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SHORT REPORT

Bronchoscopic findings for bevacizumab-related pulmonary hemorrhage in advanced non–small cell lung cancer

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Summary We report contemporaneous bronchoscopic findings for a case of bevacizumab-related pulmonary hemorrhage in a patient with advanced non–small cell lung cancer (NSCLC). Flexible bronchoscopy at diagnosis revealed abnormal capillary dilation that was suggestive of endobronchial involvement at the primary tumor location. The patient developed massive hemoptysis despite of marked tumor shrinkage achieved by bevacizumab-containing chemotherapy. Emergency flexible bronchoscopy for hemoptysis suggested that the location of the primary tumor was the source of bleeding. Subsequent follow-up flexible bronchoscopy revealed an ulcerative mucosal-like lesion associated with a white necrotic substance as well as attenuation of the dilation of submucosal vessels compared with that apparent at diagnosis. Our case report highlights the potential mechanistic insights into bevacizumab-related bleeding and importance of performing bronchoscopy at diagnosis in NSCLC patients, given that abnormal bronchoscopic findings may be a risk factor for bleeding.

Keywords Lung cancer · Bevacizumab · Pulmonary hemorrhage · Bronchoscopy

Introduction

Vascular endothelial growth factor (VEGF) plays an important role in tumor growth, invasion, and metastasis by promoting tumor angiogenesis [1, 2]. Bevacizumab, a humanized monoclonal antibody that inhibits VEGF activity, has been approved for the treatment of several types of advanced cancer, including colorectal cancer, breast cancer, renal cell carcinoma, and non–small cell lung cancer (NSCLC) [3]. In patients with NSCLC, bevacizumab is associated with an increased risk of fatal pulmonary hemorrhage, although the mechanism underlying the development of this condition has not been elucidated [4]. We now report contemporaneous bronchoscopic findings for a case of bevacizumab-related pulmonary hemorrhage in a patient with advanced NSCLC.

Case report

A 70-year-old man was diagnosed with lung adenocarcinoma of stage IV accompanied by pleural dissemination. A chest computed tomography (CT) scan revealed a 2 by 3. 4 cm mass in the inferior lobe of the left lung as well as thickened bronchial walls in the ipsilateral hilar region (Fig. 1a). Flexible bronchoscopy at diagnosis revealed a constriction in the left lower bronchial tube as well as dilation of submucosal vessels located at the bifurcation of the left upper and lower lobe bronchi (Fig. 2a, indicated by the arrow). The patient was treated with carboplatin and S-1 together with bevacizumab (15 mg/kg) [5]. Seven days after the completion of three cycles of treatment, however, the patient developed hemoptysis, with expectoration of 30 to 40 ml of bloody sputum, and was immediately referred to our hospital. At admission, he appeared in good condition despite a persistent cough that produced bloody sputum. A physical examination revealed no abnormal findings with the exception of bilateral rhonchi on chest auscultation. His hemoglobin level was 11.5 g/dL, hematocrit 32.5 %, white

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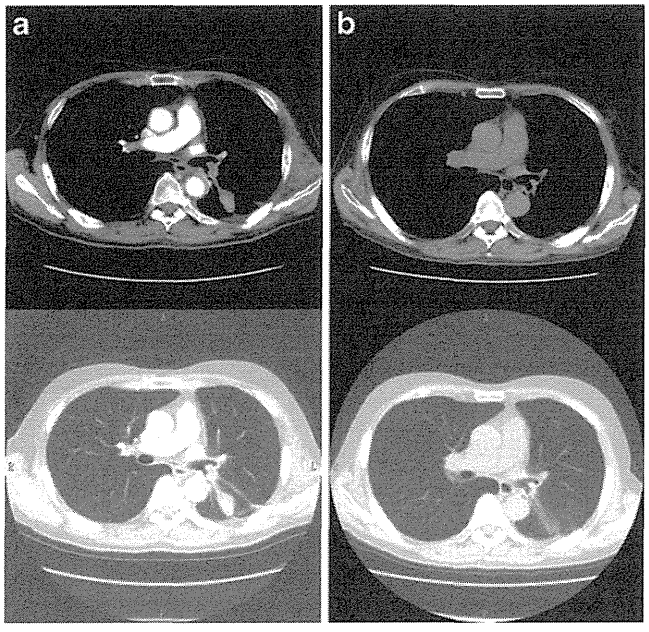

Fig. 1 **a** CT scan performed at diagnosis, shows a 2 cm×3.4 cm mass in inferior lobe of the left lung, and thickened bronchial walls of ipsilateral hilar region. **b** CT scan performed at admission by pulmonary hemorrhage, shows tumor shrinkage in inferior lobe of the left and improvement of thickened bronchial walls of left hilar region

blood cell count 3500/mm^3, and platelet count 194,000/mm^3, with coagulation analysis and biochemical findings being normal. A chest CT scan revealed tumor shrinkage in the inferior lobe of the left lung as well as amelioration of the thickening of the bronchial walls in the left hilar region (Fig. 1b). The day after admission, flexible bronchoscopy showed a large blood clot completely occluding the lower lobe bronchus (Fig. 2b, indicated by the arrow), suggesting that the location of the primary tumor was the source of bleeding. The patient was followed closely with administration of a hemostatic agent, and the bloody sputum disappeared within 6 days. Follow-up flexible bronchoscopy performed 6 days after admission showed an ulcerative mucosal-like lesion associated with a white necrotic substance along the medial wall of the left lower lobe bronchus (Fig. 2c, indicated by the arrow). At 14 days after hospitalization for hemoptysis, treatment with carboplatin and S-1 was resumed without bevacizumab. The patient underwent an additional three cycles of this treatment and did not experience a recurrence of hemoptysis.

Comment

To the best of our knowledge, there are no previously published reports of bronchoscopic findings for bevacizumab-related pulmonary hemorrhage. Recent retrospective analysis of NSCLC patients treated with bevacizumab has found that endobronchial involvement as revealed by CT is associated with the development of severe pulmonary hemorrhage [6]. In the present case, flexible bronchoscopy at diagnosis revealed irregular capillary dilation, indicative of endobronchial involvement. These observations suggest that baseline bronchoscopic information might be important for evaluation of hemoptysis in NSCLC patients undergoing therapy with bevacizumab.

We also found that the pulmonary hemorrhage was accompanied by tumor shrinkage, as confirmed by CT, in the present patient. In addition, follow-up flexible bronchoscopy revealed an ulcerative mucosal-like lesion as well as attenuation of the dilation of submucosal vessels compared with that apparent at diagnosis. Although the mechanism of bleeding associated with bevacizumab treatment is unclear, these findings suggest that such bleeding may be directly related to the inhibitory effect of bevacizumab on VEGF signaling. VEGF is important for maintenance of the architecture and integrity of the microvasculature by endothelial cells [7]. Inhibition of VEGF signaling by bevacizumab might thus impair the ability of endothelial cells to repair

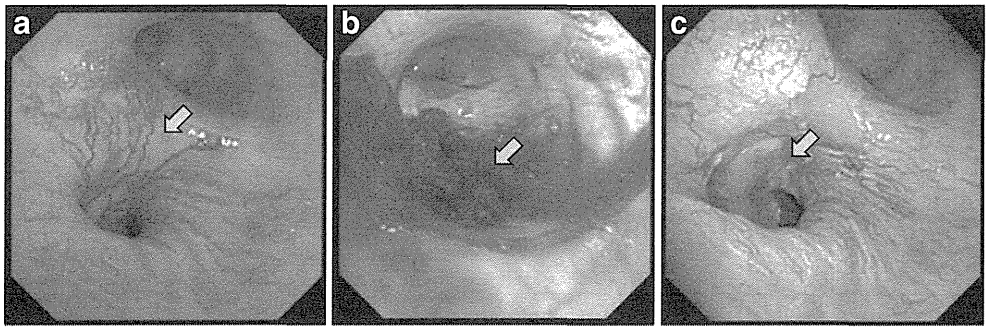

Fig. 2 **a** Bronchoscopy at diagnosis revealed the constriction in the left lower bronchial tube, and the dilatation of submucosal vessels located at the bifurcation of left upper and lower lobe bronchus. **b** Panel shows the blood clot completely abstructing the lower lobe bronchus from the bronchus intermeduis level. **c** Panel shows the scar covered with white necrotic substance is seen on the upper aspect of the lower lobe bronchusat the site of previous dilatation of submucosal vessels

or regenerate vessels after tumor shrinkage, resulting in an increased risk of bleeding. Our results suggest that prolongation of wound healing after tumor shrinkage might be an important mechanism of bevacizumab-related hemorrhage in NSCLC patients. Life-threatening hemoptysis is the most serious adverse effect of bevacizumab treatment in NSCLC patients. A squamous histology, tumor location close to major blood vessels, and tumor necrosis or cavitation are potential risk factors for bevacizumab-related pulmonary hemorrhage in such individuals, but it has not yet proved possible to prevent the development of this condition in all patients [8]. Further research is thus required to elucidate the mechanism underlying bevacizumab-related pulmonary hemorrhage and its clinical risk factors.

The present report highlights the potential importance of bronchoscopic findings for determining the risk of bevacizumab-related pulmonary hemorrhage as well as for providing insight into the mechanism of such bleeding.

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Carboplatin plus Either Docetaxel or Paclitaxel for Japanese Patients with Advanced Non-small Cell Lung Cancer

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Abstract. *Aim: Assessment of the efficacy of docetaxel plus carboplatin vs. paclitaxel plus carboplatin in Japanese patients with advanced non-small cell lung cancer (NSCLC). Patients and Methods: Chemotherapy-naïve patients were randomly assigned at a ratio of 2 to 1 to receive six cycles of either docetaxel (60 mg/m^2) plus carboplatin [area under the curve (AUC)=6 mg/ml min] or paclitaxel (200 mg/m^2) plus carboplatin (same dose), on day 1 every 21 days. The primary end-point was progression-free survival (PFS). Results: A total of 90 patients were enrolled. Overall response rate, median PFS and median survival time in the docetaxel-plus-carboplatin group and the paclitaxel-plus-carboplatin group were 23% vs. 33%, 4.8 months vs. 5.1 months, and 17.6 months vs. 15.6 months, respectively. The docetaxel-plus-carboplatin group had a higher incidence of grade 3 or 4 neutropenia (88% vs. 60%). Conclusion: Both regimens were similarly effective in Japanese patients with advanced NSCLC.*

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Key Words: Non-small cell lung cancer, chemotherapy, randomized phase 2, ethnicity, docetaxel, paclitaxel carboplatin.

Lung cancer is one of the most common malignancies and is the leading cause of cancer-related death worldwide (1). Non-small cell lung cancer (NSCLC) accounts for 85% of all cases of lung cancer. Platinum-based chemotherapy has been considered a standard treatment for advanced NSCLC. In addition, molecular-targeted therapy, including vascular endothelial growth factor (VEGF) inhibitors such as bevacizumab, epidermal growth factor receptor (EGFR) inhibitors such as gefitinib or erlotinib, and anaplastic lymphoma kinase (ALK) inhibitors, has recently become a treatment option for specific subsets of patients, especially those with non-squamous cell lung cancer (2-5). These molecular targeted therapies have led to a paradigm shift of

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treatment. Unfortunately, all patients with *EGFR*-mutant or ALK-positive lung cancer who receive EGFR or ALK inhibitors eventually experience disease relapse and require chemotherapy at some point during the course of treatment (4). Chemotherapy thus continues to play an important role in the management of NSCLC.

Docetaxel has been demonstrated to be effective against previously-untreated advanced NSCLC. Results of a large phase III trial found that docetaxel plus cisplatin was significantly superior to vindesine plus cisplatin in terms of overall response rate and overall survival (6). Carboplatin has shown broad equivalence to cisplatin in combination with chemotherapy for advanced NSCLC. To our knowledge, however, no clinical trial has directly compared docetaxel + carboplatin (DCarb) with paclitaxel plus carboplatin (PCarb) in patients with advanced NSCLC.

Fossella *et al.* reported a phase III study comparing docetaxel plus a platinum agent with vinorelbine plus cisplatin, performed by the TAX 326 Study Group (7). Docetaxel with cisplatin led to a better overall response and higher survival rate than docetaxel plus carboplatin, with a median survival time (MST) of 11.3 months, as compared with 9.4 months, respectively. However, that study was not designed to directly compare docetaxel plus cisplatin with docetaxel plus carboplatin. The therapeutic value of docetaxel with carboplatin as a front-line regimen for advanced NSCLC, thus remains unclear.

Millward *et al.* conducted a phase II study of docetaxel plus carboplatin in white and Asian patients with advanced NSCLC (8). The MST was 12.9 months, and multivariate analysis showed that ethnicity was a significant independent predictor of response and survival. Two clinical trials have evaluated docetaxel with carboplatin in Japanese patients with advanced NSCLC (9, 10). These trials reported a good MST of 12 months and 12.9 months, respectively. However, randomized phase II studies comparing docetaxel plus carboplatin with a standard regimen have yet to be performed on Asian patients with NSCLC. We therefore designed a randomized phase II study to compare the newer combination of DCarb with PCarb as standard treatment in patients with advanced NSCLC.

Patients and Methods

All patients enrolled in this study had cytologically- or histologically-confirmed diagnoses of NSCLC (adenocarcinoma, squamous cell carcinoma, large cell carcinoma, or NSCLC not otherwise specified) with advanced stage IIIB or stage IV disease or relapse after surgical resection of NSCLC (regarded as stage IV). Other eligibility criteria were as follows: chemotherapy-naïve status; an Eastern Cooperative Oncology Group performance status (PS) of 0 or 1; a neutrophil count of at least 2.0×10^9 cells/l; a platelet count higher than 100.0×10^9 cells/l; a hemoglobin concentration of at least 90 g/l; serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) concentrations of less than two-times the upper limit of normal (ULN); serum total bilirubin and creatinine concentrations of less than the ULN; a creatinine clearance of 50 ml/min or higher (as calculated by the Cockcroft-Gault equation) (11); and an alveolar partial pressure of oxygen (PaO_2) of 70 Torr or higher or an oxygen saturation on pulse oximetry (SpO_2) of 94% or higher (while breathing room air). Patients were excluded if they had any of the following conditions: severe infection, pregnancy or breastfeeding; a previous malignancy within the previous five years (except for patients with cured carcinoma *in situ*); another active cancer; an allergy to polysorbate 80 or polyoxyethylene castor oil; evidence of interstitial lung disease on a plain chest x-ray film; uncontrolled co-morbidities such as malignant hypertension, congestive heart failure, myocardial infarction within the previous six months, arrhythmia requiring treatment, bleeding tendency, or diabetes mellitus; pleural or pericardial effusion requiring drainage; symptomatic brain metastasis; or peripheral neuropathy of more than grade 1.

All patients provided written informed consent. The study protocol was approved by the Institutional Review Boards of all participating institutions and by the Japan Multinational Trial Organization (JMTO) ethical committee. This study was conducted in accordance with the Declaration of Helsinki and was registered with UMIN 000001225 on June 30, 2008.

Study design and treatment. This was a randomized, phase II, open-label study. The primary end-point was the determination of progression-free survival (PFS). The secondary end-points were tumor response, survival (1-year survival rate, overall survival), and toxic effects. Patients were randomly assigned at a ratio of 2 to 1 to receive either DCarbo or PCarbo. Central randomization to each arm was performed with the use of Pocock and Simon's method (12). Stratification factors were PS (0 or 1), more than 5% weight loss within the previous six months (yes or no), and serum lactic dehydrogenase (LDH) concentration (abnormally high or not).

Patients in the DCarbo group received intravenous docetaxel (60 mg/m^2) over the course of 60 to 90 min and carboplatin [area under the curve (AUC) 6 mg/ml min] over the course of three hours on day 1 every 21 days for six cycles. Pre-medication, such as anti-emetic agents or corticosteroids, was given as required. In the PCarbo group, patients received intravenous paclitaxel (200 mg/m^2) and carboplatin (AUC 6 mg/ml min, same as in the DCarbo group) on day 1 every 21 days for six cycles. Creatinine clearance was calculated using the Cockcroft-Gault equation. The serum creatinine level (mg/dl) used in this equation was modified by adding 0.2 mg/dl, because an enzyme assay is used in Japan, whereas Jaffe's non-enzyme assay was used to develop this equation. Patients in the PCarbo group were given pre-medication with dexamethasone, diphenhydramine, and ranitidine or cimetidine. The use of additional antiemetics was left at the physician's discretion. Use of granulocyte-colony stimulating factor (G-CSF) was permitted any time during the study (except for prophylactic use) in both groups. In the absence of progressive disease or intolerable toxicity, patients in both groups received six cycles of chemotherapy.

Treatment could be delayed for up to 14 days if the neutrophil count was less than 1.5×10^9 cells/l and the platelet count was less than 75×10^9 cells/l on day 1 of each course. In the event of prolonged or complicated grade 4 neutropenia or thrombocytopenia, the dose of docetaxel was reduced by 10 mg/m^2, that of paclitaxel by 25 mg/m^2, or that of carboplatin by AUC 1 mg/ml min for the subsequent cycle of chemotherapy. Dose reduction was allowed

twice. Treatment could be delayed for up to 14 days if AST or ALT (or both) was more than 2.5-times higher than the ULN, the serum creatinine concentration was more than 1.5-times higher than the institutional ULN, or nonhematological toxicity of grade 2 or higher developed (except for nausea, vomiting, fatigue, loss of appetite, mild electrolyte abnormalities, and alopecia) developed.

Patients were assessed every two cycles, and the objective response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.0 (13). The best response in individual patients was derived from investigator-reported data. Objective response rates were confirmed by at least one sequential tumor assessment. Toxic effects were graded in accordance with the National Cancer Institute Common Toxicity Criteria, version 2.0 (14). The numbers and frequencies of each adverse event were respectively summarized for any grade and for grade 3 or higher in each treatment group. The MST with 95% confidence intervals (CI) and the probability of 1-year survival with 95% CI were calculated by the Kaplan-Meier method for each group.

Statistical plan and analysis. The primary end-point was PFS. The main objective of the study was to estimate the PFS rate at six months in the DCarbo group. The median PFS in the DCarbo group was predicted to be about 150 days on the basis of the results of previous studies. The PFS rate at six months was thus assumed to be 45%. Given that the range of the 90% CI at six months is 0.1 or less, we estimated that at least 60 patients would be required in the DCarbo group. Because patients were randomly assigned to either the DCarbo group or PCarbo group at a ratio of 2:1, the target number of patients in the latter group (calibration group) was 30. Hazard ratios (HR) and 95% CIs were calculated with a Cox proportional-hazards model.

Results

Patients' characteristics. A total of 90 patients were enrolled between June 2007 and September 2008 at 15 institutions in Japan. All patients were eligible for analysis. Sixty patients were assigned to the DCarbo group and 30 were assigned to the PCarbo group (Figure 1). The patients' characteristics for both groups were shown in Table I. The baseline characteristics of patients in the DCarbo group were similar to those in the PCarbo group.

Tumor response and survival. The total number of administered cycles of chemotherapy was 230 in the DCarbo group and 139 in the PCarbo group. The median follow-up time was 15.8 months.

Sixty patients began chemotherapy in the DCarbo group, and 19 completed six cycles according to protocol. The mean number of administered cycles of chemotherapy was 4.0 (range, 1 to 6). Dose modification was carried out once in 17 patients (28%) and more than once in 23 patients (38%). Treatment was delayed in 11 patients (18%). The reasons for treatment discontinuation before the completion of six cycles of DCarbo were disease progression (n=18), dose modification necessitated by adverse events more than twice (n=12), and withdrawal of treatment by the patient (n=6) or investigator (n=5). In the PCarbo group, 30 patients began chemotherapy, and 14 completed six cycles. The mean number of administered cycles was 4.6 (range, 1 to 6). Dose modification was carried out once in seven patients (23%) and more than once in seven patients (23%). Treatment was delayed in 10 patients (33%). The reasons for discontinuation of PCarbo before the completion of six cycles were disease progression (n=6), withdrawal of treatment by the patient (n=5), dose modification necessitated by adverse events more than twice (n=4), and withdrawal of treatment by the investigator (n=1).

The overall response rate (based on the best confirmed response during study treatment) was 23% [14 out of 60 patients with partial response (PR); 95% CI=13%-36%] in the DCarbo group and 33% (10 out of 30 patients with PR; 95% CI=17%-53%) in the PCarbo group (Table II). No patient had a complete response. Stable disease was obtained in 31 patients (52%; 95% CI=38%-65%) in the DCarbo group and 15 patients (50%; 95% CI=31%-69%) in the PCarbo group. The Median PFS was 4.8 months (95% CI=3.9-7.2 months) in the DCarbo group and 5.1 months (95% CI=4.4-6.4 months) in the PCarbo group. The PFS rate at six months was 42% (90% CI=31%-52%) in the DCarbo group and 40% (90% CI=25%-54%) in the PCarbo group (Figure 2). The hazard ratio of DCarbo referenced to PCarbo was 0.86 (95% CI=0.55-1.36). The MST was 17.6 months (95% CI=10.2-22.9 months) in the DCarbo group and 15.6 months (95% CI=9.3-20.8 monts) in the PCarbo group (Figure 3). The 1-year survival rate was 60% in both groups (90% CI=49%-70% in the DCarbo group and 44%-73% in the PCarbo group). The hazard ratio of DCarbo compared to PCarbo was 0.77 (95%CI=0.47-1.26).

Toxicity. All patients were assessable for toxicity (Table III). Patients in the DCarbo group had a higher incidence of grade 3 or 4 neutropenia than those in the PCarbo group (88% *vs.* 60%, 95% CI=77%-95% *vs.* 41%-77%). The PCarbo group had a higher incidence of grade 2 or more sensory neuropathy (37% *vs.* 3%, 95% CI=20%-56% *vs.* 0%-12%), myalgia (13% *vs.* 0%, 95% CI=4%-31% *vs.* 0%-6%), and arthralgia (20% *vs.* 2%, 95% CI=8%-39% *vs.* 0%-9%) than the DCarbo group. There were no major differences between the two groups regarding any other toxic effects (Table III).

One treatment-related death was reported in the DCarbo group. Acute respiratory distress syndrome (ARDS) developed in a 76-year-old woman two months after the end of the fifth, final cycle of treatment. Five days after the onset of respiratory failure, the patient had an acute myocardial infarction and died two days later. The patient's attending physician judged that the relation to treatment was "not definite." An independent data monitoring committee judged

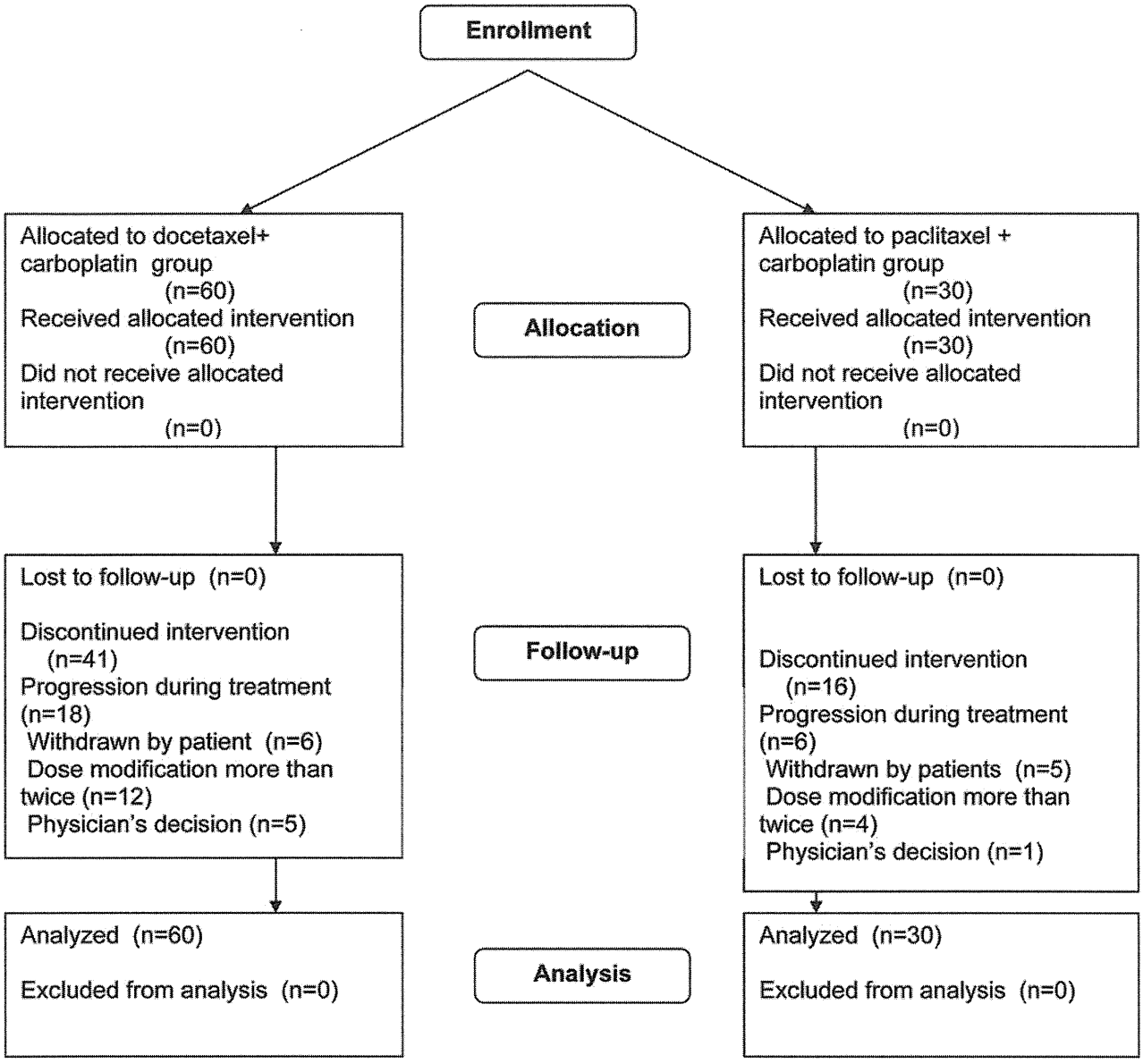

Figure 1. *Study design and patient flow. n: Number of patients.*

that the relation of death to the study treatment was not definite, but possible.

Discussion

This randomized phase II trial comparing DCarbo with PCarbo is the first of this kind to be performed in Asia. Our results suggest that both regimens are similar in terms of PFS and overall survival. The PFS of 4.8 (95% CI=3.9-7.2) months and MST of 17.6 (95% CI=10.2-22.9) months in the DCarbo group were favorable.

Asian ethnicity may contribute to some degree to better results in patients who receive DCarbo, as reported by Millward *et al.* (8). Three large phase III trials performed on Japanese patients with advanced NSCLC have included paclitaxel + carboplatin as one treatment arm (15-17). In these studies, the number of patients who received PCarbo was 281 (Okamoto *et al.*) (15), 197 (JMTO LC 00-03 study) (16), and 145 (Four-Arm Cooperative Study) (17), respectively. The dose of carboplatin was AUC 6 mg/ml min, with paclitaxel given at a dose of 200 mg/m^2 in two studies (15, 17) and 225 mg/m^2 in the other (16). The median PFS

Table I. *Patients' characteristics.*

	Docetaxel + carboplatin c (%) (n=60)	Paclitaxel + arboplatin (%) (n=30)
Age (median) (years)	67.5	65.5
Male/female	43/13 (78/22)	22/8 (73/27)
Body weight loss>5% Yes /no	11/49 (18/82)	5/25 (17/83)
Performance status 0/1	19/41 (32/68)	7/23 (23/77)
Histology Sq/Ad/La/Other	13/36/2/9 (22/60/3/15)	10/17/0/3 (33/57/0/10)
Stage IIIB/IV	24/36 (40/60)	10/20 (33/67)
Naïve/relapsed	53/7 (88/12)	26/4 (87/13)
LDH Normal/abnormally high	44/16 (73/27)	21/9 (70/30)
Prior radiotherapy	3 (5)	3 (10)

Sq: Squamous cell carcinoma, Ad: adenocarcinoma, La: large cell carcinoma, LDH: lactate dehydrogenase.

Table II. *Overall response and survival data.*

Regimen	Docetaxel + carboplatin	Paclitaxel + carboplatin
Number of patients	60	30
Response rate (95%CI)	23% (13-36%)	33% (17-53%)
Median PFS (95% CI), months	4.8 (3.9-7.2)	5.1 (4.4-6.4)
PFS rate (90% CI)*	42% (31-52)	40% (25-54)
HR (95% CI)	0.86 (0.55-1.36)	Referent
Median OS (95% CI), months	17.6 (10.2-23.0)	15.5 (9.4-20.8)
HR (95% CI)	0.77 (0.47-1.26)	Referent
1-Year survival rate (90% CI)	60% (49-70)	60% (44-73)

MST: Median survival time, CI: confidence interval, HR: hazard ratio, PFS: progression-free survival , OS: overall survival. *At six months.

Table III. *Toxicities experienced during study period.*

Toxicity	Docetaxel+ carboplatin % (95% CI) N=60	Paclitaxel+ carboplatin % (95% CI) N=30
Grade 3 or more Neutropenia	88 (77-95)	60 (41-77)
Grade 3 or more Anemia (hemoglobin)	12 (5-23)	7 (1-22)
Grade 3 or more Thrombocytopenia	0	3 (0-17)
Grade 3 or more Frbrile neutropenia	17 (8-29)	13 (4-31)
Grade 2 or more Nausea	28 (18-41)	17 (6-35)
Grade 2 or more Vomiting	12 (5-23)	10 (2-27)
Grade 2 or more Sensory neuropathy	3 (0-12)	37 (20-56)
Grade 2 or more Myalgia	0	13 (4-31)
Grade 2 or more Arthralgia	2 (0-9)	20 (8-39)
Possible TRD (ARDS)	1	0

CI: Confidence interval, TRD: treatment-related death, ARDS: acute respiratory distress syndrome.

or time to progression was 4.8, 5.8, and 4.5 months, and the MST was 13.3, 14.1, and 12.3 months, respectively. These results are similar to those of the present trial, obtaining a PFS of 5.1 months and an MST of 15.6 months, and suggest that Japanese patients have a good response to taxane-based chemotherapy. C1236T polymorphism in the ATP-binding cassette sub-family B member-1 (*ABCB1*) gene is significantly related to docetaxel clearance (18). Gandara *et al*. reported ethnic differences in the metabolism of taxanes between American and Japanese patients with lung cancer in a common-arm analysis of PCarbo, performed jointly in the United States and Japan (19).

Differences in the allelic distribution of genes involved in paclitaxel disposition or DNA repair [cytochrome *P450* 3A4 (CYP3A4)*1B and excision repair cross-complementation group 2 (*ERCC2*) K751Q] were observed between Japanese and American patients. Resulting metabolic differences in taxane metabolism may consequently contribute to better outcomes in Asian patients with lung cancer who receive taxanes.

In our study the dose of docetaxel was 60 mg/m^2 and that of carboplatin was AUC 6 mg/ml min. This dose of docetaxel is generally used in Japan to treat NSCLC. When combined with cisplatin, the dose of docetaxel used in Japan may be slightly lower the one that used in other countries (6). However, the results of Japanese studies in terms of PFS or overall survival are not inferior to those of studies performed in other countries, where docetaxel is usually given at a dose of 75 mg/m^2 (7). On the other hand, most Japanese studies have used cisplatin at a dose of 80 mg/m^2, which is slightly higher than that used in other countries (75 mg/m^2). The modest differences in the doses of chemotherapeutic agents may not have had a major influence on PFS or overall survival. Brunetto *et al*. reported that the dose intensity of platinum-doublet regimens including cisplatin or carboplatin with either vinorelbine or gemcitabine did not have an impact on survival or time-to-progression in patients with NSCLC (20).

A phase III study comparing DCarbo with PCarbo as first-line chemotherapy was performed in 1,077 patients with ovarian cancer (21). Docetaxel (75 mg/m^2) or paclitaxel (175 mg/m^2) with carboplatin to (AUC 5 mg/ml min) was administered every three weeks for six cycles.

The study also concluded that DCarbo is similar to PCarbo in terms of PFS and response, but recommended that longer follow-up is required before making a definitive statement on survival. DCarbo was considered an alternative first-line regimen for chemotherapy in patients with ovarian cancer. As for toxicity, DCarbo was associated with

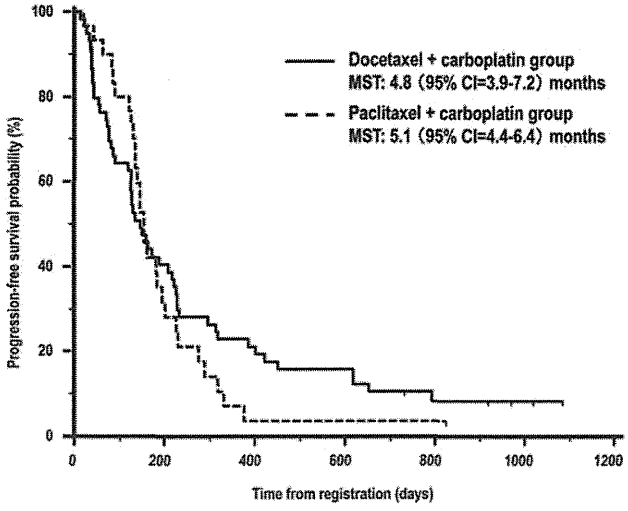

Figure 2. *Progression-free survival. MST: Median survival time, CI: confidence interval.*

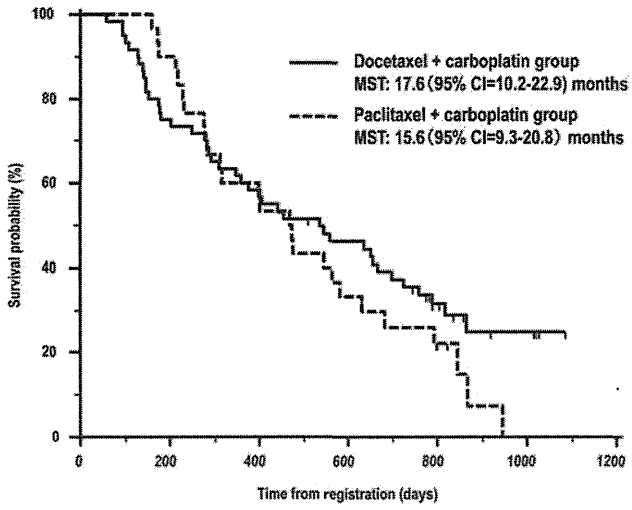

Figure 3. *Overall survival. MST: Median survival time, CI: confidence interval.*

substantially less overall and grade 2 or more neurotoxicity than PCarbo. On the other hand, DCarbo led to a higher incidence of grade 3 or 4 neutropenia than did PCarbo. Similar trends were noted in our study: DCarbo had a lower incidence of grade 2 or more sensory neuropathy (3% *vs.* 37%), but a higher incidence of grade 3 or more neutropenia (87% *vs.* 60%) as compared with PCarbo. Although myelosuppression was also frequently associated with DCarbo in our study, this adverse effect was not dose-limiting.

Recently, the survival of patients with NSCLC has improved, in part because of improved treatments or perhaps because of selection bias. The longer the survival, the more problematic is chronic toxicity such as neurotoxicity. Such toxicity negatively affects the quality of life of patients with NSCLC. This is especially true for those tested with PCarbo regimens (22). Even if the dose of paclitaxel is reduced from 225 mg/m^2 to 200 mg/m^2, the problem of neurotoxicity persists. DCarbo would, thus, be the preferred regimen to avoid severe neurotoxicity.

The treatment-related death in the DCarbo group in our study was reviewed by a safety committee. ARDS occurred as late as two months after the end of the patient's fifth, final cycle of treatment. The relation of death to chemotherapy with DCarbo was considered not definite, but possible.

Our study had several important limitations. We studied only Japanese patients, and it remains unclear whether our results can be extrapolated to other ethnic groups. Our study group comprised of patients with all histological types of NSCLC, and information on mutations in the *EGFR* gene was not obtained. In addition, the doses of docetaxel and carboplatin differed from those used in Western studies of patients with NSCLC.

Conclusion

Docetaxel plus carboplatin is considered an alternative first-line chemotherapeutic regimen for patients with newly-diagnosed advanced NSCLC, at least in Asia. In the future, this regimen might be combined with other treatments, such as molecular targeted therapy.

Conflicts of Interest

None.

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Preoperative Concurrent Chemoradiotherapy of S-1/Cisplatin for Stage III Non-Small Cell Lung Cancer

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Background. **Concurrent chemoradiotherapy using S-1 containing tegafur, an oral 5-FU prodrug, plus cisplatin has been reported to show promising efficacy against locally advanced non-small cell lung cancer with acceptable toxicity. The purpose of this study is to assess the impact of this induction treatment followed by surgery on survival for those patients.**

Methods. **Potentially resectable locally advanced non-small cell lung cancer patients were eligible. The concurrent phase consisted of S-1 (orally at 40 mg/m^2 twice a day on days 1 to 14 and 22 to 36) and cisplatin (60 mg/m^2 on days 1 and 22) with radiation of 40 Gy/20 fractions beginning on day 1 followed by surgical resection.**

Results. **Forty-two consecutive patients, between June 2005 and February 2011, were retrospectively analyzed. The median age was 59 (42 to 77) years, there were 34 males and 8 females, 26 cStage IIIA and 16 IIIB, each 21 adenocarcinomas and others. There were 26 partial responses and 16 stable disease cases after current induction treatment without uncontrollable toxicity. Of the 42 patients, 39 underwent surgical resection; 27 underwent a lobectomy and 12 pneumonectomies. One patient died due to thoracic empyema 65 days after surgery. The median follow-up time was 32.0 months. Three- and 5-year disease-free survival rates in all 39 resected patients were 52.0% and 44.0%, respectively, and 3- and 5-year overall survival rates were 77.4% and 61.7%, respectively.**

Conclusions. **Concurrent chemoradiotherapy using S-1 plus cisplatin followed by surgery may provide a better prognosis for locally advanced non-small cell lung cancer patients. Further prospective clinical investigation should be required.**

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Stage III locally advanced non-small cell lung cancer (LA-NSCLC) comprises more than 30% of cases at the time of diagnosis [1]. Recent randomized phase III trials of concurrent chemoradiotherapy have shown better locoregional control, which leads to higher survival rates and is considered to be the current standard treatment for LA-NSCLC [2].

We previously reported concurrent chemoradiotherapy using uracil-tegafur (a 5-FU prodrug, UFT; Taiho Pharmaceutical Co, Ltd, Tokyo, Japan) plus cisplatin with concurrent thoracic radiotherapy of 60 Gy (UP-RT). The response rate and median survival time for unresectable LA-NSCLC patients treated with UP-RT were 80% and 16.5 months, respectively, with a lower incidence of adverse events than those of other trials [3]. The S-1 (TS-1; Taiho Pharmaceutical Co) is a second generation oral anticancer agent based on uracil-tegafur, which has a dihydropyrimidine dehydrogenase (DPD) inhibitory fluoropyrimidine. The S-1 is composed of tegafur, 5-chloro-2,4-dihydroxypyridine (an inhibitor of DPD) and potassium oxonate (an inhibitor of phosphoribosyl transferase), in a molar ratio of 1:0.4:1, and combination treatment with S-1 and cisplatin (SP) for advanced NSCLC has shown a better response rate of 33% to 47% and a median survival time of 11 to 16 months [4, 5] compared with the usual response rate of 29.1% and median survival time of 40 weeks for combination chemotherapeutic regimens using UFT plus cisplatin [6]. Of interest, the incidence of grade 3/4 hematologic and non-hematologic adverse events was lower in our study than that of other platinum-based combination regimens [7, 8]. According to the recent results of 2 randomized phase III trials of S-1 and carboplatin or cisplatin for advanced NSCLC, this regimen is now a standard regimen for chemotherapy in Japan [9, 10]. In addition, the West Japan Thoracic Oncology Group has reported a better prognosis; a median progression-free survival of

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20 months, excellent local control with an objective response rate of 84%, and has demonstrated the safety of the SP with concurrent radiotherapy (SP-RT) [11] for patients with stage III NSCLC.

In contrast, the role of surgery for LA-NSCLC has been controversial, especially due to the heterogeneity of stage III NSCLC patients who have various numbers, stations, or conditions of mediastinal lymph node metastases, modes of tumor invasion to adjacent thoracic structures, or organs such as the great vessels, mediastinum, vertebral body, carina, esophagus, and so on, which might affect the prognosis of such patients. Such diversity of LA-NSCLC patients has precluded the establishment of an optimal treatment strategy.

We have previously reported the feasibility of SP-RT as an induction therapy that can be followed by curative intent resection for 18 patients with potentially resectable LA-NSCLC [12]. In the present study, we retrospectively analyzed the prognostic benefit for a larger number of patients treated with this strategy.

Patients and Methods

We retrospectively reviewed 42 consecutive patients with potentially resectable stage III LA-NSCLC who underwent preoperative induction concurrent chemoradiotherapy using SP-RT followed by curative-intent surgical resection between June 2005 and February 2011 in the Department of Thoracic Oncology, National Kyushu Cancer Center, Japan. The clinical or pathologic stage of the disease was diagnosed based on the general rules for the TNM Classification of Malignant Tumors (6th edition) [13]. Eligible patients had to have cytologically or histologically confirmed clinical stage III NSCLC that was considered to be potentially resectable. The other eligibility criteria were an age between 20 and 80 years, Eastern Cooperative Oncology Group performance status of 0 to 1, absence of previous chemotherapy or radiotherapy, and adequate hematologic, hepatic, and renal function. Patients with standard laboratory tests results, included the following: a leukocyte count of 3.500/μL or greater; a platelet count of 100,000/μL or greater; serum bilirubin level less than 1.5 mg/dL; serum glutamic oxaloacetic transaminase-glutamic pyruvic transaminase levels 100 IU/mL or less, a creatinine level 1.2 mg/dL or less, or a creatinine clearance level of 60 mL/minute or greater, and a blood gas oxygen tension of 60 Torr or greater, or oxygen saturation as measured by pulse oximetry equal to or greater than 95% in room air were considered to be eligible for this treatment. In addition, pulmonary function tests, chest radiography, computed tomography of the chest and the upper abdomen, computed tomography or magnetic resonance imaging of the brain, bronchoscopy using a flexible optical bronchoscope, and a bone scan or fluorodeoxyglucose-positron emission tomography were routinely performed for all patients. Patients who had malignant pleural effusion, malignant pericardial effusion, or a concomitant malignancy or serious comorbidities such as clinically significant cardiac dysfunction, active infection, or neurologic or psychiatric disorders were excluded.

Treatment Schedule

Chemotherapy With SPS-1 (40 mg/m^2 twice a day [b.i.d.]) in the form of 20 mg and 25 mg capsules containing 20 and 25 mg of tegafur, respectively, were taken orally in 2 separate doses from days 1 to 14 and days 22 to 35 as follows: in a patient with a body surface area (BSA) less than 1.25 m^2, 40 mg b.i.d.; for those with a BSA of at least 1.25 m^2 but less than 1.5 m^2, 50 mg b.i.d.; and for those with a BSA greater than 1.5 m^2, 60 mg b.i.d. was administered. Cisplatin, at a dose of 60 mg/m^2, was administered as a 120-minute infusion on days 1 and 22 while the patients were hydrated with 2,500 mL of saline by infusion. In general, this dose and schedule is equivalent of that of patients without radiotherapy. An antiemetic agent was administered at the discretion of each patient's physician.

Radiotherapy (RT)

All patients were treated with a linear accelerator photon beam of 6 MV or more from day 1. The primary tumor and involved nodes received 40 Gy in 2 Gy fractions over a period of 4 weeks. A three-dimensional treatment planning system was used. Radiation doses were specified at the center of the target volume. The delivered 40 Gy/20 fractions included the primary tumor, ipsilateral hilum, and mediastinal nodal areas from the paratracheal to subcarinal lymph nodes. For the primary tumors and the involved lymph nodes that were 1 cm or larger in the shortest diameter, a margin of at least 0.5 cm was added. The contralateral hilum was not included. The treatment of supraclavicular areas was not mandatory, but they were treated when the supraclavicular nodes were involved.

During the concurrent chemoradiotherapy period, chest X-rays, complete blood cell counts, and blood chemistry studies were repeated once a week, and the treatment was interrupted when a grade 4 hematologic or non-hematologic toxicity, including grade 3 to 4 esophagitis or dermatitis, pyrexia of 38°C or greater, or a decrease in the partial pressure of arterial oxygen of 10 Torr or more, compared with that before radiation therapy, occurred.

Surgical Resection

Immediately after completing the induction SP-RT, the patients were assessed for their response to the induction therapy and were restaged. If disease control, such as a complete response, partial response, or stable disease, was achieved a curative intent resection was planned for 3 to 6 weeks after completion of the concurrent chemoradiotherapy. The principles of resection were en bloc removal of the affected lobe or more lung parenchyma with adjacent structure(s) if necessary, with complete hilar and mediastinal lymph nodal dissection.

Evaluation of the Response and Toxicity

The response was evaluated in accordance with the Response Evaluation Criteria in Solid Tumors version 1.0 guidelines [14]. The histologic analysis of the tumor was based on the World Health Organization classification for cell types [15]. The toxicity for all patients who received any treatment was assessed and graded by using

the National Cancer Institute Common Terminology Criteria for Adverse Event version 3 [16].

Statistical Analysis

To determine the response rate, the exact binomial confidence interval was calculated. Disease-free survival was defined as the time from the starting date of induction concurrent chemoradiotherapy until disease progression or death, and was calculated for the 39 resected patients. Overall survival was defined as the time from the starting date of induction concurrent chemoradiotherapy until death from any cause. The Kaplan-Meier method was used to describe overall survival and disease-free survival curves. All statistical analyses were done with the IBM SPSS Statistics 18 software package (SPSS Japan, an IBM company, Tokyo Japan).

This retrospective analysis was approved by the Institutional Review Board of the National Kyushu Cancer Center. Written informed consent was obtained from all patients before treatment.

Results

Patient Characteristics

As shown in Table 1, there were 34 males (81.0%) and 8 females (19.0%) with the median age of 59 years (range 42 to 77) who were included in this study. Thirty-three (78.6%) patients showed an ECOG performance status of 0. Twenty-one of the 42 patients (50.0%) had adenocarcinoma, while 12 patients had squamous cell carcinoma (28.6%), 8 had non-small cell carcinoma (unclassified), and 1 had large cell carcinoma. The 26 cStage IIIA patients included 24 cases of T1-3N2 and 2 of T3N1, and the 16 cStage IIIB patients included 13 cases of T4N0-2 and 3 of T2-4N3. All N3 patients had ipsilateral supraclavicular lymph node metastasis. The location of the primary tumor was the upper lobe in 38 patients (90.5%) and other lobes in 4 patients (9.5%).

Table 1. Patient Characteristics That Were Eligible for Induction Treatment

Subject	No.	(%)
No. of patients	42	
Age, years		
Median (range)	59 (47–77)	
Gender		
Male to female	34:8	(81.0:19.0)
ECOG PS		
0:1	33:9	(78.6:21.4)
Histology		
Adenocarcinoma	21	(50.0)
Squamous cell carcinoma	12	(28.6)
Large cell carcinoma	1	(2.4)
Unclassified NSCLC	8	(19.0)
cTN[a]		
T3N1	2	
T1-2N2	20	
T3N2	4	
T4N0	2	
T4N1	5	
T4N2	6	
T2-4N3	3	
cStage[a]		
IIIA	26	(61.9)
IIIB	16	(38.1)
Primary site		
Upper lobe	38	(90.5)
Middle/lower lobe	4	(9.5)

[a] TNM Classification of Malignant Tumors (6th edition).

ECOG PS = Eastern Cooperative Oncology Group performance status; NSCLC = non-small cell carcinoma.

Induction Treatment

All patients received the planned dose of radiotherapy, and 41 (97.6%) had 2 cycles of chemotherapy as induction treatment. As shown in Table 2, no grade 4 toxicity was observed during this induction therapy. The most frequently observed adverse event was grade 3 leukopenia, but its incidence was less than 10%; the incidence of the other grade 3 adverse events was 2.4% for neutropenia and febrile neutropenia and 4.8% for thrombocytopenia. One patient received 1 cycle of chemotherapy and another patient required a dose reduction of cisplatin [CDDP] during the second cycle of chemotherapy due to grade 2 serum creatinine level elevation. After receiving the induction treatment, 26 (61.9%) of the 42 patients achieved a partial response (PR), and stable disease (SD) was observed in 16 patients (38.1%). No progressive disease was observed.

Surgical Resection

Among the 42 patients, 39 patients (92.9%) were able to undergo surgical resection. One patient proved to be unresectable after thoracotomy because of the left atrial invasion around the inferior pulmonary vein that could not be detected preoperatively, and 2 patients refused surgical treatment at the end of their induction treatment. Among the 39 patients who received the curative intent resection, 27 patients (69.2%) underwent a lobectomy, including 6 sleeve lobectomies and 12 pneumonectomies (5 in right side and 7 in left side) (30.8%) including 10 intrapericardial pneumonectomies. Sixteen of the 39 patients (41.0%) required combined resection of an adjacent structure or organ: the chest wall with rib(s) in 12 cases; combined partial resection of the vertebra in 3 cases; the internal jugular or brachiocephalic vein that required vascular replacement with a vascular prosthesis each in 1 case; the superior vena cava in 1 case; and the left atrium in 1 case (Table 3). Complete resection was performed in all patients. Of the 3 patients with ipsilateral supraclavicular lymph node metastasis, two underwent a systemic mediastinal and supraclavicular lymph nodal dissection via a median sternotomy, and the other one was confirmed to have no metastasis in his supraclavicular lymph nodes by a pathological examination during surgery, and subsequently underwent systemic

Table 2. Toxicities (n = 42); National Cancer Institute Common Terminology Criteria for Adverse Event Version 3

	Grade		Frequency of 3 or 4 (%)
	3	4	
Hematologic			
Leukopenia	3	0	7.1
Neutropenia	1	0	2.4
Thrombocytopenia	2	0	4.8
Anemia	0	0	/
Non-hematologic			
Febrile neutropenia	1	0	2.4
Nausea	0	0	/
Vomiting	0	0	/
Creatinine	0	0	/
AST to ALT	0	0	/
Diarrhea	0	0	/
Stomatitis	0	0	/
Pneumonitis	0	0	/
Esophagitis	0	0	/

ALT = alanine aminotransferase; AST = aspartate aminotransferase.

mediastinal lymph nodal dissection via posterolateral thoracotomy.

Surgical Morbidity and Mortality

The postoperative morbidity in this series of patients were the following: 3 cases each of postoperative bleeding and arterial fibrillation; 2 cases of chylothorax; and 1 each of prolonged air leakage, pulmonary edema, empyema, heart failure, and spinal cord injury. Among these cases, 3 patients underwent re-thoracotomy; 2 for postoperative bleeding and 1 for chylothorax. One patient who had undergone a left upper lobectomy experienced postoperative thoracic empyema without a bronchopleural fistula and died on the 65th postoperative day due to massive intrathoracic bleeding.

Table 3. Type of Resection (n = 39)

Subject	No. (%)
Pneumonectomy	12 (30.8)
Intrapericardial pneumonectomy	10
Lobectomy[a]	27 (69.2)
Sleeve lobectomy	6
Combined resection	16 (41.0)
Site of combined resection (redundant)	
Chest wall (ribs)	12
Vertebra	3
Internal jugular or brachiocephalic vein	2
SVC (replacement with graft)	1
Left atrium	1

[a] One patient with a bilobectomy was included.

SVC = superior vena cava.

Pathologic Findings

Concerning the clinical and pathologic response to induction concurrent chemoradiotherapy using SP-RT in the 39 patients who underwent surgical resection, 9 of the 39 (23.1%) patients showed a complete pathologic response in both the primary tumor and involved lymph nodes, while 6 of these 9 presented clinical PR and 3 clinical SD. Among the other 30 patients (76.9%) with partial pathologic response, 18 showed clinical PR and 12 clinical SD.

Adjuvant Chemotherapy

Twenty-five (64.1%) patients received adjuvant chemotherapy, mainly with cisplatin-based regimens. The regimens were determined by the attending surgeon. Ten of these 25 patients received more than 3 cycles of adjuvant chemotherapy.

Survival and Recurrence

The median follow-up time was 32.0 months. One-, 3-, and 5-year disease-free survival rates in all 39 surgically resected patients were 73.8% (95% CI: 59.95% to 87.7%), 52.0% (95% CI: 34.9% to 69.1%), and 44.0% (95% CI: 26.4% to 61.6%), respectively (Fig 1A). One-, 3- and 5-year overall survival rates were 84.3% (95% CI: 72.7% to 95.9%), 77.4% (95% CI: 63.3% to 91.5%), and 61.7% (95% CI: 42.1% to 81.3%), respectively (Fig 1B). When patients were stratified into those with cStage IIIA versus cStage IIIB, pN0 versus pN1-3, clinical response (ie, PR versus SD and lobectomy versus pneumonectomy), there were no statistically significant differences in either disease-free survival or overall survival (data not shown). However, when patients were stratified by their pathologic response, 3-year disease-free survival rates in the 9 patients with pathologic complete response were 76.2% (95% CI: 47.2% to 100%), while those of the other 30 patients with any pathologic response were 44.5% (95% CI: 24.7% to 64.3%) (Fig 2A). Three-year overall survival rates were 88.9% (95% CI: 68.3% to 100%) in the 9 patients with pathologic complete response, whereas those of the other 30 patients were 74.0% (95% CI: 56.9% to 91.1%) (Fig 2B).

Of the 39 resected patients, recurrence developed in 18 patients. The first site of recurrence in 16 patients was a distant region. The most common first recurrence site was the brain (7 cases) and the lungs (6 cases). Two patients had recurrence in the contralateral mediastinal lymph nodes that was out of the irradiated field during induction treatment. One of the 9 patients who achieved a pathologic complete response experienced recurrence in the contralateral lung.

Comment

The data presented here imply that treatment with concurrent chemoradiotherapy using SP-RT followed by surgery might provide better local disease control and better survival in patients with potentially resectable LA-NSCLC. Because LA-NSCLC is associated with a high risk of local and systemic recurrence of approximately 80% and 60%, respectively [17], combined local and systemic treatments are warranted. In this regard, the

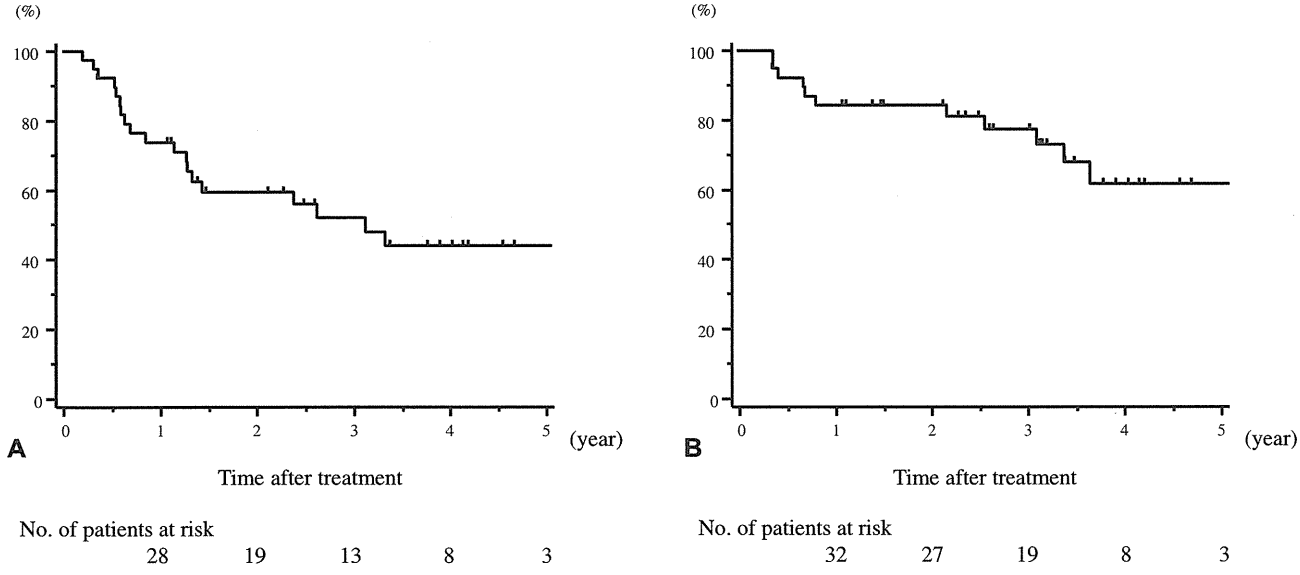

Fig 1. The survival curve of all 39 resected patients. (A) Disease-free survival and (B) overall survival.

optimal treatment strategy for LA- NSCLC is generally considered to be concurrent chemoradiotherapy [18]; however, the most frequent relapse site after concurrent chemoradiotherapy is at a distant region. A possible reason for this type of relapse is that the full-dose chemotherapeutic regimens developed for metastatic-NSCLC in the 1990s cannot be used at the full doses concurrently with radiotherapy due to the associated acute toxicities. Recently, Ichinose and colleagues [11] showed that the combination of full dose SP and concurrent radiotherapy of 60 Gy could be administered with acceptable toxicity, and the treatment with this regimen demonstrated a favorable survival, with a median progression-free survival of 20 months and an ORR of 84%.

Some phase III trials of concurrent chemoradiotherapy with radiation doses ranging from 56 to 66 Gy have shown good response rates of approximately 55% to 80% [19, 20]. In the present study, we observed that 59.5% of patients had a partial response and 40.5% had stable

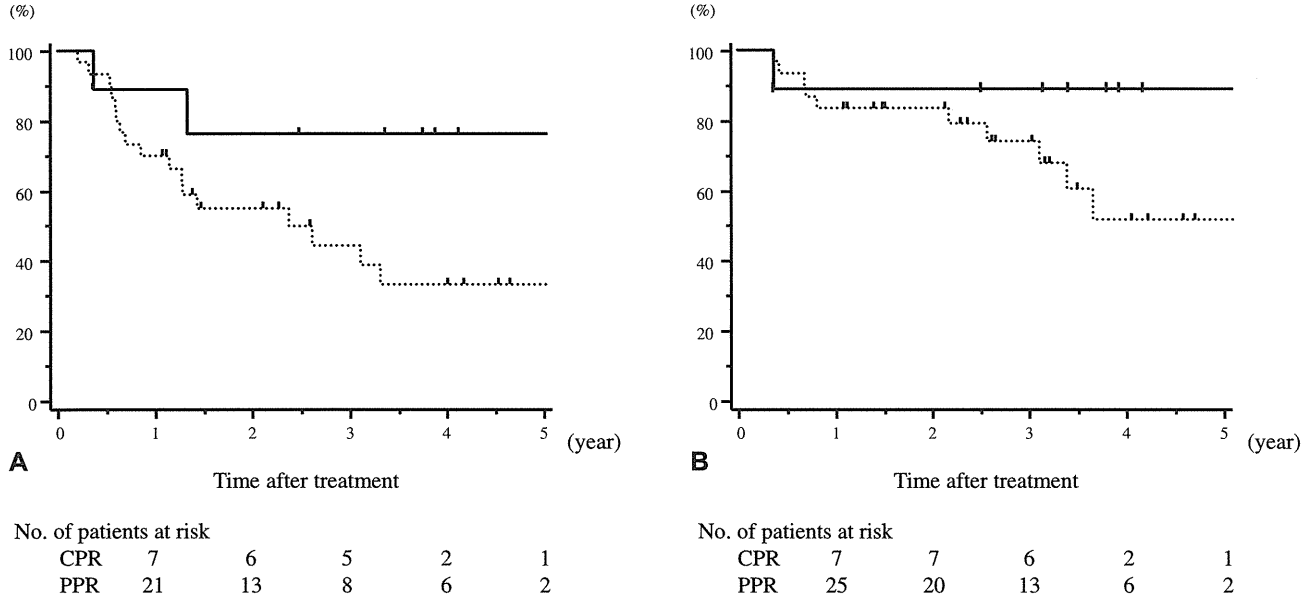

Fig 2. The prognosis of patients stratified by the pathologic response of the resected specimen. Solid line represents patients with complete pathologic response (CPR), while dashed line represents the patients with partial pathologic response (PPR). (A) Disease-free survival; (B) overall survival.

disease after using SP, even with 40 Gy of concurrent radiation therapy. The toxicity of our SP-RT induction treatment was also excellent, without any grade 4 events, which allowed patients to safely undergo the subsequent surgical resection.

Concerning the survival benefit of concurrent chemoradiotherapy for LA-NSCLC, Segawa and colleagues (OLCSG 0007) [19] compared docetaxel plus cisplatin to mitomycin, and vindesine plus cisplatin with concurrent radiotherapy in their phase III study, and reported better 1- and 3-year progression-free survival rates of 53.4% and 24.9%, respectively, and 1- and 3-year overall survival rates of 82.8% and 38.1%, respectively, in the docetaxel plus cisplatin group. Yamamoto and colleagues [20] (WJOG 0105) also compared mitomycin, vindesine plus cisplatin, irinotecan plus carboplatin and paclitaxel plus carboplatin, and demonstrated that a median progression-free survival rate was 9.5 months and a median overall survival was 22.0 months in their docetaxel plus cisplatin group. Focusing on induction concurrent chemoradiotherapy followed by surgery for LA-NSCLC, some phase I and II studies demonstrated promising results in their surgery arm; Friedel and colleagues [21] showed a better median overall survival of 39 months in the subset analysis of their phase II study, and an improved 5-year overall survival rate of 43.1% in patients who underwent surgical resection after induction chemoradiotherapy with carboplatin and paclitaxel with 45 Gy of concurrent radiotherapy for stage III NSCLC compared with those treated without surgical resection, which were 29.6 months and 0%, respectively. Edelman and colleagues [22] reported a good median overall survival of 55.8 months in their series of stage III NSCLC patients with negative mediastinal nodes after induction concurrent chemoradiotherapy using carboplatin and vinorelbine in their phase I/II study. We also previously showed the impact of induction concurrent chemoradiotherapy with cisplatin and UFT on the survival of stage IIIB NSCLC patients who underwent surgical resection, with 1- and 3-year overall survival rates of 82% and 67%, respectively [23].

In their recent report, Albain and colleagues (INT 0139) [24] reported no significant overall survival difference between patients who received induction concurrent chemoradiotherapy with or without surgery; however, the patients who underwent lobectomy showed significant better survival. Additionally, in their resected pT0N0 patients, an excellent median survival of 39 · 8 months was observed. In the present study, a considerably better prognosis was observed; 1-, 3-, and 5-year disease-free survival rates were 73.8%, 52.0%, and 44.0%, respectively (Fig 1A), and 1-, 3-, and 5-year overall survival rates were 84.3%, 77.4%, and 61.7%, respectively (Fig 1B). Our study also indicated that pathologic good responders (ie, patients with complete pathologic response) showed a 3-year disease-free survival rate of 76.2% and 3-year overall survival of 88.9%. We did not evaluate the relationship between the pre-induction and post-induction treatment TNM stage because we believe that one of the important predictive factors for postoperative survival is the pathologic response. That is the reason why we focused on this issue and did not show the correlation between pre-induction and post-induction staging. These results seem to indicate that SP-RT can provide a sufficient systemic dose to prevent occult distant metastasis. In addition, 5-FU is known to have a radiosensitizing effect [25] and S-1 was orally administered for 14 consecutive days twice during the radiotherapy in the present study.

The limitations of the present study are the retrospective nature of the analysis and the relatively small number of patients. We are currently performing a single institutional phase II study of SP-RT as an induction concurrent chemoradiotherapy, followed by surgical resection, for LA-NSCLC patients.

In conclusion, SP-RT followed by surgery may provide a better prognosis for LA-NSCLC patients. Further clinical investigations are warranted.

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GENERAL THORACIC

INVITED COMMENTARY

To date, 5-fluorouracil (5-FU) has not been utilized in the treatment of non-small cell lung cancer (NSCLC) because of its bioavailability profile, providing lower levels outside the gastrointestinal system. S-1 is an oral fluoropyrimidine drug that combines tegafur, a prodrug of 5-FU, with gimeracil (CHDP) and potassium oxonate (OXO), to increase serum 5-FU levels and minimize gastrointestinal toxicity, respectively. Usually, approximately 80% to 90% of 5-FU administered intravenously is rapidly catabolized by liver dihydropyrimidine dehydrogenase (DPD), and others have also shown high levels of DPD may exist in lung tumors. With S-1, CHDP inhibits both liver and tumor DPD more than 150 times more effectively than uracil and OXO inhibits 5-FU phosphorylation by gastrointestinal mucosal cells. Capecitabine is another oral 5-FU prodrug, but its metabolism is different from that of than tegafur, relying on a final step requiring the enzyme thymidine phosphorylase, which is expressed variably in NSCLC tumors [1].

Although early reports of S-1 in the treatment of NSCLC are now more than a decade old, the clinical use of S-1 has not gained significant traction worldwide yet. Although S-1, in combination with platinum, exhibits antitumor effects in NSCLC as shown in a recent multicenter phase II study (overall response rate 20%, median time to progression 4 months), these results were comparable but not superior to those of other current platinum doublets [2]. This North American study [3], however, used lower doses of S-1 (25 mg/m^2) than in previous studies from Japan in combination with cisplatin at 75 mg/m^2. Yet, S-1 plus platinum demonstrated 50% fewer grade 4 toxicities as compared with other standard platinum doublets for NSCLC. In the present study by Yamaguchi and colleagues [3], S-1 given at 40 mg/m^2 with cisplatin (60 mg/m^2) resulted in a very favorable toxicity profile. The radiosensitizing effects of 5-FU are well known and the higher S-1 dose in the present study likely contributes to the overall results. However, the cohort size here is small, and additional studies will be needed to further explore the optimum dose levels and most effective drug combinations with S-1 for NSCLC.

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Solid tumors versus mixed tumors with a ground-glass opacity component in patients with clinical stage IA lung adenocarcinoma: Prognostic comparison using high-resolution computed tomography findings

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Objective: This study aimed to compare malignant behavior and prognosis between solid tumors and mixed tumors with a ground-glass opacity component on high-resolution computed tomography.

Methods: We examined 436 of 502 consecutive patients with clinical stage IA adenocarcinoma who had undergone preoperative high-resolution computed tomography and F-18-fluorodeoxyglucose positron emission tomography/computed tomography; 66 patients with tumors with pure ground-glass opacity components were excluded. Tumor type (solid, n = 137; mixed, n = 299) and surgical results were analyzed for all patients and their matched pairs.

Results: In all patients, solid tumors showed a significantly greater association ($P < .001$) with lymphatic, vascular, and pleural invasion and lymph node metastasis compared with mixed tumors. The disease-free survival was also worse in patients with solid tumors ($P = .0006$). Analysis of 97 pairs matched for solid component size confirmed that solid tumors were significantly associated with lymphatic, vascular, and pleural invasion ($P = .008$, $P = .029$, $P = .003$, respectively) and poor prognosis. When maximum standardized uptake value and solid component size were matched (n = 79), the differences in pathologic prognostic parameters and disease-free survivals between patients with solid and mixed tumors disappeared.

Conclusions: Solid tumors exhibit more malignant behavior and have a poorer prognosis compared with mixed tumors, even when the solid component size is the same in both tumor types. However, differences in malignant behavior can be identified using maximum standardized uptake values determined by F-18-fluorodeoxyglucose positron emission tomography/computed tomography. (J Thorac Cardiovasc Surg 2013;146:17-23)

The recent development of high-resolution computed tomography (HRCT) and low-dose computed tomography (CT) screening has improved the detection of small lung cancers, especially lung adenocarcinomas.[1-3] These often contain a nonsolid component that presents as a ground-glass opacity (GGO) on HRCT and is closely associated with bronchioloalveolar carcinoma.[4,5] We have previously reported the benefits of comparing solid component size (the maximum dimension of the solid component excluding GGO) on HRCT with whole tumor size for predicting the pathologic invasiveness of tumors or the prognosis of clinical stage IA lung adenocarcinomas.[6] It remains unclear whether GGO-containing tumors have the same malignant behavior and prognosis as pure solid tumors after matching for solid component size.

Whether or not differences exist in malignant behavior between pure solid tumors and mixed tumors with a GGO component on HRCT remains controversial. Therefore, we used HRCT to compare malignant behavior, including lymphatic, vascular, and pleural invasion, and prognosis between solid tumors and mixed tumors having a GGO component in patients with clinical stage IA lung adenocarcinoma.

PATIENTS AND METHODS

Between August 1, 2005, and December 31, 2009, we enrolled 502 patients with clinical T1N0M0 stage IA lung adenocarcinoma who were admitted to 1 of the following 4 institutions: Hiroshima University, Kanagawa Cancer Center, Cancer Institute Hospital, and Hyogo Cancer Center. HRCT and F-18-fluorodeoxyglucose positron emission tomography/CT

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GTS

Abbreviations and Acronyms

CT = computed tomography
DFS = disease-free survival
FDG-PET = F-18-fluorodeoxyglucose positron emission tomography
FOV = field of view
GGO = ground-glass opacity
HRCT = high-resolution computed tomography
SUV = standardized uptake value
SUVmax = maximum standardized uptake value

(FDG-PET/CT) followed by curative R0 resection were performed in all patients, who were staged according to the seventh edition of the TNM classification of malignant tumors.[7] Mediastinoscopy and endobronchial ultrasonography were not routinely performed because HRCT revealed no swelling of mediastinal or hilar lymph nodes and FDG-PET showed no accumulation in these lymph nodes in all patients. Sublobar resections (segmentectomy or wedge resection) were performed if the tumor mainly comprised a GGO component or had no lymph node metastasis on intraoperative assessment. Tumors with pure GGO were excluded from the analyses because they are noninvasive and have an extremely good prognosis.[8,9] We obtained appropriate approval for this multicenter study from the institutional review board of each institution, which waived the requirement for informed consent from individual patients because this was a retrospective review of medical records from a prospective database.

High-Resolution Computed Tomography

Chest images were obtained using 16-row multidetector CT independently of subsequent FDG-PET/CT examinations. High-resolution images of the tumors were acquired using the following parameters: 120 kVp; 200 mA; section thickness, 1 to 2 mm; pixel resolution, 512 × 512; scanning time, 0.5 to 1 seconds; a high spatial reconstruction algorithm with a 20-cm field of view (FOV); and mediastinal (level, 40 HU; width, 400 HU) and lung (level, −600 HU; width, 1600 HU) window settings. GGO was defined as a misty increase in lung attenuation that did not obscure underlying vascular markings. We defined solid component size as the maximum dimension of the solid component in the lung windows after excluding the GGO component.[6] Solid tumors were defined as pure solid tumors without a GGO component, whereas mixed tumors were defined as tumors with a GGO component regardless of the GGO proportion.

F-18-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography

Patients were instructed to fast for more than 4 hours before intravenous injection of 74 to 370 MBq of FDG. After injection, they were instructed to relax for at least 1 hour before FDG-PET/CT scanning. Blood glucose was calculated before tracer injection to confirm a level of less than 150 mg/dL.[10] Patients with blood glucose values 150 mg/dL or greater were excluded from PET/CT image acquisition. Images were obtained using Discovery ST (GE Healthcare, Little Chalfont, UK), Aquiduo (Toshiba Medical Systems Corporation, Tochigi, Japan), or Biograph Sensation16 (Siemens Healthcare, Erlangen, Germany) integrated PET/CT scanners. Low-dose, unenhanced CT images of 2- to 4-mm section thickness for attenuation correction and localization of lesions identified by PET were obtained from the head to the pelvic floor of each patient using a standard protocol. Immediately after CT, PET covered the identical axial FOV for 2 to 4 minutes per table position depending on the condition of the patient and scanner performance. All PET images with a 50-cm FOV were reconstructed using an iterative algorithm with CT-derived attenuation correction. Variations in standardized uptake values (SUVs) among institutions were minimized using an anthropomorphic body phantom. A calibration factor was obtained by dividing the actual SUV by the gauged mean SUV in the phantom background to decrease interinstitutional SUV inconsistencies; the final SUV used is referred to as the revised maximum SUV (SUVmax).[11,12] Adjustment of interinstitutional variability in SUV narrowed the range from 0.89 to 1.24 to 0.97 to 1.18 when the SUVmax ratio was expressed as the SUVmax reported by each institute relative to the SUVmax reported by the control institute.

Follow-up Evaluation

All patients who underwent lung resection were followed up from the day of surgery. Postoperative follow-up procedures, including physical examination and chest roentgenography every 3 months and chest and abdominal CT examinations every 6 months, were performed for the first 2 years. Thereafter, physical examination and chest roentgenography were performed every 6 months, whereas chest CT examination was performed every year. Recurrence was determined by radiographic features or histologic evidence.

Statistical Analysis

Data are presented as numbers (%) or mean ± standard deviation unless otherwise stated. Frequencies were compared using the chi-square test for categoric variables, and the Fisher exact test was applied to small samples in all cohort patients. McNemar tests were used for analyses of matched-pair patients. Mann–Whitney U tests and t tests were used to compare continuous variables in all cohort patients. Wilcoxon tests were used for analyses of matched-pair patients. Disease-free survival (DFS) was defined as the time from the date of surgery until the first event (relapse or death from any cause) or last follow-up. The duration of DFS was analyzed using the Kaplan–Meier method. Differences in DFS were assessed using the log-rank test. We applied matching to balance the assignment of the included patients and correct for tumor type (solid or mixed), which confounded survival. The variables were solid component size or SUVmax. Solid and mixed tumor pairs with an equivalent solid component size or SUVmax were selected by a 1-to-1 match. All 436 patients were pooled and sorted in ascending order according to their solid component size or SUVmax. The selection process began from the first 2 cases with the lowest solid component size or SUVmax. If 1 case exhibited a solid tumor and the other case exhibited a mixed tumor, both were selected as a matched pair. If this was not the case, then 4 cases were included. In the same way, solid and mixed tumors were matched by their solid component size or SUVmax in 1:1, 2:2, 3:3, or 4:4 blocks. A patient who did not have a suitable match within the acceptable rank range was excluded from further analysis, and the matching process moved down the sort list until all possible matched pairs were included. The selected patients formed well-matched 1:1 pairs in both groups. Data were analyzed using the Statistical Package for the Social Sciences (v 10.5; SPSS Inc, Chicago, Ill).

RESULTS

Of the 502 patients, 66 who had tumors with pure GGO components were excluded; the remaining 436 patients were included in this analysis. Of the 436 study patients, 137 had solid tumors and 299 had mixed tumors. The mean follow-up period after surgery was 20.2 ± 12.5 months, during which the disease recurred in 29 patients (6.7%). The mean follow-up period was similar for solid and mixed tumors (21.4 ± 12.8 months and 19.7 ± 12.4 months, respectively, $P = .235$). Of the 29 cases of recurrence, 9 (2.1%) were local (including mediastinal lymph node metastasis), 3 (0.7%) were local and distant, and 17