Table 1 Clinicopathological features of pleomorphic carcinoma

Patient	Age (years)	Gender	Carcinoma size (cm)	Other component	p-Stage	IHC Podoplanin	IHC Calretinin	IHC CEA
1	61	Male	1.8	Ad	IA	—	2+	—
2	66	Male	6.0	Ad	IIB	—	1 + (F)	—
3	78	Male	2.1	Ad + P/D	IB	1 + (D)	1 + (F)	—
4	44	Male	6.1	Ad + P/D	IB	—	1 + (F)	—
5	78	Male	3.1	P/D	IIIA	—	2 + (D)	—
6	69	Male	2.4	Ad + P/D	IB	1 + (F)	1 + (D)	1 + (F)
7	79	Male	4.7	Ad + P/D	IIB	—	—	—
8	70	Male	6.9	Ad + P/D	IIIA	—	—	—
9	56	Female	3.1	Sq	IIIA	2 + (D)	2 + (F)	—
10	70	Male	6.5	Sq	IIIA	—	1 + (D)	—
Present case	80	Male	5.3	Ad + P/D	IIIB	1 + (F)	1 + (D)	—

Carcinoma size was measured along the major axis.

Ad, adenocarcinoma; D, diffuse; F; focal; IHC, immunohistochemistry; P/D, poorly differentiated carcinoma; Sq, squamous cell carcinoma; p-Stage, pathological stage.

calretinin. The surgical pathology databases of the National Cancer Center Hospital East, Chiba, Japan, were searched, and 11 cases of PC located in the peripheral lung and resected between January 2005 and December 2007, including the present case, were retrieved. The institutional review board approved the analysis. Some tumors had a malignant history, and five patients died of their PC. Sections 5 μm thick were cut from paraffin-embedded tissue blocks of the 10 other tumors, mounted on slides, and deparaffinized with xylene and ethanol. Endogenous peroxidase was blocked for 15 min with 0.3% H_2O_2 in methanol. Immunohistochemical staining with D2-40 (mouse polyclonal, 1:50, Signet Laboratories, Dedham, MA, USA) and calretinin antibody (rabbit polyclonal, 1:50, Zymed, San Francisco, CA, USA) was performed on every tumor. The podoplanin and the calretinin antigens were retrieved by immersing the sections in 10 mmol/L citric buffer solution (pH 6.0) and heating to 95°C by exposure to microwave irradiation for 30 min.[12] The intensity (0, none; 1+, weak; 2+, strong) and distribution (focal, diffuse) of immunostaining in the sarcomatoid component of the PC were evaluated and recorded by two pathologists (HK and GI). Strong staining intensity was defined as staining comparable to that of lymphatic endothelium, and diffuse distribution was defined as staining of ≥50% of the tumor cells.

The clinical data and immunohistochemistry findings are summarized in Table 1. Podoplanin immunostaining of the sarcomatoid component was positive in four cases (36%), and calretinin immunostaining was positive in nine cases (82%). In addition, CEA was positive in only one case.

DISCUSSION

This is the first report of a PC of the lung that was immunoreactive for both podoplanin and calretinin, well-known markers for mesothelioma. PC is composed of non-small cell carcinoma and spindle and/or giant cells, or of only spindle and giant cell components.[1] PC of the lung were found to have a predilection to occur in the periphery of the lung, and they frequently invade the chest wall or pleura.[13,14] Because PC frequently have a spindle cell component and invade the pleura, they are sometimes confused with mesothelioma in small biopsy specimens.

Although podoplanin and calretinin have recently been reported to be of diagnostic value for the sarcomatoid component of mesothelioma, there has been controversy in the staining results. Hinterberger *et al.* reported that immunostaining for calretinin was superior to immunostaining for podoplanin as a means of diagnosing both epithelioid and sarcomatoid mesotheliomas (calretinin was positive in 57% of sarcomatoid mesothelioma, and D2-40 was positive in 30% of those).[3] In contrast, Padgett *et al.* suggested that podoplanin is a valuable marker for the diagnosis of sarcomatoid mesothelioma (72% of sarcomatoid mesothelioma was positive), and was superior to calretinin (43% of sarcomatoid mesothelioma was positive).[5] Staining with D2-40 has been reported to be less intense and more focal, and to have a cytoplasmic distribution in sarcomatoid mesotheliomas and the sarcomatoid areas of biphasic mesotheliomas.[3,5,15] With regard to sarcomatoid lung carcinoma, D2-40 (8%) was reported to be rarely positive.[5] In contrast, although calretinin was also reported to be frequently positive (42–67%),[16–18] Padgett *et al.* reported that calretinin was negative in the sarcomatoid carcinoma.[5] In the present patient both the membrane and cytoplasm of the sarcomatoid component stained positive for podoplanin. Four of the 11 PC stained in the present study were immunoreactive for podoplanin, and nine were immunoreactive for calretinin. Thus, even when both podoplanin and calretinin were positive, the markers did not appear to be useful for differentiating between sarcomatoid mesothelioma and peripheral pulmonary PC. Special care is required when diagnosing biopsy specimens of

peripheral lung spindle-cell tumors that are positive for podoplanin and calretinin, and when making the differential diagnosis between PC and sarcomatoid mesothelioma.

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ORIGINAL ARTICLE

Phase II study of nedaplatin and irinotecan followed by gefitinib for elderly patients with unresectable non-small cell lung cancer

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Abstract
Purpose We conducted a phase II study of combination chemotherapy with nedaplatin (NP) and irinotecan (CPT) followed by gefitinib to determine the effects and toxicities in patients 70 years or older with unresectable non-small cell lung cancer (NSCLC).
Methods Eligible patients were entered to receive 3 courses of 50 mg/m^2 NP and 60 mg/m^2 CPT on days 1 and 8 every 4 weeks and sequential gefitinib 250 mg po once a day was followed until tumor progression.
Results Twenty-eight patients received NP and CPT combination chemotherapy. One patient achieved CR, 10 PR, 14 SD and 3 PD, and the response rate was 39.3%. Twenty-one patients received gefitinib 250 mg per day until tumor progression after completion of the NP and CPT chemotherapy. Two patients with SD after NP and CPT chemotherapy achieved PR. For the 3-drug combination, there were 13 responders and the overall response rate was 42.9%. Of the toxicities associated with NP and CPT chemotherapy, grade 4 neutropenia, and grade 3 febrile neutropenia were observed in 24 (33.8%) and 3 (4.2%) courses, respectively. Of the toxicities associated with gefitinib treatment, grade 3 anemia, and SGOT and SGPT elevation were observed in one patient (4.8%) each, respectively. The median survival time was 8.7 months, and the 1- and 2-year survival rates were 42.9 and 32.1%, respectively.
Conclusion NP and CPT followed by gefitinib is feasible for elderly patients with unresectable NSCLC.

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Introduction

Current chemotherapy regimens for metastatic non-small cell lung cancer (NSCLC) are not particularly effective. Regimens based on combinations of new anticancer agents such as vinorelbine, gemcitabine, docetaxel and paclitaxel with platinum compounds have emerged as a gold standard for such patients [1].

In a subset analysis of randomized trials, the response rate, toxicity and survival rates in fit, elderly patients with NSCLC receiving platinum-based treatment appeared to be similar to those in younger patients [2]. However, elderly patients with normal organ function had been selected as subjects for the analysis. A feasibility study of standard cisplatin-based chemotherapy in elderly lung cancer patients with normal organ function showed that only 29% satisfied the eligibility criteria, and that these patients experienced severe neutropenia after cisplatin-based chemotherapy [3]. It is generally believed that elderly patients are less able to tolerate aggressive chemotherapy than their younger counterparts. The randomized Elderly Lung Cancer Vinorelbine Study Group trial demonstrated that elderly patients treated with vinorelbine—in combination with best supportive care (BSC)—have a significantly improved chance of survival and quality of life in comparison with patients treated with BSC alone [4]. The Multicenter Italian Lung Cancer in the Elderly Study trial demonstrated that the use of a combination of gemcitabine plus vinorelbine in this patient population did not further improve the survival rate or quality of life in comparison with either vinorelbine or gemcitabine monotherapy [5]. Thus, standard combination chemotherapy

has not been established for elderly patients with advanced NSCLC.

Three-dimensional analysis models have demonstrated a remarkable synergistic interaction of concurrently administered nedaplatin (NP) and irinotecan (CPT) [6]. In our previous phase I/II study, a combination of NP and CPT showed high activity against NSCLC: the response rate was 31.0%, and the 1-year survival rate was 45.2% [7]. A phase II study of combination chemotherapy with NP and CPT in 38 patients aged 70 years or older with advanced NSCLC demonstrated a 65.8% response rate, a median survival time of 418 days, and a 1-year survival rate of 55.3% [8]. However, seven of the 38 patients could not receive a second cycle of the chemotherapy because of toxicities such as vomiting, diarrhea and febrile neutropenia. Dose or schedule modifications are therefore required to make the NP and CPT combination safe for elderly patients.

The epidermal growth factor receptor (EGFR) superfamily was identified early on as a potential target for therapy of solid tumors. Given the biological importance of the EGFR molecular network in carcinomas, several molecules that can inhibit the EGFR tyrosine kinase domain have been synthesized. The inhibitor gefitinib at 250 mg per day demonstrated an 18.4% objective response in 103 patients with previously treated advanced NSCLC [9]. Adverse events associated with use of the drug were mainly skin reactions and diarrhea. As no hematological adverse events or infections related to chemotherapy safety in elderly patients with NSCLC were observed in a trial of gefitinib at 250 mg per day, gefitinib treatment is considered to be feasible for such patients.

Here we report a phase II study of combination chemotherapy with NP and CPT followed by sequential gefitinib treatment for elderly patients with advanced NSCLC. We modified the NP arm so that it was divided on days 1 and 8, in order to ensure safety and to allow continuous use of gefitinib after completion of the NP and CPT chemotherapy until tumor progression.

Patients and methods

The Institutional Review Board of Kanagawa Cancer Center reviewed and approved this study prior to commencement.

Patients

Patients with histologically or cytologically proven unresectable NSCLC were registered for the NP and CPT combination followed by gefitinib chemotherapy. Eligibility criteria for the chemotherapy were: no prior chemotherapy, expected survival of at least 6 weeks, age $\geq$ 70 years, Eastern Cooperative Oncology Group PS score $\leq$ 2, leukocyte count $\geq$ 4,000/μl, hemoglobin count $\geq$ 9 g/dl, platelet count $\geq$ 100,000/μl, total serum bilirubin $\leq$ 1.5 mg/dl, aspartate aminotransferase and alanine aminotransferase $\leq$ 90 IU/l, serum creatinine $\leq$ 1.5 mg/dl, and creatinine clearance more than 40 ml/min. We did not attempt their geriatric assessment in the present study. Patients experiencing postoperative recurrence and patients who had received radiotherapy for metastatic lesions were eligible for the present study, and at least 4 weeks' rest was required after prior surgery or radiation therapy. Patients with massive pleural effusion, pericardial effusion, symptomatic brain metastasis, paralytic ileus, severe infection or pneumonitis were excluded. Patients with uncontrolled ischemic heart disease, severe cardiac insufficiency, hypertention or diabetes mellitus were also excluded. Written informed consent was obtained in every case.

Chemotherapy

Patients exhibiting no progression of the disease were treated every 4 weeks with 60 mg/m^2 CPT and 50 mg/m^2 NP on days 1 and 8. Patients received 5-HT$_3$ antagonist IV and 8 mg dexamethasone IV before administration of the anticancer drugs. Both drugs were administered on day 8 when the following criteria were satisfied: leukocyte count $\geq$ 3000/μl, neutrophil count $\geq$ 1,500/μl, platelet count $\geq$ 75,000/μl, non-hematologic toxicity of less than grade 2 except for alopecia, and leukocyte or neutrophil count greater than 1,000/μl or 500/μl respectively during the period between day 2 and 8. Recombinant human granulocyte colony-stimulating factor (G-CSF), 50 mg/m^2 per day or 2 μg/kg per day, was administered subcutaneously once a day when the patient's leukocyte or neutrophil counts were below 1,000 and 500/μl, respectively. Subsequent cycles of chemotherapy were started when patients were able to satisfy the organ function eligibility criteria, with the exceptions of hemoglobin count and creatinine clearance, for entry to the study. The doses of CPT and NP were reduced by 10 mg/m^2 for the subsequent cycle if dose-limiting toxicities (DLT) were observed, such as grade 4 neutropenia lasting $\geq$4 days or grade 4 neutropenia with fever $\geq$38°C, grade 4 thrombocytopenia, other grade 4 blood/bone marrow toxicities, except for leukocyte and hemoglobin toxicities, grade 4 vomiting, grade 4 anorexia, grade 4 constipation, grade 4 stomatitis/pharyngitis, grade 4 metabolic/laboratory toxicities, grade 4 coagulation toxicities, or grade 3 or 4 other non-blood/bone marrow toxicities, except for nausea and vomiting. The NP and CPT chemotherapy was repeated for a maximum of three cycles unless the disease progressed, or if severe toxicities developed, such as septic shock, irreversible renal failure, grade 4 hepatic toxicity, grade 4 cardiovascular toxicity, grade 4 pulmonary toxicity, grade 4 diarrhea, grade 4 CNS cerebrovascular

ischemia, or grade 4 CNS hemorrhage/bleeding. Tumor responses were evaluated according to the RECIST criteria [10]. Toxicities were evaluated according to the NCI-CTC ver.2 criteria [11].

Sequential chemotherapy with gefitinib 250 mg po once a day was started after completion of the NP and CPT combination chemotherapy when the following criteria were satisfied: PS score ≤ 2, leukocyte count $\geq 4{,}000/\mu l$, hemoglobin count ≥ 9 g/dl, platelet count $\geq 100{,}000/\mu l$, total serum bilirubin ≤ 1.5 mg/dl, aspartate aminotransferase and alanine aminotransferase ≤ 90 IU/l, serum creatinine ≤ 1.5 mg/dl. Sequential gefitinib treatment was interrupted for a maximum 14 days until the toxicities became less than grade 2, if grade 4 hematological toxicities, grade 3 skin toxicity, grade 3 diarrhea, or grade 3 other non-hematological toxicities appeared. The sequential chemotherapy was stopped if the disease progressed, toxicities did not recover to grade 0 or 1 within 14 days, 2 breaks of treatment were required due to toxicities, or patients refused the treatment.

Study design

We chose a 60% response rate as a desirable target level for the NP and CPT regimen, and considered a 40% response rate as not significant. The study design had the power to detect responses greater than 90%, with less than 10% error. Therefore, we required 28 assessable patients in the first stage and 13 in the second stage, according to the Minimax design of Simon [12]. We decided to stop the study if less than 11 patients responded to NP and CPT in the first stage. This regimen was defined as active if the number of responders out of 41 patients was $\geqq 21$, and inactive if the number of responders was $\leqq 20$ [12, 13]. Overall survival was estimated using the method of Kaplan and Meier.

We also defined toxic regimen when one-third patients experienced grade 4 thrombocytopenia, grade 3 neutropenic fever or other grade 3 non-hematological toxicities in this study.

Results

Between November 2002 and July 2005, 28 patients were registered in the study. Patient characteristics are summarized in Table 1. Twenty patients were male and 8 were female, with a median age of 74 years (range 70–81 years). Six patients had a performance status (PS) of 0 and the other 22 patients had a PS of 1. Twenty-three patients had adenocarcinoma, 4 had squamous cell carcinoma, and 1 had non-small cell carcinoma. Seven and 21 patients were stage IIIB and stage IV, respectively. All 28 patients were assessed for response, toxicities and survival. Twenty-five patients received 2 or 3 cycles of NP and CPT combination chemotherapy. Three patients dropped out the study after the first cycle of NP and CPT chemotherapy: 1 with disease progression, 1 with febrile neutropena requiring 15 days for improvement, and 1 with grade 2 diarrhea and grade 3 CNS cerebrovascular ischemia. Treatment-related toxicities during the total 71 courses of NP and CPT chemotherapy are listed in Table 2. Of the hematological toxicities, grade 4 anemia and neutropenia were observed during 2 (2.8%) and 24 (33.8%) courses, respectively. There was no grade 4 thrombocytopenia, and none of the patients required transfusion. Of the non-hematological toxicities, grade 3 febrile neutropenia was observed in three courses (4.2%). Grade 3 diarrhea and grade 3 CNS cerebrovascular ischemia was observed in 1 course (1.4%) each, respectively. Other non-hematological toxicities were mild. The outcome of the NP and CPT regimen in 28 patients were 1 CR, 10 PR, 14 SD and three PD, and the response rate was 39.3%. Thus, the study was stopped in the first stage.

Twenty-one patients received sequential gefitinib treatment, and 7 patients were unable to do so, 3 because of decreased PS, 3 due to refusal, and 1 because of the need for whole brain irradiation for progressive brain metastasis. The median duration of sequential gefitinib treatment was 68 days (range 21–932 days). Two patients, whose

Table 1 Patient characteristics

	No. of patients
Total	28
Age (years)	
Median	74
Range	70–81
Gender	
Male	20
Female	8
Performance status (ECOG)	
0	6
1	22
Smoker	22
Clinical stage	
IIIB	7
IV	18
Postoperative recurrence	3
Histology	
Adenocarcinoma	23
Others	5
No. of metastatic organs	
1	16
$\geqq 2$	5
Brain metastasis	1

Table 2 Toxicities in NP and CPT combination chemotherapy

	Grade (NC I-CTC ver.2)					
	0	1	2	3	4	Grade 3, 4 (%)
Hemogbbin	7	21	27	14	2	22.5
Leukocytes	10	9	24	23	5	39.4
Neutrophils	10	5	10	22	24	64.8
Platelets	19	27	9	16	0	22.5
Bilirubin	68	1	2	0	0	–
SGOT	56	15	0	0	0	–
SGPT	63	7	1	0	0	–
Creatinine	62	7	2	0	0	–
Fatigue	2	48	16	5	0	7.0
Fever	65	6	0	0	0	–
Alopecia	48	22	1	0	0	–
Rash/desquation	68	3	0	0	0	–
Diarrhea	37	27	6	1	0	1.4
Nausea-vomiting	40	25	6	0	0	–
Febrile neutrophenia	62	6	0	3	0	4.2
CNS cerebrovascular ischemia	70	0	0	1	0	1.4
Neuropathy	71	0	0	0	0	–
Pneumonitis	71	0	0	0	0	–

response to NP and CPT was SD, responded to gefitinib treatment, and the overall response rate for NP and CPT followed by gefitinib was 42.9%. Treatment-related toxicities for the total of 21 patients who received gefitinib treatment are listed in Table 3. Of the hematological toxicities, grade 3 anemia was observed in one patient (4.8%). Of the non-hematological toxicities, infection with grade 3 SGOT and SGPT elevation was observed in one patient (4.8%). Other hematological and non-hematological toxicities were mild.

The overall survival curve is shown in Fig. 1. Five patients survived and the other 23 patients died during the follow-up period. The median survival time was 8.7 months. The 1- and 2-year survival rates were 42.9 and 32.1%, respectively.

Discussion

The combination of NP with CPT followed by gefitinib treatment showed activity against NSCLC in the present study. We chosen 60% response rate as a desirable target level in NP and CPT regimen. The responders in 28 entered patients of first stage were required 12 patients, the responders were 11 and this regimen was concluded inactive. However, two patients, whose response to NP and CPT was SD, responded to gefitinib treatment. Thus, overall response rate 42.9% for NP and CPT followed by gefitinib was considered to be active. A previous study of NP and CPT combination chemotherapy showed that it was effective for elderly patients with advanced NSCLC, although 29% of patients experienced febrile neutropenia [8]. In the present study design, we defined toxic when one third patients experienced grade 4 thrombocytopenia, grade

Table 3 Toxicities in gefitinib treatment

	Grade (NC I-CTC ver.2)					
	0	1	2	3	4	Grade 3, 4 (%)
Hemogbbin	1	12	7	1	0	4.8
Leukocytes	16	4	1	0	0	–
Neutrophils	18	2	1	0	0	–
Platelets	15	4	2	0	0	–
Bilirubin	19	2	0	0	0	–
SGOT	13	7	0	1	0	4.8
SGPT	16	4	0	1	0	4.8
Creatinine	17	3	1	0	0	–
Fatigue	1	18	2	0	0	–
Fever	21	0	0	0	0	–
Alopecia	19	2	0	0	0	–
Dry skin	12	9	0	0	0	–
Nail change	20	1	0	0	0	–
Pruritis	13	8	0	0	0	–
Rash/desquation	7	12	2	0	0	–
Anorexia	20	1	0	0	0	–
Diarrhea	15	6	0	0	0	–
Gastritis	20	1	0	0	0	–
Nausea-Vomiting	19	2	0	0	0	–
Epistaxix	20	1	0	0	0	–
Infection	20	0	1	0	0	–
Neuropathy	21	0	0	0	0	–
Pneumonitis	21	0	0	0	0	–

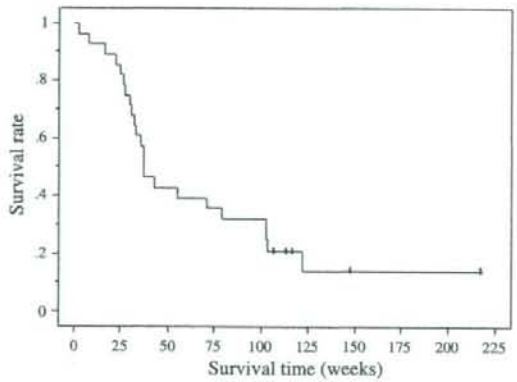

Fig. 1 Survival curves constructed by the Kaplan–Meier method. Five of the 28 patients were alive, the MST was 8.7 months, and the 1- and 2-year survival rates were 42.9 and 32.1%, respectively

3 neutropenic fever or other grade 3 non-hematological toxicities. Only five patients (17.9%) experienced these toxicities and the treatment was concluded to be safe. We also considered the incidence of 33% for grade 4 neutropenia and 4.2% for grade 3 neutropenic fever to be acceptable in this study. Although the response rate of 39.3% for NP and CPT chemotherapy was not high, 25 of 28 patients (89.3%) were able to receive 2–3 cycles of the combination chemotherapy. Division of the NP arm on days 1 and 8 with CPT was confirmed to be safe for elderly patients with NSCLC.

Sequential gefitinib treatment resulted in tumor regression in only 2 of 21 patients (9.5%) achieving SD or PD with NP and CPT treatment. We considered that this small adjuvant effect of gefitinib after NP and CPT treatment may have been due to gefitinib resistance in most of the elderly patients who entered the trial. However, the response rate in the present study was higher than that in a study of gefitinib monotherapy for 40 elderly patients with pretreated NSCLC, which demonstrated a 5% objective response [14]. Responsiveness to gefitinib has been demonstrated in distinct subgroups of patients, such as women, patients who have never smoked, patients with adenocarcinoma, and Asians [15–17]. Twenty-two and 21 of the 28 patients registered in this study were smokers and males, respectively. Only four patients in this study were women who had never smoked, and were sensitive to gefitinib. This may have accounted for the small impact of gefitinib treatment in this study. Median survival time was 8.7 months, but nine patients (32.1%) survived more than 2 years. The presence of such long survivors suggested that gefitinib treatment could be effective for some elderly patients who are gefitinib-sensitive. Although the level of EGFR protein expression is not associated with the response to gefitinib, specific missense and deletion mutations in the tyrosine kinase domain of the EGFR gene have been reported to be associated with gefitinib sensitivity [18, 19]. A retrospective study demonstrated that NSCLC patients with EGFR mutations had a better outcome with gefitinib treatment than patients with the wild-type EGFR gene [20]. Our recent study has also demonstrated a significantly higher gefitinib response in patients with EGFR mutation than in those with wild-type EGFR (90.9 vs. 14.3%), and significantly longer overall and progression-free survivals in patients with EGFR mutation [21]. Unfortunately, the patients in the present study were not analyzed their EGFR genetic status, gefitinib treatment seems to be of some benefit to patients with EGFR mutation.

In conclusion, sequential gefitinib treatment added to NP and CPT combination chemotherapy does not improve the response rate but can have a longer survival benefit for at least some elderly patients with advanced NSCLC. Gefitinib treatment can be considered when candidate patients have EGFR mutation in NSCLC.

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Prognosis of Small Adenocarcinoma of the Lung Based on Thin-Section Computed Tomography and Pathological Preparations

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Objective: We investigated the relationship between findings from tumor opacity in the mediastinal window image and solid lesions in pathological preparations and related the results to tumor recurrence.
Methods: The subjects were 115 patients with a lung adenocarcinoma of 20 mm or smaller who underwent surgical resection. The proportion of the reduction in the tumor opacity in the mediastinal window image maximum diameter to the maximum diameter of the tumor opacity was calculated as the reduction percentage, and the proportion of the maximum solid lesions in pathological preparation diameter to the maximum tumor diameter was calculated as the pathological ratio.
Results: The incidence of relapse was significantly higher in patients with a reduction percentage of less than 50% and in patients with a pathological ratio of less than 50%.
Conclusions: Measurement of the reduction percentage and the pathological ratio may allow prediction of prognosis of small adenocarcinoma of the lung.

Key Words: small adenocarcinoma, lung, thin-section CT, solid lesion, prognosis

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Early detection and early treatment of lung cancer is of importance to improve therapeutic outcomes. Introduction of computed tomography (CT) screening and advancement of diagnostic CT imaging have enabled early detection and early diagnosis of small peripheral-type lung cancers,[1] and such cases are mostly adenocarcinoma. The potential to diagnose and treat peripheral small adenocarcinoma is likely to increase, and qualitative diagnosis is important for establishment of therapeutic policies. Although a small diameter is one of the characteristics of early cancers, a subgroup of small peripheral-type lung cancers are already invasive despite early detection. Patz et al[2] reported that the tumor diameter is not correlated with disease extent or prognosis of small lung cancers of 30 mm or less in diameter, suggesting that other criteria are necessary for prediction of prognosis of peripheral-type early cancers. The current standard therapy for peripheral-type lung adenocarcinoma is lobectomy with lymph node dissection if applicable. However, a subgroup of cases with small adenocarcinoma of the lung have a good prognosis even with limited surgery, and if the prognostic factors in early cancer could be defined, the indication for limited surgery may expand.

A study performed at Kanagawa Cancer Center previously found that the tumor opacity in the mediastinal window image (TOM) of thin-section CT (TS-CT) is associated with the prognosis of patients with lung adenocarcinoma of 20 mm or smaller in diameter.[3,4] However, the pathology of the TOM has not been fully investigated; therefore, in this study, we examined whether TS-CT findings reflect pathological findings in detail and determined the association of tumor opacity with prognosis.

MATERIALS AND METHODS

This study was approved by the institutional Review Boards of Kanagawa Cancer Center and St. Marianna University School of Medicine. Informed consent was obtained from each patient before operation. The subjects were 115 patients with peripheral-type adenocarcinoma of the lung who underwent surgical resection at the Kanagawa Cancer Center between January 1997 and October 2003. Patients with bronchioloalveolar carcinoma (BAC) undetectable in the mediastinal window image were excluded. Contrast-enhanced CT scans were performed using an Aquilion M/16 or X-Vigor/Real system (Toshiba Medical Systems, Tokyo, Japan). High-resolution images targeted to the tumor were obtained at 120 kV (peak) and 200 mA using sections of 2-mm thickness. Images were photographed on each sheet of film using mediastinal (level, 40 Hounsfield unit [HU]; width, 400 HU) and lung (level, −600 HU; width, 1600 HU) window settings.

The findings of TS-CT was evaluated and measured the maximum diameter of the TOM in TS-CT. The proportion of the reduction in the maximum TOM diameter relative to the

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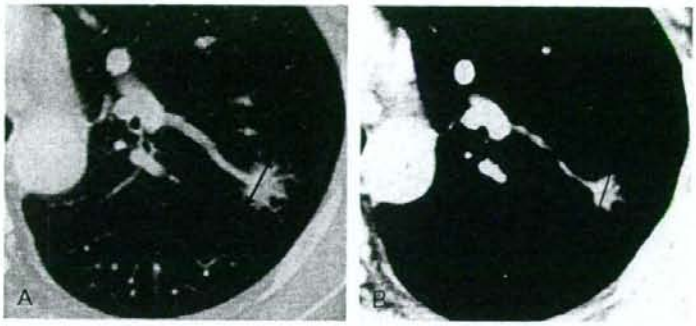


FIGURE 1. Adenocarcinoma with mixed subtypes. TS-CT lung window image (A) and TS-CT mediastinal window image (B). Reduction percentage (%) = {[Tumor diameter (lung window: black arrow) − Tumor diameter (mediastinal window: black line)]/ Tumor diameter (lung window)} ×100.

maximum diameter of the tumor opacity in the lung window was calculated as the reduction percentage (Fig. 1).

The excised lung was distended and fixed by infusion of formalin from the bronchus. The specimen including the maximum cross-sectional area of the tumor was sliced into several sections at intervals of a few millimeters and stained with hematoxylin and eosin. The maximum diameter of the solid lesion in the pathological preparation (SLP) observed under a magnifying glass was measured. The SLP was defined as follows: (1) regions with alveolar collapse, (2) regions accompanied by destruction of the alveolar framework, and (3) regions described in (2) accompanied by collagen fibrotic foci. The proportion of the maximum SLP diameter to the maximum tumor diameter in the pathological preparation was calculated as the pathological ratio (Fig. 2).

Comparisons between the maximum diameters of the tumor opacity in the lung window in TS-CT and the maximum diameters in the pathological preparation, between the maximum TOM and SLP diameters, and between the reduction percentage and pathological ratio were performed using Pearson correlation coefficient.

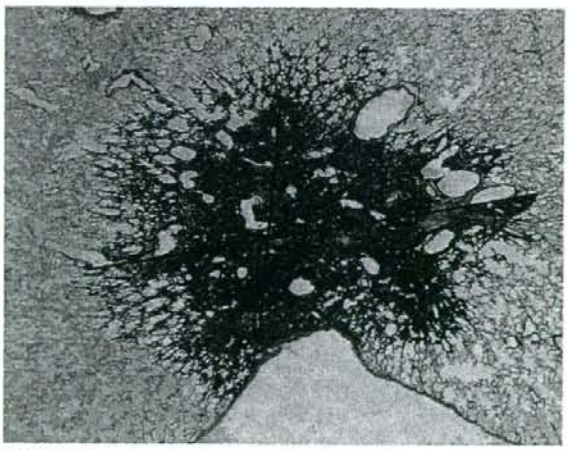


FIGURE 2. Adenocarcinoma with mixed subtypes. Pathological ratio (%) = {[Tumor diameter (black line) − Maximum diameter of solid lesion (black arrow)]/Tumor diameter} ×100.

To investigate the association with prognosis, the relationships of relapse with the maximum TOM and SLP diameters, reduction percentage, and pathological ratio were analyzed by the Kaplan-Meier method and subjected to log-rank tests.

RESULTS

The background characteristics of the patients are shown in Table 1. The patients comprised 52 men and 63 women and had a median age of 67 years. The disease stage was Ia in 95 patients, Ib in 10, IIa in 2, IIb in 3, IIIa in 4, and IIIb in 1, and cancer recurred in 16 patients (13.9%). Of the 115 patients, 99 patients underwent lobectomy with systemic hilar and mediastinal lymph node dissection, whereas 16 patients underwent wedge resection. There were no recurrences in patients who underwent wedge resection. None of the cases had been treated by radiotherapy or chemotherapy.

Pathological findings are shown in Table 2. All cases included alveolar collapse, destruction of the alveolar framework, or collagen fibrotic foci. The histological types were determined according to the World Health Organization classification: the tumor was of the acinar type in 1 case, papillary type in 8, BAC in 12, adenocarcinoma with mixed subtypes in 80, and solid adenocarcinoma with mucin in 14. The Noguchi classification[5] was type B (localized BAC [LBAC] with foci of structural collapse of alveoli) in 12 cases, type C (LBAC with foci of active fibroblastic proliferation) in 80, type D (poorly differentiated adenocarcinoma) in 14, type E (tubular adenocarcinoma) in one, and type F (papillary adenocarcinoma with a compressive growth pattern) in 8. Lymphatic invasion was noted in 21

TABLE 1. Patient Characteristics

Characteristic	No.
No. patients	115
Sex (male/female)	52/63
Age (median, range)	67 (29–82)
p-stage	
I (Ia/Ib)	95/10
II (IIa/IIb)	2/3
III (IIIa/IIIb)	4/1
Relapse	16

TABLE 2. Pathological Findings

	No. (%)
Subtypes of adenocarcinoma	
Acinar	1 (0.9)
Papillary	8 (7.0)
BAC	12 (10.4)
Adenocarcinoma with mixed subtypes	80 (69.6)
Solid adenocarcinoma with mucin	14 (12.1)
Noguchi classification	
Type B	12 (10.4)
Type C	80 (69.6)
Type D	14 (12.1)
Type E	1 (0.9)
Type F	8 (7.0)
Lymphatic permeation	21 (18.3)
Vascular invasion	33 (28.7)
Pleural involvement	17 (14.8)
Nodal involvement	9 (7.8)

Type A indicates LBAC; type B, LBAC with foci of structural collapse of alveoli; type C, LBAC with foci of active fibroblastic proliferation; type D, poorly differentiated adenocarcinoma; type E, tubular adenocarcinoma; type F, papillary adenocarcinoma with a compressive growth pattern.

cases (18.3%), vascular invasion in 33 (28.7%), pleural invasion in 17 (14.8%), and lymph node metastasis in 9 (7.8%).

Tumor diameter-related parameters are shown in Table 3. In TS-CT findings, the median tumor diameter was 18 mm, the median maximum TOM diameter was 12 mm, and the median reduction percentage was 25%. In the pathological preparation, the median tumor diameter was 14 mm, the median maximum SLP diameter was 10 mm, and the median pathological ratio was 24.1%. An analysis of the correlation between the TS-CT and pathological findings gave correlation coefficients of 0.714 ($P < 0.0001$) for the relationship between the maximum diameter of the tumor opacity in the lung window and the pathological maximum tumor diameter, 0.874 ($P < 0.0001$) for the relationship between the maximum TOM and SLP diameters, and 0.903 ($P < 0.0001$) for the relationship between the reduction percentage and pathological ratio.

Analysis of the association of relapse with the maximum TOM and SLP diameters, reduction percentage,

TABLE 3. Maximum Diameters in TS-CT and in Pathological Preparations and the Reduction Percentage and Pathological Ratio (n = 115)

	Size, mm
TS-CT	
Tumor diameter in lung window images, median (range)	18 (8–28)
Tumor diameter in mediastinal window images, median (range)	12 (1–22)
Reduction percentage, median (range)	25 (0–88.9)
Pathological preparation	
Pathological tumor diameter, median (range)	14 (4–20)
Maximum diameter of solid lesions, median (range)	10 (1–20)
Pathological ratio, median (range)	24.1 (0–84.5)

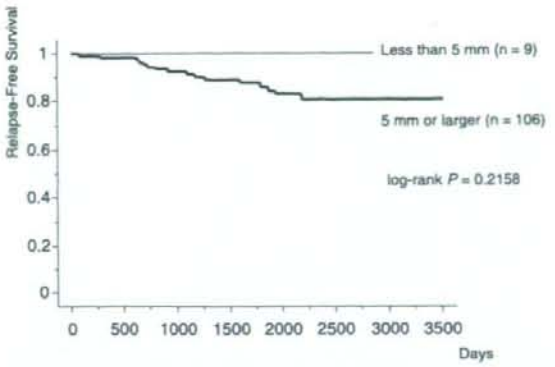


FIGURE 3. Maximum TOM diameter in TS-CT and relapse-free survival.

and pathological ratio gave the following results. Relapse did not occur in patients with a maximum TOM diameter of less than 5 mm, but the difference in incidence of relapse between these patients and those with a maximum TOM diameter of 5 mm or greater was not significant by log-rank test (Fig. 3). The maximum TOM diameter was less than 5 mm in 9 cases, accounting for 7.8% of all cases. Statistically, no significant difference was noted in the incidence of relapse examined at various cutoff values with maximum TOM diameter. However, the incidence of relapse was significantly higher in patients with a reduction percentage of less than 50% compared with those with a reduction percentage of 50% or greater (log-rank test, $P = 0.0203$); no relapse occurred in patients with a reduction percentage of 50% or greater (Fig. 4). No relapse was prominent for in the 28 cases with a reduction percentage of 50% or greater, which accounted for 24.3% of all cases. Regarding the pathological preparations, relapse occurred in only 1 patient with a maximum SLP diameter of less than 5 mm, but there was no significant difference in the incidence of relapse between patients with maximum SLP diameters of less than 5 mm and 5 mm or greater (Fig. 5). The maximum SLP diameter was less than 5 mm in 15 cases, accounting for 13.0% of all cases. Statistically, there was no

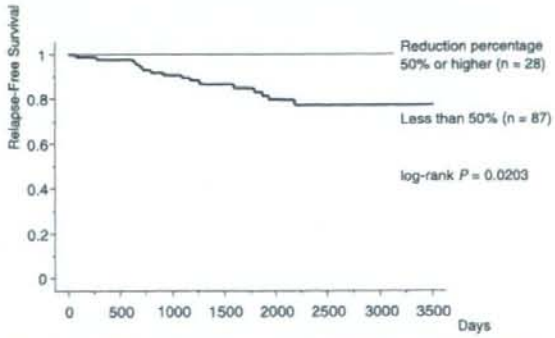


FIGURE 4. Reduction percentage in TS-CT and relapse-free survival.

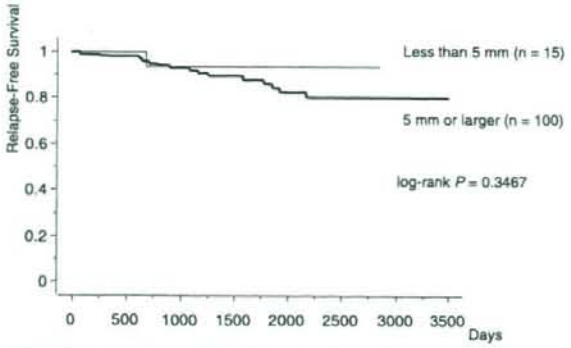


FIGURE 5. Maximum SLP diameter in pathological preparations and relapse-free survival.

significant difference in the incidence of relapse examined at various cutoff values with the maximum SLP diameter. However, the incidence of relapse was significantly higher in patients with a pathological ratio of less than 50% compared with those with a pathological ratio of 50% or greater (log-rank test, $P = 0.0493$); no relapse occurred in patients with a pathological ratio of 50% or greater (Fig. 6). No relapse occurred in the 20 cases with a pathological ratio of 50% or greater, which accounted for 17.4% of all cases.

No acinar, papillary, or solid adenocarcinoma with mucin subtype was noted pathologically when the reduction percentage and pathological ratio exceeded 50%, nor was there vascular, lymphatic, or pleural invasion or lymph node metastasis in such cases (Tables 4 and 5).

DISCUSSION

A previous report from Kanagawa Cancer Center showed that cases of lung adenocarcinoma of 20 mm or smaller in diameter can be divided into 2 groups with different prognoses, based on the reduction percentage of the area in the mediastinal window image in TS-CT compared with the area in the peripheral window image in TS-CT being 50% or greater (air-containing type) and less than 50% (solid-density type).[3,4] Relapse did not occur in patients with tumors

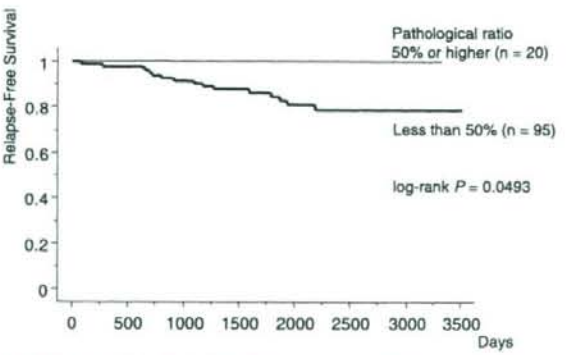


FIGURE 6. Pathological ratio in pathological preparations and relapse-free survival.

TABLE 4. Relationship Between a Reduction Percentage of Less Than 50% in TS-CT and the Pathological Findings

	Reduction Percentage ≥50% (n = 28)	Reduction Percentage <50% (n = 87)
Subtypes of adenocarcinoma		
Acinar	0	1
Papillary	0	8
BAC	8	4
Adenocarcinoma with mixed subtypes	20	60
Solid adenocarcinoma with mucin	0	14
Noguchi classification		
Type B	8	4
Type C	20	60
Type D	0	14
Type E	0	1
Type F	0	8
Lymphatic permeation	0	21
Vascular invasion	0	33
Pleural involvement	0	17
Nodal involvement	0	9

of the air-containing type, whereas recurrence was noted in approximately 25% of solid-density type cases, suggesting that a reduction percentage of 50% or greater is a positive prognostic factor. Tumors of the air-containing type belonged to BAC, whereas tumors of the solid-density type belonged to acinar, papillary, adenocarcinoma with mixed subtypes, or solid adenocarcinoma with mucin. Evaluation of the reduction percentage in the major axis of the tumor, which is a simpler approach, may also be a positive prognostic factor. In this study, we investigated the pathological validity of these

TABLE 5. Relationship Between a Pathological Ratio of Less Than 50% in the Pathological Preparation and Pathological Findings

	Pathological Ratio ≥50% (n = 20)	Pathological Ratio <50% (n = 95)
Subtypes of adenocarcinoma		
Acinar	0	1
Papillary	0	8
BAC	8	4
Adenocarcinoma with mixed subtypes	12	68
Solid adenocarcinoma with mucin	0	14
Noguchi classification		
Type B	8	4
Type C	12	68
Type D	0	14
Type E	0	1
Type F	0	8
Lymphatic permeation	0	21
Vascular invasion	0	33
Pleural involvement	0	17
Nodal involvement	0	9

imaging studies by comparing the maximum diameters of tumor opacity in the lung window (TOM) and the reduction percentage in TS-CT with the maximum diameters of the tumor (SLP) and the pathological ratio in the pathological preparation.

The air-containing category includes ground-glass opacity (GGO) tumors whose reduction percentage is 100%; GGO tumors have been identified as BAC with good prognosis.[6–10] Actually, relapse did not occur in all 53 cases with a reduction percentage of 100% that underwent surgical resection at Kanagawa Cancer Center between January 1997 and October 2003. Therefore, we excluded these cases. With exclusion of GGO tumors, differentiation of lesions into good and poor prognosis groups using TS-CT may be useful,[11] but the prognostic factors have not been fully investigated. Based on Pearson correlation coefficients, our data suggest a strong relationship between TS-CT findings and pathological findings for the relationships between the maximum TOM and SLP diameters and between the reduction percentage and pathological ratio. However, the relationship between the maximum tumor diameters in the TS-CT image and pathological preparation was slightly weaker. These findings suggest that the tumor opacity in the TS-CT mediastinal window faithfully reflects the SLP. The correlation coefficient between the reduction percentage and the pathological ratio was particularly high, showing that contrasting the mediastinal window image with the lung window image faithfully reflects the pathological findings. We note that slicing the excised lung in the same direction as that used for CT is difficult, and alteration of the size of air-containing lesions by formalin fixation is likely; however, the influence of these variables on the relationship between the reduction percentage and pathological ratio seems to be negligible.

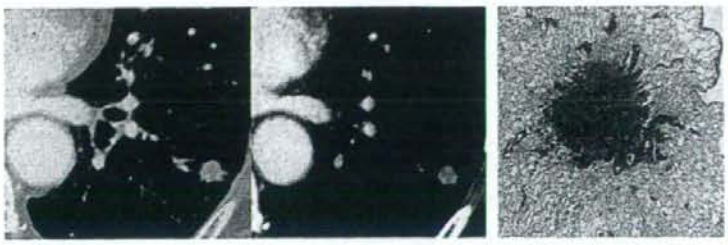
Suzuki et al[12] and Yokose et al[13] have reported that the maximum diameter of the central scar may be associated with the prognosis of lung adenocarcinoma of 30 mm or lesser in diameter; these studies indicated that carcinoma did not recur, and qualitative diagnosis of cancer was possible in cases with a central scar diameter of 5 mm or smaller.

Definitions differ in SLP and the central scar. However, in our patients, recurrence did occur in some cases, although the maximum SLP diameter was 4 mm, suggesting that the maximum SLP diameter alone is insufficient for judgment of good prognosis (Fig. 7). The recurrent cases were solid adenocarcinoma with mucin, which did not show a lepidic growth pattern. Because the incidence of relapse is high in this type, the maximum SLP diameter may not serve as a prognostic factor.[5] In fact, there was no significant difference in the incidence of relapse between cases with a maximum SLP diameter of 5 mm or greater and less than 5 mm. In contrast, there was a significant difference in the incidence of relapse between cases with a pathological ratio of 50% or greater and less than 50%. These findings suggest that the pathological ratio may be more useful than the maximum SLP diameter for prediction of relapse.

In TS-CT, there was no significant difference in the incidence of relapse between cases with a maximum TOM diameter of 5 mm or greater and less than 5 mm. Although a significant difference was found in the incidence of relapse between cases with a reduction percentage of 50% or greater and less than 50%. Ohde et al[14] have reported that the prognosis was significantly better when the major axis of the tumor consolidation on the lung window image in TS-CT was 50% or less of the entire tumor diameter, and our results suggest that the reduction percentage is more useful than the maximum TOM diameter for prediction of relapse.

The pathological examination indicated that the solid lesions were the following: (1) regions with alveolar collapse, (2) regions accompanied by destruction of the alveolar framework, and (3) regions described in (2) that were accompanied by collagen fibrotic foci. Noguchi et al[5] classified the histopathology of small adenocarcinoma of the lung and found that destruction of the alveolar framework and collagen fibrotic foci were associated with prognosis; therefore, solid lesions in the pathological preparation may have contained a region associated with invasiveness of lung adenocarcinoma. Goto et al[15] reported that prognosis varied depending on the condition of the alveolar framework in lung adenocarcinoma of 20 mm or smaller in diameter and that prognosis was significantly poorer in cases with destruction of the alveolar framework associated with destruction of the basement membrane, suggesting that destruction of the basement membrane is the first step in tumor invasion. Because tumor invasion is accompanied by destruction of the alveolar framework and collagen fibrosis, the alveolar air space may be lost, resulting in formation of a solid region in the pathological preparation.

A lepidic growth and advancement pattern of the adenocarcinoma was noted in 80% of our cases, supporting the hypothesis that the early stage of lung adenocarcinoma is often BAC. In this growth and advancement pattern, the air-containing region is initially retained because the lesion



A B

FIGURE 7. A recurrent case with a maximum SLP diameter of 4 mm. Solid adenocarcinoma with mucin: TS-CT (A); pathological preparation (B).

grows by replacement of alveolar lining cells, but acquisition of invasiveness is accompanied by destruction of the alveolar framework and collagen fibrosis, which decreases the air-containing region and increases the solid region. Therefore, decreases in the reduction percentage and pathological ratio may represent a state in which increased invasiveness has caused a decreased air-containing region and an increased solid region. Acinar, papillary, or solid adenocarcinoma with mucin are tumors with nonlepidic growth pattern, and prognosis of them is worse than tumors with lepidic growth pattern (BAC).[5] Pathological ratio and reduction percentage of tumors with nonlepidic growth pattern were less than 50% (Tables 4 and 5).

The correlation coefficient between the reduction percentage in TS-CT and the pathological ratio was very high, and no relapse occurred in cases with a reduction percentage exceeding 50%, confirming that the reduction percentage accurately reflects the pathological findings. Therefore, use of the reduction percentage in TS-CT to roughly divide lesions into 2 groups with different prognoses may be valid based on the pathological investigation. Measurements of the reduction percentage and pathological ratio may allow identification of lung adenocarcinoma with good prognosis. Such measurements are straightforward during intraoperative rapid diagnosis and may be useful for prediction of relapse and judgment of the indication for clinical treatment of early cancer. These findings suggest that prospective investigations of the indications for limited surgery and postoperative adjuvant therapy should be performed for small adenocarcinoma of the lung.

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Prognostic Significance of Thin-Section CT Scan Findings in Small-Sized Lung Adenocarcinoma*

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Objectives: **The purpose of this study is to evaluate the prognostic importance of thin-section (TS) CT scan findings in small-sized lung adenocarcinomas.**

Patients and methods: **We reviewed TS-CT scan findings and pathologic specimens from 359 consecutive patients who underwent surgical resection for peripheral lung adenocarcinomas ≤ 20 mm in diameter during the period from July 1997 to May 2006. By using TS-CT scan images, tumors were defined as air-containing types if the maximum diameter of tumor opacity on mediastinal window images was less than or equal to half of that seen on lung window images, and as a solid-density type if the maximum diameter on the mediastinal window images was more than half of that on lung window images. We compared TS-CT scan findings to pathologic findings (*ie*, lymph node metastasis, pleural invasion, vessel invasion, and lymphatic invasion) and prognosis. The following prognostic factors were analyzed by χ^2 test and Cox proportional hazard model: age; gender; tumor size; pathologic stage; TS-CT scan findings; histologic subtypes defined by Noguchi et al (*ie*, Noguchi type); pleural involvement; lymphatic invasion; and vascular invasion.**

Results: **No pathologic invasive findings or recurrence were found in patients with air-containing-type tumors. Pathologic invasive findings and recurrence were found in 10 to 30% of patients with solid-density-type tumors. The air-containing type tumors seen on TS-CT scans and Noguchi type A or B tumors were demonstrated as prognostic factors for good outcome by χ^2 test ($p < 0.001$). Multivariate analyses revealed lymphatic permeation as a significant prognostic factor.**

Conclusion: **The TS-CT scan findings were important predictive factors for postsurgical outcome in patients with lung adenocarcinoma.** ***(CHEST 2008; 133:441–447)***

Key words: bronchioloalveolar cell carcinoma; ground-glass opacity; limited surgery; noninvasive cancer

Abbreviations: BAC = bronchioloalveolar cell carcinoma; GGO = ground-glass opacity; HU = Hounsfield units; TS = thin section

The number of patients with small-sized lung carcinoma has been increasing due to the routine clinical use of CT scanning and the increasing use of helical CT scan screening for lung cancer. Adenocarcinoma is the most common histologic type of lung cancer in those cases. The population of lung adenocarcinoma is heterogeneous, and many subtypes of adenocarcinoma have been advocated.[1,2] For example, Noguchi et al[1] classified small-sized lung adenocarcinoma into six subtypes based on tumor growth patterns. In this study, a type A or B tumor was localized bronchioloalveolar cell carcinoma (BAC), which showed no lymph node metastasis, rare vascular and pleural invasion, and excellent prognosis (5-year survival rate, 100%). A type C tumor was BAC with foci of active fibroblast proliferation, and showed pathologic invasive findings, and poor prognosis (5-year survival rate, 74.8%). A type D, E, or F tumor was adenocarcinoma without BAC and showed worst prognosis (5-year survival rate, 52.4%). Although these pathologic characteristics are useful as prognostic indicators, the results are defined only after surgery. If we have techniques by which we know the biological behavior of the tumor

and prognosis before treatment, they may be useful for planning therapy.

Many investigators reported that preoperative CT scan findings were related to the pathologic features and prognosis after resection of the tumor. The ratio of ground-glass opacity (GGO), defined as a hazy increase in lung attenuation without obscuring the underlying vascular marking on the CT scan, was associated with the histologic type of the tumor and survival. One of the purposes of these studies was to determine noninvasive carcinoma, defined as a tumor without lymph node metastasis, pleural invasion, vascular invasion, and lymphatic invasion by using thin-section (TS) CT scan images. However, there are few articles accurately determining noninvasive carcinoma by TS-CT scan images. If we determine a diagnosis of noninvasive carcinoma using CT scan images, they are useful for deciding on the surgical procedure to be used, especially lesser resection. This study was carried out to determine whether TS-CT scan findings were good indicators of noninvasive carcinoma of the lung, and also to clarify whether TS-CT scan findings were related to the prognosis.

Materials and Methods

We reviewed TS-CT scan findings and pathologic specimens from 359 consecutive patients who underwent surgical resection for peripheral adenocarcinomas ≤ 20 mm in diameter during the period from July 1997 to May 2006. All patients underwent physical examination, chest roentgenography, CT scan of the chest and abdomen, bone scintigraphy, and MRI of the brain for the staging and evaluation of resectability before the operation. The patients with disease of clinical stage IIB or less underwent surgery. We also surgically treated the patients with clinical N2 disease without evidence of mediastinal lymph node metastasis proven by mediastinoscopy. This study was approved by our institutional review board after confirmation of informed consent by the patients for us to review their records and images. Chest CT scan images were obtained by a commercially available scanner (X-Vigor/Real or Aquilion M/16 CT scanner; Toshiba Medical Systems; Tokyo, Japan). Conventional CT scan images were obtained serially from the thoracic inlet to the lung bases at 120 kV peak spacing, 512 × 512 pixel resolution, and 1-s scanning time. TS images targeted to the tumor were obtained serially at 120 kVp and 200 mA, with 2-mm section thickness, pitch 1, section spacing of 1 to 2 mm, 512 × 512 pixel resolution, and 1-s scanning time, using a high-spatial-reconstruction algorithm with a 20-cm field of view. These images were printed as photographs on each sheet of films using a mediastinal window level setting (level, 40 Hounsfield units [HU]; width, 400 HU) and a pulmonary window level setting (level, −600 HU; width, 1,600 HU).

While contrast medium (60 mL) was infused IV during imaging, lesion sites were translocated in a helical scan mode with a CT scan table speed of 2 mm/s; TS-CT scan images were obtained at one breath hold (120 kVp; 200 mA). The time interval between CT scan examination and subsequent surgery was ≤ 2 weeks in all patients. All CT scan images were reviewed by four thoracic oncologists who were not informed of the pathologic findings. They obtained the maximum dimension of the tumor using a pulmonary window level setting and the maximum dimension of the tumor using a mediastinal window level setting from the TS-CT scan images.

Tumors were defined as air-containing types if the ratio of the maximum dimension of the tumor using a mediastinal window level setting to the maximum dimension of the tumor using a pulmonary window level setting was ≤ 50%, and were defined as solid-density types if it was > 50%. Examples of CT scan images of the two groups are shown in Figures 1 and 2.

Each pattern based on TS-CT scan images was evaluated in terms of pathologic findings and survival outcome. We evaluated pathologic stage (TNM system), pleural involvement, vascular invasion, and lymphatic invasion. In addition, pathologic subtypes defined by Noguchi et al[1] (called hereafter *Noguchi type*) were evaluated.

The statistical significance of the difference between the incidence of relapse and TS-CT scan findings or Noguchi type was assessed by χ^2 tests. Relapse-free survival was calculated by the Kaplan-Meier method. Log-rank tests were used to compare the Kaplan-Meier curves. The Cox proportional hazards model was applied for multivariate analysis. Significance was defined as $p < 0.05$.

Results

Patient and tumor characteristics are listed in Table 1. There were 60 cases in which the largest diameter of the lesion was ≤ 10 mm, 130 cases in which it was 11 to 15 mm, and 169 cases in which it was 16 to 20 mm. There were 152 patients with air-containing-type tumors, and 207 patients with solid-density-type tumors. Table 2 shows the relationship between TS-CT scan findings and pathologic findings. No patients with air-containing-type tumors had lymph node metastasis, pleural involvement, vascular invasion, or lymphatic permeation. Among patients with solid-density-type tumors, 23 (11%) had lymph node metastasis, 45 (22%) had pleural involvement, 69 (33%) had vascular invasion, and 41 (20%) had lymphatic permeation. Table 3 shows the relationship between TS-CT scan findings and

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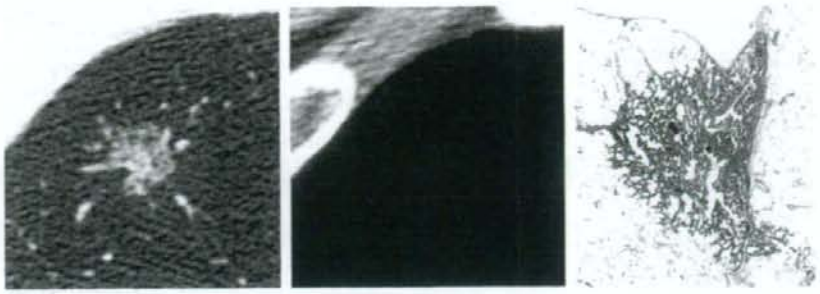

FIGURE 1. TS-CT scan findings of an air-containing-type tumor (diameter, 13 mm) on lung window setting images (*left*, *a*) and on mediastinal window setting images (*center*, *b*). The histologic specimen (*right*, *c*) shows BAC (hematoxylin-eosin, original × 6).

pathologic stage. All patients with air-containing-type tumors had pathologic stage IA disease. In contrast, 39 patients (19%) with solid-density-type tumors had pathologic stage IB or greater disease. Table 5 shows the relationship between TS-CT scan findings and Noguchi type tumors. Among 152 patients with air-containing-type tumors, 79 patients received lobectomy, while 73 underwent limited resections (*ie*, segmentectomy or wedge resection) because of their small size (median tumor diameter, 11 mm). Among 207 patients with solid-density-type tumors, 3 patients underwent pneumonectomy and 155 underwent lobectomy, while 49 underwent limited resections because of their being elderly or having pulmonary hypofunction.

Table 2 shows the relationship between TS-CT scan findings and cancer relapse after surgery. No postoperative cancer relapse was seen in patients with air-containing-type tumors; in contrast, relapse was found in 31 patients (15%) with solid-density-type tumors. The relapse-free survival of 207 patients for whom ≥ 3 years have passed since surgery is shown in Figure 3. Patients with air-containing-type tumors had a 100% 5-year relapse-free survival rate, which was significantly better than that for patients with solid-density-type tumors ($p < 0.001$).

We assessed prognostic factors in 207 patients for whom ≥ 3 years had passed since undergoing surgery. Table 5 shows the relationship between cancer relapse and TS-CT scan findings or Noguchi type. No cancer relapse was seen patients with air-containing-type tumors or patients with Noguchi type A or B tumors. The presence of both air-containing-type and Noguchi type A or B tumors were demonstrated as significant prognostic factors for good outcome by χ^2 tests ($p < 0.001$). The reason for using χ^2 tests but not Cox proportional hazards models to analyze the prognostic factors for TS-CT scan findings and Noguchi type tumors was due to the difficulty in conducting a statistical analysis at the time of no relapse event in the patient group with air-containing-type tumors or Noguchi type A or B tumors. Then, a multivariate analysis with a Cox pro-

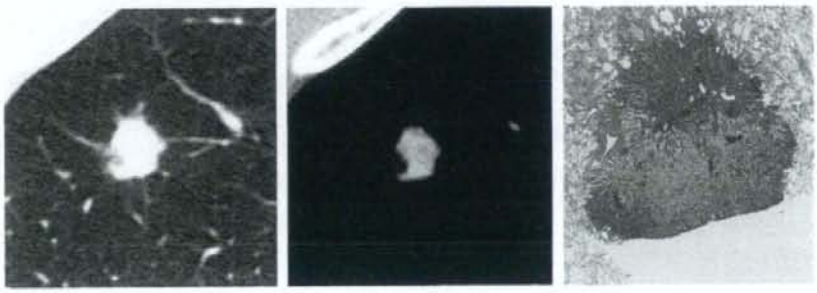

FIGURE 2. TS-CT scan findings for a solid-density-type tumor (diameter, 14 mm) on lung window setting images (*left*, *a*) and on mediastinal window setting images (*center*, *b*). The histologic specimen (*right*, *c*) shows poorly differentiated adenocarcinoma (hematoxylin-eosin, original × 6).

Table 1—*Patient and Tumor Characteristics

Variables	Values
Patients, No.	359
Age, yr	29–86 (65)
Gender, No.	
Male	159
Female	200
Tumor size, mm	5–20 (15)
Noguchi type tumor, No.	
Type A	52
Type B	75
Type C	162
Type D	39
Type E	5
Type F	25
TS-CT scan findings, No.	
Air-containing-type tumor	152
Solid-density-type tumor	207

*Values are given as range (median) or No.

portional hazard model was performed in 116 patients without air-containing type tumors or Noguchi type A or B tumors. The results showed that lymphatic permeation was a significant prognostic factor (Table 6).

Discussion

In patients with small-sized lung adenocarcinomas, several authors[1,2] have shown that pathologic characteristics are correlated with prognosis. Noguchi et al[1] have used tumor growth patterns to classify small-sized adenocarcinomas into six subtypes (*ie*, types A to F). Small, localized BACs (*ie*, types A and B) have not yet metastasized to lymph nodes or invaded vessels or pleura, and are associated with an excellent prognosis (5-year survival rate, 100%). Localized BAC with central fibrosis formation (*ie*, type C) is thought to be advanced carcinoma, which progresses from type A or B and is associated with a poorer prognosis than before (5-year survival rate, 74.8%). The prognosis for patients with nonreplacement-type adenocarcinomas (*ie*, types D, E, or F) is worse than that for patients with replacement-type adenocarcinomas (*ie*, types A, B, and C) [5-year survival rate, 52.4%]. Suzuki et al[3] showed that the size of the central fibrosis was a prognostic factor among peripheral lung adenocarcinomas that were ≤ 3.0 cm in size. In this study, the patients with adenocarcinoma having central fibrosis ≤ 5 mm in the maximum dimension had a 5-year survival rate of 100%, whereas the other patients had a 5-year survival rate of 70%. Higashiyama et al[4] showed that the component area of BAC was correlated with postoperative survival in patients with small peripheral adenocarcinomas ≤ 2.0 cm in diameter. Patients with adenocarcinoma having a BAC component comprising < 50% of the tumor tissue showed a significantly poorer prognosis than those with ≥ 50%.

In TS-CT scan images, consolidation areas represent mostly the foci of fibrosis or tumors of a solid growth pattern, whereas GGO areas reflect areas of a growth pattern of tumor cells replacing alveolar lining cells such as BAC. Because the fibrotic foci increase with the progression of the tumor, and because these areas and advanced adenocarcinomas with a solid growth pattern demonstrate consolidation areas on CT scans, it is suggested that the percentage of the consolidation or GGO areas relative to the tumor is a prognostic indicator. Many investigators[5–22] have reported on the correlation among TS-CT scan findings, pathologic findings, and prognosis. These studies have shown that GGO ratios were very much associated with BAC ratios and had favorable prognostic factors. However, the methods used to calculate the percentage of GGO areas (*ie*, GGO ratio) differ in different articles. Besides, we have few articles that have accurately determined the presence of noninvasive carcinoma, which was defined as a tumor without lymph node

Table 2—*Relationship Between TS-CT Findings and Both Pathologic Findings and Recurrence*

	TS-CT Scan Findings	
Pathologic Findings	Air-Containing-Type Tumors (n = 152)	Solid-Density-Type Tumors (n = 207)
Lymph node metastasis	0	23
Pleural involvement	0	45
Lymphatic permeation	0	41
Vascular invasion	0	69
Recurrence	0	31

Table 3—*Relationship Between TS-CT Findings and Pathologic Stage*

	Pathologic Stage					
TS-CT Scan Findings	IA	IB	IIA	IIB	IIIA	IIIB
Air-containing-type tumor	152	0	0	0	0	0
Solid-density-type tumor	167	16	5	3	15	1

Table 4—*Relationship Between TS-CT Findings and Noguchi Type*

	Noguchi Type					
TS-CT Scan Findings	A	B	C	D	E	F
Air-containing-type tumor	49	53	49	0	0	1
Solid-density-type tumor	3	22	113	39	5	24

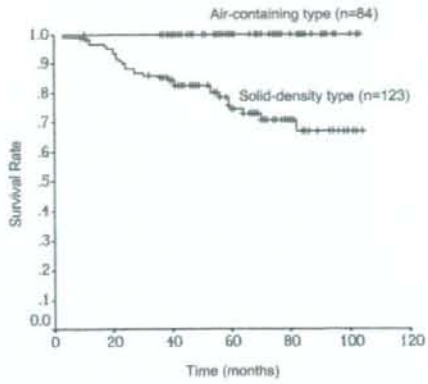

FIGURE 3. Relapse-free survival curves in patients with air-containing-type tumors and solid-density-type tumors.

metastasis, pleural invasion, vascular invasion, and lymphatic invasion, by TS-CT scan images. The parameters used to calculate the GGO ratio that have previously been reported are as follows: a GGO/tumor area ratio[5–10]; a consolidation/tumor dimension ratio[11–14]; a GGO/tumor volume ratio[15]; an area ratio of tumor on mediastinal window to that on the lung window[16,17]; a product of the dimension ratio of the tumor on the mediastinal window to that on lung window[18–20]; and a maximum dimension of tumor on the mediastinal window.[21] Matsuguma et al[8] reported on the relation between the proportion of the GGO and both clinicopathologic characteristics and tumor recurrence in patients with clinical T1N0M0 adenocarcinoma. In this study, the patients with a GGO ratio of ≥ 50% seen on high-resolution CT scans had neither lymph node metastasis nor lymphatic invasion and were alive without cancer recurrence. Ohde et al[12] reported the relation between the proportion of consolidation to GGO and pathologic invasive findings in patients with lung adenocarcinomas ≤ 3.0 cm. They showed that all tumors in which the ratio of the greatest diameter of consolidation to that of the tumor was ≤ 50% had neither lymph node metastasis nor vessel invasion and 5-year survival rate of 95.7%. Although only one cancer relapse was seen in tumors with a ratio of the greatest diameter of consolidation to that of the tumor of ≤ 50% in the study by Ohde et al[12]; the methods used to calculate the GGO ratio in these two studies[8,12] may be useful in defining noninvasive cancer. On the other hand, several investigators[16–20] used not only lung window images but also mediastinal window images to classify the tumors on TS-CT scan images. Kondo et al[16] used a ratio of the tumor area on the mediastinal window images to that on lung window images in patients with pulmonary adenocarcinoma of ≤ 2.0 cm, and showed that the tumors with a ratio of ≤ 50% had no lymph node metastasis, rare vascular invasion, and no cancer relapse. Okada et al[18] and Shimizu et al[20] used the tumor shadow disappearance rate, which was determined from the product of the maximum dimension of the tumor and the largest dimension perpendicular to the maximum axis on both pulmonary and mediastinal window images on TS-CT scan, as previously described by Takamochi et al.[22] They showed that the tumors with a tumor shadow disappearance rate of ≥ 50% had no lymph node metastasis, rare vascular invasion, and no cancer relapse in patients with lung adenocarcinomas ≤ 2.0 cm in diameter. However, the methods used to classify the tumors in these studies with both pulmonary and mediastinal window images could not completely discriminate the tumor without invasive findings (*ie*, vascular, lymphatic, and pleural involvement) from the other. In contrast, the present study showed that the air-containing-type tumor did not have lymph node metastasis, pleural involvement, vessel invasion, or lymphatic permeation, and did not recur after resection. These results suggest that the air-containing-type tumor should be defined as a noninvasive cancer.

Table 5—*Relationship Between Recurrence and Both TS-CT Findings and Noguchi Type Tumor in 207 Patients for Whom 3 Years or More Have Passed Since Surgery*

TS-CT Scan Findings	Recurrence		p Value
	No	Yes	
Tumors			0.000
Air-containing type	84	0	
Solid-density type	93	30	
Noguchi type tumor			0.000
Type A or B	66	0	
Type C, D, E, or F	111	30	

The GGO area is sometimes neither clear nor objective. We sometimes experienced cases in which the border of consolidation and the GGO shadow on the TS-CT scan was unclear, and it was difficult or impossible to measure this size accurately. To select noninvasive cancer more simply and more objectively, we measured the maximum dimensions of tumors on both the lung and mediastinal windows. Our classification has the advantage of simplicity and objectiveness. We have only to compare the greatest dimension of the tumor on lung window images with that on mediastinal images of the TS-CT scan.

Although a number of prognostic indicators have been proposed such as TNM staging, tumor differentiation, molecular expression, and vascular inva-

Table 6—*Multivariate Analysis of Relapse-Free Survival*

Variables	Hazard Ratio	95% Confidence Interval	p Value
Age	0.968	0.923–1.014	0.170
Gender (male vs female)	2.372	0.986–5.707	0.054
Tumor size	1.062	0.947–1.192	0.305
Pathologic stage (≥ II vs I)	1.795	0.598–5.389	0.297
Noguchi type tumor (type D, E, or F vs type C)	2.169	0.842–5.586	0.109
Pleural involvement (positive vs negative)	2.181	0.951–5.001	0.066
Lymphatic permeation (positive vs negative)	2.819	1.094–7.265	0.032
Vascular invasion (positive vs negative)	0.864	0.289–2.588	0.795
Operation mode (lobectomy vs wedge resection)	0.453	0.188–1.094	0.079

sion, the final results are defined only after surgery. As yet, no definite preoperative indicators have been discovered for the postoperative outcome of patients with adenocarcinomas. This study showed that preoperative TS-CT scan findings had prognostic importance. The air-containing-type tumor defined in this study showed no cancer relapse and was revealed as an independent prognostic factor for relapse-free survival. The identification of prognostic variables, especially before the operation is important to decide on the operative procedure and adjuvant therapy. Although lobectomy and pneumonectomy with systemic mediastinal lymphadenectomy is the standard surgical treatment for non-small cell lung cancer, if noninvasive lung cancers are distinguishable on CT scans, limited surgery can be indicated before the operation. Since patients with the air-containing-type tumor showed neither pathologic invasion nor relapse after surgery, we think it is reasonable that we can treat patients with lesser resection for tumors of this type. Treating patients with limited resection leads to a reduction in operative complications and the maintenance of pulmonary function. The number of both elderly patients with lung cancer and patients with a second lung cancer has been increasing. Lesser invasive techniques such as limited resection and stereotactic radiotherapy will play an important role in the future. Studies[23,24] have shown the results of the attempt to apply limited surgery for small lung tumors ≤ 2.0 cm in diameter, in which a small number of local relapses was seen in patients who underwent limited resections. Our study also showed that 11% of solid-density-type tumors had lymph node metastasis. We think that it is not the size of the tumor but the findings of the CT scan of the tumor that is a good indicator for determining whether to use limited resection. Nakata et al[25] reported the results of limited resection of pure GGO selected by the CT scan, in which no cancer relapse was seen in 33 patients who underwent limited resection. In the selection of a candidate for limited surgery, it is important to select patients with noninvasive cancers that not only have high specificity but also high sensitivity. In our study, among 162 patients with Noguchi type C tumor, which is thought to be advanced carcinoma, 49 patients had air-containing-type tumors (Table 4). This result means that our classification using TS-CT scans can preoperatively determine the presence of type C tumors without invasive findings. A prospective study is needed to clarify whether patients with air-containing-type tumors defined preoperatively on TS-CT scan images are candidates for limited surgery. In conclusion, the presence of air-containing-type tumors in patients with peripheral adenocarcinomas < 2.0 cm in diameter means noninvasive cancer and that such patients are candidates for limited surgery.

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