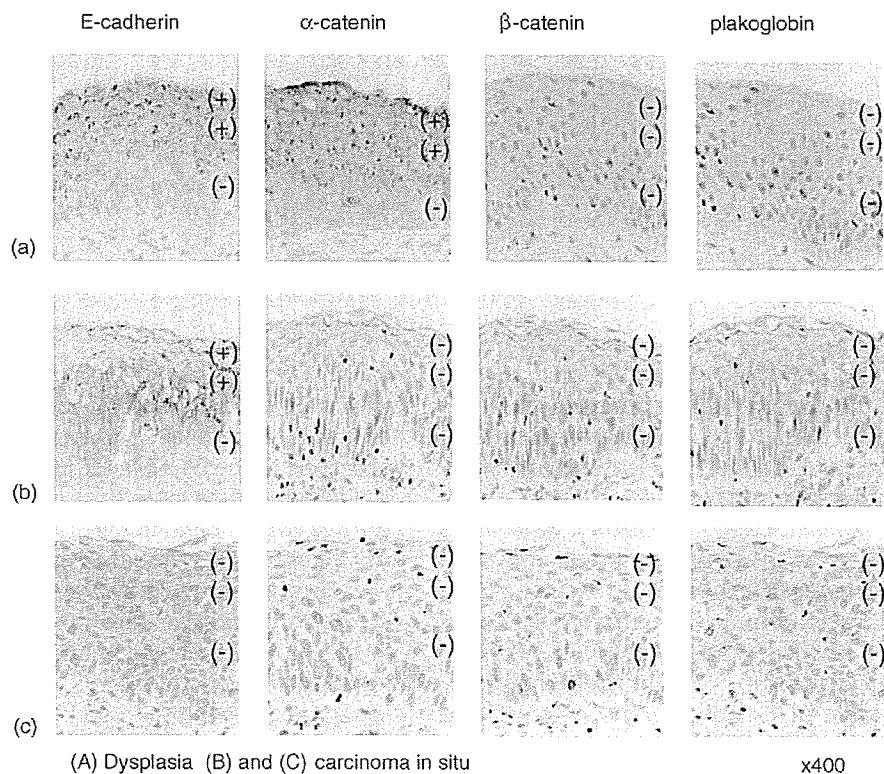


Fig. 1 (A) Representative immunohistochemical staining for E-cadherin, α -catenin, β -catenin, and plakoglobin in biopsy specimens of dysplasia (a) and carcinoma in situ (b and c). Evaluation for each layer of the intrabronchial lesions is shown at the right side of each picture $\times 400$. (B) A borderline area between carcinoma in situ and dysplasia. Evaluation for each layer of the carcinoma in situ area is shown at the left side of each picture, and that for each layer of the dysplasia area at the right side of each picture.

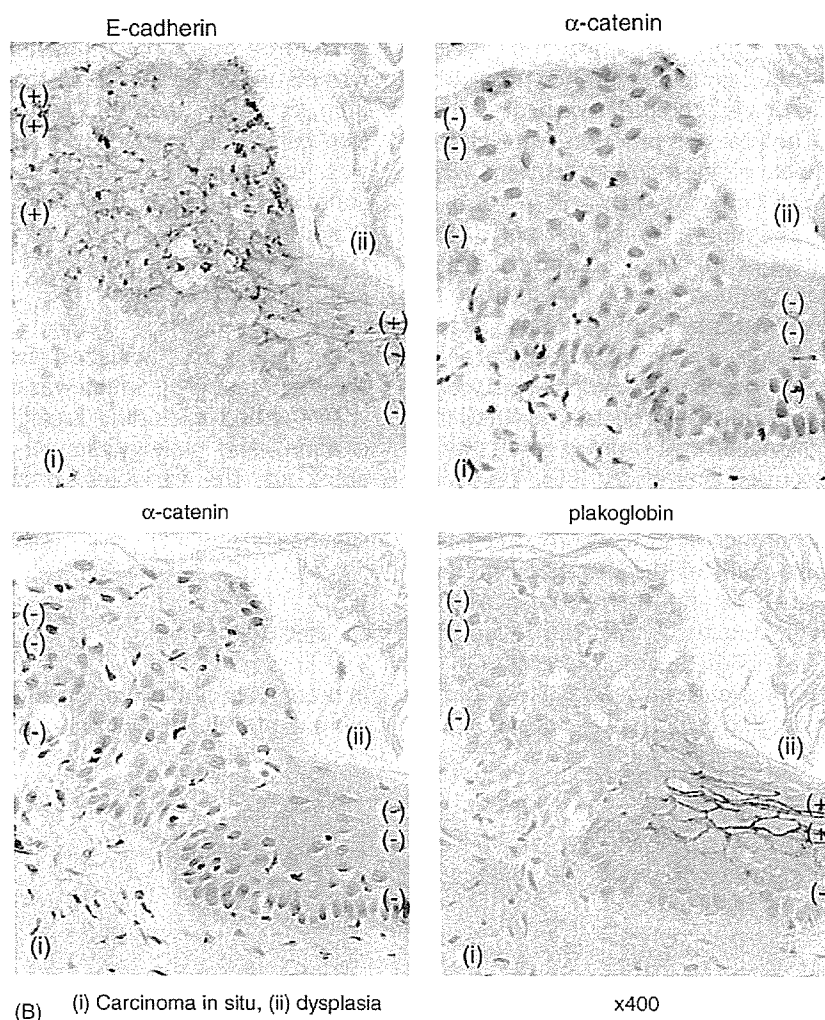


Fig. 1 (Continued).

ical findings for representative intrabronchial lesions are shown in Fig. 1. Cases with reduced expression of either E-cadherin or catenins in intrabronchial lesions are summarized in Table 1. Reduced expression of E-cadherin and/or catenins was closely correlated with an atypical grade of dysplasia in the basal layer ($p < 0.05$). In particular, down-regulation of E-cadherin and/or catenins was associated with an atypical grade of BSM with atypia in intrabronchial lesions ($p < 0.01$). Additionally, reduced expression of E-cadherin and catenins was observed in squamous cell carcinoma, as shown in Table 2.

In BMS without atypia ($n = 32$ cases), loss of expression of α -catenin, β -catenin or plakoglobin was observed in the basal layer in six cases (18%), in the intermediate layer in two cases (6%), and in the superficial layer in three cases (9%). In BSM

with atypia ($n = 25$ cases), loss of expression of E-cadherin, α -catenin, β -catenin or plakoglobin was observed in the basal layer in seven cases (28%), in the intermediate layer in seven cases (28%), and in the superficial layer in five cases (20%). In dysplasia ($n = 5$ cases), loss of expression of these molecules was observed in the basal layer in two cases (40%), in the intermediate layer in one case (20%), and in the superficial layer in one case (20%). In carcinoma in situ ($n = 21$ cases), loss of expression was observed in the basal layer in 10 cases (48%), in the intermediate layer in 9 cases (43%), and in the superficial layer in 8 cases (38%). In microinvasion to bronchial wall ($n = 4$), loss of expression was observed in the basal layer in four cases (100%), in the intermediate layer in three cases (75%), and in the superficial layer in two cases (50%). These results are presented in Fig. 2 and Table 3.

Table 1 Aberrant expression of E-cadherin and catenins in intrabronchial lesions

	E-cadherin			α-Catenin			β-Catenin			Plakoglobin			Rate ^a (%)
	B	I	S	B	I	S	B	I	S	B	I	S	
BSM without atypia n = 32	+	+	+	-	-	+	+	+	+	-	-	-	21
	+	+	+	+	+	+	-	+	+	+	+	+	
	+	+	+	+	+	+	-	+	+	+	+	+	
	+	+	+	+	+	+	+	+	+	-	+	+	
	+	+	+	+	+	+	+	+	+	+	+	+	
	+	+	+	+	+	+	+	+	+	-	-	-	
BSM with atypia n = 25	-	-	+	+	+	+	+	+	+	+	+	+	28
	+	+	+	-	-	-	-	-	-	+	+	+	
	+	+	+	+	+	+	-	-	-	+	+	+	
	+	+	+	+	+	+	-	-	-	+	+	+	
	+	+	+	+	+	+	-	-	+	-	-	+	
	-	-	-	-	-	-	-	-	-	-	-	-	
Dysplasia n = 540%	-	+	+	-	+	+	-	-	-	-	-	-	40
	-	+	+	-	+	+	+	+	+	+	+	+	
	+	+	+	+	+	+	-	-	+	+	+	+	
Carcinoma in situ n = 21	+	+	+	+	+	+	-	-	+	+	+	+	48
	+	+	+	+	+	+	-	+	+	-	+	+	
	+	+	+	-	-	-	-	-	-	-	-	-	
	+	-	+	-	-	+	-	-	-	+	+	+	
	-	+	+	-	-	-	-	-	-	-	-	-	
	-	-	+	-	-	-	+	+	+	+	+	+	
Microinvasion to bronchial wall n = 4	-	-	-	-	-	+	-	-	-	-	+	+	100
	-	-	-	-	-	-	-	-	-	+	+	+	
	+	+	+	-	-	+	-	-	+	+	+	+	
	+	+	+	+	+	+	-	-	-	-	-	-	
+	+	+	+	+	+	+	+	+	-	+	+		

Variable	Contrast	p-Value
BSM without atypia	BSM with atypia	0.097
BSM without atypia	Dysplasia	0.043
BSM without atypia	Carcinoma in situ	0.003
BSM without atypia	Microinvasive to bronchial wall	0.001

B: basal layer; I: intermediate layer; S: superficial layer.

^a Reduced expression rate of either E-cadherin or catenins in intrabronchial lesions.

Table 2 Reduced expression rate of E-cadherin and catenins in advanced stage of squamous cell carcinoma

	Squamous cell carcinoma, n = 32
E-cadherin	21 (67%)
α-Catenin	26 (81%)
β-Catenin	27 (84%)
Plakoglobin	14 (44%)
Rate ^a	100%

^a Reduced expression rate of either E-cadherin or catenins in squamous cell carcinoma.

4. Discussion

It has been established that malignant transformation can arise from an accumulation of genetic alterations. This stepwise transformation is known as multistep carcinogenesis. In general, it is known that primary lung carcinoma is one of the most malignant solid tumors, and that it has a wide range of invasive and metastatic behavior. There is a high possibility that alterations in genotype are reflected in the morphological phenotype of the bronchial epithelium. In this context, bronchial

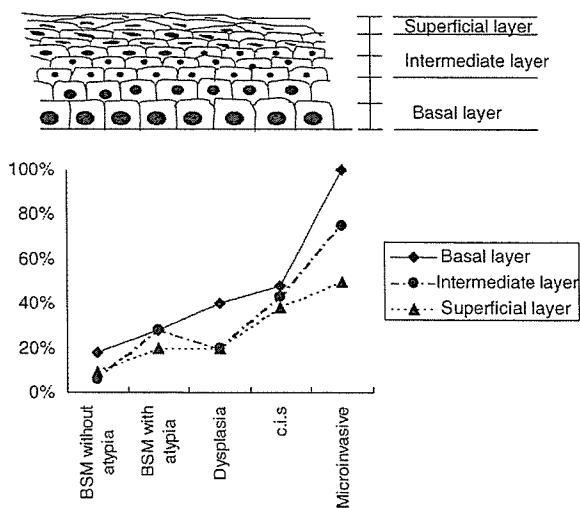


Fig. 2 Proportion of cases with reduced expression of either E-cadherin or catenins within the basal layer (◆), the intermediate layer (●) or the superficial layer (▲) of the intrabronchial lesions. The relative distribution of the different layers is shown in the upper part of the figure.

squamous metaplasia and dysplasia can be considered as precancerous lesions, mutation of the p53 tumor suppressor gene, and deletion of chromosome 17p have been reported in such lesions [39–42]. We have reported sequential changes in cell proliferation, DNA aneuploidy and accumulation of mutant p53 protein during carcinogenesis in the bronchial epithelium, and that these histochemical changes initially occurred in the basal layer [43]. We believe that the ability of cancerous cells to invade the bronchial wall will be acquired in a sequential manner during carcinogenesis. Therefore, we investigated the reduction of expression of E-cadherin and/or catenins in intrabronchial precancerous lesions and the early stages of bronchial squamous cell carcinoma. In intrabronchial lesions and squamous cell carcinoma, expression of either E-cadherin or catenins was reduced in 21% of BSM without atypia, 28% of BSM with atypia, 40% of dysplasia, 48% of carcinoma in situ, 100% of carcinoma microinvasive to the

bronchial wall, and 100% of squamous cell carcinoma. We also demonstrated a positive correlation between the expression of these molecules and the grade of atypia of intrabronchial lesions. Our previous studies showed that reduced expression of E-cadherin and catenins occurs frequently in non-small cell lung carcinoma [35]. Hence, our present findings indicate that downregulation of E-cadherin and catenins may play an important role in the progression of human intrabronchial lesions and squamous cell carcinoma.

Studies on cell–cell adhesion molecules may help to clarify the mechanisms of local invasion and metastasis. Investigations of the cadherin–catenin complex have been carried out at the cellular and molecular levels [14,22,44]. It has already been reported that reduction of E-cadherin expression is caused by mutation and by inactivation of the E-cadherin gene by hypermethylation in the promoter region [45]. Dysfunction of the cadherin–catenin complex caused by reduction of the expression of these molecules implies an increased ability of cancer cells to disperse, which is the probable early step of local invasion and metastasis. Reduction of expression of E-cadherin and α -catenin is associated with local invasion and metastasis of scirrhous carcinoma in gastric cancer, breast cancer, and esophageal cancer [20,22].

In BSM with atypia and dysplasia, cells showing reduction of E-cadherin and/or catenin expression were localized mainly in the basal layer. As histological atypia increased, reduced expression of each molecule also became evident in the intermediate and superficial layers. This observation parallels the finding that proliferating cells and cells with accumulation of mutant p53 protein appeared from the basal layer to the superficial layer during carcinogenesis in the bronchus [43]. Therefore, we hypothesize that these cellular changes indicate an increased risk of eventual malignant transformation, and also that cells in the basal layer are the first to acquire the capacity for local invasion.

Our present study suggests that reduction of expression of E-cadherin and/or catenins is a rela-

Table 3 Aberrant expression rate of E-cadherin and/or catenins in intrabronchial lesions

	BSM without atypia	BSM with atypia	Dysplasia	c.i.s	Microinvasion to bronchial wall	Sq.c.ca.
Basal layer	6 (18%)	7 (28%)	2 (40%)	10 (48%)	4 (100%)	100%
Intermediate layer	2 (6%)	7 (28%)	1 (20%)	9 (43%)	3 (75%)	
Superficial layer	3 (9%)	5 (20%)	1 (20%)	8 (38%)	2 (50%)	
Whole layer	7 (21%)	7 (28%)	2 (40%)	10 (48%)	4 (100%)	
Total (cases)	32	25	5	21	4	32

tively early event in the genesis of bronchial squamous cell carcinoma, and that increasing histological atypia is accompanied by further diminution in the expression of these molecules. Finally, reduced levels of E-cadherin and/or catenins might play a critical role in local invasion beyond the basement membrane and the development of the advanced stage of squamous cell lung carcinoma.

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Phase II trial of postoperative adjuvant cisplatin and etoposide in patients with completely resected stage I-IIIa small cell lung cancer: The Japan Clinical Oncology Lung Cancer Study Group Trial (JCOG9101)

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Objective: Indications for surgical intervention for very limited small cell lung cancer have not yet been determined. The objective of this study is to determine whether resection followed by cisplatin and etoposide is feasible.

Methods: From September 1991 through December 1996, 62 patients with completely resected small cell lung cancer who were less than 76 years of age from 17 centers were entered in the trial. Of 62 patients, 61 were eligible, with a median follow-up of 65 months. Chemotherapy consisted of 4 cycles of cisplatin (100 mg/m², day 1) and etoposide (100 mg/m², days 1-3). There were 49 (80%) male patients, 44 with clinical stage I disease, 10 with stage II disease, and 6 with stage IIIa disease.

Results: Forty-two (69%) patients received 4 cycles of cisplatin and etoposide. No treatment-associated mortality was noted. Median survival time was not reached in patients with pathologic stage I disease, was 449 days in patients with stage II disease, and was 712 days in patients with stage IIIa disease. Three-year survival was 61% overall, 68% in patients with clinical stage I disease, 56% in patients with stage II disease, and 13% in patients with stage IIIa disease ($P = .02$). Recurrence was noted in 26 (43%) patients overall. Local failure was noted in 6 (10%) patients. Locoregional recurrence tends to be found more frequently in patients with stage IIIA disease. Distant failure was found in 21 (34%) patients overall. Brain metastasis was found in 15% of the patients.

Conclusion: Major lung resection followed by postoperative cisplatin and etoposide is feasible, with a favorable survival profile. Because nodal metastasis appears to be a major prognostic factor, preoperative evaluation of nodal status remains a major concern.

The prognosis of lung cancer remains poor, and this disease is the leading cause of cancer mortality worldwide. Small cell lung cancer (SCLC) comprises approximately 20% of lung cancer cases. Without treatment, SCLC has the most aggressive clinical course of any other type of lung cancer, resulting in a very short median survival time of approximately 2 to 4 months. Although surgical resection is generally indicated for early stage non-small cell lung cancer, this is not always the case with SCLC. This can be explained by the fact that

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dissemination to regional lymph nodes or distant organs would be found in most patients with SCLC at the time of initial presentation.¹ Therefore, localized forms of treatment, such as surgical resection or radiation therapy, rarely produce long-term survival, and systemic treatment with current chemotherapy regimens is usually incorporated into the treatment program.

Indications for surgical resection for SCLC have not yet been determined, although several authors have reported that a small minority of patients with limited-stage disease and adequate lung function might benefit from surgical resection.¹⁻⁹ According to these reports, the prognosis of resected SCLC was not so poor, especially when no pathologic nodal involvement was observed. The 5-year survival ranged from 26% to 61% in these trials if the tumor was stage I. Because SCLC tends to be disseminated and the results of surgical intervention alone for this disease have been reported to be poor,^{1,10} postoperative chemotherapy has been used in most studies. However, the chemotherapy was not standardized, and various chemotherapy protocols were often used. Furthermore, most previous studies were retrospective and thus suffered from the inherent weakness of any retrospective assessment of a given treatment.

Because the combination of cisplatin and etoposide has been considered to be standard in the treatment of SCLC,¹¹ this combination was selected as a postoperative adjuvant regimen. We conducted a prospective study of surgical resection plus adjuvant chemotherapy for stage I through IIIA SCLC to investigate the efficacy of this treatment strategy.

Patients and Methods

Eligibility

Patients who were given postoperative diagnoses of SCLC histologically or cytologically were eligible for enrollment in the study. The patients had to have completely resected pathologic stage I, II, or IIIA disease according to the TNM classification of the International Union Against Cancer.¹² Histologic typing was determined according to the World Health Organization classification.¹³ Inclusion criteria included an Eastern Cooperative Oncology Group performance score of 0 or 1, age between 20 and 75 years, no prior treatment for lung cancer, no other concurrent or previous malignancies, a leukocyte count of greater than 3500/ μ L, a platelet count of greater than 100,000/ μ L, a hemoglobin level of greater than 9.5 g/dL, a serum creatinine level of less than 1.5 mg/dL, and aspartate aminotransferase–alanine aminotransferase values of less than twice the institutional upper limit of normal. Exclusion criteria included a history of myocardial infarction within the past 3 months, hepatic cirrhosis, and/or severe cardiopulmonary dysfunction that required oxygen therapy. The following preoperative investigations were performed before entry into the study: computed tomographic (CT) scanning of the chest, upper abdomen, and brain; bronchoscopy; chest plain film; radionuclide bone scanning; complete blood cell count and serum chemistry; and physical examination. Preoperative mediastinoscopy was performed in

some cases. All patients provided written informed consent before entering the study.

Treatment Schedule

Major lung resection, such as pulmonary lobectomy or pneumonectomy, was required as a surgical procedure for SCLC. Complete hilar and mediastinal lymph node dissections were recommended on the basis of the lymph node map defined by Naruke and colleagues.¹⁴ After confirming complete resection and histologic typing of SCLC histologically, eligible patients were registered in the study.

Chemotherapy consisted of cisplatin (100 mg/m² on day 1) and etoposide (100 mg/m² on days 1-3; PE regimen). This regimen was repeated every 4 weeks and was administered in 4 courses. The dose was modified according to the blood cell count and renal function on the day of chemotherapy. Chemotherapy was administered unless the leukocyte count was less than 3000/ μ L or the platelet count was less than 75,000/ μ L. Chemotherapy was withheld until the counts recovered. If grade 4 hematologic toxicity, according to World Health Organization (WHO) criteria,¹⁵ was seen, the dose of etoposide was reduced to 75%. Chemotherapy was permanently discontinued at any time when the serum creatinine level was 2.0 mg/dL or greater or the blood urea nitrogen level was 30 mg/dL or greater. To assess toxicity, we subjected all patients to complete blood cell counts and blood chemistry evaluations, such as for aspartate aminotransferase–alanine aminotransferase, blood urea nitrogen, and serum creatinine, as well as chest plain film and urinalyses at least once per week during treatment. Toxicity criteria were evaluated on the basis of the WHO criteria.¹⁵

Patients were followed up at the outpatient department every 3 months postoperatively and underwent CT scans of the chest, upper abdomen, and brain, as well as radionuclide bone scanning every 6 months, even when they were asymptomatic. No postoperative radiotherapy was applied until relapse was apparent.

Sites of relapse were determined by clinical, radiologic, or histologic criteria at initial recurrence. Local failure was defined as recurrence at the primary lung site or hilar-mediastinal lymph nodes. Distant failure was defined as recurrence in the contralateral lung, bone, brain, liver, or other extrathoracic regions.

Statistical Analysis

The trial was designed as a prospective phase II trial. The primary goal of the study was to estimate the survival. A sample size of 30 was considered to provide a power of 90% for detecting a significant improvement in the 3-year survival (from 20% to 50%) in a 1-sided test with an α value of .025 and a β value of .10. The median follow-up period for 35 surviving patients was 65 months. The length of survival was defined as the interval in months between the day of surgical resection of lung cancer and the date of death from any cause or the last follow-up. The survival curves were constructed by using the Kaplan-Meier method,¹⁶ and curves were compared with the log-rank test.

Results

Patient Characteristics

Between September 1991 and December 1996, 62 patients were entered in this phase II trial at the 16 institutions that

TABLE 1. Patient characteristics

Total	61
Sex	
Male	49
Female	12
Age (y)	
Range	22-74
Median	64
Histologic subtype defined by WHO*	
Oat cell type	9
Intermediate type	45
Combined type	7
Clinical stage	
I	44
II	9
IIIA	8
Side of primary tumor	
Right	32
Left	29
Operative procedure	
Lobectomy	57
Pneumonectomy	4
Extent of lymph node dissection†	
Complete hilar and mediastinum	59
Only hilar	2
Pathologic stage	
I	35
II	8
IIIA	18
Performance status	
0	32
1	29

*Histologic subtyping was determined on the basis of the World Health Organization (WHO) classification. †The extent of lymph node dissection was defined by Naruke and associates.¹⁴

participated in the study. One patient was excluded because his final histologic category was changed from SCLC to large cell carcinoma. Thus, 61 patients were eligible for assessment of survival data, and their characteristics are shown in Table 1. The median age was 64 years (range, 22-74 years). According to histologic typing defined by the WHO, oat cell, intermediate, and combined types were found in 9, 45, and 7 patients, respectively. Forty-four patients had clinical stage I disease, 9 had stage II disease, and 8 had stage IIIA disease. Pathologically, stage I, II, and IIIA disease was found in 35, 8, and 18 patients, respectively.

Treatment Administration

As a surgical procedure, pulmonary lobectomy was performed in 57 (93%) patients, and pneumonectomy was performed in the other 4 patients. Among 4 pneumonectomies, 3 were on the left side, and 1 was on the right side. Complete hilar and mediastinal lymph node dissection was performed in 59 (97%) patients.

TABLE 2. Treatment delivery

Total no. of patients	61
No. of chemotherapy courses	
0	1 (2%)
1	5 (8%)
2	8 (13%)
3	5 (8%)
4	42 (69%)

A total of 204 courses were administered (Table 2). Forty-two (69%) patients underwent a full course of chemotherapy. The other 19 patients did not complete postoperative chemotherapy because of progressive disease in 3 patients, adverse effects in 7 patients, refusal of chemotherapy in 8 patients, and death from pneumonia in 1 patient.

Treatment-Related Toxicity

No treatment-associated deaths were found. Postoperative bronchopulmonary fistula was found in 1 (2%) patient who underwent pulmonary lobectomy after completion of the first cycle of chemotherapy. Chemotherapy-related toxicity is shown in Table 3. Grade 4 toxicity was found in 9 (15%) patients: leukopenia in 4 patients, thrombocytopenia in 2 patients, nausea in 2 patients, and cardiac failure in 1 patient. One patient died of pneumonia 2 months after the first course of chemotherapy, but this was not considered to be chemotherapy related.

Survival

Survival data are shown in Table 4. Among the 61 eligible patients, 35 were still alive after a median follow-up of 65

TABLE 3. Chemotherapy-related toxicity in 60 eligible patients treated for resected stage I to IIIA SCLC

Toxicity	WHO grade				
	1	2	3	4	4 (%)
Anemia	9	29	16	0	0
Leukocytopenia	7	17	26	4	6.5
Thrombocytopenia	11	8	14	2	3.2
Infection	2	1	0	0	0
Nausea	24	13	13	2	3.3
Diarrhea	8	2	2	0	0
Azotemia	35	0	0	0	0
Renal failure	18	0	0	0	0
Stomatitis	14	1	1	0	0
Dyspnea	5	0	0	0	0
Fever	10	7	0	0	0
Skin	4	2	0	0	0
Alopecia	13	23	11	0	0
Cardiac dysfunction	5	2	1	1	1.7
CNS	1	1	1	0	0
Peripheral neuropathy	5	1	0	0	0

WHO, World Health Organization; CNS, central nervous system.

TABLE 4. Survival in patients with resected SCLC who underwent postoperative chemotherapy

	Median survival time (d)	Survival	
		3 y	5 y
Clinical stage			
IA	Not reached	70%	66%
IB	Not reached	65%	65%
II	Not reached	56%	56%
IIIA	530	13%	13%
Pathologic stage			
IA	Not reached	78%	73%
IB	Not reached	67%	67%
II	449	38%	38%
IIIA	712	39%	39%

months. The overall estimated 3- and 5-year survivals were 61% and 57%, respectively (Figure 1). The 5-year survival was 66%, 56%, and 13% in patients with clinical stage I, II, and IIIA disease, respectively (Figure 2). Among the 44 patients with clinical stage I disease, 27 were classified as having clinical stage IA disease, and the other 17 were classified as having clinical stage IB disease. There was no significant difference in prognosis between clinical stage IA and IB disease. Similar results were obtained regarding the pathologic stage. Pathologic stage I disease showed a significantly better prognosis (Figure 3). The 5-year survivals in the 23 patients with pathologic stage IA disease and the 12 patients with stage

IB disease were 73% and 67%, respectively. No significant differences in survival were observed between patients with pathologic stage IA and IB disease.

Patterns of failure. Recurrence was noted in 26 (43%) patients, and the sites of initial relapse at a median follow-up time of 65 months are shown according to the pathologic stage in Table 5. Recurrence was found in 30% of patients with stage IA disease, 25% of patients with stage IB disease, 50% of patients with stage II disease, and 67% of patients with stage IIIA disease.

Local failure was noted in 6 (10%) patients: 4 in the mediastinal lymph nodes and 2 in the bronchial stump. Locoregional recurrence tended to be found more frequently in patients with stage IIIA disease (22%) than in patients with stage I or II disease. Relapse at the bronchial stump was only seen in patients with stage IIIA disease.

Distant failure was found in 22 (36%) patients overall: 6 (26%) with stage IA disease, 2 (17%) with stage IB disease, 4 (50%) with stage II disease, and 9 (50%) with stage IIIA disease. Distant failure was most frequently noted in the brain, followed by the liver. The incidence of brain metastasis was 15% overall, 17% in patients with stage IA disease, and 11% in patients with stage IIIA disease. Bone metastasis was noted exclusively in patients with stage IIIA disease.

Discrepancy between clinical and pathologic stages. Table 6 shows the relationship between the clinical stage and the pathologic stage. Among 44 patients with clinical stage I disease, only 33 (75%) had pathologic stage I disease, and

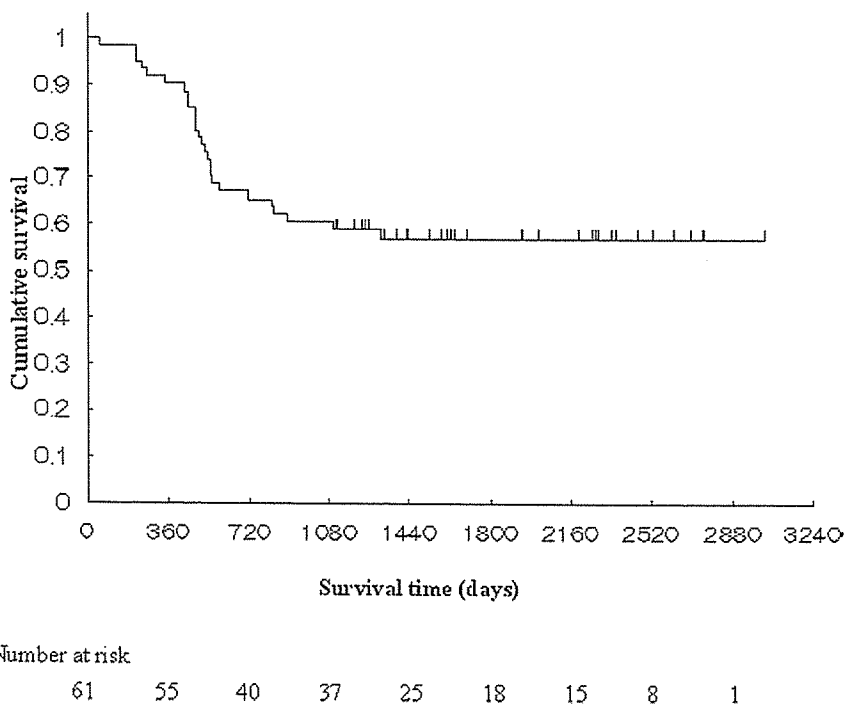


Figure 1. Survival curve for overall patients with resected SCLC.

GTS

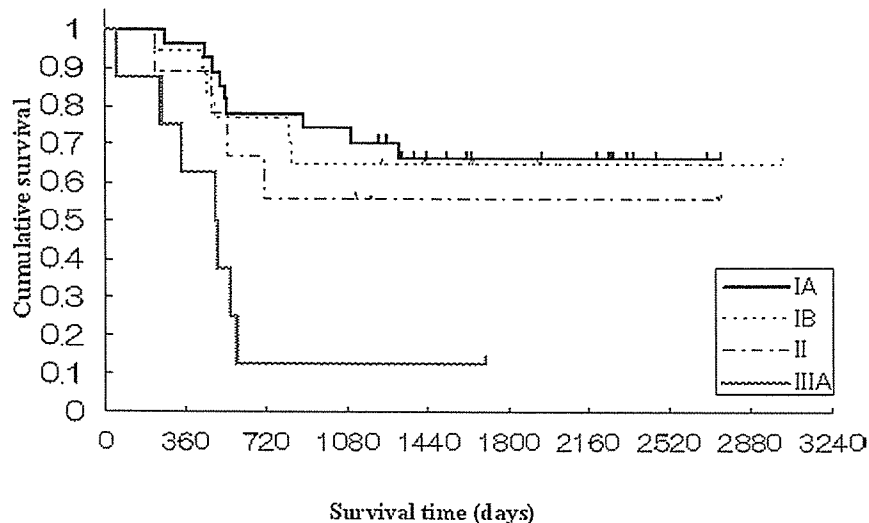


Figure 2. Survival curves for patients with resected SCLC by clinical stages.

GTS

6 had stage IIIA disease. Five patients with clinical stage IA disease had mediastinal lymph node metastasis. According to the Bowker test of symmetry, these differences were statistically significant.

Discussion

This phase II trial showed that postoperative PE for patients who underwent surgical resection of stage I to IIIA SCLC was feasible, and the outcome was acceptable. Survival was excellent in patients with stage I disease and did not appear

to be inferior to that with chemoradiotherapy in patients with stage II or IIIa disease.

On the basis of the results of the British Medical Research Council, radical radiotherapy has been preferable to surgical intervention for SCLC,^{17,18} and the indications for surgical resection for SCLC are still controversial. An operation would be indicated for limited SCLC because the most common relapse site after radiotherapy was locoregional, and surgical intervention might improve local control.¹⁹ Several authors have reported that a small minority of

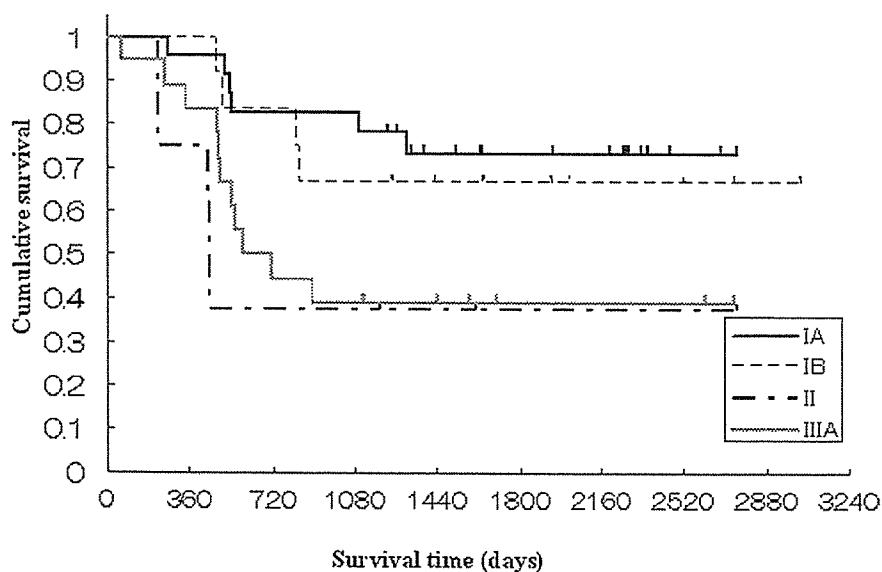


Figure 3. Survival curves for patients with resected SCLC by pathologic stage.

TABLE 5. Site of the first relapse by pathologic stages*

Variables	Overall	Stage IA	Stage IB	Stage II	Stage IIIA
No. of patients	61	23	12	8	18
No. of recurrence	26 (43%)	7 (30%)	3 (25%)	4 (50%)	12 (67%)
Recurrence					
Local					
Overall	6 (10%)	1 (4%)	1 (8%)	0 (0%)	4 (22%)
Mediastinum	4	1	1	0	2
Bronchial stump	2	0	0	0	2
Distant					
Overall	22 (36%)	6 (26%)	2 (17%)	4 (50%)	9 (50%)
Brain	9 (15%)	4 (17%)	0 (0%)	3 (38%)	2 (11%)
Bone	3	0	0	0	3
Liver	7	1	1	1	4
Lung	2	0	1	0	1
Small intestine	2	1	0	0	1

limited-stage SCLCs could be managed with an operation and postoperative chemotherapy.¹⁻⁹ According to those reports, the 5-year survivals were 28% to 36% overall and 26% to 61% in patients with stage I disease. However, most of those reports were retrospective and used various combinations of chemotherapy. Therefore, a prospective trial of adjuvant chemotherapy for patients with resected SCLC using standardized chemotherapy has been needed. Our survival data suggest that postoperative PE after major lung resection and hilar and mediastinal lymph node dissection is a feasible and promising treatment, especially for patients with stage I SCLC. The 3- and 5-year survivals for patients with stage I disease were 78% and 73%, respectively, and the median survival time was not reached. As for patients with stage II or IIIA disease, the results were not definitive, and a further prospective study is needed. This study dealt with postoperatively proved SCLC. As to the indication for surgical intervention for preoperatively diagnosed SCLC, controversies still remain. Our recommendation is as follows. When a patient has SCLC of clinical N1 or N2 status, chemoradiotherapy should be considered because a survival after an operation alone would not be good enough. Surgical intervention should be considered, however, for patients with clinical stage I disease because an operation followed by chemotherapy offers a good prognosis, as shown in this

study, and because such SCLC sometimes turns out to be non-SCLC postoperatively. A phase III trial comparing chemoradiotherapy with surgical intervention followed by chemotherapy is interesting. However, the number of patients with SCLC with clinical stage I or II disease is very small, and we do not think it is possible to perform the phase III trial in this population.

Because clinical stage and pathologic stage were significant prognostic factors in our trial, preoperative staging, intraoperative staging, or both should be a major concern for the treatment of very limited SCLC. Actually, the following preoperative investigations were performed before entry into the study in this cohort: CT scans of the chest, upper abdomen, and brain; bronchoscopy; chest plain film; radio-nuclide bone scans; complete blood cell count and serum chemistry; and physical examination. If the diagnosis of SCLC was made preoperatively, we recommend the same preoperative workup as done by us in this study. Furthermore, if swollen lymph nodes are detected on thoracic CT scans, we absolutely recommend mediastinoscopy for such cases. As for positron emission tomography, we have no recommendation thus far because this modality has recently begun to be evaluated, although it could be useful for staging N1 disease. Intraoperatively, hilar and mediastinal lymph node sampling or dissection was performed in 59 (97%) patients. This intraoperative staging is also important for deciding on the treatment strategy.

The site of the first relapse was another fruit of our study. This clinical trial did not use postoperative mediastinal irradiation or prophylactic cranial irradiation (PCI). We should discuss the importance of these strategies for very limited SCLC. As to locoregional recurrence, approximately 10% of the patients showed relapse in the mediastinal lymph nodes, bronchial stump, or both. Five percent of patients with stage I or II disease eventually have locore-

TABLE 6. Relationship between clinical and pathologic stages

Clinical stage	Pathologic stage			P value*
	I	II	IIIA	
I	33	5	6	.011
II	1	3	5	
IIIA	1	0	7	

*P value in Bowker's test of symmetry.

gional recurrence, whereas this is seen in 22% of patients with stage IIIA disease. These results suggest that patients with stage IIIA disease, at least, could benefit from postoperative mediastinal irradiation, whereas those with stage I or II disease might not need to undergo radiotherapy. Thus, postoperative chemoradiotherapy might be used in a future trial for stage IIIA disease.

Auperin and associates²⁰ reported that PCI improved both overall survival and disease-free survival among patients with SCLC in complete remission. Surgically resected SCLC would be considered SCLC in complete remission, and PCI would be indicated. Overall, 15% of the patients in our study showed brain metastasis. Even among patients with stage IA disease, more than 10% of the patients had brain metastasis. Therefore, PCI might be necessary for all patients with completely resected SCLC, whereas some authors have insisted that patients with pathologic stage IA SCLC can be cured without any adjuvant treatment.¹⁹

Noda and coworkers²¹ reported that combination chemotherapy consisting of irinotecan (CPT-11) and cisplatin was superior to PE for extensive SCLC. Although concurrent radiotherapy with CPT-11 would be harmful, we would use the new regimen for very limited SCLC, especially for stage II or IIIA SCLC.

Major lung resection with complete hilar and mediastinal lymph node dissection followed by postoperative PE is a feasible treatment and results in a favorable survival profile. Survival was especially good for patients with stage I disease. Our strategy could be used as a standard treatment arm in a future trial for very limited SCLC.

We thank Ms Mieko Imai and Dr Haruhiko Fukuda, JCOG Data Center, National Cancer Center Research Institute, for their technical support in statistical analyses. We also thank Dr Hideo Kunitoh, Medical Oncology and Internal Medicine Division, National Cancer Center Hospital, for his critical discussion.

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7196 General Poster Session (Board #U5), Sun, 8:00 AM - 12:00 PM

Prognostic value of blood levels of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) in advanced non-small cell lung cancer (NSCLC) patients. V. Alberola, C. Camps, R. Sirera, L. Llobat, A. Blasco, M. J. Safont, J. Garde, M. Taron, J. J. Sanchez, R. Rosell; Hospital Arnau de Vilanova, Valencia, Spain; Hospital General de Valencia, Valencia, Spain; Hospital Germans Trias i Pujol, Badalona, Spain; Universidad Autonoma de Madrid, Madrid, Spain

Background: VEGF and bFGF are among the most important angiogenic factors. We have explored these angiogenesis mediators in plasma and its prognostic significance in advanced NSCLC. **Methods:** Were enrolled 451 patients with advanced NSCLC, stages IIIB and IV and treated with cisplatin and docetaxel. Blood was collected before chemotherapy. Plasma VEGF and bFGF levels were assessed by commercial ELISA (sensitivity 5 pg/ml). In parallel plasma from 32 age and gender-matched controls was used. **Results:** Median age was 61 years (35-82) and 84% were males. 99% had performance status 0-1. 84% were in stage IV and 16% in stage IIIB. The histological subtypes were: 32% squamous cell carcinoma, 50% adenocarcinoma, 14% anaplastic large cell, and 4% undifferentiated. 41% of the patients received second line chemotherapy. 1% achieved complete response (CR), 36% partial response (PR), 35% had stable disease (SD) and 28% progressive disease (PD). Patient's median plasma levels of VEGF (20 pg/ml, [6-203]) differ significantly ($p = 0.04$) from controls (14 pg/ml, [7-53]), but in contrast bFGF levels were not different, 14 pg/ml [5-960] vs 10 pg/ml [6-278] respectively. There were not differences in patients according to histology, site of metastasis and ECOG; however we could observe a tendency with stage for both factors: bFGF 9 pg/ml [5-24] in stage IIIB vs 15 pg/ml [6-960], $p = 0.071$ and VEGF 17 pg/ml [6-145] in IIIB vs 21 pg/ml [6-203] in IV, $p = 0.086$. It could not be observed any differences in response to therapy for both angiogenic factors; CR+PR patients presented median VEGF of 18 pg/ml [6-71] and bFGF 11 pg/ml [6-960] vs 20 pg/ml of VEGF [6-203] and 15 pg/ml of bFGF [5-395] in the SD+PD group. In the multivariate analysis we could not find that VEGF and bFGF plasma levels were predictors for time to progression (TTP) and overall survival (OS). **Conclusions:** VEGF but not bFGF levels in patients are significantly higher in patients than in controls. In our cohort of patients with advanced NSCLC we have not found any relationship between serum VEGF and bFGF levels with stage, histology, response, site of metastasis, TTP and OS.

7198 General Poster Session (Board #U7), Sun, 8:00 AM - 12:00 PM

Elevated osteopontin (OPN) plasma levels are highly prognostic in advanced non-small cell lung cancer (NSCLC): Analysis of SWOG S0003. P. C. Mack, M. W. Redman, K. Chansky, S. K. Williamson, N. Farneth, P. N. Lara Jr, Q. Le, P. H. Gumerlock, J. J. Crowley, D. R. Gandara; UC Davis Cancer Center, Sacramento, CA; Southwest Oncology Group Statistical Center, Seattle, WA; SWOG Statistical Center, Seattle, WA; University of Kansas Medical Center, Kansas City, KS; Stanford University, Stanford, CA

Background: OPN is a secreted glycoprotein with a diverse array of functions, including induction of uPA & increased cell migration. OPN has been shown to be elevated in a number of tumor types, & its downregulation reduces tumorigenicity & metastasis in tumor models. High levels have also been associated with tumor hypoxia/angiogenesis, as are vascular endothelial growth factor (VEGF) & plasminogen activator inhibitor (PAI-1). We hypothesized that secreted levels of these biomarkers would correlate with clinical outcome after treatment. **Methods:** Plasma concentrations of OPN, VEGF & PAI-1 were measured by ELISA in 160 NSCLC patients enrolled on the Southwest Oncology Group (SWOG) trial S0003 (paclitaxel/carboplatin \pm the hypoxic cytotoxin tirapazamine). Post-treatment plasma samples were available in 56 patients. **Results:** Baseline OPN plasma levels correlated significantly with patient overall survival (OS). High interpatient variability was observed, with levels ranging from undetectable to 2560 ng/ml, (median: 606.5 ng/ml). When dichotomized, median OS was 11 months for patients below median OPN levels & 7 months for those above ($p = 0.004$). Survival decreases with increasing OPN concentration. Furthermore, OPN levels correlated with response rate (RR) (median responders: 497; median non-responders: 698 ng/ml. Wilcoxon rank-sum $p = 0.03$). No association between baseline levels of either VEGF or PAI-1 with RR or OS was observed. However, plasma levels of both PAI-1 & VEGF were significantly inter-related & trended together ($p < 0.0001$), & both decreased significantly after treatment ($p = 0.0004$ & 0.04 , respectively). Median decrease: OPN: 17%, PAI: 44%, VEGF: 42%. No significant differences were observed between study arms, suggesting that OPN is prognostic in NSCLC, but not predictive for response to tirapazamine. **Conclusions:** 1) There is a great need for development of tumor biomarkers which can be serially assessed pre- & post-therapy. 2) High OPN plasma levels were significantly associated with reduced RR & OS for patients on this trial. OPN is a strong candidate for inclusion in a panel of prognostic (& perhaps predictive) markers for NSCLC. Supported by the Hope Foundation & RO1-CA107228.

7197 General Poster Session (Board #U6), Sun, 8:00 AM - 12:00 PM

The influence of tumor size, histological differentiation and smoking history in patients with completely resected stage I adenocarcinoma of the lung. M. Tsuboi, H. Kato, Y. Ichinose, M. Ohta, E. Hata, N. Tsubota, H. Tada, H. Wada, N. Hamajima, M. Ohta, the Japan Lung Cancer Research Group on Postsurgic; Tokyo Medical University, Tokyo, Japan; National Kyushu Cancer Center, Fukuoka, Japan; National Okinawa Hospital, Okinawa, Japan; Mitsui Memorial Hospital, Tokyo, Japan; Hyogo Medical Center, Akashi, Japan; Osaka City General Hospital, Osaka, Japan; Kyoto University, Kyoto, Japan; Nagoya University, Nagoya, Japan

Background: To test the hypothesis that patients with completely resected p-stage I adenocarcinoma [Ad.] of the lung contain a favorable subgroup of patients with well differentiated histology and tumor 2.0 cm or less in greatest dimension, we analyzed the results of the JLCRG trial (a randomized prospective trial of adjuvant chemotherapy with Uracil-Tegafur for stage I adenocarcinoma of the lung) by tumor size, smoking history, degree of histological differentiation and more. **Methods:** Patients were randomized to receive either oral uracil-tegafur (250 mg of tegafur m^2/day) for 2 years postoperatively or no adjuvant treatment. Multivariate analyses and interactions with the Cox proportional-hazards model were used to estimate the simultaneous effects of prognostic factors on survival. **Results:** The 5-year survival rate of the 412 patients with tumor 2cm or less in size was 89.8% (95% confidence interval [CI]: 86.8 to 92.8) versus 84.4% (95% CI: 81.3-87.4) for the 569 patients with tumor more than 2cm in size (median follow-up 72 months, $p = 0.002$). Although univariate analysis demonstrated improved survival for the patients with no smoking history and female gender, the selected covariates by multivariate analysis were as follows: age (hazard ratio [HR] for patients aged 70 years or more, 2.25; 95% CI: 1.58 to 3.14, $p < 0.0001$), tumor size (HR for more than 2cm in size, 1.55; 95% CI: 1.10 to 2.21, $p = 0.012$), histological differentiation (HR for moderate and poor differentiation, 1.75, 95% CI: 1.25 to 2.47, $p = 0.001$), and treatment group (HR for the uracil-tegafur group, 0.68; 95% CI: 0.49 to 0.94, $p = 0.02$). For these prognostic factors, there was only one significant interaction between tumor size and the adjuvant treatment. **Conclusions:** 1) Patients with completely resected stage I Ad. of the lung contain a favorable subgroup of patients with aged less than 70 years, well differentiated histology, and a maximum tumor dimension of 2.0 cm or less. 2) Adjuvant chemotherapy with oral uracil-tegafur should also be considered for stage I Ad. patients more than 2 cm in tumor size. 3) 2cm in tumor size might be a good benchmark candidate of the description of T factor to facilitate treatment strategies and revisions of the TNM staging system.

7199 General Poster Session (Board #U8), Sun, 8:00 AM - 12:00 PM

The relationship between RASSF1A aberrant methylation and survival in small sized lung adenocarcinoma. K. Miyajima, T. Ohira, J. Usuda, H. Saji, M. Tsuboi, T. Hirano, H. Kato, M. Suzuki, S. Toyooka, A. F. Gazdar; Tokyo Medical University, Tokyo, Japan; University of Texas Southwestern Medical Center, Dallas, TX

Background: Aberrant methylation of CpG islands in promoter regions of tumor suppressor cells is one of the major mechanisms for silencing of tumor suppressor genes. The RAS association domain family 1A (RASSF1A) gene was isolated from the 3p21.3 region homozygously deleted in lung cancer cell lines, and it was shown to be inactivated by hypermethylation of the promoter region in lung cancers. In this study, we investigated the clinicopathological significances of RASSF1A methylation in the development and/or progression of small-sized (less than 2.0cm) lung adenocarcinoma. It is important to identify a marker for high-risk early stage patients who should benefit from new investigational adjuvant therapies. **Methods:** Surgically resected specimens from 77 cases of small-sized primary lung adenocarcinoma. We determined the frequency of aberrant promoter methylation of the RASSF1A genes in small-sized adenocarcinoma. Aberrant promoter methylation was examined using methylation-specific PCR (MSP). **Results:** Twenty-five of 77 (32.5%) tumors showed RASSF1A methylation. RASSF1A methylation was dominantly detected in smoker ($P < 0.03$). There was no significant correlation of RASSF1A methylation with gender, age, T stage, N stage and pathological stage. RASSF1A methylation correlated with adverse survival by univariate analysis ($P < 0.005$) as well as multivariate analysis ($P = 0.0062$; RR 4.251; 95% C.I., 1.507-11.993). Furthermore, RASSF1A promoter hypermethylation in resected stage I small-sized lung adenocarcinoma was associated with impaired patient survival ($P < 0.01$). **Conclusions:** Aberrant promoter methylation of the RASSF1A was present in 25 of 77 (32.5%) of small-sized lung adenocarcinoma by MSP assay. These results indicated that epigenetic inactivation of RASSF1A plays an important role in the progression of small-sized lung adenocarcinoma, and that RASSF1A hypermethylation appears to be a useful molecular marker for the prognosis of patients with small-sized and stage I lung adenocarcinoma. RASSF1A is a potential tumor suppressor gene that undergoes epigenetic inactivation in lung adenocarcinoma through hypermethylation of its promoter region. RASSF1A methylation was significantly related to unfavorable prognosis in small-sized lung adenocarcinoma.

Gefitinib in the adjuvant setting: safety results from a phase III study in patients with completely resected non-small cell lung cancer

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Standard therapy for stage I–IIIA non-small cell lung cancer (NSCLC) is surgery, although adjuvant therapies are required to prevent disease recurrence and improve patient survival. This is the first study that planned to administer adjuvant gefitinib (Iressa) 250 mg/day or placebo to randomized patients with completely resected NSCLC (stage IB–IIIA) 4–6 weeks following surgery, for 2 years, until recurrence/withdrawal. However, recruitment was stopped after the randomization of 38 patients, because interstitial lung disease (ILD)-type events were being increasingly reported in Japan in the advanced disease setting. Finally, the trial was halted. Safety data for 38 recruited patients (18 gefitinib and 20 placebo) showed no unexpected adverse drug reactions (ADRs), with the most common being grade 1/2 gastrointestinal and skin disorders in 12 and 16 patients receiving gefitinib and in five and six patients receiving placebo, respectively. Grade 3/4 ADRs occurred in four patients receiving gefitinib and one patient receiving placebo. ILD-type events were reported in one patient receiving gefitinib (concomitantly with other ILD-inducing drugs) who died and two patients receiving placebo. Eight patients receiving gefitinib withdrew due to ADRs compared with three patients receiving placebo. Adverse events associated with surgical complications were reported for six patients receiving

gefitinib and four patients receiving placebo. In the adjuvant setting there were no unexpected adverse events observed. Gefitinib had no impact on surgery-related complications when given within 4–6 weeks post-operatively. *Anti-Cancer Drugs* 16:1123–1128 © 2005 Lippincott Williams & Wilkins.

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Sponsorship: This trial was coordinated and supervised by the Study Coordinating Committee (principal investigators plus AstraZeneca personnel), and the Independent Data Monitoring Committee (lung cancer and statistical experts independent of AstraZeneca), with funding and organizational support from the trial sponsor AstraZeneca.

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Introduction

Non-small cell lung cancer (NSCLC) is generally not diagnosed until the disease is symptomatic, by which time more than two-thirds of patients are in the advanced stages of disease and have a poor prognosis [1]. Approximately 25% of patients with NSCLC are diagnosed when their disease is in the early stages; however, as many of these patients frequently have undetectable metastases, disease often recurs in distant sites [2]. Adjuvant therapies are therefore required to help prevent disease recurrence and as they will need to be given to patients post-operatively for a prolonged period, they should be well tolerated.

Although some clinical trials in NSCLC have shown a significant survival benefit with adjuvant uracil plus tegafur (UFT) and cisplatin-based chemotherapy [3–7], others have not observed a significant improvement in

survival [5,8,9]. At the time of commencing this study, there were no standard adjuvant treatment regimens for NSCLC.

Gefitinib (Iressa), an orally active epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), was approved in Japan for the treatment of inoperable or recurrent NSCLC in 2002. Two large phase II trials, IDEAL (Iressa Dose Evaluation in Advanced Lung cancer) 1 and 2, observed objective responses and stable disease in more than 40% of pre-treated patients with NSCLC receiving 250 mg/day gefitinib, with the majority of adverse events (AEs) being mild to moderate gastrointestinal and skin disorders [10,11]. Gefitinib was not associated with the well-recognized AEs observed with cytotoxic chemotherapy (e.g. bone marrow depression, neurotoxicity, nephrotoxicity). The tolerability profile of gefitinib has been confirmed by data from the

Expanded Access Programme, through which more than 39 000 patients have received gefitinib 250 mg/day on a compassionate-use basis. Furthermore, a retrospective analysis of 9515 US patients who had received gefitinib for 1 year or more via the Expanded Access Programme showed a 1-year survival rate of 33% [12], which compares with the IDEAL studies [10,11]. Recently, Onn *et al.* observed efficacy (16% with objective responses and 45% with stable disease) and a low incidence of grade 3/4 AEs in Japanese patients with NSCLC, most of whom had been treated with second-line gefitinib or above (99% of patients) [13].

To date, there is no experience of using gefitinib in the post-operative adjuvant setting. This phase III trial was initially undertaken to compare survival rates in patients with completely resected stage IB–IIIA NSCLC who had been treated with adjuvant gefitinib 250 mg/day or placebo. However, in October 2002, recruitment was halted following high-profile media activity around reports of gefitinib-related interstitial lung disease (ILD)-type events in patients with advanced or metastatic NSCLC in Japan. In March 2003, the trial was halted because of an increased withdrawal rate. As enrollment could not be resumed until the prospective investigation into gefitinib-related ILD-type events in Japan was completed, the trial was closed. Consequently survival data are not available, although data from patients recruited to the study have been subsequently analyzed for safety.

Methods

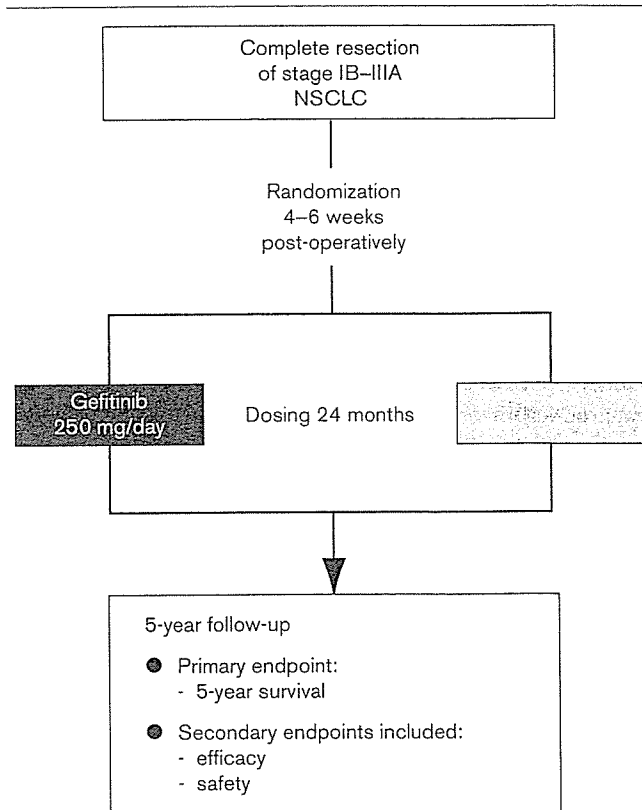
Patients

Patients were eligible for inclusion in the trial if they had histologically confirmed NSCLC (post-operative stage IB–IIIA) that had been completely resected 4–6 weeks before the start of treatment. Patients were required to be 20–75 years of age, with a WHO performance status (PS) 0–1, no previous history of chemotherapy, radiotherapy or immunotherapy for NSCLC and no co-malignancies within the past 5 years. All patients gave written, informed consent to participate in the trial, which was conducted in accordance with the Declaration of Helsinki [14] and Good Clinical Practice guidelines.

Study design

This randomized (1:1), double-blind, placebo-controlled, phase III multicenter survival study planned to recruit 670 patients (335 per group) and randomize them to receive either gefitinib (250 mg) or placebo (Fig. 1). Treatment was to be continued for 2 years, or until recurrence/secondary carcinoma or withdrawal criteria were met. An Independent Data Monitoring Committee (IDMC) was set up to assess the efficacy and safety of gefitinib post-operatively, and would advise whether the study should be continued, changed or discontinued.

Fig. 1



Trial design schema.

Assessments

Efficacy

Disease recurrence or secondary carcinogenesis were assessed using X-rays every 3 months during treatment and every 6 months during the follow-up period. Computed tomography (CT) scans were carried out 8 weeks after the first dose (where necessary, the pre-operative thoracoabdominal CT scan could be used), at week 48 during treatment, at week 104 after withdrawal/completion and every 52 weeks thereafter, unless disease recurrence was observed.

Safety

AEs were to be recorded and coded using MedDRA (Medical Dictionary for Regulatory Activities) version 6.0, graded using National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0 and assigned causality by the investigators. AEs associated with post-operative complications were defined as events occurring within 90 days after surgery and were recorded without regard to causality. Treatment could be interrupted for up to 14 days, although the IDMC later recommended that drug interruption could be allowed for more than 14 days in cases where ILD-type events were suspected, but could not be confirmed, in order to ensure the safety of

patients who remained in the trial after recruitment was halted. Hematology, biochemistry and urinalysis were also measured at baseline and during the study.

Role of the funding source

This trial was coordinated and supervised by the principal investigators, the IDMC and AstraZeneca personnel, with funding and organizational support from the trial sponsor AstraZeneca.

Results

Patients

Between August and October 2002, 38 patients were randomized into the trial – 18 received gefitinib and 20 received placebo. Patient demography was well balanced between the treatment arms, with the majority of patients having adenocarcinoma histology and WHO PS 1 (Table 1). When the trial was stopped, four patients in the gefitinib arm and 11 patients in the placebo arm were

still receiving treatment (Fig. 2). Of the 23 patients who withdrew, 13 did so because of AEs (10 in the gefitinib arm and three in the placebo arm), five were unwilling to continue with treatment (three in the gefitinib arm and two in the placebo arm), two had disease recurrence (both in the placebo arm) and three withdrew for other reasons (one patient in the gefitinib arm had incomplete recovery from surgery that was not drug related, and two patients in the placebo arm had pre-existing interstitial pneumonia and were withdrawn at the request of the sponsor).

Efficacy

From the limited efficacy data, disease recurrence was not seen in patients receiving gefitinib at data cutoff. Three patients who received placebo (one with stage IB and two with stage IIB) experienced disease recurrence – two patients recurred during the trial and one patient recurred after the trial had stopped.

ADRs

No unexpected ADRs were observed and, in general, the frequency of all ADRs was higher for gefitinib versus placebo (Table 2). The most common ADRs were mild to moderate grade 1/2 gastrointestinal and skin disorders. Grade 3/4 ADRs were seen in four patients in the gefitinib arm and one patient in the placebo arm (Table 3), all of whom had treatment withdrawn (the patient with grade 3 eczema had treatment withdrawn due to grade 2 impetigo).

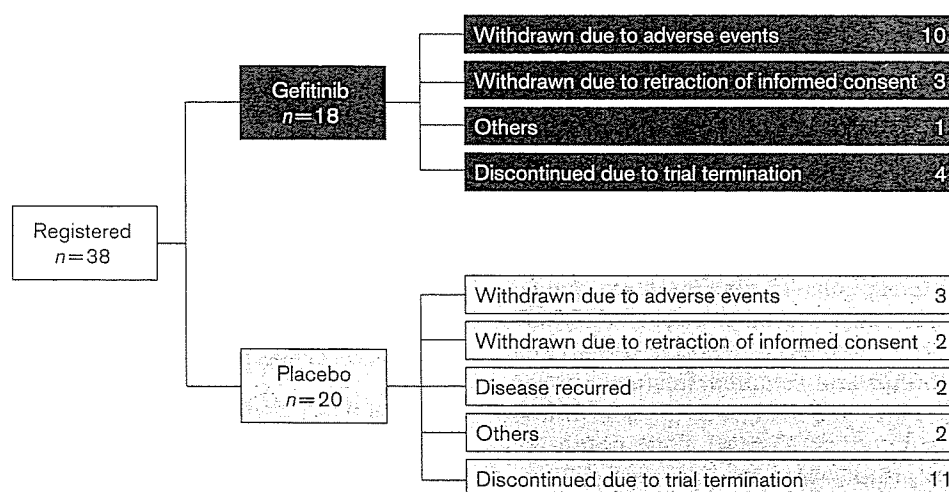
Respiratory ADRs

The majority of respiratory ADRs were grade 1/2 and occurred within 1 month of treatment. In the gefitinib arm, two patients experienced cough (associated with post-operative complications), one patient had dyspnea,

Table 1 Patient demography

	Gefitinib 250 mg/day (n=18)	Placebo (n=20)
Sex [n (%)]		
male	14 (77.8)	15 (75.0)
female	4 (22.2)	5 (25.0)
Median age [years (range)]	64.0 (49–73)	62.5 (52–73)
WHO PS [n (%)]		
0	5 (27.8)	9 (45.0)
1	13 (72.2)	11 (55.0)
Histology [n (%)]		
squamous cell carcinoma	4 (22.2)	6 (30.0)
adenocarcinoma	14 (77.8)	14 (70.0)
Stage [n (%)]		
IB	7 (38.9)	8 (40.0)
IIA	2 (11.1)	1 (5.0)
IIB	3 (16.7)	5 (25.0)
IIIA	6 (33.3)	6 (30.0)

Fig. 2



Trial outcome.

Table 2 Common ADRs occurring in two or more patients

AE (MedDRA term) ^a	Gefitinib 250 mg/day (n=18)	Placebo (n=20)
Abnormal hepatic function	4	0
Acne	2	0
Anorexia	5	1
Cough	2 ^b	1
Diarrhea	9	2
Dry skin	3	0
Eczema	8	2
Elevated ALT/AST	2	0
Fatigue	2	0
Gastritis	3 ^b	0
Loose stools	4	0
Nausea	3	0
Rash	5	3
Sputum	0	2
Stomatitis	2	0

^aA patient could have more than one AE.^bAll were associated with post-operative complications.

Table 3 Grade 3/4 ADRs

AE (MedDRA term)	Grade	Gefitinib 250 mg/day (n=18)	Placebo (n=20)
Abnormal hepatic function	3	1	0
Eczema	3	1	0
Elevated ALT	3	1	0
Neutropenia	3	0	1
Pneumonitis	4	1	0

and one patient experienced grade 4 ILD-type events (pneumonitis) 107 days after starting gefitinib and was withdrawn from the study. The patient with pneumonitis had taken concomitant shosaikoto, a Chinese herbal medicine, and loxoprofen, both of which have previously been shown to induce pneumonitis [15,16]. Twenty-one days later bacterial pneumonia related to methylprednisolone therapy was diagnosed, and the patient subsequently died 37 days later due to both pneumonitis and bacterial pneumonia. In the placebo arm, one patient who experienced cough and grade 1 pulmonary fibrosis had had interstitial changes on their chest X-ray at enrollment, and in a second patient, pre-existing non-specific interstitial pneumonia was exacerbated resulting in grade 1 ILD. In both patients, these conditions persisted following withdrawal of study drug.

Interruptions and withdrawals due to ADRs

ADRs requiring interruptions in therapy were similar between patients receiving gefitinib or placebo (Table 4) and were usually for less than 14 days, although four patients in the gefitinib arm required treatment to be interrupted for 14 days (including one patient whose treatment was interrupted for 20 days). The majority of ADRs leading to withdrawal were usually mild-to-moderate grade 1/2 in severity (Table 5). Grade 3 ADRs leading to withdrawal occurred in two patients receiving gefitinib (hepatic function abnormalities, elevated ALT)

Table 4 Exposure of patients to gefitinib

	Gefitinib 250 mg/day (n=18)	Placebo (n=20)
Median duration of treatment [days (range)]	86.5 (4–195)	144.0 (20–197)
Dosing period (n)		
<60 days	6	2
60–120 days	9	4
≥ 120 days	3	14
No. dose interruptions (n)		
1	5	6
2	2	2
≥ 3	2	2

Table 5 ADRs leading to patient withdrawals

Adverse event (MedDRA term)	Grade	Gefitinib 250 mg/day (n=18)	Placebo (n=20)
Eczema	2	1	0
Elevated ALT/AST	2	1	0
	3	1	0
Hepatic function abnormalities	2	1	0
	3	1	0
ILD	1	0	1
Impetigo	2	1	0
Neutropenia	3	0	1
Paronychia	2	1	0
Pneumonitis	4	1	0
Pulmonary fibrosis	1	0	1

and in one patient receiving placebo (neutropenia), and grade 4 pneumonitis led to the withdrawal of one patient who was receiving gefitinib. Following withdrawal of gefitinib treatment, grade 3 abnormal hepatic function and elevated ALT resolved, and grade 3 neutropenia persisted.

AEs associated with post-operative complications

As there are no safety data regarding the use of gefitinib in the post-operative setting, AEs associated with the healing process were examined to provide preliminary safety data on the start of the dosing timing in the adjuvant setting for gefitinib. AEs related to post-operative complications were observed in six patients in the gefitinib arm and four patients in the placebo arm. In the gefitinib arm, the most frequent AEs were grade 1/2 cough (four patients) and gastritis (three patients), and in the placebo arm grade 1/2 pain (three patients). Grade 1 cough, grade 1 supraventricular arrhythmia and grade 2 dyspnea were also experienced by three out of four patients receiving placebo.

Discussion

This trial was designed to compare survival rates in patients with completely resected stage IB–IIIA NSCLC who had received adjuvant therapy with gefitinib 250 mg day or placebo. However, incidences of ADRs of ILD

type events in the advanced disease setting have been increasingly reported since gefitinib was launched in Japan, and new recruitment was put on hold on 23 October 2002 at the request of the Ministry of Health, Labor and Welfare. In order to evaluate the ILD and ensure the safety of the trial patients, two separate Co-ordination Committee and IDMC meetings (December 2002 and January 2003) were conducted to discuss the feasibility of continuing the study and management of the trial patients. Based on the updated information on ADRs of interstitial pneumonia, the committees concluded that the study could be continued because the possibility of risk did not exceed that of benefit to enrolled patients. The IDMC also suggested that top priority should be given to assure the safety of the patients receiving gefitinib, and that discontinuation should be considered if flu-like symptoms including difficulty in breathing, fever and coughing occurred.

A 'Supplemental Explanation Sheet and Informed Consent Form' was provided four times to enrolled patients, offered updated information and methods to assure and manage any safety issues, and confirmed the patients' willingness to continue participating in the study. In December 2002, AstraZeneca KK gave the principal investigators the option to suspend gefitinib treatment at once. With the extensive monitoring of the trial patients in terms of safety, there were still an increasing number of withdrawals. In addition, enrollment could not be resumed until the prospective investigation on gefitinib-related ILD was completed. Based on these facts, the sponsor finally decided to terminate the trial in March 2003.

The types of AEs reported in this trial were similar to that already reported in the large phase II IDEAL 1 and 2 trials for patients with locally advanced or metastatic NSCLC [10,11]. Three patients experienced ILD-type events – two in the placebo arm and one patient in the gefitinib arm (this patient was also taking two other medications known to induce ILD) [15,17]. It has generally been observed that a higher frequency of ILD-type events are reported in Japanese patients taking gefitinib compared with those in other south-east Asian countries and the rest of the world (1.6, 0.3, and 0.3%, respectively) [18]. The occurrence of ILD in Japanese patients and the reasons for such an ethnic stratification in ILD incidence following gefitinib treatment require further clarification.

The most common reason for withdrawal in both treatment arms was due to toxicity, with the majority of drug-related AEs being grade 1/2 in severity. In the advanced or metastatic disease setting, few patients who experience grade 1/2 drug-related AEs withdraw from treatment with gefitinib, and in IDEAL 1, which

recruited Japanese patients, two out of 103 patients who received gefitinib 250 mg/day withdrew from therapy due to ADRs [18]. Several factors may explain the high number of withdrawals (including withdrawal of treatment for less severe ADRs) reported in this trial data compared with previously reported studies. These reasons include the fact that patients with early-stage NSCLC may be less tolerant of AEs compared with patients with advanced NSCLC who have received prior chemotherapy. In contrast to the other studies, the impact of heavy media coverage surrounding gefitinib-related ILD cannot be ignored.

It has been suggested that the dosage and schedule of gefitinib used in this study may not best suit patients with completely resected NSCLC in terms of tolerability and a number of adjustments may need to be taken into consideration when planning an adjuvant study of gefitinib in the future. It is unlikely that the time frame of 4–6 weeks is too short before starting adjuvant treatment, as other adjuvant trials conducted in Japanese patients have used similar time frames [3,4]. It may be possible to lengthen the duration by which gefitinib could be interrupted for toxicity, since 14 days may be too short for patients recovering from AEs such as hepatic enzyme elevation, or to reduce the dose following toxicity to perhaps 250 mg every other day, although this would require further study into the efficacy of such an approach.

With no experience of using gefitinib in post-operative patients there was a concern that EGFR-TKIs might impact on surgery-related complications (especially on the healing process) due to their mode of action. In order to assess this, the trial was designed to allow a safety review of the first 60 patients. Due to the early termination of the study, we have only 38 patients' (18 on gefitinib) data for review; however, there does not seem to be any impact on surgery-related complications when gefitinib was administered within 4–6 weeks after surgery, as evidenced by a similar number of these AEs that occurred in both groups. This indicates that it may be feasible to administer gefitinib in the adjuvant setting within this time frame.

In conclusion, this is the first study to investigate the use of EGFR-TKIs as adjuvant therapy. Despite the absence of survival data, there were no unexpected AEs seen in the adjuvant setting compared with those already reported for patients with locally advanced or metastatic NSCLC. However, it was observed that there were more AEs leading to withdrawal in the gefitinib arm, even though the majority of AEs were grade 1/2 in severity, suggesting that a daily dose of gefitinib 250 mg may not best suit patients with completely resected NSCLC in terms of tolerability.

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