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Phase I study of olaratumab in Japanese patients with advanced solid tumors

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Key words

IMC-3G3, monoclonal antibody, olaratumab, phase 1, platelet-derived growth factor receptor

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Olaratumab (IMC-3G3) is a fully human IgG1 monoclonal antibody that selectively binds the external domain of human platelet-derived growth factor receptor-α with high affinity and blocks ligand binding. This was a single-center, dose-escalation, phase I trial of olaratumab in Japanese patients with advanced/refractory solid malignancies. Three to six patients were enrolled into each of three cohorts: Patients received i.v. olaratumab: 10 mg/kg on days 1 and 8 every 3 weeks (cohort 1); 20 mg/kg every 2 weeks (cohort 2); and 15 mg/kg on days 1 and 8 every 3 weeks (cohort 3). Doses were escalated from cohort 1 through cohort 3. The primary objective was to establish the safety and pharmacokinetic profile of olaratumab. Sixteen patients were treated across three cohorts. There were no dose-limiting toxicities, so the maximum tolerated dose was not reached. The most common olaratumab-related treatment-emergent adverse events (TEAEs) were proteinuria (25.0%) and elevated aspartate transaminase (12.5%). One patient (cohort 2) had two olaratumab-related Grade 3 TEAEs (increased aspartate aminotransferase and tumor hemorrhage); otherwise, olaratumab-related TEAEs were Grade 1/2. Seven patients (43.8%) had a best response of stable disease. Based on the pharmacokinetic concentration profile of olaratumab, the trough concentrations following single and multiple doses at 15 mg/kg on days 1 and 8 every 3 weeks (cohort 3) and multiple doses at 20 mg/kg every 2 weeks (cohort 2) were above the 155 μg/mL target. Thus, these two doses could represent an acceptable schedule for future trials in Japanese patients. Olaratumab had an acceptable safety profile and was well tolerated.

The platelet-derived growth factor receptor family (PDGFR) consists of PDGFRα and PDGFRβ.[1] These receptors and their ligands are involved in normal organ development and function, wound-healing, and the pathogenesis of malignant and non-malignant diseases.[1] The PDGFRα/platelet-derived growth factor (PDGF) axis is required for vascular endothelial growth factor production by tumor stroma and the regulation of tumoral angiogenesis.[2]

Platelet-derived growth factor receptor-α is expressed in several types of cancer on transformed cells and in tumor stroma.[3–6] PDGFRα expression is associated with disease progression, diminished patient survival, and metastases to lymph nodes and bone.[7–10] Due to the effects of the PDGFRα/PDGF axis on tumor growth and tumor-associated vasculature, there is interest in developing therapeutic inhibitors of this pathway.[11,12] Most of these inhibitors are small molecule tyrosine kinase inhibitors (TKIs) that typically inhibit multiple kinases.[11,12]

Olaratumab (IMC-3G3) is a fully human IgG1 monoclonal antibody that selectively binds human PDGFRα with high affinity (approximately 40 pM) and blocks ligand-binding.[13] This antibody inhibits the proliferation and growth of a variety of human tumor cell lines both *in vitro* and *in vivo*.[5,6,13] Based on its activity in preclinical models involving human cells,[5,6,13] olaratumab entered clinical development. One phase I trial in patients with advanced tumors is complete (CP15-0601; I5B-IE-JGDC)[14] and several phase II trials are ongoing. Here, we report the results of a phase I trial of olaratumab in a cohort of Japanese patients (CP15-0907; I5B-IE-JGDF) with advanced solid tumors.

Materials and Methods

Patients. Patients (≥20 years old) with advanced primary or recurrent solid tumors not responding to standard therapy, or for whom no standard therapy was available, were eligible. Other enrollment criteria included Eastern Cooperative Oncology Group Performance Status of 0–1; estimated life expectancy >3 months; and adequate hematologic, hepatic, renal, and coagulation function.

Patients with known brain metastases were excluded due to risk of bleeding. Other exclusion criteria included chemotherapy or radiotherapy within 28 days (6 weeks for nitrosoureas or mitomycin C) prior to entering the study or presence of ongoing side effects ≥Grade 2 due to agents administered >28 days prior to study entry; uncontrolled intercurrent illness; participation in clinical trials of unapproved agents within 4 weeks of study entry for small molecules or within 8 weeks for monoclonal antibodies; and hepatitis B virus antigen, hepatitis C virus antibody, or human immunodeficiency virus antibody positivity.

This study was conducted in accordance with the Good Clinical Practices, Japanese Good Clinical Practices, the Declaration of Helsinki, and approval by the medical institution's Ethical Review Board. Patients provided written informed consent prior to inclusion. The ClinicalTrials.gov identifier is NCT01199822.

Study design. This was a single-center, open-label, dose-escalation, phase I trial. The primary objective was to establish the safety and pharmacokinetic (PK) profile of olaratumab administered on day 1 every 2 weeks (q2w) or on days 1 and 8 every

Table 1. Baseline demographics and disease characteristics

	Number of patients, *n* (%) (unless otherwise indicated)			
	Cohort 1 (10 mg/kg) *n* = 3	Cohort 2 (20 mg/kg) *n* = 7	Cohort 3 (15 mg/kg) *n* = 6	All cohorts *N* = 16
Age, years				
Median (range)	69.6 (59.6–71.4)	60.9 (35.6–70.3)	59.1 (50.5–69.7)	60.7 (35.6–71.4)
Sex				
Male	3 (100.0)	5 (71.4)	2 (33.3)	10 (62.5)
Female	0	2 (28.6)	4 (66.7)	6 (37.5)
Race				
Asian (Japanese)	3 (100.0)	7 (100.0)	6 (100.0)	16 (100.0)
Type of cancer†				
Colorectal	1 (33.3)	5 (71.4)	1 (16.7)	7 (43.8)
Gastric	1 (33.3)	0	1 (16.7)	2 (12.6)
Gastrointestinal stroma	0	2 (28.6)	2 (33.3)	4 (25.0)
Head and neck	1 (33.3)	0	1 (16.7)	2 (12.5)
Sarcoma	0	0	1 (16.7)	1 (6.3)
Duration of disease, months‡				
Median (range)	45.6 (2.4–61.4)	66.3 (32.5–90.4)	48.5 (25.5–102.5)	49.6 (2.4–102.5)
ECOG performance status				
0	3 (100.0)	7 (100.0)	5 (83.3)	15 (93.8)
1	0	0	1 (16.7)	1 (6.3)
Metastatic site				
Lung	2 (66.7)	2 (28.6)	3 (50.0)	7 (43.8)
Liver	1 (33.3)	6 (85.7)	3 (50.0)	10 (62.5)
Lymph nodes	1 (33.3)	2 (28.6)	3 (50.0)	6 (37.5)
Peritoneal	1 (33.3)	1 (14.3)	2 (33.3)	4 (25.0)
Pleural	1 (33.3)	0	0	1 (6.3)
Other	0	3 (42.9)	3 (50.0)	6 (37.5)
Prior disease-related therapy				
Chemotherapy§	2 (66.7)	7 (100.0)	6 (100.0)	15 (93.8)
Other¶	0	2 (28.6)	1 (16.7)	3 (18.8)
Missing	1 (33.3)	0	0	1 (6.3)
Prior disease-related radiotherapy				
Yes	0	0	1 (16.7)	1 (6.3)
No	3 (100.0)	7 (100.0)	4 (66.7)	14 (87.5)
Missing	0	0	1 (16.7)	1 (6.3)
Prior disease-related surgery				
Yes	2 (66.7)	6 (85.7)	6 (100.0)	14 (87.5)
No	0	1 (14.3)	0	1 (6.3)
Missing	1 (33.3)	0	0	1 (6.3)

†Not coded and was presented as reported. ‡Duration of disease is time (in months) from date of histologic/cytologic confirmation of advanced solid tumor to date of first dose. If the day of first confirmation of cancer is unknown, it was replaced by 15MMMYYYY. §Includes agents such as cetuximab, sunitinib, imatinib, aflibercept, and bevacizumab. ¶Other than chemotherapy, hormonal therapy, immunotherapy, and biologic therapy. ECOG, Eastern Cooperative Oncology Group.

Table 2. Olaratumab-related treatment-emergent adverse events across all cycles†,‡

Preferred term	Number of patients, *n* (%)		
	Cohort 1 (10 mg/kg) *n* = 3	Cohort 2 (20 mg/kg) *n* = 7	Cohort 3 (15 mg/kg) *n* = 6
Patients with any AE	1 (33.3)	6 (85.7)	1 (16.7)
Hematologic			
Anemia	0	1 (14.3)	0
Leukopenia	0	1 (14.3)	0
Non-hematologic			
Aspartate aminotransferase increased	0	2 (28.6)	0
Cough	1 (33.3)	0	0
Dermatitis	0	0	1 (16.7)
Diarrhea	0	1 (14.3)	0
Fatigue	0	1 (14.3)	0
Fibrin D-dimer increased	0	1 (14.3)	0
Hyperglycemia	0	1 (14.3)	0
Hypertension	0	1 (14.3)	0
Proteinuria	0	3 (42.9)	1 (16.7)
Rash	0	1 (14.3)	0
Tumor hemorrhage	0	1 (14.3)	0

†For each preferred term, each patient is counted only once per preferred term. ‡AEs with missing relationship to study drug were considered as related. AE, adverse event.

Table 3. Efficacy of olaratumab

	Cohort 1 (10 mg/kg) *n* = 3	Cohort 2 (20 mg/kg) *n* = 7	Cohort 3 (15 mg/kg) *n* = 6
Best overall tumor response, *n* (%)			
CR	0	0	0
PR	0	0	0
SD	2 (66.7)†	3 (42.9)‡	2 (33.3)§
PD	1 (33.3)	3 (42.9)	4 (66.7)
NE	0	1 (14.3)	0
Objective response rate (CR+PR), %	0.0	0.0	0.0
Disease control rate (CR+PR+SD), %	66.7	42.9	33.3
95% CI¶	9.4–99.2	9.9–81.6	4.3–77.7
Duration of SD, *n* (%)			
Median, months	2.8	2.8	4.9
95% CI	–	2.8–N/A	4.2–5.6

†Carcinoid tumor of rectum; parotid tumor. ‡Colon cancer; gastrointestinal stromal tumor; rectal. §Hypopharyngeal cancer; leiomyosarcoma of inferior vena cava origin. ¶Binomial exact confidence interval. CI, confidence interval; CR, complete response; N/A, not attainable; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

3 weeks (q3w) in this patient population. Exploratory analyses included preliminary assessment of antitumor activity and assessment of the pharmacodynamic effect of olaratumab.

Patients received i.v. olaratumab (infusion rate not exceeding 25 mg/min) q2w or on days 1 and 8 q3w. One cycle was defined as 6 weeks. Tumor response was evaluated radiographically every 6 weeks, starting from the first drug administration and independently from the treatment cycle. After cycle 1, patients experiencing a complete response (CR), partial response (PR), or stable disease (SD) received olaratumab at their cohort dose and schedule until there was evidence of progressive disease (PD) or until other withdrawal criteria were met.

Treatment cohorts. Olaratumab dosing was based on baseline body weight; the dose was recalculated if there was a ≥10% weight change from baseline. A minimum of three patients were enrolled in each cohort. The cohort 1 dose was 10 mg/kg administered on days 1 and 8 q3w. Dose escalation from cohort 1 to cohort 2 (20 mg/kg q2w) occurred after all cohort 1 patients completed the first cycle of therapy or discontinued due to a dose-limiting toxicity (DLT). Enrollment into cohort 3 (15 mg/kg q3w) occurred after all cohort 2 patients completed the first cycle of therapy or discontinued due to a DLT. Intrapatient dose escalations were not permitted. Patients who did not complete the first 6 weeks (one cycle) of treatment for reasons other than a DLT were replaced.

If one DLT was observed in any cohort during cycle 1, 3 additional patients were enrolled into that cohort. If no additional DLTs were observed, dose escalation continued. If a patient did not recover from the DLT to ≤ Grade 1 within 2 weeks, the patient was discontinued from the study.

A DLT was defined as one of the following conditions: if considered by the investigator to be definitely, probably, or possibly related to olaratumab; grade 4 neutropenia lasting >7 days; grade ≥3 thrombocytopenia with bleeding or requiring platelet transfusions; grade ≥3 neutropenia associated with fever; grade 3 or 4 non-hematologic toxicity; grade ≥3 skin toxicity (despite pre-emptive and supportive care); and/or grade ≥3 diarrhea, nausea, or vomiting (despite pre-emptive and supportive care).

Dose adjustments. Dose reductions were not permitted. Dose delays were permitted after cycle 1 for patients with non-life-threatening, reversible grade 3–4 adverse events (AEs) that resolved to grade ≤1 within 2 weeks. For these AEs, treatment could resume within 2 weeks and could continue until PD or other withdrawal criteria were met.

Determination of maximum tolerated dose. This trial used a conventional 3 + 3 design. If ≥2 patients in cohort 1 experienced a DLT, the study was to be discontinued. If ≥2 patients in cohort 2 or 3 experienced a DLT, then the cohort 1 dose was to be the maximum tolerated dose (MTD). If no MTD was determined, both cohorts 2 and 3 were to be expanded to six patients, with the goal of obtaining enough data for a PK analysis.

Pharmacokinetic assessments. Serum olaratumab was quantitated by using a validated ELISA. For the 10 mg/kg (cohort 1) and 15 mg/kg (cohort 3) (dosed on day 1 and day 8 every 3 weeks) q3w groups, PK samples were collected up to 168 h post end of day 1 infusion and 336 h post end of day 8 infusion. For the 20 mg/kg q2w group (cohort 2), PK samples were collected up to 336 h post end of infusion following the first (cycle 1, day 1) and fifth (cycle 2, day 1) infusions. Beginning cycle 3, samples were collected prior to and 1 h after completion of the first infusion in every subsequent cycle. The PK parameters were calculated from individual serum concentrations versus time profiles by noncompartmental analysis method by using WINNONLIN (Version 5.3; Certara, St. Louis, MO, USA).

Pharmacodynamic assessments. Human PDGF-AA and PDGF-BB in sodium heparin plasma collected at pre-specified

time points was quantitatively determined by using an ELISA at Intertek Laboratories (Houston, TX, USA).

For cohorts 1 and 3, PD markers were analyzed using plasma samples (from approximately 7 mL of blood) obtained prior to the first infusion; immediately after the first infusion; and 1, 4, 8, 24, and 168 h following the completion of the first infusion, prior to and 1 h following the completion of the fifth infusion and ninth infusion, and prior to and 1 h following the completion of the infusion every 6 weeks thereafter. A blood sample for PD assessment was also taken at the end of study visit.

For cohort 2, PD markers were analyzed using plasma samples obtained prior to the first infusion; immediately after the end of the first infusion; 1, 4, 8, 24, 168, and 336 h following the completion of the first infusion; prior to and 1 h following the completion of the fourth infusion and seventh infusion; and prior to and 1 h following the completion of the infusion every 6 weeks thereafter. A blood sample for PD assessment was also taken at the end of study visit.

Safety assessments. Adverse events were coded by the Medical Dictionary for Regulatory Activities and graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events, Version 4.02.[15]

Disease assessment. Baseline tumor burden was assessed within 28 days prior to study registration. Patients were evaluated for response according to the Response Evaluation Criteria in Solid Tumors (v 1.0) after every cycle.[16] Confirmatory scans were obtained ≥4 weeks following initial documentation objective response.

Data and statistical analysis. The anticipated sample size was 18 patients. This sample size was based on cohort size. Data were analyzed using SAS® software (Cary, NC, USA), version 9.2.

Analysis populations. The safety population included all enrolled patients who received any olaratumab, regardless of study eligibility, and was based on the actual initial therapy that a patient received, regardless of any other cohort to which the patient was assigned. The safety population was used for the analysis of baseline characteristics, safety data, and efficacy data. The MTD population included all enrolled patients who completed cycle 1 or discontinued during cycle 1 due to a DLT.

Results

Patient characteristics and treatment. Sixteen patients at one Japanese center received olaratumab. One additional patient signed an informed consent form and was enrolled in the study, but was considered a screen failure and was not treated due to pneumonia at the time of study entry. Across all cohorts, the median age was 60.7 years (range 35.6–71.4). The majority of patients were male (62.5%) and had colorectal or gastric type cancers (81.3%); all patients were Asian (Japanese). Table 1 shows the baseline demographics and disease characteristics.

Dose. The median duration of treatment was 13.1 (range 7.0–13.6), 6.0 (range 3.0–13.4), and 7.0 (range 7.0–25.1) weeks in cohort 1 (n = 3), cohort 2 (n = 7), and cohort 3 (n = 6), respectively. The median number of infusions was 8.0 (range 4.0–8.0), 3.0 (range 2.0–6.0), and 4.0 (range 4.0–16.0) in cohort 1, cohort 2, and cohort 3, respectively. The median relative dose intensity was >85% in all three cohorts.

Safety. There were no DLTs in this trial; therefore, the MTD was not reached, consistent with the previous phase I trial.[14] One patient experienced an AE that met DLT definitions (grade 3 olaratumab-related tumor hemorrhage), but this event occurred outside the DLT assessment period (patient discontinued treatment prior to the completion of cycle 1 because, in the investigator's opinion, continued treatment was inappropriate); thus, the event was not considered a DLT.

There were four dose delays; two occurring in cohort 2 and 1 each occurring in cohorts 1 and 3. Two dose delays were caused by AEs in cohort 2 (grade 1 olaratumab-related proteinuria) and

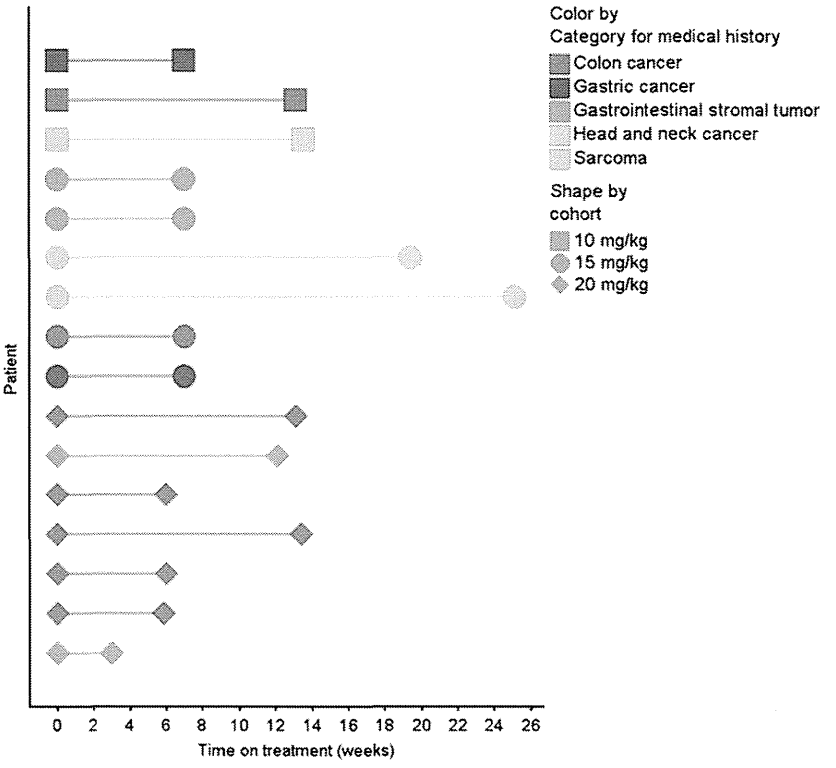

Fig. 1. Time on treatment. The duration of treatment for each patient is shown.

cohort 3 (fatigue/anorexia/weight loss). There were no infusion interruptions. No AE led to treatment discontinuation.

All patients experienced at least one AE of any grade. Across all cohorts and cycles, the most frequently reported treatment-emergent adverse events (TEAEs) regardless of causality were pyrexia (4 [25.0%]), proteinuria (4 [25.0%]), constipation (3 [18.8%]), and anorexia (3 [18.8%]). During cycle 1, the most frequently reported TEAEs regardless of causality were pyrexia (4 [25.0%]), constipation (3 [18.8%]), and proteinuria (3 [18.8%]).

Table 2 shows TEAEs that were assessed as olaratumab-related occurring through all cycles. The most common olaratumab-related TEAEs were proteinuria (4 [25.0%]) and elevated aspartate aminotransaminase (2 [12.5%]). One patient (cohort 2) had two grade 3 olaratumab-related AEs (i.e., increased aspartate aminotransferase and tumor hemorrhage); both AEs occurred in cycle 1.

Two serious AEs, both occurring in cycle 1, were reported during the trial (malignant neoplasm and tumor hemorrhage). The tumor hemorrhage was considered by the investigator to be olaratumab-related. There were no patient deaths due to AEs on study or within 30 days of the last olaratumab dose. One patient (cohort 3) died due to PD, approximately 2 months after the patient's last olaratumab dose.

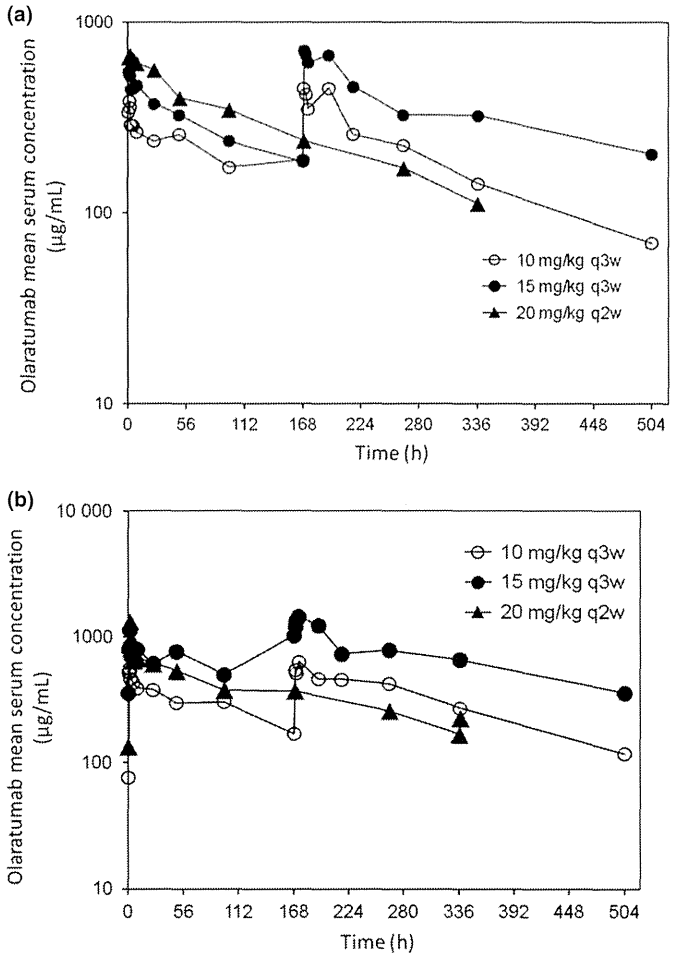

Fig. 2. Arithmetic mean olaratumab serum concentration versus time profiles following the first dose (a) and multiple (b) doses of olaratumab. Semi-log scales are shown in each plot. h, hour; q2w, every 2 weeks; q3w, every 3 weeks.

Efficacy. The best overall response was SD (Table 3). The disease control rate (CR+PR+SD) was 66.7% in cohort 1, 42.9% in cohort 2, and 33.3% in cohort 3. The median duration of SD was 2.8 months in cohort 1 and cohort 2, and 4.9 months in cohort 3.

Of the seven patients with a best response of SD, two patients in cohort 3 experienced disease stabilization >4 months; these patients had hypopharyngeal cancer (4.2 months) and leiomyosarcoma of inferior vena cava origin (5.6 months). The others experienced disease stabilization that lasted approximately 2.8 months each. Figure 1 shows time on treatment for each patient.

Pharmacokinetics. Non-compartmental PK analysis was conducted for three patients from cohort 1, six patients from cohort 2, and six patients from cohort 3; one patient was excluded from PK analysis due to a dosing error (protocol deviation). The mean serum concentration versus time profiles following the first and multiple doses of olaratumab infusion are shown in Figure 2(a,b) respectively. The second peak, occurring at approximately 169 h for the 10 mg/kg (cohort 1) and 15 mg/kg (cohort 3) dose groups, is associated with the second infusion of olaratumab given on day 8 (168 h).

The PK parameters following the first infusion and multiple infusions of olaratumab at 10 mg/kg q3w (cohort 1), 15 mg/kg q3w (cohort 3), and 20 mg/kg q2w (cohort 2) are summarized in Table 4. After a single infusion, PK parameters, including area under the serum concentration versus time curve from zero to infinity ($AUC_{(0-\infty)}$), total body clearance of drug calculated after intravenous administration (CL), and terminal phase volume (V_z), were not calculated for the 10 mg/kg (cohort 1) and 15 mg/kg (cohort 3) dose groups; the terminal elimination $t_{1/2}$ was calculated following day 8 infusion because of the unique dosing schedules of these cohorts (patients received first infusion on day 1 and second infusion on day 8 q3w). The individual terminal elimination $t_{1/2}$ following the first and multiple doses ranged from 4.42 to 9.38 days and 4.06 to 8.83 days, respectively, across all dose groups and dosing schedules. Due to the relatively short PK sampling time (336 h) post end of infusion, the true terminal elimination phase may not have been completely captured and accurately estimated. Therefore, $t_{1/2}$ and its associated parameters, including $AUC_{(0-\infty)}$ and CL, should be interpreted with caution. The olaratumab maximum observed serum drug concentration (C_{max}) following the first infusion appeared to increase with dose.

Individual serum concentration-time profiles exhibited a multi-phasic decline (data not shown). Following the multiple doses (fifth dose for the 10 mg/kg [cohort 1] and 15 mg/kg [cohort 3] dose groups and fourth dose for the 20 mg/kg [cohort 2] dose group), individual serum concentrations were higher than the first dose, reflecting some accumulation of olaratumab following multiple infusions (individual patient accumulation ratio, calculated using AUC [$R_{A,}$ AUC] ranged from 1.30 to 1.72) (data not shown).

Following multiple infusions of olaratumab at 10 mg/kg q3w and 20 mg/kg q2w, the geometric mean trough concentrations (C_{last}) were close to or above the target trough concentration (155 μg/mL) associated with antitumor activity in preclinical xenograft studies.[14] However, olaratumab infusion at 15 mg/kg q3w generated geometric mean pre-dose serum concentrations above 155 μg/mL (target trough concentration) throughout the study (Table 4).

Comparative analyses of clearance (steady state clearance; CLss) and exposure (area under the concentration versus time curve during one dosing interval; AUCτ), following multiple

Table 4. Summary of olaratumab pharmacokinetic parameters

Regimen	Geometric mean (CV%)†		
	10 mg/kg (*N* = 3)‡,§ q3w	15 mg/kg (*N* = 6)§ q3w	20 mg/kg (*N* = 6) q2w
After the first dose			
C_{max} (μg/mL)	362.322; 436.172	587 (40)	735 (29)¶
t_{max} (h)††	1.20; 1.73	1.45 (1.18–9.14)	2.22 (1.27–3.28)¶
C_{last} (μg/mL)	203.320; 176.762	173 (46)	110 (19)
$AUC_{(0-168)}$ (μg/h/mL)	NC	48 000 (47)§§	63 400 (21)
$AUC_{(0-tlast)}$ (μg/h/mL)	35 500; 35 600	43 600 (45)	92 500 (20)‡‡
$AUC_{(0-\infty)}$ (μg/h/mL)	NC	NC	126 000 (12)¶
$t_{1/2}$ (days)‡‡	5.33; 6.38	7.29 (6.04–9.38)¶¶	6.42 (4.42–8.00)¶
CL (mL/h/kg)	NC	NC	0.159 (12)¶

Regimen	Geometric mean (CV%)†		
	10 mg/kg (*N* = 3)††† q3w	15 mg/kg (*N* = 6)†††‡‡‡ q3w	20 mg/kg (*N* = 6)¶¶ q2w
After multiple doses			
C_{max} (μg/mL)	658.391; 546.854§§§	920.832§§§	1160 (91)
t_{max} (h)‡‡	1.74; 2.21§§§	2.18§§§	2.21 (1.70–3.30)
C_{last} (μg/mL)	151.101; 121.188	360.948	181 (37)
$AUC_{(0-168)}$ (μg/h/mL)	53 500; 44200	82 800	77 400 (30)
AUC_{τ} (μg/h/mL)	NC	NC	123 000 (29)¶¶¶
$t_{1/2}$ (days)‡‡‡	4.06; 7.33††††	8.25††††	7.33 (5.42–8.83)
CL_{ss} (mL/h/kg)	NC	NC	0.163 (29)
R_A (AUC)‡‡‡‡	1.55	1.38	1.46 (15)

†The single value is reported when *n* = 1; values are separated by semicolon when *n* = 2. ‡*n* = 2 for all parameters. One patient, whose samples were not collected for the initial 168 h, was excluded from PK analysis. §C_{max}, C_{last}, AUC_{0-168}, and $AUC_{0-tlast}$ are calculated following the first infusion (day 1) and $t_{1/2}$ is calculated following the second infusion (day 8) in day-1 and day-8 dosing in 21-day cycles (q3w). ¶*n* = 5. ††Median (range). ‡‡Geometric mean (range). §§*n* = 4. ¶¶*n* = 3. †††Patient received first infusion on day 1 and second infusion on day 8 in 21-day cycles (q3w). ‡‡‡*n* = 1 for all parameters. §§§C_{max}, t_{max}, and $AUC_{(0-168)}$ are calculated following the first infusion (day 1) in day 1 and day 8 dosing in 21-day cycles (q3w). ¶¶¶Dosing interval (τ) is 336 h. ††††$t_{1/2}$ is calculated following the second infusion (day 8) in day 1 and day 8 dosing in 21-day cycles (q3w). ‡‡‡‡Intercycle accumulation of olaratumab calculated as $AUC_{(0-504)}$ (Cycle 2)/$AUC_{(0-504)}$ (Cycle 1) for 10 and 15 mg/kg (q3w) and $AUC_{(0-336)}$ (Cycle 2)/$AUC_{(0-336)}$ (Cycle 1) for 20 mg/kg (q2w). $AUC_{(0-168)}$, area under the concentration versus time curve from zero to 168 h; $AUC_{(0-336)}$, area under the concentration versus time curve from zero to 336 h; $AUC_{(0-504)}$, area under the concentration versus time curve from zero to 504 h; $AUC_{(0-\infty)}$, area under the serum concentration versus time curve from zero to infinity; $AUC_{(0-tlast)}$, area under the concentration versus time curve from zero to time *t*, where t is the last scheduled sampling time point with a measurable drug concentration; AUC_{τ}, area under the concentration versus time curve during one dosing interval; C_{last}, last quantifiable serum drug concentration; C_{max}, maximum observed serum drug concentration; CL, total body clearance of drug calculated after intravenous administration; CL_{ss}, total body clearance of drug calculated after intravenous administration at steady state; CV, coefficient of variation; *N*, number of patients with assessable PK; NC, not calculated; PK, pharmacokinetic; q2w, every 2 weeks; q3w, every 3 weeks; R_A, accumulation ratio; $t_{1/2}$, terminal elimination half-life; t_{max}, time of maximal concentration.

infusions of olaratumab 20 mg/kg q2w, were conducted between this study of Asian patients and the US phase 1 study of non-Asian patients.[14] The results of this analysis are presented in Figure 3. As shown in the figure, the PK parameters CLss and AUCτ appear to be comparable between Asian and non-Asian patients. However, due to the small sample size, a statistical analysis was not conducted.

Circulating biomarkers. For PDGF-BB, all samples were below the limit of quantitation, so no further analysis was performed.

Prior to the initial olaratumab dose, the median PDGF-AA expression was 11.30 ng/mL for cohort 1, 11.00 ng/mL for cohort 2, and 17.35 ng/mL for cohort 3. Until 24 h following the first infusion, the median PDGF-AA expression increased to 42.15, 62.35, and 48.18 ng/mL for cohort 1, cohort 2, and cohort 3, respectively. However, no trend was identified for the biomarker level change over time for any cohort at later time points. When analyzed by patient, the best overall responses did not seem to be related to the largest change from baseline in PDGF-AA (data not shown).

Discussion

Inhibitors of the PDGF/PDGFR axis are being sought as anticancer agents.[11,12] Most of these agents are small molecule TKIs that inhibit multiple kinases and have complex toxicities.[11,12,17,18] Monoclonal antibodies specifically targeting PDGFR are expected to offer an advantage in terms of specificity and minimizing AEs.

This is the first report of the use of olaratumab, a fully human IgG1 monoclonal antibody that selectively binds human PDGFRα,[13] in Japanese cancer patients. As an IgG1 antibody, olaratumab has the potential to induce antibody-dependent cellular cytotoxicity;[19] however, this has not been experimentally tested. This report follows an earlier report of a phase I trial conducted in the United States.[14] In the current report, 16 Japanese patients with advanced solid tumors, who had not responded to standard therapy or for whom no standard therapy was available, were treated with olaratumab in an open-label, dose-escalation, phase 1 trial. This study met

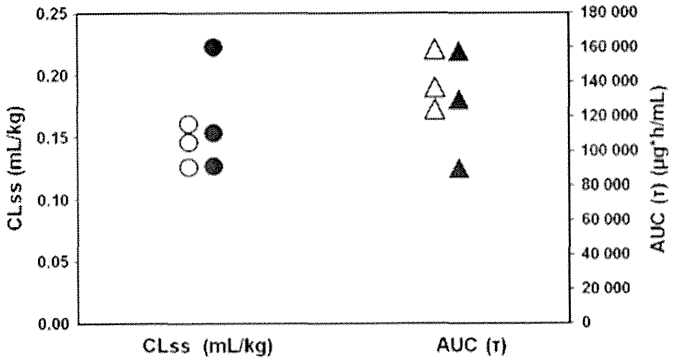

Fig. 3. Comparison of PK parameters clearance and exposure between non-Asian and Asian patients following multiple infusions of olaratumab. Shown are CLss (circles) and AUC_τ (triangles) for the 20 mg/kg-every-2-weeks groups. White circles (○) = CLss, non-Asian patients; black circles (●) = CLss, Asian patients; white triangles (△) = AUC_τ, non-Asian patients; black triangles (▲) = AUC_τ Asian patients. AUC_τ, area under the concentration versus time curve during one dosing interval; CLss, total body clearance of drug calculated after intravenous administration at steady state.

its objectives to establish the safety and PK profile of olaratumab.

In this trial, most AEs were mild to moderate in severity. The most frequently reported olaratumab-related AEs were proteinuria (25.0%) and increased aspartate aminotransferase (12.5%). These AEs were distributed across the three cohorts, and thus did not appear to be dose-related. There were only two grade 3 olaratumab-related non-laboratory AEs (elevated aspartate transaminase and tumor hemorrhage) during the trial, both occurring in cycle 1 and in the same patient. No infusion reactions or interruptions were reported and the majority of patients in the safety population received a relative dose intensity of at least 80%.

In this trial, no fluid retention, ascites, or edemas were reported. The PDGFR may be involved in the control of interstitial fluid pressure through PDGF-BB.[20] The use of small molecule multi-kinase TKIs that inhibit PDGFR is sometimes associated with fluid retention,[17,18] and blockade of PDGFRβ in cancer patients by a humanized, pegylated di-Fab was associated with ascites and fluid retention.[21] Fluid retention was not observed in our trial with selective PDGFRα blockade, even in patients with prolonged exposure (up to 25 weeks). This observation supports the hypothesis that PDGFRα is less likely to be involved in the fluid retention observed with non-specific PDGFR blockade by small molecules or with a selective PDGFRβ blockade.

In this trial, there were no DLTs and the MTD was not reached, which is consistent with the previous US trial.[14] Over the three dose ranges, olaratumab had an acceptable safety profile and was well tolerated in this patient population.

Based on the PK concentration profile of olaratumab, the trough concentrations following single and multiple doses of olaratumab at 15 mg/kg on days 1 and 8 every 3 weeks (cohort 3), and multiple doses at 20 mg/kg every 2 weeks (cohort 2), were above 155 μg/mL, the concentration that was efficacious in preclinical xenograft studies.[14] Thus, olaratumab dosed at 15 mg/kg on days 1 and 8 every 3 weeks and at 20 mg/kg every 2 weeks could represent an acceptable schedule for future trials in Japanese patients. Based on the comparative analysis of both the clearance (CLss) and exposure (AUCτ), the observed PK in the Asian patient population appears to be similar to the non-Asian patient population observed in the previous US phase I trial.[14]

The best overall response in this trial was SD, achieved by 7 of 16 patients (43.8%). Of these seven patients, four had tumors that were located in the gastrointestinal tract; the remaining three patients had tumors of diverse origins. Two patients, both in cohort 3, experienced disease stabilization >4 months (hypopharyngeal cancer [SD = 4.2 months]) and leiomyosarcoma of inferior vena cava origin [SD = 5.6 months]), which indicates some preliminary antitumor activity.

In nude mice, treatment with olaratumab inhibited the growth of human glioblastoma (U118) and leiomyosarcoma (SKLMS-1) xenografts and decreased the amount of tumor-associated phosphotyrosyl-PDGFRα in the glioblastoma model.[13] In cultured cells, olaratumab inhibited PDGF-induced mitogenesis, PDGFRα autophosphorylation, and the phosphorylation of downstream signaling molecules. At this time, it is not known if the same changes occur in patient tumors or whether pharmacologically active concentrations can be achieved in human tumor tissue. Our trial showed that the median plasma PDGF-AA expression increased for 24 h after the first infusion in all three cohorts, but no trend was noted at later time points and best overall responses seemed unrelated to the largest change in PDGF-AA from baseline. Because biomarker studies were not performed in the US trial, comparisons cannot be made with this trial; nonetheless, an increase in PDGF-AA may be a compensatory mechanism that results from PDGFRα inhibition and/or sequestration.

Based on its safety and preliminary efficacy in this trial and the previous phase 1 trial,[14] olaratumab has advanced to phase II trials. Olaratumab is being tested as monotherapy and in combination with other agents in several tumor types.

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Disclosure Statement

Aruna Dontabhaktuni is an employee of ImClone Systems, a wholly-owned subsidiary of Eli Lilly and Company and owns stock in Eli Lilly and Company. Cornelia Nippgen is an employee of Eli Lilly and Company. Johannes Nippgen and Yan Ma were employed by ImClone Systems, a wholly-owned subsidiary of Eli Lilly and Company, during the conduct of this trial. Toshihiko Doi and Atsushi Ohtsu report no conflicts of interest.

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Clinicopathological characteristics and surgical results of lung cancer patients aged up to 50 years: The Japanese Lung Cancer Registry Study 2004

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ABSTRACT

Objective: The clinicopathological characteristics and surgical results of young lung cancer patients were investigated.
Materials and methods: Seven hundred and four (6.0%) patients with lung cancer, aged up to 50 years, were enrolled from among the 11,663 patients registered in the Japanese Lung Cancer Registry Study 2004, and their clinical data were compared with those of 10,959 patients older than 50 years. This epidemiological study is based on the single year registration of surgically treated patients in the major institutes in Japan.
Results: The 5-year overall survival rate (5Y-OS) and the 5-year lung cancer-related survival rate was 79.2%/69.0% ($p < 0.001$) and 81.3%/76.6% ($p = 0.005$) in the young/old groups, respectively. In the young/old groups, lobectomy and pneumonectomy was performed in 76.9%/78.0% and 5.7%/3.2%, respectively; adjuvant therapies were given preoperatively in 10.4%/4.7% ($p < 0.001$) and postoperatively in 31.4%/24.5% ($p < 0.001$). The proportions of patients with p-stage IIIA (18.2%) and adenocarcinoma histology (78.7%) were higher in the young group. The 5Y-OS was 94.8%/86.2% for p-stage IA ($p < 0.001$), 87.0%/73.2% for p-stage IB ($p = 0.001$), 61.0%/61.6% for p-stage IIA ($p = 0.595$), 71.0%/48.4% for p-stage IIB ($p = 0.003$), 49.6%/39.4% for p-stage IIIA ($p = 0.020$), and 80.0%/24.8% for p-stage IIIB ($p = 0.012$); it was 83.5%/80.7% for females ($p = 0.106$) and 75.1%/62.3% for males ($p < 0.001$) in the young/old groups. The postoperative survival was significantly better with all operative procedures in the young group. The 5Y-OS after recurrence was 17.9%/13.4% in the young/old groups ($p = 0.016$). In the young group, the 5Y-OS was better in females (83.5%) than in males (75.1%, $p = 0.002$), and for patients with adenocarcinoma (80.3%) than for those with squamous cell carcinoma (68.5%, $p = 0.013$). Age up to 50 years was identified as an independent better prognostic factor on multivariate analysis.
Conclusions: The postoperative survival in lung cancer patients aged up to 50 years was better than that in patients older than 50 years.

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1. Introduction

Lung cancer is a leading cause of malignancy-related death. The American Cancer Society estimates that 226,160 people will be diagnosed and 160,340 patients will die of lung cancer in the United States in 2012 [1]. Lung cancer occurs mainly in older people, and fewer than 2% of all cases are found in people younger than 45 years in the USA [1]. The Ministry of Health, Labor, and Welfare, Japan, reported that 69,813 people died of lung cancer in 2010 in Japan, and the number is still increasing. According to the Japanese Lung Cancer Registry Study, the number of patients younger than 50 years ranged from 5.0% to 8.2% of all resected cases since 1994 [2]. Because of the small size of the young population, the clinical features of young lung cancer patients remain unclear.

Better survival of lung cancer patients in the middle-aged group (45–60 years) as compared to the young (<45 years) or old group (>60 years) was reported by a multicenter study [3]. Several previous studies also revealed better postoperative survival rate in the young lung cancer patients [4–6], while other reports showed equivalent survival outcome to the old patients [7,8]. So, the survival superiority of the young patients is still controversial in lung cancer. Active treatment with multiple modalities was recommended in young patients in association with these results, while the study cohort included all lung cancer patients treated with surgery, chemotherapy, and irradiation [3]. However, the clinicopathological characteristics and surgical results of young patients with lung cancer have not yet been identified. Recent developments in chemotherapy and molecular targeted therapy might contribute to prolonged survival and improvement of results with multimodality management, especially in young patients, who are expected to be able to tolerate active treatments.

Patients aged up to 50 years extracted from the Japanese Lung Cancer Registry Study 2004 who underwent surgical resection were evaluated in order to clarify their clinicopathological characteristics and the results of surgical intervention in the present study [2].

2. Materials and methods

2.1. Patients

A total of 704 lung cancer patients aged up to 50 years were extracted from among the 11,663 patients listed in the Japanese Lung Cancer Registry Study 2004, which was conducted as a multicenter surveillance study of patients who underwent surgery by the Japanese Joint Committee of the Lung Cancer Registry (JJCLCR) [2]. JJCLCR is officially authorized by The Japan Lung Cancer Society, The Japanese Association for Chest Surgery, The Japanese Respiration Society, and The Japan Society for Respiratory Endoscopy. Of the 605 teaching hospitals certified by the Japanese Board of General Thoracic Surgery, 253 participated in this registry. All patients analyzed in the present study underwent surgery in 2004 and the single year registration included the following data: (1) demographic background (age and sex), (2) preoperative status (Eastern Cooperative Oncology Group performance status (ECOG PS), preoperative comorbidity, smoking status, tumor markers), (3) clinical TNM, (4) induction therapy, (5) operative procedure, (6) postoperative morbidity, (7) tumor histology, (8) adjuvant therapy, (9) pathological TNM. The clinicopathological characteristics and the results of surgical intervention in patients aged up to 50 years were analyzed in detail and compared to those of 10,959 patients older than 50 years. The data collected using the UICC-TNM staging system (version 6) were converted to the UICC-TNM staging system (version 7) to assess the extent of lung cancer [9].

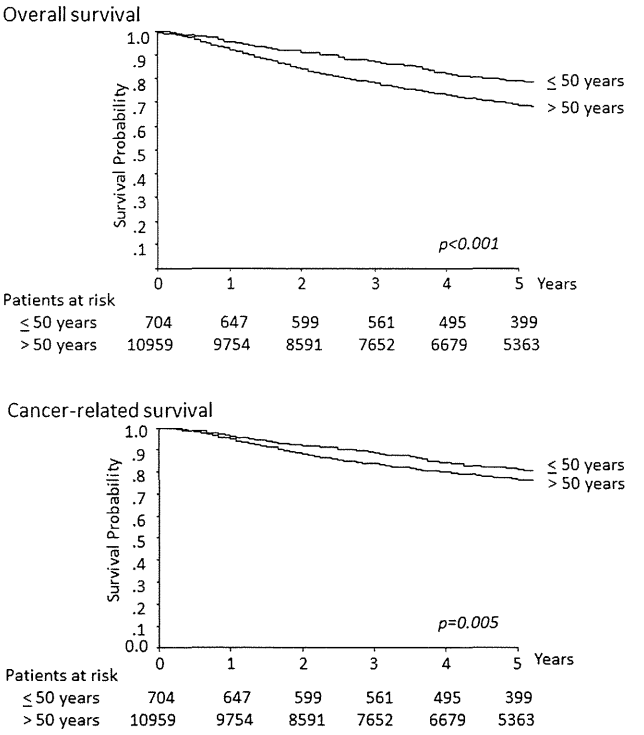

Fig. 1. The overall and lung-cancer related survival rates for patients aged up to and older than 50 years with surgical intervention. The postoperative survival rate was significantly better in the young group.

2.2. Statistical analyses

All data were extracted and analyzed by a JJCLCR member biostatistician (EM). Survival after pulmonary resection was estimated according to the Kaplan–Meier method, and survival differences were tested using the log-rank test. The prognostic effect of variables on survival was analyzed using the multivariate Cox regression model with variables of sex, ECOG-PS, smoking history, comorbidity, operative procedure, p-stage, histology, adjuvant chemotherapy. The χ^2-test was used to compare the rates between groups. A p value less than 0.05 was considered significant.

3. Results

Patients' characteristics, with a comparison of patients aged up to 50 years and older than 50 years, are shown in Table 1. The proportion of females was significantly higher in the young group than in the old group ($p < 0.001$). Performance status (ECOG) was significantly better in the young group ($p < 0.001$). Smoking history and preoperative comorbidity were significantly more frequent in the old group ($p < 0.001$). The operative procedure was significantly different ($p = 0.013$) and the rate of pneumonectomy was higher in the young group. The distribution of p-stage showed the significant difference, and the proportion of p-stage IB and IIA was lower and that of locally advanced disease with p-stage IIIA was higher in the young group as compared to the old group. The proportion of histopathology was significantly different ($p < 0.001$) and the rate of adenocarcinoma was higher in the young group. Young patients received both preoperative and postoperative adjuvant therapy more frequently than old patients.

The 5-year overall survival rate (5Y-OS) was 79.2% and 69.0% in the young and old groups, respectively ($p < 0.001$), as shown in Fig. 1. The 30-days mortality was 1/704 (0.1%) and 47/10959 (0.4%), and the hospital mortality was 2/704 (0.3%) and 134/10959 (1.2%) in the young and old groups, respectively. The morbidity was

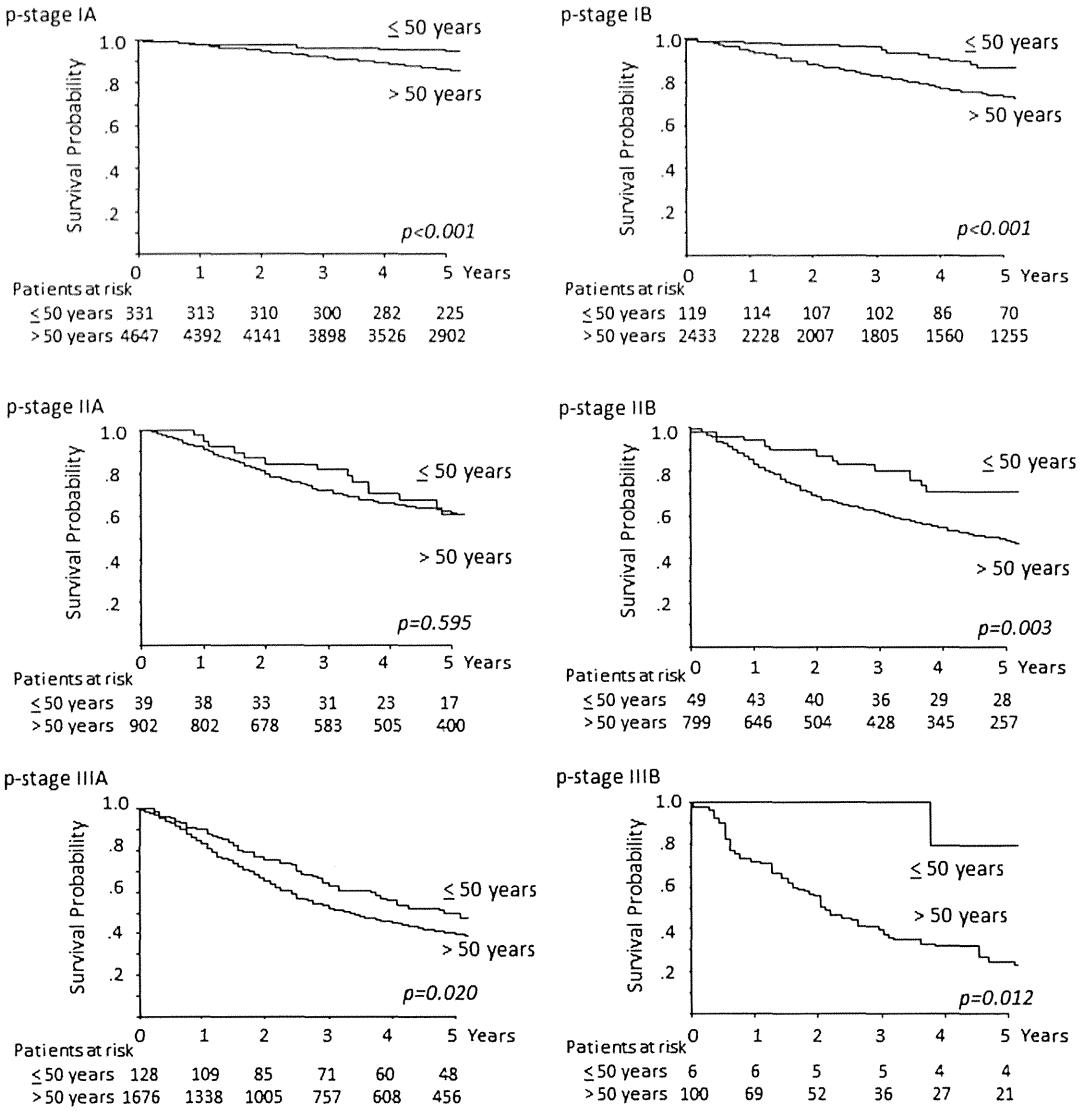

Fig. 2. The survival curves of patients aged up to and older than 50 years with surgery according to p-stage using UICC version 7. The postoperative survival was significantly better in the young group for each p-stage IA – IIIB except stage IIA.

58/704 (8.2%) and 1921/10959 (17.5%) in the young and old groups, respectively ($p < 0.001$). When analyzing disease-specific outcome, the 5-year lung cancer-related survival rate was 81.3% and 76.6% in the young and old groups, respectively ($p = 0.005$), as shown in Fig. 1. According to p-stage, the 5Y-OS was 94.8% and 86.2% for IA ($p < 0.001$), 87.0% and 73.2% for IB ($p < 0.001$), 61.0% and 61.6% for IIA ($p = 0.595$), 71.0% and 48.4% for IIB ($p = 0.003$), 49.6% and 39.4% for IIIA ($p = 0.020$), and 80.0% and 24.8% for IIIB ($p = 0.012$), in the young and old groups, respectively, as shown in Fig. 2.

Among male patients, the 5Y-OS was 75.1% and 62.3% in the young and old groups, respectively ($p < 0.001$), although there was no significant difference among female patients and the 5Y-OS was 83.5% and 80.7%, respectively (Fig. 3). The cause of death, preoperative comorbidities, smoking history, and adjuvant therapy were examined by age and sex. Lung cancer-unrelated death was higher (25.3%) in the old group than that in the young group (6.8%) in males ($p < 0.001$), while no significant difference was observed in females. Preoperative comorbidities were frequent in the old group in both male and female patients. Smoking history was significantly more frequent in the old group in males, while it was less frequent in females. Male patients in the young group more frequently had both preoperative and postoperative adjuvant therapies as compared to the old group, while no significant difference was found in female patients.

According to operative procedure, the 5Y-OS was better in the young group than in the old group for all procedures: 59.1% and 42.0% for pneumonectomy ($p = 0.050$), 79.9% and 71.7% for lobectomy ($p < 0.001$), 87.3% and 73.1% for segmentectomy ($p = 0.034$), and 93.5% and 65.9% for wedge resection ($p < 0.001$), in the young and old groups, respectively (Fig. 4). According to histological type, the 5Y-OS for adenocarcinoma was 80.3% in the young group which was significantly better than 74.5% in the old group, though no significant survival difference was observed for squamous cell carcinoma. The 5Y-OS after recurrence was 17.9% and 13.4% in the young and old groups, respectively ($p = 0.016$). In the young group, the 5Y-OS was significantly better for female patients (83.5%) than for male patients (75.1%, $p = 0.002$). 5Y-OS was better for the histology of adenocarcinoma (80.3%) than for squamous cell carcinoma (68.5%, $p = 0.013$).

Since the comparison of survival difference between young and old patients might be affected by patients older than 70 years, who are expected to have poor long-term survival, another comparison of survival difference between patients aged up to 50 years ($n = 704$) and those 50–70 years ($n = 6152$), which was a young elderly cohort,

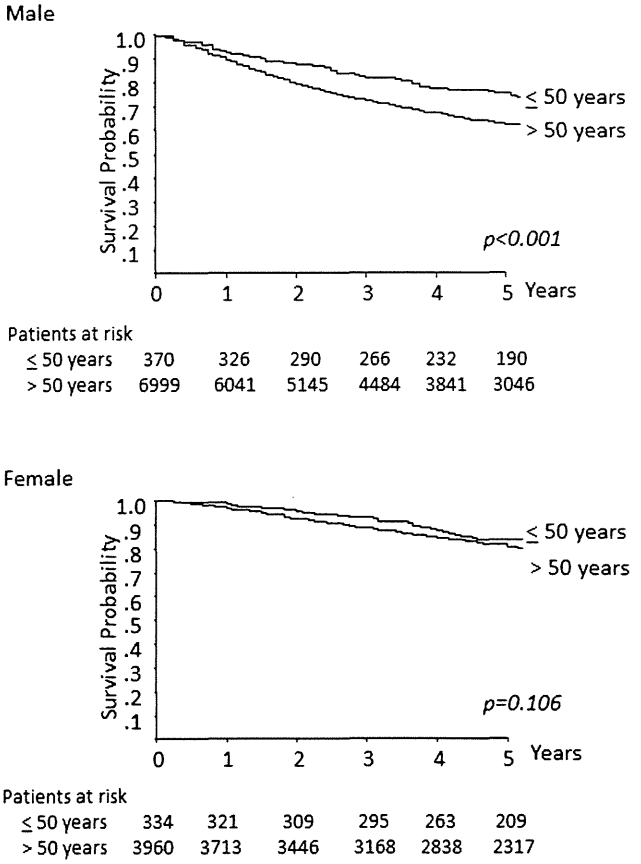

Fig. 3. The survival curves of patients aged up to and older than 50 years with surgery according to sex. Among male patients, the overall survival in patients aged up to 50 years was significantly better than that in patients older than 50 years. No significant difference was found in female patients.

were also performed. The 5Y-OS was 79.2% and 73.7% in the young and young elderly groups, respectively ($p = 0.002$). According to p-stage, the 5Y-OS was 94.8% and 90.6% for IA ($p = 0.022$), 87.0% and 79.0% for IB ($p = 0.027$), 61.0% and 66.9% for IIA, 71.0% and 54.7% for IIB ($p = 0.027$), 49.6% and 44.7% for IIIA, and 80.0% and 27.7% for IIIB ($p = 0.023$), in the young and young elderly groups, respectively. These differences showed a similar tendency to have a better survival rate in the young group as seen with the comparative results between those aged up to and those older than 50 years shown above. However, survival after postoperative recurrence did not show a significant difference between the young and young elderly groups.

The prognostic factors were tested by multivariate analyses using the variables of age, sex, ECOG-PS, smoking history, comorbidity, operative procedure, p-stage, histology, adjuvant therapy (Table 2). Age up to 50 years was identified to be an independent prognostic factor with a hazard ratio of 1.451. Female, good ECOG-PS, no smoking history, no comorbidity, early p-stage, and no preoperative adjuvant therapy were also identified as predictors of a better prognosis. When analyzing age as continuous variable in multivariate analysis, age was identified as an independent prognostic factor with the hazard ratio 1.026 (CI: 1.022–1.030).

4. Discussion

The postoperative survival of young lung cancer patients remains unclear due to their low numbers, though several studies have been reported so far [3–10]. Radzikowska et al. and Minami et al. investigated patients younger than 50 years and showed significantly better survival as compared to old patients [4,6]. Among several studies with definition of the young group as up to 40 years, Tian et al. reported higher 5Y-OS in young patients, though no superior survival was shown in the study by Hanagiri et al. or by Maruyama et al. [5,7,8]. In the present epidemiological study, cancer patients aged up to 50 years who underwent surgery were extracted from the Japanese Lung Cancer Registry Study 2004 [2],

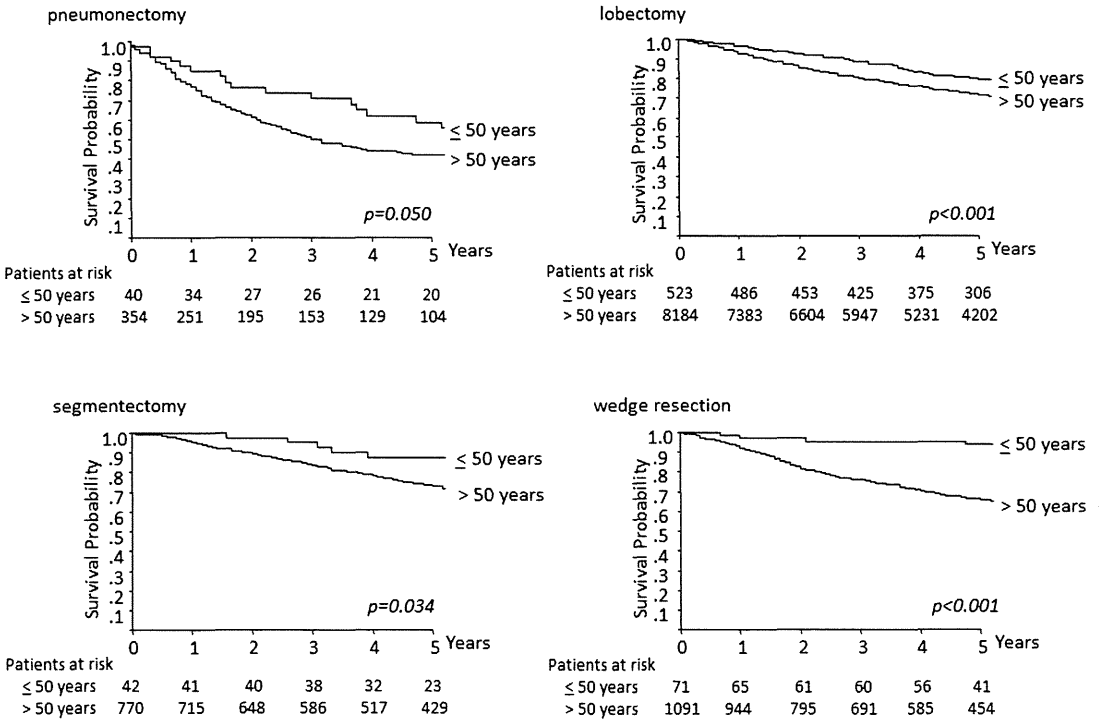

Fig. 4. The survival curves of patients aged up to and older than 50 years with surgery according to operative procedure. The postoperative survival was significantly better in the young group for each procedure.

Table 1
Patients' characteristics.

	Age ≤ 50 years	Age > 50years	p value
Sex			p < 0.001
Male	370(52.6%)	6999(63.2%)	
Female	334(47.4%)	3960(36.8%)	
PS			p < 0.001
0	665(94.5%)	8943(81.6%)	
1	27(3.8%)	1661(15.1%)	
Others	12(1.7%)	355(3.3%)	
Smoking history			p < 0.001
No	308(43.8%)	3777(34.5%)	
Yes	334(47.4%)	6290(57.4%)	
Unknown	62(8.8%)	892(8.1%)	
Comorbidity			p < 0.001
No	562(79.8%)	7151(65.3%)	
Yes	79(11.2%)	3048(27.8%)	
Unknown	63(8.9%)	760(6.9%)	
c-stage			p < 0.001
Stage IA	420(59.7%)	5875(53.6%)	
Stage IB	88(12.5%)	2700(24.6%)	
Stage IIA	36(5.1%)	167(1.5%)	
Stage IIB	45(6.4%)	854(7.8%)	
Stage IIIA	84(11.9%)	856(7.8%)	
Stage IIIB	13(1.8%)	394(3.6%)	
Stage IV	18(2.6%)	113(1.0%)	
Operative procedure			p < 0.001
Pneumonectomy	40(5.7%)	354(3.2%)	
Bilobectomy	18(2.6%)	357(3.3%)	
Lobectomy	523(74.3%)	8184(74.7%)	
Segmentectomy	42(6.0%)	770(7.0%)	
Wedge resection	71(10.1%)	1091(10.0%)	
Others	10(1.3%)	203(1.9%)	
p-stage			p < 0.001
Stage IA	331(47.0%)	4647(42.4%)	
Stage IB	119(16.9%)	2433(22.2%)	
Stage IIA	39(5.5%)	902(8.2%)	
Stage IIB	49(7.0%)	799(7.3%)	
Stage IIIA	128(18.2%)	1676(15.3%)	
Stage IIIB	6(0.9%)	100(0.9%)	
Stage IV	32(4.5%)	402(3.7%)	
Histology			p < 0.001
Adenocarcinoma	554(78.7%)	7367(67.2%)	
Squamous cell carcinoma	52(7.4%)	2548(23.3%)	
Large cell carcinoma	30(4.3%)	357(3.3%)	
Small cell carcinoma	11(1.6%)	232(2.1%)	
Others	57(8.0%)	455(4.1%)	
Preoperative adjuvant therapy			p < 0.001
Yes	73(10.4%)	520(4.7%)	
No	631(89.6%)	10,439(95.3%)	
Postoperative adjuvant therapy			p < 0.001
Yes	221(31.4%)	2682(24.5%)	
No	483(68.6%)	8277(75.5%)	
Total	704(100%)	10,959(100%)	

PS, Eastern Cooperative Oncology Group performance status; Smoking history, including both current and ex-smokers; Comorbidity, including current smoking history, obesity with BMI > 30 kg/m^2, cerebrovascular disease, chronic obstructive pulmonary disease, interstitial pneumonia, ischemic heart disease, renal dysfunction with creatinine> 2.0 g/dL, liver cirrhosis with Child-Turcotte classification > B, diabetes mellitus with HbA1c > 8%, anemia with Hb < 8 g/dL, and treatment for other malignancy within a year.

Table 2
Results of multivariate analysis in lung cancer patients with surgical resection.

Variables		Hazard ratio	95% Confidence Interval	p value
Age				
≤50 years		1.000		
>50 years		1.451	1.211–1.739	<0.001
Sex				
Male		1.000		
Female		0.664	0.593–0.744	<0.001
ECOG PS				
PS 0		1.000		
PS 1		1.582	1.441–1.736	<0.001
PS 2		2.041	1.600–2.604	<0.001
PS 3		2.706	1.717–4.266	<0.001
Smoking history				
No		1.000		
Yes		1.150	1.026–1.289	0.016
Comorbidity				
No		1.000		
Yes		1.232	1.135–1.338	<0.001
Operative procedure				
Pneumonectomy		1.000		
Bilobectomy		1.089	0.873–1.358	0.450
Lobectomy		0.782	0.665–0.920	0.003
Segmentectomy		0.978	0.786–1.218	0.844
p-stage				
IA		1.000		
IB		1.958	1.741–2.203	<0.001
IIA		2.878	2.488–3.329	<0.001
IIB		4.031	3.505–4.637	<0.001
IIIA		6.940	5.288–9.108	<0.001
Histology				
Pre-invasive lesion		1.000		
Squamous cell carcinoma		1.280	0.318–5.151	0.728
Small cell carcinoma		1.961	0.481–7.994	0.348
Adenocarcinoma		1.166	0.291–4.682	0.828
Large cell carcinoma		1.721	0.425–6.978	0.447
Adjuvant therapy				
Preoperative	No	1.000		
	Yes	1.169	1.018–1.342	0.027
Postoperative	No	1.000		
	Yes	0.923	0.850–1.002	0.055

ECOG, Eastern Cooperative Oncology Group; PS, Performance Status; Adjuvant therapy includes systemic chemotherapy and radiation therapy.

and better postoperative survival was observed in these young lung cancer patients, although the proportion of advance disease was higher as compared to the old group. It was also found that, among young patients, women and those with adenocarcinoma had a better survival, which was similar to the results of all-generation analyses [2].

The higher proportion of young patients who underwent pneumonectomy could imply that they were better able to tolerate surgery, as a previous report showed similar results [5]. Pneumonectomy was, however, reported to increase the perioperative morbidity in elderly patients in a case-control study [11], and sleeve lobectomy, if possible, is recommended as an alternative procedure to pneumonectomy, with lower mortality and better survivals [12].

The results of the present study might indicate the importance given to curative intention over the preservation of pulmonary function in young patients. The superior 5Y-OS in young group treated with a pneumonectomy in the present study could suggest that pneumonectomy is still a considerable option for resectable locally advanced disease in the young patients.

Higher rates of both preoperative and postoperative adjuvant therapy in the young group could reflect the higher proportion of stage IIIA advanced disease, which is a prime indication for induction therapy [13], in addition to the ability of young patients to tolerate such treatment. Radzikowska et al. also reported similar results with more aggressive treatment in young patients [4]. The rate of preoperative adjuvant therapy in the young group was more than 2-fold that in those old group (Table 1). These results indicate a planned active multimodal strategy in young patients with good performance status, while the clinical effect to the survival is unclear. Since postoperative adjuvant chemotherapy was adopted as an evidence-based treatment in a practice guideline for lung cancer treatment in 2005 in Japan, quoting several meta-analyses and randomized studies [14–17], only a proportion of patients with stage IB-IIIA analyzed in the present study had received adjuvant therapy. Thus, it might be expected that postoperative survival in patients with locally advanced disease has potentially become better with postoperative chemotherapy, though further investigation is necessary to identify the issue.

The overall survival rates for patients with stages IA, IB, IIB, IIIA, and IIIB were better for patients aged up to 50 years than for

patients older than 50 years. We added another comparison of survival between patients aged up to 50 years and those 50–70 years, because it is expected that patients older than 70 years could have more frequent lung cancer-unrelated death. The similar results to the comparison between patients aged up to and older than 50 years might suggest other factors in addition to the natural aging bias. Though we could not analyze the treatment after recurrence in the present study, young patients with good performance status might have more chance to receive second and third lines of chemotherapy. Further investigation is required to clarify the clinical impact on survival of the aggressive multimodality therapy in young patients with postoperative recurrence using recent cases.

The worse postoperative survival in males older than 50 years was probably due to the greater number of lung cancer-unrelated deaths in that group. This cohort with more comorbidities and smoking history could have cardiopulmonary diseases or second primary malignancies related to tobacco exposure. The poor general status of the old patients might also be related to the less frequent use of adjuvant therapies. As a result, the young male patients without comorbidity or smoking history might improve the survival of the entire patient group. The death rate of male is reported to be twice higher than that of female in 30–84 year-old population by Statistics and Information Department, Minister's Secretariat, Ministry of Health, Labor and Welfare, Japan. Thus, such natural biological bias might also influence to the results.

The tendency for favorable survival in female patients and in patients with adenocarcinoma histology was the same as that seen with all-generation analyses [2]. Bronchioloalveolar carcinoma (BAC) showing ground glass opacity on CT scanning, which is currently classified as adenocarcinoma in situ or minimally invasive adenocarcinoma [18], is generally recognized to be a slow growing, low-grade adenocarcinoma and a unique subtype related to a never-smoking history, female sex, and Asian race [19]. Though CT findings were not analyzed in the present study cohort, higher proportions of adenocarcinoma and females in the Japanese young patients' group might change the patients' characteristics, with a higher rate of BAC and low-grade malignant behavior. Further investigations including CT findings are necessary to resolve these issues.

The present epidemiological study has several limitation and speculation for the results. The retrospective study cannot clarify the prognostic effect of multimodal therapy in young patients due to the lack of data for chemotherapy regimens or molecular target therapy. Younger age is well-known better prognostic predictor in other malignancies and the influence of other factors except the variables analyzed in this study cannot be completely denied. Further prospective analyses using high volume surgically and non-surgically treated lung cancer patients are required to clarify the cause for the better prognosis of young patients treated surgically.

5. Conclusion

In conclusion, surgically treated young lung cancer patients showed the highest rate of locally advanced disease and received active multimodality therapies. Their postoperative survival was better than that of patients older than 50 years, and age was identified as an independent better prognostic factor. Even when comparing cancer-related survival, the outcome was significantly better in young lung cancer patients.

Conflict of interest statement

All authors contributing to this work have no other conflict of interest to declare.

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ORIGINAL ARTICLE

Clinical predictor of pre- or minimally invasive pulmonary adenocarcinoma: possibility of sub-classification of clinical T1a

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Abstract

OBJECTIVES: A new pathological classification for pre- and minimally invasive adenocarcinoma has been established, with distinction prior to surgery crucial because of the extremely good prognosis.

METHODS: Of 412 patients who underwent surgery for lung cancer from 2008 to 2011, 110 classified as c-stage I had each of the following four parameters assessed for predictive power for pre- or minimally invasive adenocarcinoma and relapse-free survival (RFS): (i) whole tumour size (WS) shown by computed tomography (CT) , (ii) size of the solid (SS) component in CT findings, (iii) maximum standard uptake value in fluorodeoxyglucose positron emission tomography (FDG-PET)/CT scan images (SUV_{max}) and (iv) serum level of carcinoembryonic antigen.

RESULTS: For prediction of pre- or minimally invasive adenocarcinoma, the area under the receiver-operating curve was >0.7 for all the four parameters, while only SS was found to be an independent factor in multivariate logistic regression analysis. In Cox proportional hazard model analysis, SS and SUV_{max} were statistically significant, and SS was exclusively independent in multivariate analysis. Differences in RFS between T1a and T1b were more pronounced when using SS compared with WS. In the sub-classification of T1a, we used a break-point of 1.0 cm in SS (T1a-α and T1a-β), which resulted in a 2-year RFS rate of 1.00 for T1a-α ($n = 21$), 0.89 for T1a-β ($n = 27$) and 0.68 for T1b ($n = 26$) ($P = 0.002$ between T1a-β and T1b).

CONCLUSIONS: The SS parameter was useful to distinguish pre- and minimally invasive adenocarcinoma from other types of lung cancer, and set a T1a sub-classification.

Keywords: Non-small-cell lung cancer • Computed tomography • Invasive adenocarcinoma • SUV_{max} • Carcinoembryonic antigen • Surgery

INTRODUCTION

Among patients with lung cancer who undergo surgery, the proportion of those with an adenocarcinoma or small lesions has been increasing, while the prognosis of clinical stage I non-small-cell lung cancer (NSCLC) has improved [1]. The histological classification of pulmonary adenocarcinoma has been revised according to the extent of invasiveness, such as pre-, minimally invasive and invasive [2], and is similar to the method used to calculate tumour size in breast cancer [3]. This is because the prognosis of pulmonary adenocarcinoma is well distinguished by the amount of invasion [2], which dominantly appears as a solid region in computed tomography (CT) findings, contrary to the ground glass opacity (GGO) appearance of a lepidic adenocarcinoma [2, 4]. In addition to CT findings, other clinical parameters including maximum standard uptake value (SUV_{max}) in fluorodeoxyglucose positron emission tomography (FDG-PET) images [5] and serum carcinoembryonic antigen (CEA) level [6, 7] are used as predictors of aggressiveness and/or prognosis in cases of NSCLC. Therefore, it is crucial to evaluate those clinical parameters prior to surgery in order to distinguish patients with a pre- or minimally invasive adenocarcinoma, because of the extremely good survival [2].

MATERIALS AND METHODS

Of 412 patients with lung cancer who underwent surgery from 2008 to 2011 at Osaka University Medical Hospital, 110 classified as clinical stage I underwent a segmentectomy or lobectomy (video-assisted thoracic surgery in 72 cases) with removal of lymph nodes, which was greater than the minimal requirement noted in Union for International Cancer Control (UICC) Tumor Node Metastasis (TNM) classification ver. 7, which states the following: 'Histological examination of hilar and mediastinal lymphadenectomy specimens(s) will ordinarily include 6 or more lymph

nodes/stations. Three of these nodes/stations should be mediastinal including the subcarinal nodes and 3 from N1 nodes/stations' [3]. The number of lymph nodes removed ranged from 6 to 31, with a median of 20. The tumour histology of the p-N2 cases varied (invasive adenocarcinoma $n = 3$, squamous cell carcinoma $n = 1$ and pleomorphic carcinoma $n = 1$). Cyto-pathological staging of the affected lymph nodes was not performed prior to surgery, and thus clinical staging was accomplished mainly using CT and FDG-PET findings. In these cases, each of the following four parameters was assessed for their predictive power for pre- or minimally invasive adenocarcinoma and relapse-free survival (RFS): (i) WS shown by thin section CT, (ii) size of the solid (SS) component in CT findings, (iii) SUV_{max} in FDG-PET/CT scan findings (SUV_{max}) and (iv) CEA (Tables 1 and 2). For the WS parameter, the size (mean ± standard deviation (SD)) according to tumour histology was 2.9 ± 1.0 cm for adenocarcinoma and 3.1 ± 1.3 cm for non-adenocarcinoma. There were no missing data for any of the four parameters. Representative appearances in thin-sliced CT are shown in Fig. 1. The pathological diagnosis of each tumour was defined according to clinical records, except for adenocarcinoma lesions that required rediagnosis according to the new classification [2], which was performed by a pathologist (E.M.). Adjuvant therapy was carried out in 17 cases (oral administration of tegafur-uracil for pathological stage IB in 9, platinum doublet for pathological stage II or III in 8).

The follow-up periods ranged from 12 to 44 months, with a median of 23 months. In the follow-up examinations, all the patients were evaluated at 3-month intervals, which included a physical examination, chest X-ray and blood tests including tumour markers, while additional thoraco-abdominal CT scans were generally performed at 6-month intervals. During the follow-up period, cancer relapse occurred in 19 cases (pathological stage IA in 9 cases, IB in 6, IIA in 2, IIIA in 1, and V in 1), which included local recurrence in 8, distant recurrence in 6, local plus distant recurrence in 5 and death in 8 (original lung cancer in 6, heart attack in 1 and suicide in 1).

Assessment of prediction of pre- or minimally invasive adenocarcinoma

The area under the curve (AUC) of the receiver-operating curve (ROC) was calculated using JMP 9 (SAS Institute Japan, Tokyo, Japan) for WS, SS, SUV_{max} and CEA. In addition, the relative risk (RR) of the four parameters was calculated by logistic regression analysis, while multivariate analysis was performed using variables that showed statistical significance in the individual analysis using StatView 5.0 (HULINKS, Tokyo, Japan).

Assessment of survival

RFS was defined as the period from the day of initial surgery to the day of relapse shown in clinical findings (primarily radiography). Survival curves were figured with the Kaplan–Maier method and a log-lank test was used to assess statistical significance. The hazard ratio (HR) was calculated using Cox proportional hazard model analysis and multivariate analysis was performed using variables that showed statistical significance in the individual analysis. These analyses were done using StatView 5.0 (HULINKS, Tokyo, Japan).

Table 1. Patient characteristics

Total number	110
Gender	
Male	63
Female	47
Age in years	
Median	69
Minimum	40
Maximum	88
Mean ± SD	67.8 ± 9.8
Tumour histology	
Adenocarcinoma	81
preinvasive	8[a]
Minimally invasive	12
Invasive	61
Squamous cell carcinoma	23
Other	6
GGO status by CT	
Pure GGO	4
Mixed GGO	33
Pure Solid	73
c-T factor	
T1a	26
T1b	38
T2a	41
T2b	5
c-stage	
IA	72
IB	38
p-T factor	
T1a	38
T1b	31
T2a	39
T2b	0
T3	2
p-N factor	
N0	102
N1	3
N2	5
p-M factor	
M0	109
M1a	1
p-stage	
IA	64
IB	35
IIA	2
IIB	3
IIIA	5
IV	1
Operation	
Lobectomy	103
Segmentectomy	7

[a]There were no cases of atypical adenomatous hyperplasia.
GGO: ground glass opacity; CT: computed tomography.

This retrospective investigation was approved by the institutional review board of Osaka University Medical Hospital.

RESULTS

RFS curves for pre- or minimally invasive adenocarcinoma

The present pre- and minimally invasive cases had 100% RFS, confirming extremely good prognosis (Fig. 2).

Prediction of pre- or minimally invasive adenocarcinoma

For prediction of pre- or minimally invasive adenocarcinoma, the AUC of the ROC was >0.7 for all the four parameters (0.80 for WS, 0.95 for SS, 0.91 for SUV_{max} and 0.70 for CEA) (Fig. 3). In logistic regression analysis, each parameter was statistically significant (Table 3), while SS was exclusively independent in multivariate analysis (Table 4).

Table 2: Variables examined as clinical prognostic indicators

WS (n = 110)	
Median	2.6
Minimum	0.9
Maximum	6.6
Mean ± SD	2.8 ± 1.1
SS (n = 110)	
Median	2.2
Minimum	0
Maximum	6.6
Mean ± SD	2.4 ± 1.4
SUV_{max} (n = 110)	
Median	2.9
Minimum	0
Maximum	20.6
Mean ± SD	4.2 ± 4.0
CEA (n = 110)	
Median	3
Minimum	0
Maximum	137
Mean ± SD	5.5 ± 13.5

WS: whole size of tumour in CT; SS: size of the solid component in CT; SUV_{max}: maximum standard uptake value in FDG-PET/CT images; CEA: serum level of carcinoembryonic antigen.

RFS based on clinical-T classification using WS or SS

When analysing survival, SS provided a better distinction between T1b and T2a compared with WS. In our assessment of RFS according to clinical T classification based on WS, the 2-year RFS rate was 89% for T1a (n = 26), 79% for T1b (n = 38), 78% for T2a (n = 41) and 80% for T2b (n = 5). There were no statistically significant differences between any neighbouring groups. As for assessment of RFS according to clinical T classification by SS, the 2-year RFS rate was 95% for T1a (n = 48), 68% for T1b (n = 26), 72% for T2a (n = 32) and 75% for T2b (n = 4). There was no statistically significant difference between any neighbouring groups, except between T1a and T1b (P = 0.002).

In the sub-classification T1a, we used 1.0 cm as the breakpoint to provide a suitable sensitivity of 0.91 and specificity of 0.85 for

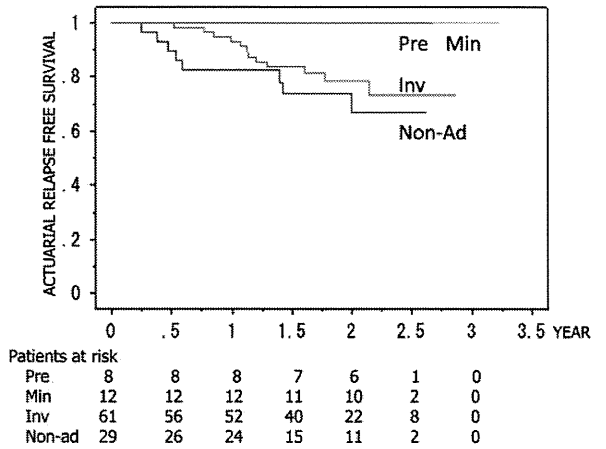

Figure 2: RFS curves according to histology type. Pre: preinvasive adenocarcinoma (n = 8); Min: minimally invasive adenocarcinoma (n = 12), Inv: invasive adenocarcinoma (n = 61); Non-AD: non-adenocarcinoma (n = 29). The 2-year RFS rate (95% CI) was 1.00 (1.00–1.00) for Pre, 1.00 (1.00–1.00) for Min, 0.79 (0.67–0.91) for Inv and 0.74 (0.54–0.94) for Non-AD.

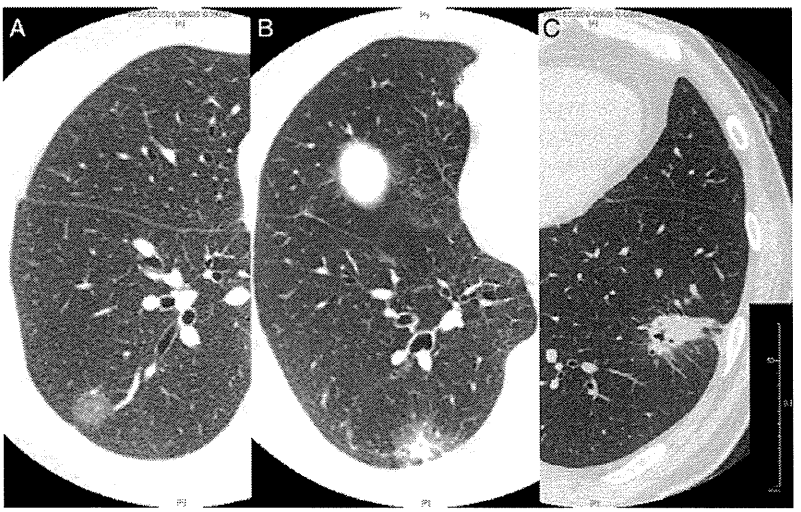

Figure 1: Representative appearances of pure GGO lesion (**A**), GGO with solid component lesion (**B**) and pure solid lesion (**C**) in thin-sliced CT. Whole size of the lesion is 1.8 cm in (A), 2.8 cm in (B) and 2.8 cm in (C), and size of the solid component is 0 cm in (A), 1.5 cm in (B) and 2.8 cm in (C).

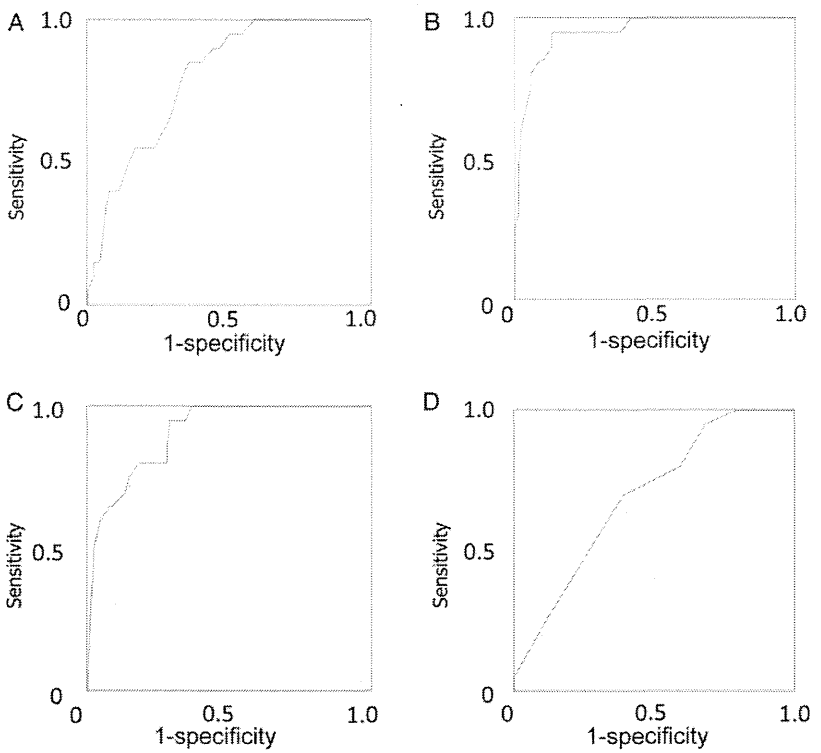

Figure 3: Receiver-operating curves. The AUC was 0.80 for the entire size of the tumour in CT findings (**A**), 0.95 for the SS (**B**), 0.91 for SUV_{max} in FDG-PET)/CT images (**C**) and 0.70 for serum level of CEA (**D**).

Table 3: Results of logistic regression analysis for prediction of pre- or minimally invasive adenocarcinoma

Variables	Univariate			Multivariate		
	RR	95% CI	*P*-value	RR	95% CI	*P*-value
WS (n = 110)	0.217	0.095–0.497	0.0003	0.377	0.105–1.351	0.1
SS (n = 110)	0.051	0.013–0.198	<0.0001	0.067	0.011–0.421	0.004
SUV_{max} (n = 110)	0.239	0.108–0.529	0.0004	0.725	.0322–1.631	0.4
CEA (n = 110)	0.647	0.443–0.957	0.03	0.702	0.440–1.119	0.1

WS: whole size of the tumour in CT; SS: size of the solid component in CT; SUV_{max}: maximum standard uptake value in FDG-PET/CT images; CEA: serum level of carcinoembryonic antigen; CI: confidence interval.

Table 4: Results of Cox proportional hazards model analysis for disease-free survival

Variables	Univariate			Multivariate		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
WS (n = 110)	1.397	0.089–1.908	0.2			
SS (n = 110)	1.574	1.171–2.115	0.003	1.434	1.006–2.044	0.04
SUV_{max} (n = 110)	1.123	1.035–1.219	0.005	1.063	0.959–1.178	0.2
CEA (n = 110)	1.006	0.948–1.066	0.9			

WS: whole size of the tumour in CT; SS: size of the solid component in CT; SUV_{max}: maximum standard uptake value in FDG-PET/CT images; CEA: serum level of carcinoembryonic antigen; HR: hazard ratio; CI: confidence interval.

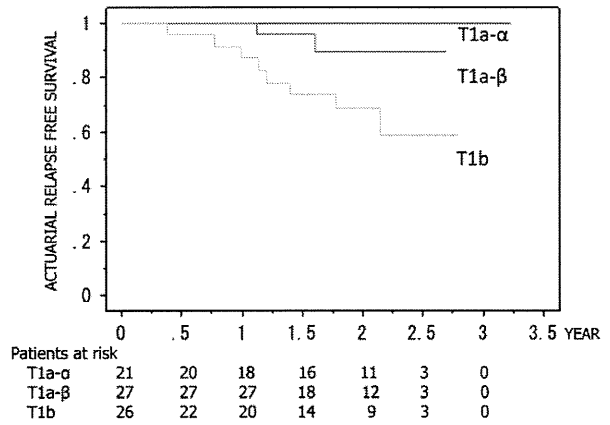

Figure 4: RFS curves according to clinical T1 sub-classification. T1a-α, SS < 1.0 cm (n = 21); T1a-β, SS < 2.0 cm (n = 27); T1b, SS < 3.0 cm (n = 26) in CT findings. The 2-year RFS rate (95% CI) was 1.00 (1.00–1.00) for T1a-α, 0.89 (0.74–1.04) for T1a-β and 0.68 (0.48–0.88) for T1b. There was a statistically significant difference between T1a-β and T1b (P = 0.002).

the SS parameter (T1a-α and T1a-β) (Fig. 4). As a result, the 2-year RFS rate was 1.00 in the T1a-α group (n = 21), 0.89 in the T1a-β group (n = 27) and 0.68 in the T1b (n = 26) group (P = 0.002 between T1a-β and T1b).

DISCUSSION

Pre- and minimally invasive are known to be associated with scant cancer spreading and a very low chance of recurrence following surgery [2], and thus, prediction of such histology type is crucial for important decisions related to surgical treatment. In this investigation of clinical parameters reported to be predictive indicators of cancer spread and recurrence, we found that SS, which indicates the SS, was an independent predictor and indicated a subclassification of T1a.

At present, the entire tumour size without exclusion of the GGO region in CT findings is employed for detecting the clinical T factor [3]. However, the GGO region corresponds to the lepidic component of an adenocarcinoma and possesses a very low level of invasiveness, and thus has a very low chance of causing cancer relapse [8]. Okada *et al.* [9] reported results of a multicentre prospective study and showed that SUV_{max} and bronchioloalveolar carcinoma ratio, tumour disappearance rate and GGO ratio mirrored the pathological aggressiveness of tumour malignancy, nodal metastasis, recurrence and prognosis. In addition, Tsutani *et al.* [10] found that cases with a pure solid adenocarcinoma had inferior prognosis compared with those with a mixed GGO adenocarcinoma, though when SUV_{max} and solid component size were matched, the differences in pathological prognostic parameters and disease-free survivals between patients with solid and mixed tumours disappeared. Those results led us to consider SS as an effective parameter for tumour invasiveness and prognostic factor, in addition to SUV_{max}.

Some have reported that SUV_{max} is a predictive indicator of the aggressiveness of pulmonary carcinoma as well as prognosis [5, 11, 12], even though SUV_{max} is difficult to calculate with GGO lesions [5] and underestimated in small tumours [13]. The strong clinical implication of SUV_{max} noted above [9, 10] may be due to use of an absorption revision technique for small lesions. In the present study, SUV_{max} was shown to be a predictive indicator of pre- and minimally invasive adenocarcinomas as well as poor prognosis, though it was not found to be an independent factor. This may have been because our specimens included a large number of lesions with SS <1 cm and we did not employ an absorption revision technique. Tsutani *et al.* [10] reported the clinical usefulness of both SS and SUV_{max} using an absorption revision technique for patients with a large number of exclusive pulmonary adenocarcinoma tumours. However, that technique is not universally applied.

Tumour markers are also predictive indicators of the aggressiveness of pulmonary carcinoma and patient prognosis [14], with CEA the most frequently employed. Sawabata *et al.* [15] reported a concept that used a sub-normal level of less than half of the maximum point of normal and showed that a low serum CEA level can be useful clinically to predict prognosis. Their observations may indicate a relationship between serum CEA and adenocarcinoma invasiveness. In the current study, serum CEA level was shown to be a predictive indicator of a pre- or minimally invasive adenocarcinoma, even though serum CEA levels were normal in a large number of our patients.

We performed an intentional segmentectomy procedure in cases with small peripheral GGO dominant lesions and that on an emergency basis in high-risk patients. In all cases, sufficient tumour margin distance and negative margin cytology are mandated based on a concept of previous reports [16–18].

For the present study, we used the clinical parameters: entire size of the tumour in thin section CT findings, SS in CT findings, SUV_{max} in FDG-PET/CT findings and serum level of CEA, as they have been reported to be predictive factors of tumour aggressiveness and prognosis. Among those, only SS was shown to be an independent predictive factor of pre- or minimally invasive (RR, 0.067; 95% CI, 0.011–0.421 and P-value, 0.004 in multivariate analysis), and chance of recurrence (H.R., 1.434; 95% C.I., 1.006–2.044 and P-value, 0.04 in multivariate analysis).

Since this is a retrospective clinical investigation with a limited number of patients and the observation period was rather short, there are some limitations that must be seriously considered. Above all, care should be taken with assessing prognosis using only RFS. In addition, analysis of RFS using a specific T factor or 1.0 cm as the breakpoint for solid portion size may not show a significant distinction between RFS curves. Therefore, additional analysis of a greater number of patients is mandatory prior to establishment of a classification. Although this is a very crucial limitation of this study, we consider that our findings may be helpful for a future prospective investigation.

In summary, in our assessment of surgical patients with clinical stage I NSCLC, the SS showed high potential to distinguish pre- and minimally invasive adenocarcinoma from other types of lung cancer, and may provide important information for a subclassification of T1a.

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Conflict of interest: none declared.

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