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Feasibility trial for adjuvant chemotherapy with docetaxel plus cisplatin followed by single agent long-term administration of S-1 chemotherapy in patients with completely resected non-small cell lung cancer: Thoracic Oncology Research Group Study 0809

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Background: We conducted a multicentre feasibility study for single agent long-term S-1 chemotherapy following docetaxel plus cisplatin in patients with curatively resected stage II–IIIA non-small cell lung cancer.

Methods: Patients received three cycles of docetaxel (60 mg m^{-2}) plus cisplatin (80 mg m^{-2}) and then received S-1 (40 mg m^{-2} twice daily) for 14 consecutive days with a 1-week rest for >6 months (maximum, 1 year). The primary end point was feasibility, which was defined as the proportion of patients who completed eight or more cycles of S-1 chemotherapy. If the lower 95% confidence interval (CI) of this proportion was 50% or more, then the treatment was considered as feasible. The sample size was set at 125 patients.

Results: One hundred and thirty-one patients were enrolled, of whom 129 patients were eligible and assessable. In all, 109 patients (84.5%) completed 3 cycles of docetaxel plus cisplatin and 66 patients (51.2%, 95% CI: 42.5–59.8) completed 8 or more cycles of S-1 treatment. Grade 3/4 toxicities during the S-1 chemotherapy included anaemia (7.3%), neutropaenia (3.7%), and anorexia (3.7%).

Conclusion: The toxicity level was acceptable, although the results did not meet our criterion for feasibility. Modification of the treatment schedule for S-1 chemotherapy might improve the treatment compliance.

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Primary surgery is the standard of care for resectable clinical stage I or II non-small cell lung cancer (NSCLC). The 5-year survival rate for patients with clinical stage IB and stage II surgically resected NSCLC was ~66% and 50%, respectively. The majority of patients with recurrences have distant metastases, indicating that systemic micrometastases are common in patients with completely resected NSCLC. To control distant micrometastasis and to improve patients' survival, adjuvant chemotherapy has been examined in patients with completely resected NSCLC of pathological stage I–III. Several randomised studies and meta-analyses have demonstrated that cisplatin-based adjuvant chemotherapy improved the overall survival (OS) in patients with pathological stage IB to III NSCLC (Arriagada *et al*, 2004; Hotta *et al*, 2004; Winton *et al*, 2005; Douillard *et al*, 2006; Pignon *et al*, 2006). However, the absolute increase in survival was only 4% at 5 years. Thus, new treatment strategies or drugs are needed to improve the clinical outcome in patients with resectable NSCLC.

A randomised phase III study demonstrated that adjuvant chemotherapy with uracil-tegafur (UFT) improved survival among patients with completely resected pathological stage I adenocarcinoma of the lung. The 5-year OS was 88% in the UFT group and 85% in the control group (hazard ratio 0.71, 95% confidence interval (CI) 0.52–0.98) (Kato *et al*, 2004). S-1 is an oral anticancer agent comprises tegafur, gimeracil (an inhibitor of dihydropyrimidine dehydrogenase, which degrades fluorouracil), and oteracil (which inhibits the phosphorylation of fluorouracil in the gastrointestinal tract, thereby reducing the gastrointestinal toxicity of fluorouracil) in a molar ratio of 1 : 0.4 : 1 (Shirasaka *et al*, 1996). S-1 is approved for the treatment of NSCLC as well as gastric, colorectal, head and neck, breast, pancreatic, and biliary tract cancer in Japan. In a phase II trial, S-1 monotherapy produced a response rate of 22% as a first-line treatment in patients with advanced NSCLC (Kawahara *et al*, 2001). S-1 is believed to have a stronger antitumour activity against NSCLC than UFT, since UFT monotherapy produced a response rate of only 6% in another phase II study (Keicho *et al*, 1986). A randomised phase III trial demonstrated that S-1 plus carboplatin (CBDCA) was non-inferior in terms of OS, compared with paclitaxel plus CBDCA, in patients with advanced NSCLC (Okamoto *et al*, 2010). Another randomised phase III trial also demonstrated that S-1 plus CDDP was non-inferior in terms of OS, compared with docetaxel plus CDDP, in patients with advanced NSCLC (Katakami *et al*, 2012). Previous phase II trials demonstrated that S-1 monotherapy produced a response rate of 7–14% as a second-line treatment for advanced NSCLC (Totani *et al*, 2009; Govindan *et al*, 2011; Shiroyama *et al*, 2011).

Recent phase III trials have demonstrated that switch maintenance chemotherapy consisting of pemetrexed or erlotinib prolonged the OS of patients with advanced NSCLC who showed no signs of progression after four cycles of platinum-based chemotherapy (Ciuleanu *et al*, 2009; Cappuzzo *et al*, 2010). Continuation maintenance with pemetrexed also prolonged the OS in patients with non-squamous NSCLC in another randomised trial (Paz-Ares *et al*, 2012a,b). Maintenance chemotherapy has thus received considerable attention.

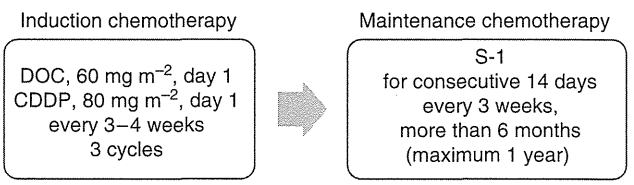
The Thoracic Oncology Research Group (TORG) conducted a randomised phase II study comparing docetaxel (DOC) plus CDDP with paclitaxel (PTX) plus CBDCA as an adjuvant chemotherapy in patients with completely resected stage IB to IIIA NSCLC (TORG 0503). This study showed that DOC plus CDDP had a promising activity with a favourable 2-year recurrence-free survival (RFS) rate (74.1% *vs* 72.5%, respectively) (Ohira *et al*, 2011). Taking these rationales into consideration, we conducted a feasibility study for adjuvant chemotherapy consisting of DOC plus CDDP followed by single agent long-term S-1 chemotherapy in patients with completely resected NSCLC (TORG 0809).

PATIENTS AND METHODS

Patient population. Patients were required to have completely resected stage II or IIIA (according to the Union Internationale Contre le Cancer (UICC) fifth TNM edition) NSCLC, an age of 20–74 years, and an ECOG performance status (PS) of 0 or 1. Other criteria included a PaO_2 at room air $\geqslant 70$ torr or an SpO_2 at room air $\geqslant 95\%$, and adequate organ function (i.e., total bilirubin $\leqslant 1.2\,mg\,dl^{-1}$, AST and ALT $\leqslant 100\,IU\,l^{-1}$, serum creatinine $\leqslant 1.2\,mg\,dl^{-1}$, creatinine clearance $\geqslant 60\,ml\,min^{-1}$, leukocyte count $\geqslant 4000$ per mm^3 and $\leqslant 12\,000$ per mm^3, neutrophil count $\geqslant 2000$ per mm^3, haemoglobin $\geqslant 10.0\,g\,dl^{-1}$, and platelets $\geqslant 100\,000$ per mm^3). Patients were required to start the protocol treatment within 10 weeks after surgical resection.

Key exclusion criteria were a lack of recovery from surgical complications; active infection; interstitial pneumonia as determined using computed tomography (CT) of the chest; acute cardiac infarction within 6 months; uncontrolled heart disease, liver dysfunction, or diabetes mellitus; grade 2 or worse peripheral neuropathy; active concomitant malignancy; pregnancy or breast-feeding; a history of hypersensitivity to drugs including polysorbate-80; and the concurrent use of flucytosine. Patients who had undergone a pneumonectomy were also excluded. All the patients were required to provide written informed consent.

Treatment plan. The treatment schema is shown in Figure 1. Treatment was started within 1 week after enrolment in the study. Patients received adjuvant chemotherapy with DOC ($60\,mg\,m^{-2}$, day 1) and CDDP ($80\,mg\,m^{-2}$, day 1) every 3–4 weeks for up to three cycles. After the completion of adjuvant chemotherapy with DOC plus CDDP, if the leukocyte count was $\geqslant 3000$ per mm^3, the neutrophil count was $\geqslant 1500$ per mm^3, the platelet count was $\geqslant 100\,000$ per mm^3, the AST and/or ALT level was $\leqslant 100\,IU\,l^{-1}$, the total bilirubin level was $\leqslant 1.5\,mg\,dl^{-1}$, the serum creatinine level was $<1.5\,mg\,dl^{-1}$, and all other non-haematological toxicities were grade 1 or better with the exception of alopecia, body weight loss, and hyponatraemia, then the patients were treated with oral S-1 at a dose of $40\,mg\,m^{-2}$ twice daily for 14 consecutive days, followed by a 1-week rest. The actual dose of S-1 was selected as follows: patients with a body surface area (BSA) of $<1.25\,m^2$ received 80 mg daily; those with a BSA of $1.25\,m^2$ or more but $<1.5\,m^2$ received 100 mg daily; and those with a BSA of $1.5\,m^2$ or more received 120 mg daily. If the serum creatinine level was $1.2\,mg\,dl^{-1}$ or more but $<1.5\,mg\,dl^{-1}$ before the initiation of S-1 chemotherapy, then the S-1 dose was reduced to a lower level. This 3-week cycle was repeated for 6 months (maximum, 1 year) if neither unacceptable toxicity nor tumour recurrence was observed. In the event of a leukocyte count of <2000 per mm^3, a platelet count of $<75\,000$ per mm^3, an AST and/or ALT level of $\geqslant 100\,IU\,l^{-1}$, a total bilirubin level of $\geqslant 2.5\,mg\,dl^{-1}$, a serum



	S-1
BSA < 1.25 m²	40 mg, b.i.d.
1.25 m² ⩽ BSA < 1.5 m²	50 mg, b.i.d.
1.5 m² ⩽ BSA	60 mg, b.i.d.

BSA, body surface area.

Figure 1. **Treatment schema for this study.**

creatinine level of $\geqslant 1.5\,mg\,dl^{-1}$, appetite loss, diarrhoea, mucositis, nausea/vomiting of grade 2 or worse despite appropriate antiemetic therapy, and/or other grade 2 non-haematological toxicities other than body weight loss, alopecia, or hyponatraemia, the daily dose of S-1 was reduced from 120 to 100 mg, 100 to 80 mg, or 80 to 50 mg in the next cycle. If the patients experienced the above-mentioned toxicities after the dose reduction, then their daily dose of S-1 was reduced from 100 to 80 mg, or 80 to 50 mg. If a patient with a BSA of $<1.25\,m^2$ experienced the above toxicities at 50 mg, then the S-1 chemotherapy was terminated. If the adjuvant chemotherapy of DOC + CDDP was terminated after one or two cycles, then a shift to S-1 chemotherapy was allowed. However, these patients were not considered to have completed the protocol treatment.

Safety assessment and follow-up. For the toxicity assessment, blood samples were obtained before the start of each cycle. A chest X-ray examination was performed monthly throughout the study period. Toxicities were graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. A CT examination of the chest was performed at 1, 2, 3, and 5 years after the initiation of the protocol treatment.

Study design and statistical analysis. This trial was designed as a multicentre, prospective, single-arm, feasibility study and the study protocol was approved by the institutional review board of each participating institution. All the study data were managed by the TORG0809 data centre at Kitasato University Research Center for Clinical Pharmacology.

The primary end point of this study was feasibility, which was defined as the proportion of patients who had completed eight or more cycles of S-1 chemotherapy. If the lower 95% CI of this proportion was 50% or more, then the treatment was considered as feasible. If a patient received 75% or more of S-1 in a cycle, that is, 21 times per cycle, this patient was considered to have completed the treatment cycle. If 72 out of 120 patients (60%) completed the protocol treatment, then the 95% CI of the proportion of the treatment completion was 51.2–68.8%. Considering the possibility of ineligible patients, the sample size was set at 125 patients.

The secondary end points included adverse events, OS, RFS, and recurrence pattern. Because of the short follow-up period, we will report the OS and RFS data elsewhere. We plan to analyse the OS and RFS at 5 years after the last enrolment, as described in the study protocol. The statistical analysis was performed using SAS version 9.2 (SAS Institute, Cary, NC, USA).

This study was registered with the UMIN Clinical Trials Registry (number UMIN000001779).

RESULTS

Patient population. A total of 131 patients were enrolled in this study between January 2009 and November 2010 from 20 institutions in Japan. One patient did not receive any protocol treatment at the patient's request. Another patient was enrolled as p-stage IIIA according to the UICC 7th edition; however, the p-stage corresponded to IIIB according to the UICC 5th edition, making this patient ineligible. This patient received three cycles of docetaxel plus cisplatin and two cycles of S-1 chemotherapy, and she was included in the safety analysis. A total of 129 patients were eligible (Figure 2). The patient characteristics are listed in Table 1. Sixty-four percent of the patients were male; the median age was 63 years. Seventy-eight percent of the patients had an adenocarcinoma histology.

Treatment delivery and protocol compliance. Overall, 114 patients received two cycles or more of DOC + CDDP. Of these, 67 patients (58.8%) required a dose reduction of DOC or CDDP. The most common reason for the dose reduction of DOC and CDDP was grade 4 neutropaenia ($n = 63$), followed by a fever of 38.0 °C or higher ($n = 16$). The dose of CDDP was reduced because of anorexia, nausea, and/or vomiting of grade 2 or worse for more than a week ($n = 16$) and an elevated serum creatinine level of $1.5\,mg\,dl^{-1}$ or more ($n = 6$).

In total, 109 patients (84.5%) completed three cycles of adjuvant chemotherapy consisting of DOC + CDDP (Table 2). The main reasons for the discontinuation of the adjuvant chemotherapy were toxicity ($n = 15$) and patient refusal because of toxicity ($n = 7$) (Table 3). One patient terminated the DOC + CDDP treatment after one cycle and completed eight cycles of S-1 chemotherapy. Another patient terminated the DOC + CDDP treatment after two cycles and received three cycles of S-1 chemotherapy.

One hundred and eight patients received S-1 chemotherapy. Of these, 34 patients (31.5%) required the interruption of S-1 during a treatment cycle. Thirty-one patients (28.7%) required a dose reduction of S-1. The majority of the reasons for the interruption

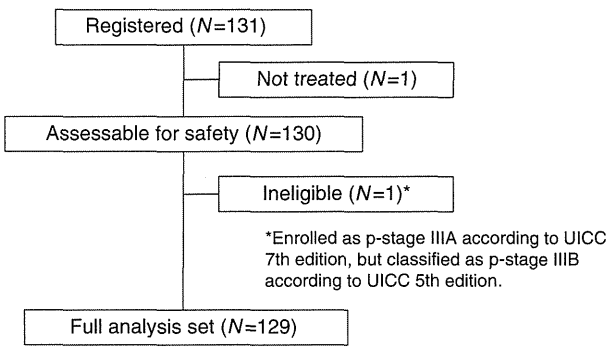


Figure 2. **CONSORT diagram.**

Table 1. Patient characteristics of 129 eligible patients

Characteristic	Number of patients
Sex	
Male	83
Female	46
Age (years)	
Median	63
Range	23–74
PS status	
0	107
1	22
Pathological stage[a]	
IIA	17
IIB	32
IIIA	80
Histological type	
Adenocarcinoma	100
Squamous cell carcinoma	25
Others	4

Abbreviations: PS = performance status; TNM = tumour-node-metastasis.
[a]Pathological stage was based on the Union Internationale Contre le Cancer fifth TNM edition.

or dose reduction of S-1 were appetite loss, diarrhoea, mucositis, or nausea/vomiting of grade 2 or worse ($n = 27$), followed by other non-haematologic toxicities of grade 2 or worse ($n = 20$).

One hundred and six patients (82.2%) completed three cycles of DOC + CDDP and subsequently switched to S-1 chemotherapy. Of these, 31 patients terminated the S-1 chemotherapy after receiving 3 or fewer cycles. A total of 66 patients (51.2%; 95% CI, 42.5–59.8%) completed 8 cycles or more of S-1 treatment (Table 2). The lower limit of the 95% CI for the completion rate was 42.5%, which was less than our previously defined criterion for treatment feasibility. The reasons for the discontinuation of the S-1 chemotherapy included toxicity ($n = 17$), patient refusal because of toxicity ($n = 15$), and recurrence ($n = 6$) (Table 3).

Safety and toxicity. The most common grade 3 or 4 toxicity experienced during the DOC + CDDP treatment was neutropaenia (78.5%) (Table 4). Ten patients (7.7%) developed febrile neutropaenia; however, all these patients recovered after receiving appropriate antibiotic therapy. Two patients experienced grade 3 or 4 allergic reactions to DOC during the first cycle, resulting in treatment termination.

Grade 3 or 4 toxicities during the S-1 chemotherapy included anaemia (7.3%), neutropaenia (3.7%), anorexia (3.7%), dyspnoea (1.8%), and infection with neutropaenia of grade 0–2 (1.8%). Febrile neutropaenia was not observed. One treatment-related death occurred during the study. This patient was a 63-year-old man. After two cycles of S-1 chemotherapy, he developed grade 3 fatigue. On day 36 of the second cycle of S-1, grade 3 dyspnoea was observed, and his SpO_2 was 92% in room air. A CT scan of the chest revealed bilateral diffuse ground-glass opacities. Prednisolone (80 mg day^{-1}; 1 mg kg^{-1} per day) was administered, and an improvement in the opacities was observed.

Table 2. Treatment delivery in 129 eligible patients

Treatment	Cycle	Number of patients	%	95% Confidence interval
Docetaxel + cisplatin	1	129	100	
	2	114	88.4	
	3	109	84.5	
Maintenance chemotherapy using S-1	1	106	82.2	
	2	97	75.2	
	3	86	66.7	
	4	75	58.1	
	5	73	56.6	
	6	72	55.8	
	7	71	55	
	8	67	51.9	
Completion		66	51.2	42.5–59.8

Table 3. Reason for discontinuation of the treatment

Reasons	Docetaxel + cisplatin	Maintenance chemotherapy using S-1
Recurrence	1	6
Toxicity	15	17
Patient refusal because of toxicity	7	15
Others	0	2

The prednisolone was tapered to 30 mg day^{-1} for 6 weeks; however, multiple cavity lesions were visible on a chest CT image obtained 2 months after the initiation of the steroid therapy. Multiple abscesses at the neck, axilla, chest, and femur were noted, and the patient developed hypotension. *Nocardia* was isolated in blood and abscess samples, with a diagnosis of disseminated nocardiosis. Sulfamethoxazole/trimethoprim and antibiotics were administered and artificial ventilation therapy was performed. The patient was taken off the respirator once, but the pneumonitis recurred and disseminated intravascular coagulation also developed, leading to death.

DISCUSSION

This feasibility study was designed to evaluate the tolerability, safety, and efficacy of single agent long-term administration of S-1 chemotherapy following three cycles of DOC plus CDDP in patients with completely resected stage II or IIIA NSCLC. Fifty-one percent of the patients (95% CI, 42.5–59.8%) completed three cycles of DOC plus CDDP and eight cycles or more of S-1 chemotherapy. The lower limit of the CI for this proportion was lower than the predefined criterion of 50%. Grade 3–4 haematologic toxicities were observed in 7.3% of patients, while grade 3–4 non-haematologic toxicities were observed in only 4%. However, grade 1–2 anorexia and/or fatigue were common, with rates of ~50–60%. S-1 was administered for 2 weeks with a 1-week rest. The long duration of S-1 administration might have been responsible for the low-grade but extended non-haematologic toxicities and might have been too intensive for patients especially after platinum-doublet chemotherapy. In a previous phase III study of adjuvant chemotherapy for gastric cancer with single agent of S-1, 78% of patients received S-1 for at least 6 months (Sakuramoto *et al*, 2007). Adjuvant chemotherapy of DOC + CDDP probably affected the compliance of S-1 chemotherapy negatively in our study. A modification of the treatment schedule for S-1 chemotherapy, such as a 2-week rest period rather than a 1-week rest period, might improve treatment compliance.

Efficacious treatment for advanced stage disease has been introduced and investigated in an adjuvant setting, such as bevacizumab plus platinum-doublet chemotherapy in patients with non-squamous cell carcinoma or erlotinib in patients with a mutated epidermal growth factor receptor gene. Recent phase III trials have demonstrated that switch maintenance chemotherapy consisting of pemetrexed or erlotinib, which were efficacious for second-line chemotherapy, prolonged the OS in patients with advanced NSCLC (Ciuleanu *et al*, 2009; Cappuzzo *et al*, 2010). Switch maintenance chemotherapy can be recognised as an early second-line chemotherapy. The purpose of adjuvant chemotherapy is to control micrometastasis and to prevent recurrence. Switch maintenance chemotherapy is considered to enhance the efficacy of adjuvant chemotherapy. Previous phase II trials have demonstrated that S-1 monotherapy produced a response rate of 7–14%, a median progression-free survival (PFS) of 3–4 months, and a median OS of 7–16 months as a second-line treatment for advanced NSCLC (Totani *et al*, 2009; Govindan *et al*, 2011; Shiroyama *et al*, 2011). Pemetrexed is effective against non-squamous NSCLC; on the other hand, S-1 is effective against both non-squamous and squamous NSCLC. A randomised trial comparing S-1 and docetaxel as a second- or third-line chemotherapy is now underway in Asia. Switch maintenance chemotherapy using S-1 is also being evaluated as a first-line chemotherapy for patients with advanced NSCLC in a phase II study (UMIN000003676). If promising RFS or OS data in this trial are obtained, then a prospective randomised trial will be warranted to compare adjuvant chemotherapy with or without single agent long-term administration of S-1 chemotherapy.

Table 4. Toxicity

	Docetaxel + cisplatin ($n = 130$)					Maintenance chemotherapy using S-1 ($n = 109$)					
Toxicity	**Toxicity grade**					**Toxicity grade**					
	1	2	3	4	%3–4	1	2	3	4	5	%3–5
Haematologic											
Neutropaenia	4	14	39	63	78.5	20	18	4	0	0	3.7
Anaemia	52	31	1	0	0.8	26	38	6	2	0	7.3
Thrombocytopaenia	30	6	0	0	0	35	0	0	0	0	0
Gastrointestinal											
Anorexia	55	47	22	0	16.9	43	21	4	0	0	3.7
Vomiting	23	20	5	0	3.8	11	5	1	0	0	0.9
Diarrhoea	35	11	15	0	11.5	19	3	1	0	0	0.9
Mucositis	12	4	0	0	0	23	7	0	0	0	0
Hepatic											
AST	14	5	2	0	1.5	25	5	0	0	0	0
ALT	25	9	1	0	0.8	24	4	0	0	0	0
Renal											
Creatinine	39	9	0	0	0	30	8	0	0	0	0
Neurologic											
Neuropathy (sensory)	9	4	0	0	0	19	2	2	0	0	1.8
Others											
Hyponatraemia	57	—	18	5	17.7	16	—	0	0	0	0
Fatigue	57	21	5	0	3.8	41	9	2	0	0	1.8
Allergic reaction	7	0	1	1	1.5	1	0	0	0	0	0
Dehydration	0	0	2	0	1.5	0	0	0	0	0	0
Alopecia	68	29	0	0	0	35	10	0	0	0	0
Febrile neutropaenia	—	—	10	0	7.7	—	—	0	0	0	0
Infection with G3–4 neutropaenia	0	3	5	0	3.8	0	0	0	0	0	0
Infection with G0–2 neutropaenia	0	3	2	1	2.3	1	3	1	0	1	1.8
Pneumonitis	1	0	0	0	0	0	1	1	0	0	0.9
Dyspnoea	0	1	0	0	0	8	2	2	0	0	1.8

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; G = grade.

A recent phase III trial has also demonstrated that continuation maintenance chemotherapy consisting of pemetrexed prolonged the OS and PFS in patients with advanced non-squamous NSCLC. However, concurrent chemoradiotherapy consisting of pemetrexed plus CDDP followed by four cycles of pemetrexed did not improve OS over concurrent chemoradiotherapy consisting of etoposide plus CDDP in patients with stage III non-squamous NSCLC (PROCLAIM study). Up to four cycles of pemetrexed in the PROCLAIM study, comparable to S-1 chemotherapy in our study, might be unable to enhance curative treatment effect. We might have to distinguish strategy for stage IV disease from that for curative situations in completely resected stage II/III disease.

Combination chemotherapy consisting of DOC plus CDDP is a standard regimen for the treatment of patients with advanced NSCLC. A randomised trial demonstrated that DOC + CDDP resulted in a more favourable response rate and OS than vinorelbine (VNR) plus CDDP in chemo-naïve patients with advanced NSCLC. The median OS period was 11.3 months for patients treated with DOC plus CDDP and 10.1 months for patients treated with VNR plus CDDP. The hazard ratio was 1.183 (97.2% CI, 0.989–1.416) (Fossella *et al*, 2003). A higher incidence of grade 3–4 anaemia, nausea, and vomiting was observed in VNR + CDDP arm, compared with DOC + CDDP arm. Febrile neutropaenia occurred in <5% of patients in both regimens. Furthermore, the single agent DOC had a more favourable OS period than the single agent VNR in both first-line and second-line settings in patients with advanced NSCLC (Fossella *et al*, 2000). TORG0503 study demonstrated that >90% of patients completed three planned cycles of adjuvant chemotherapy in both DOC + CDDP and PTX + CBDCA arms. On the other hand, the most common regimen for adjuvant chemotherapy for pathological stage II or III NSCLC is VNR + CDDP, because most randomised trials, which resulted in positive results, adopted VNR + CDDP. Considering the promising results of clinical trials for advanced NSCLC, it might be reasonable to select DOC + CDDP as an adjuvant chemotherapy in patients with completely resected stage II or III NSCLC. Indeed, DOC + CDDP has been selected as one of the standard adjuvant chemotherapy regimens in ECOG1505 study, which is a randomised phase III trial of adjuvant chemotherapy with or without bevacizumab in patients with completed resected early-stage NSCLC (Wakelee *et al*, 2011). However, 7.7% of patients experienced grade 3 febrile neutropaenia

during the chemotherapy of DOC + CDDP in our study. Relatively high incidence of febrile neutropaenia could not support the use of adjuvant chemotherapy with DOC + CDDP as a new alternative. Four cycles of VNR + CDDP followed by long-term administration of S-1 might be a better strategy in a future study.

The treatment cycle for DOC plus CDDP was set at three because the actual median numbers of cycles delivered in previous phase III studies of adjuvant chemotherapy were three or four (Winton *et al*, 2005; Douillard *et al*, 2006), and a randomised study demonstrated that four cycles or more of platinum-based chemotherapy did not improve the OS in patients with advanced NSCLC (Smith *et al*, 2001). In the TORG0503 study, the number of treatment cycles for DOC plus CDDP or for PTX plus CBDCA as an adjuvant chemotherapy was also set at three, and a favourable 2-year RFS rate was observed (Ohira *et al*, 2011).

A previous randomised phase II study demonstrated that adjuvant chemotherapy with pemetrexed plus CDDP was safe and feasible with less toxicity and superior dose delivery compared with VNR + CDDP (Kreuter *et al*, 2013). Pemetrexed plus CDDP is considered as suitable for adjuvant chemotherapy because of relatively less toxic and promising antitumour activity in patients with non-squamous NSCLC. A randomised phase III study is underway comparing pemetrexed plus CDDP and VNR + CDDP in patients with completely resected stage II–IIIA non-squamous NSCLC in Japan. However, it is difficult to conduct a randomised phase III study of adjuvant chemotherapy in patients with NSCLC, because large sample size and long-term follow-up are needed. Therefore, a randomised phase II study containing control arm should be taken into consideration to select appropriate experimental treatment.

Aprepitant, a standard antiemetic drug for cisplatin therapy, was approved in December 2009 in Japan. As a result, ~20 patients did not receive aprepitant. If aprepitant had been available for all the enrolled patients, then the treatment compliance might have improved. Furthermore, 2 out of the 129 patients experienced grade 3 or 4 allergic reactions to DOC during the first cycle, resulting in treatment termination. Premedication for DOC + CDDP included dexamethasone only on day 1 in this study. The administration of dexamethasone on the day before the initiation of DOC + CDDP and an antihistamine on day 1 might be recommended in future clinical trials to prevent anaphylaxis in response to DOC.

In conclusion, the toxicity level of S-1 chemotherapy was acceptable, although the treatment completion rate did not meet our criterion for feasibility. A modification of the treatment schedule for S-1 chemotherapy, such as a 2-week rest period rather than a 1-week rest period, might improve treatment compliance. After referring to the results for OS and RFS, we would like to plan a randomised trial to investigate whether platinum-based chemotherapy followed by single agent long-term administration of S-1 chemotherapy improves survival in patients with completely resected stage II or III NSCLC.

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First Case of Combined Small-Cell Lung Cancer with Adenocarcinoma Harboring *EML4-ALK* Fusion and an Exon 19 *EGFR* Mutation in Each Histological Component

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A 72-year-old male exsmoker of 60-pack-years had undergone a high anterior resection, followed by chemotherapy (Leucovorin+5-Fluorouracil, S-1, FOLFOX-4+Bevacizumab, FOLFIRI+Bevacizumab) for rectal cancer with liver and sacral bone metastases 6 years ago. Because a nodal shadow had appeared in the right lower lobe of the lung, despite the disappearance of the liver and sacral metastases, he was referred to our department for a treatment of the pulmonary nodule.

Computed tomography showed an irregular nodule in the right lower lobe, which was confirmed as active by positron emission tomography, although there were no active lesions on the liver or sacral bone (Fig. 1*A*). The pulmonary lesion was assumed to be primary lung cancer, and right lower lobectomy with lymphadenectomy was performed. The cut sections revealed a whitish solid nodule encircled by a gray-whitish component with a maximum diameter of 4.5 cm (Fig. 1*B*). The central component was pathologically diagnosed as small-cell lung cancer (SCLC), which was 30% of the entire tumor, and the surrounding area was adenocarcinoma (70%) with papillary, acinar and lepidic components (formerly nonmucinous bronchioloalveolar carcinoma, 10%; Fig. 2 *A– C*). Both the components showed immunoreactivity to thyroid transcriptional factor 1, whereas synaptophysin and CD56 were detected only in the SCLC component. The pathological stage was finally determined to be IB. Each of the components was separately examined for mutations of epidermal growth factor receptor (*EGFR*) and anaplastic lymphoma kinase (*ALK*) by the direct sequencing method. A deletion in exon 19 of *EGFR* was detected only in the lepidic component, whereas only the SCLC component harbored variant 1 of echinoderm microtubule-associated protein-like 4 (*EML4*)-*ALK* fusion (Fig, 3*A*, *B*) and those were confirmed by immunohistochemistry (Fig. 3*C*, *D*). Figure. 3*E* shows gene mapping of the mutations in each component.

DISCUSSION

Gene mutations in tyrosine kinases play crucial roles in the pathogenesis of adenocarcinoma. Tumors with the *EGFR* gene, the most well-known tyrosine kinase which

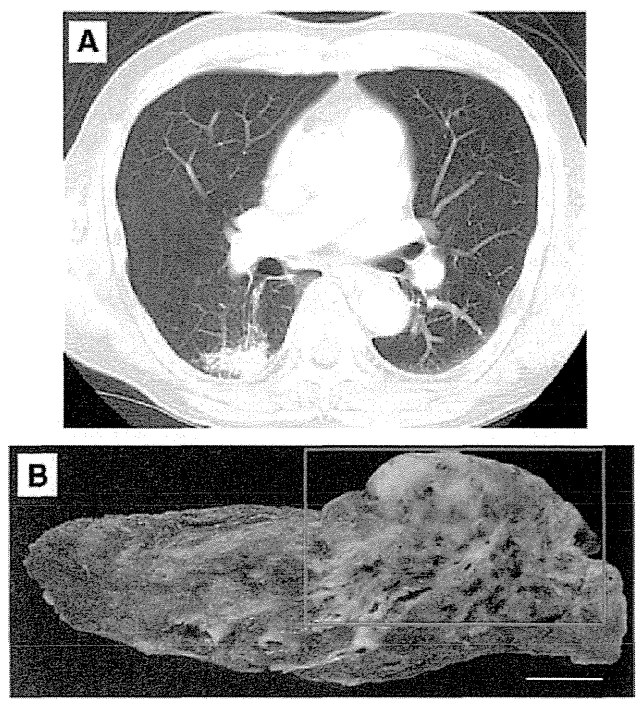

FIGURE 1. *A,* Computed tomography showing an irregular nodule in the right lower lobe of lung. *B,* Cut sections of the tumor are seen by the encircled part.

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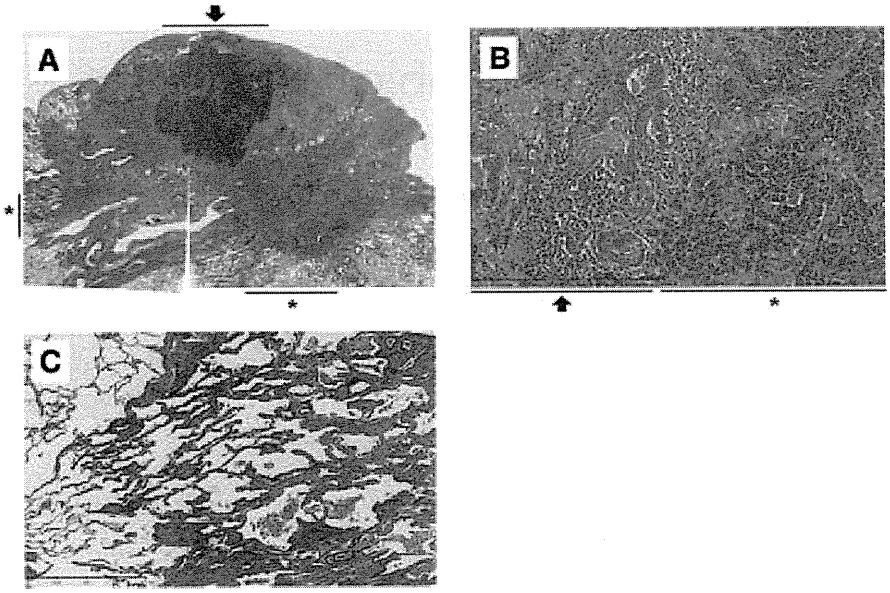

FIGURE 2. Microscopic findings. *A*, Microscopic findings of the tumor consisting of SCLC (arrow) surrounded by adenocarcinoma with papillary, acinar and lepidic components (asterisk). Highly magnified images of (*B*) the SCLC (asterisk), the adenocarcinoma (arrow), and (*C*) the lepidic components. SCLC, small-cell lung cancer.

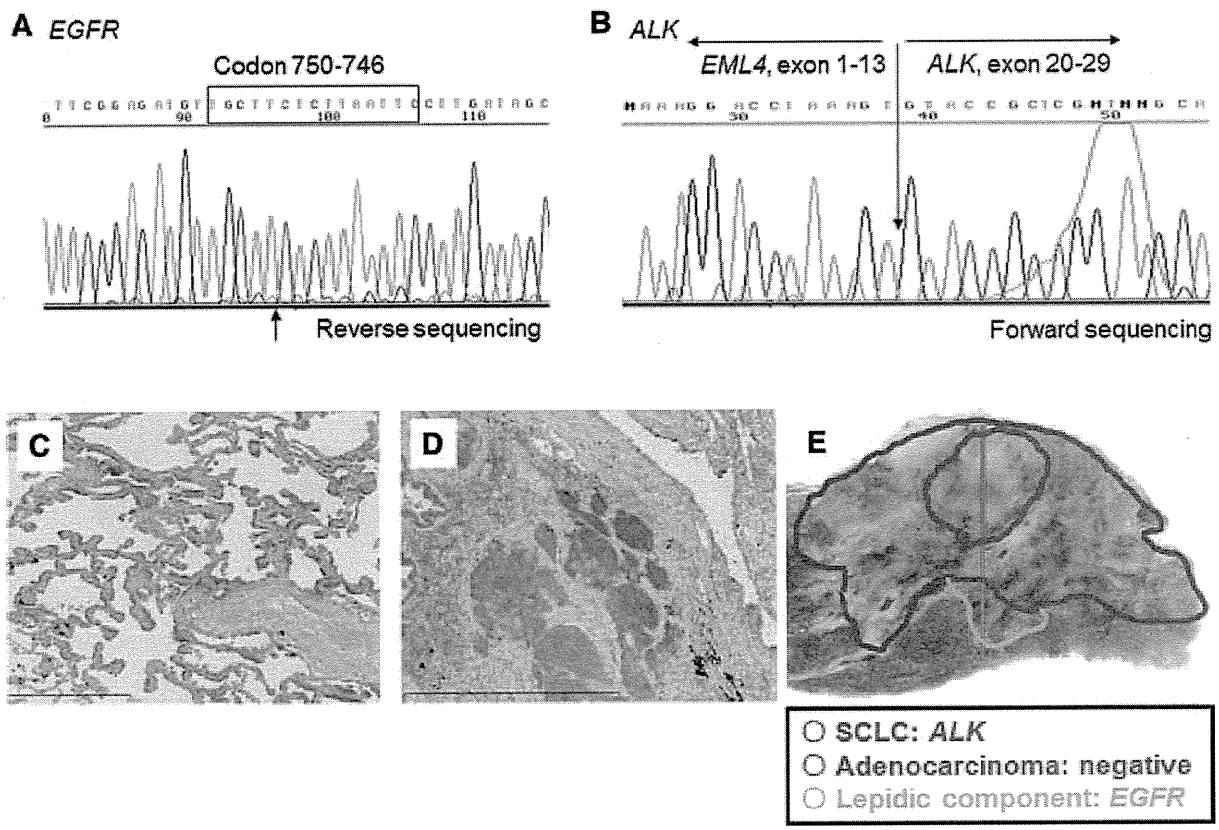

FIGURE 3. A direct sequence analysis revealing (*A*) a deletion in exon 19 of *EGFR* in the adenocarcinoma and (*B*) a variant 1 mutation of *EML4-ALK* in the SCLC. Immunoreactivity of the lepidic component to the deletion in exon 19 of EGFR using an antibody that specifically detects deleted EGFR (E746-A750del) (6B6, Cell Signaling, Danvers, MA) (*C*) and of the SCLC to ALK using primary antibody against ALK (5A4, Nichirei, Tokyo, Japan) (*D*). A polymer method was used for the immunohistochemical analysis, specifically, an intercalating antibody-enhanced polymer method was used for the detection of ALK. *E*, Gene mapping of the driver mutations in each component. EGFR, epidermal growth factor receptor; EML4-ALK, echinoderm microtubule-associated protein-like 4; SCLC, small-cell lung cancer; ALK, anaplastic lymphoma kinase.

harbors activating mutations in exon 19 and 21, can be successfully treated by EGFR-tyrosine kinase inhibitors (TKIs) in comparison to cytotoxic reagents.[1] The *EML4-ALK* fusion gene also possesses a transforming activity[2] and has attracted much attention because it might be a potential therapeutic target of ALK inhibitors in the treatment of adenocarcinoma.[3] Although *EGFR* mutations have already been identified in SCLCs (4%),[4] there are no reports on the *EML4-ALK* translocation in SCLCs. Intriguingly, *ALK* translocation was detected in the SCLC component in the present case, whereas the exon 19 *EGFR* mutation was shown only in the lepidic component.

Adenocarcinoma with sensitive *EGFR* mutations can transform into SCLC in the process of acquiring resistance to EGFR-TKIs.[5] This mechanism does not apply to the current case, because the patient had not received EGFR-TKIs. Although the complexity of the combined histology and driver mutations in the present case has not been elucidated, this phenomenon suggests that *ALK* rearrangements could be involved in the pathogenesis of SCLC, which could be successfully treated with ALK inhibitors.

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Impact of age on epidermal growth factor receptor mutation in lung cancer

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ABSTRACT

Aging is one of the best, but rarely referred, risk factors for various types of cancer including lung cancer, because age could be a surrogate for accumulation of genetic events in cancers. Smoking inversely associates with the presence of epidermal growth factor receptor (*EGFR*) mutation in lung cancer, but its strong confounding with age and sex makes it difficult to evaluate sole impact of age. To clarify an impact of age on *EGFR* mutation, we conducted a cross-sectional study based on data of 1262 lung cancer patients. The associations between *EGFR* mutation and age, considering sex, smoking and histology, were evaluated using logistic regression models. In multivariate analysis, we found a significant increase of *EGFR* mutation prevalence by increase of age (p-trend = 0.0004). Consistent trend was observed among never-smoking females (p-trend = 0.011) and never-smoking males also showed similar trend although not significant. These were consistently observed when we limit the subject to those with adenocarcinoma. In conclusion, age independently associates with *EGFR* mutation among lung cancer. Positive association between *EGFR* mutation and age among never-smokers regardless of sex might indicate that *EGFR* mutation occurs cumulatively by unidentified internal/external factors other than smoking.

1. Introduction

Recent advancement of molecular oncology has uncovered some critical alterations in lung cancers [1]. Epidermal growth factor receptor (EGFR) is a receptor tyrosine kinase that is highly expressed in cancer cells [2]. Mutations in the *EGFR* gene that are frequently present in exons 18–21 have been reported to be critical gene mutations in non-small-cell lung cancers (NSCLCs), especially in adenocarcinoma [2–5]. Gefitinib and erlotinib are reversible *EGFR* tyrosine kinase inhibitors (EGFR-TKIs) and are used for the treatment of NSCLC [6]. Of particular interest is the fact that exon 19 deletions and exon 21 L858R mutations of the *EGFR* gene have been demonstrated to be associated with significant sensitivity to EGFR-TKIs [7–10]. This fact strongly suggest the importance of *EGFR* mutation in NSCLC and understanding the clinicopathological feature of *EGFR* mutation is necessary.

Previous studies have shown that the following patients have a higher chance of harboring *EGFR* mutations than their respective counterparts: females, never-smokers, and individuals with adenocarcinoma histology and East Asians [3,4]. We have previously focused on smoking dose to show how it is useful for predicting the presence of *EGFR* mutations using receiver-operator-characteristic analysis [11]. Our findings indicate that cumulative exposure to cigarette smoke inversely associated with the presence of *EGFR* mutations [11]. One of the limitations in evaluation of cumulative exposure to cigarette smoke is that it strongly confounds with age. Aging is one of the best known, but is rarely referred, risk factor for various type of cancer including lung cancer [12]. This is because age could be a surrogate for accumulation of genetic events in local tissues resulting from cumulative exposures to known and unknown risk factors. To date, it is scarcely evaluated whether age solely associated with risk of *EGFR* mutation.

In this study, we evaluated the associations between *EGFR* mutation and age in combination with other factors like sex, smoking and histology for the presence of *EGFR* mutations.

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Table 1
Patient characteristics and *EGFR* mutation rate by demographic factors.

Variables	Total patients (*n*)	Patients with EGFR mutation			Cross-sectional OR	*p*-Value	*p*-Values for heterogeneity test by institution
		n	%	(95% CI)			
Sex							0.37
Male	768	157	20.4	(17.6–23.5)	1.00 (reference)		
Female	494	260	52.6	(48.1–57.1)	4.32 (3.35–5.59)	<0.001	
Smoking status							0.28
Ever-smoker	771	127	16.5	(13.9–19.3)	1.00 (reference)		
Never-smoker	491	290	59.1	(54.6–63.4)	7.32 (5.58–9.59)	<0.001	
Histological subtype							0.12[a]
AD	964	406	42.1	(39.0–45.3)	1.00 (reference)		
ADSQ	23	4	17.4	(5.0–38.8)	0.29 (0.07–0.88)	0.017	
SQ	202	5	2.5	(0.8–5.7)	0.03 (0.01–0.08)	<0.001	
LA	54	2	3.7	(0.5–12.7)	0.05 (0.01–0.20)	<0.001	
SCLC	12	0	0.0	(0.0–27.0)	NE	NE	
Other	7	0	0.0	(0.0–41.0)	NE	NE	
p-stage[b]							0.82[c]
I	783	298	38.1	(34.6–41.6)	1.00 (reference)		
II	173	37	21.4	(15.5–28.3)	0.44 (0.29–0.66)	<0.001	
III	256	74	28.9	(23.4–34.9)	0.66 (0.48–0.91)	0.008	
IV	50	8	16.0	(7.2–29.1)	0.31 (0.12–0.68)	0.002	

n, number; CI, confidence interval; OR, Odds ratio; AD, adenocarcinoma; ADSQ, adenosquamous carcinoma; SQ, squamous cell carcinoma; LA, large cell carcinoma; SCLC, small-cell lung cancer. NE indicates not estimated because of no subject with *EGFR* mutation in the category.
[a] Heterogeneity test by institution for AD or non-AD.
[b] Pathological stage was determined according to International Union against Cancer TNM classification of malignant tumors (6th edition).
[c] Heterogeneity test by institution for one level increase of categories.

2. Materials and methods

2.1. Study design, subjects and data of this study

This study was designed as a cross-sectional study to evaluate the association between age at diagnosis and harboring of *EGFR* mutation in lung cancer. Subjects analyzed in this study were consecutive 1262 patients with primary lung cancer who had undergone surgical resection between 2000 and 2009 at two institutions, the Aichi Cancer Center Hospital (737 patients), Nagoya, Japan, and the Okayama University Hospital (525 patients), Okayama, Japan. Institutional Review Board permission and informed consent were obtained at each site.

The clinicopathological information (age at diagnosis, sex, smoking, histology and stage) and *EGFR* mutation status of these patients were obtained. We defined never-smokers as those patients with a lifetime exposure of 100 cigarettes or less and rest were defined as ever-smokers.

2.2. Detection of EGFR mutations in primary lung cancers

DNA-based analysis using direct sequencing or polymerase chain reaction-based length polymorphisms (exon 19) or restriction fragment length polymorphism (exon 21) assays were performed to detect *EGFR* mutation in samples from Okayama University [13]. The RNA-based analysis using one-step reverse transcription-polymerase chain reaction for *EGFR* mutation detection or direct sequencing was carried out at the Aichi Cancer Center [14]. In this study, a deletional mutation in exon 19 and a L858R mutation in exon 21 were considered to be *EGFR* mutations.

2.3. Statistical analysis

A primary endpoint of this study was to evaluate cross-sectional association between increasing of age and *EGFR* mutation stratified by clinicopathological parameters. We applied cross-sectional odds ratios (ORs) and 95% confidence intervals (CIs) estimated by logistic regression models. In stratified analysis, we examined strata-pair wise heterogeneity by Mantel–Haenzel tests.

The exact 95% CIs for *EGFR* mutation rates in each category of clinicopathological parameters, such as age, sex, smoking, histology and pathological stage were calculated. The difference of *EGFR* mutation prevalence by clinicopathological parameters was tested by using Fisher's exact tests. Inter-institutional heterogeneity for each clinicopathological parameter was assessed by Cochran–Mantel–Haenszel tests. All statistical analyses were carried out using STATA ver11 (STATA Corp., College Station, TX, USA).

Table 2
Impact of age increase in harboring of *EGFR* muation by uni- and multi-variate[a] models.

Age group	Total (*n*)/EGFR mutated (*n*) (%)	Univariate OR	95% CI	*p*-Value	Multivariate OR	95% CI	*p*-Value
≤45	44/12 (27.3%)	1	Reference		1	Reference	
≤55	195/57 (29.2%)	1.10	0.53–2.29	0.796	1.28	0.58–2.80	0.542
≤65	411/133 (32.4%)	1.28	0.64–2.56	0.492	1.76	0.84–3.72	0.137
≤75	441/161 (36.5%)	1.53	0.77–3.07	0.225	2.24	1.14–5.07	0.021
>75	171/54 (31.6%)	1.23	0.59–2.57	0.581	2.01	0.90–4.48	0.087
				p-trend[b] = 0.116			*p*-trend[b] = 0.0004

n, number; OR, odds ratio; CI, confidence interval.
[a] Adjusted for sex, cumulative exposure to smoking (pack year, continuous) and histology (adenocarcinoma vs. non-adenocarcinoma) in logistic regression models.
[b] Trend was assessed by putting age as continuous variable in the models. The ORs for age categories (≤45(–45), ≤55(46–55), ≤65(56–65), ≤75(66–75) and >75(76–)) or 10-years age increase indicate that relative likelihood of harboring *EGFR* mutation in each age category compared to age equal or less than 45 years (≤45) inuni- and multi-variate analyses.

3. Results

3.1. Patient characteristics

The characteristics of the 1262 patients are shown in Table 1. A total of 1262 patients consisted of 494 (39.1%) females and 768 (60.9%) males; 491 (38.9%) never-smokers and 771 (61.1%) ever-smokers; 964 (76.4%) adenocarcinomas and 298 (23.6%) non-adenocarcinomas. The median age was 65 years (range, 26–90); the median pack-year of tobacco smoking was 22.5 (range, 0–324).

3.2. EGFR mutation rate from each clinicopathological factor

Of 1262 cases, *EGFR* mutations were found in 417 (33.0%) cases, which consisted of 200 (15.8%) exon 19 deletions and 217 (17.2%) exon 21 L858R mutations. The *EGFR* mutation prevalence and 95% CI in each category of patient characteristics are shown in Table 1. Prevalence of *EGFR* mutation is higher in patients with the following factors: females, never-smokers and Aden carcinoma as expected. There was no significant difference in *EGFR* mutation rate and the clinicopathological factors between the two institutions, using heterogeneity test (Table 1).

3.3. Impact of age increase in harboring of EGFR mutation

Table 2 shows results of uni- and multi-variate analyses to evaluate an impact of age at diagnosis. Increase of age is associated with higher likelihood of harboring *EGFR* mutation especially in multivariate analysis adjusted for sex, cumulative exposure to cigarette and histology (p-trend = 0.0004).

To further evaluate consistency of association with age across subgroup by sex, smoking status and histology, we conducted stratified analyses by these factors. Table 3 and Fig. 1 show stratified analysis by sex and smoking status. Interestingly, among never-smoking females, age showed significantly positive association with *EGFR* mutation (p-trend = 0.011, OR for 10 years increase of age: 1.28, 95% CI: 1.06–1.55). Not significant but similar trend was observed with never-smoking males and ever-smoking males. In contrast, age showed inverse association with *EGFR* mutation among ever-smoking females. The heterogeneity test indicated significant difference pattern of association by age between never-smoking females and ever-smoking females (p-heterogeneity = 0.0476). To rule out potential impact of the pathological stage on the association between age and *EGFR* mutation, we explored the heterogeneity by the factor and confirmed no statistically significant impact. When we further stratify the analyses by histology, we observed consistent pattern of association among adenocarcinoma (Fig. 2). As small number of subjects among non-adenocarcinoma could be limitation, we observed increased prevalence of *EGFR* mutation among never-smoking females, supporting consistency of association across histologic subtype.

4. Discussion

This large-scale cross-sectional study with 1262 patients evaluated the associations between *EGFR* mutation and age in combination with other factors like sex, smoking and histology for the presence of *EGFR* mutations. We found age independently increased likelihood of harboring *EGFR* mutation. When we further stratify the analyses by histology, we observed consistent pattern of association among adenocarcinoma. Our result is consistent with a recent study with 98 female patients with NSCLC [15]. The study showed that only 30% of patients younger than 45 years harbored *EGFR* mutation, whereas 70% of patients older than 65 years harbored *EGFR* mutation. This result might indicate that *EGFR* mutation rate increased in both male and female among NSCLC patients in

Table 3
Odds ratio for *EGFR* mutation by age according to sex and smoking status.

Sex	Smoking status	Age at diagnosis										Each 10 years age increase	Pairwise examination of heterogeneity of Impact of age on EGFR mutation by Mantel-Haezel heterogeneity test			
		≤45		≤55		≤65		≤75		>75			Male ever	Male never	Female ever	Female never
		Total (n)/EGFR mutated (n)		Total (n)/EGFR mutated (n)		Total (n)/EGFR mutated (n)		Total (n)/EGFR mutated (n)		Total (n)/EGFR mutated (n)		OR (95% CI, p-Value)				
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI					
Male	Ever	18/2		102/11		227/37		249/39		100/16			-			
		1	Reference	0.97	0.20–4.78	1.56	0.34–7.06	1.49	0.33–6.72	1.52	0.32–7.28	1.12 (0.90–1.40, p = 0.310)				
Male	Never	3/1		9/6		20/15		27/21		13/9						
		1	Reference	4	0.25–63.9	6	0.44–81.2	7	0.54–91.1	4.5	0.31–65.2	1.34 (0.86–2.09, p =0.203)	0.4699	-		
Female	Ever	3/1		20/8		24/5		22/7		10/2						
		1	Reference	1.33	0.10–17.3	0.53	0.04–7.05	0.93	0.07–12.1	0.5	0.03–8.71	0.78 (0.50–1.23, p =0.285)	0.1597	0.0951	-	
Female	Never	20/8		64/32		140/76		143/94		48/27						
		1	Reference	1.5	0.54–4.16	1.78	0.69–4.63	2.88	1.10–7.51	1.93	0.67–5.57	1.28 (1.06–1.55, p =0.011)	0.3581	0.8408	0.0476	-

Ever, ever-smoker; Never, never-smoker; n, number; OR, Odds ratio; CI, confidence interval. The odds ratios (ORs) for age categories (≤45(–45), ≤55(46–55), ≤65(56–65), ≤75(66–75) and >75(76–)) or 10-years age increase were estimated by multivariate logistic regression models by strata of sex and smoking status. The ORs for age categories indicate that relative likelihood of harboring *EGFR* mutation in each age category compared to age equal or less than 45 years (≤45). Pairwise examination of heterogeneity tests whether the association between age increase and harboring *EGFR* mutation differs or not by combination of sex and smoking status.

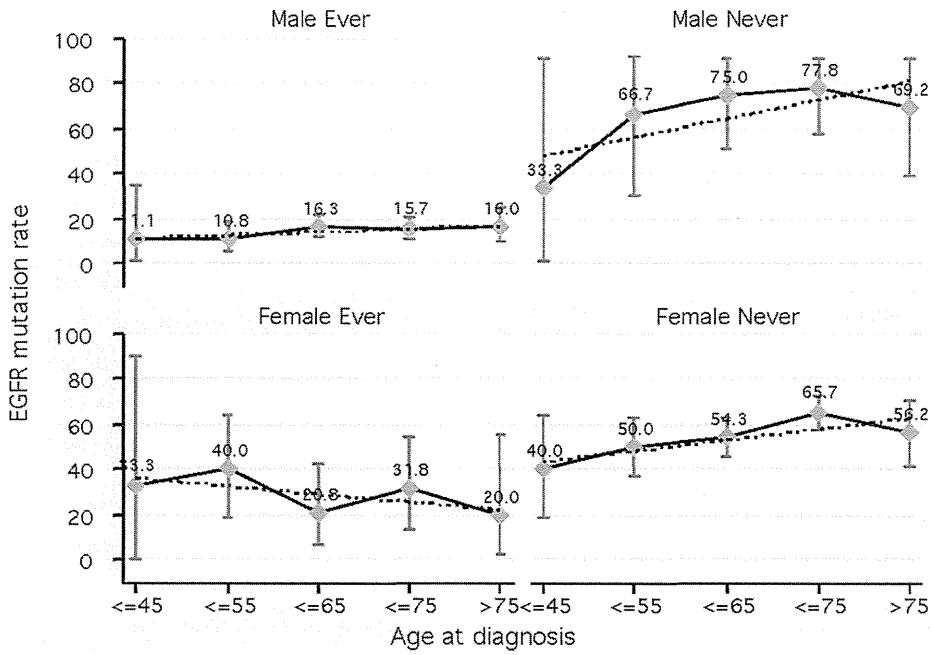

Fig. 1. *EGFR* mutation rates by sex, smoking status and five categories (≤45(−45), ≤55(46–55), ≤65(56–65), ≤75(66–75) and >75(76–)) of age at diagnosis.

never smokers by unidentified internal/external factors related to aging other than smoking.

NSCLCs with *EGFR* mutation themselves are generally dormant tumors and thus they confer favorable prognosis compared with wild-type NSCLCs even without EGFR-TKI treatment [16,17]. Therefore, it is anticipated that NSCLC with *EGFR* mutations would take a longer time to become a clinically detectable disease, resulting in relative accumulation of *EGFR* mutant tumors in patients of older age. In contrast, more aggressive NSCLCs would grow faster and would take a shorter time to become an overt disease, resulting in relative accumulation in the younger generation. This group of patients may include those with recently identified NSCLCs with *echinoderm microtubule-associated protein-like 4* (*EML4*) and *anaplastic lymphoma kinase* (*ALK*) fusion. *EML4-ALK* fusion genes are known to be frequently present in younger NSCLC patients [18,19].

Aging plays one of the important roles in the oncogenesis. Aging accumulates genetic alterations by leading to eventual reduction in stem cell fitness [20]. In young healthy individual, the high fitness of stem cell population represents a powerful barrier to tumor development, by creating an environment that is not conducive for

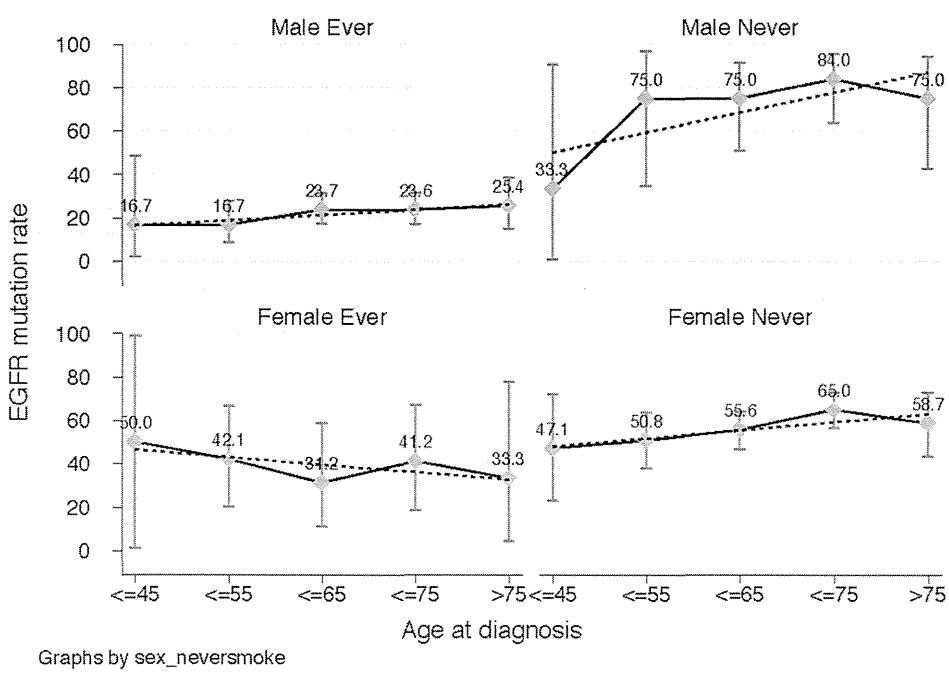

Fig. 2. *EGFR* mutation rates by sex, smoking status and five categories (≤45(−45), ≤55(46–55), ≤65(56–65), ≤75(66–75) and >75(76–)) of age at diagnosis among adenocarcinoma.

selection of oncogenic mutations. The stem cell fitness is reduced with age, and oncogenic mutations have an increased chance. This is supported by observations in various types of cancer. In colorectal cancer, *K-ras* mutation was positively associated to age [21,22]. *K-ras* mutation was much less frequent in colonic tumors from male at younger ages than 40 years and older men had more mutation [21]. It is preferentially involved in carcinoma developing from adenoma, which preserves differentiation, and codon12 of *K-ras* mutation has a role mucinous differentiation pathway. In childhood malignant glioma, TP53 mutations were observed in 11.8% from < 3 years of age at diagnosis versus 40% from older children, a difference that was significant [23]. Our results revealed same phenomenon for *EGFR* mutation in NSCLC with substantially large number of cases.

Our results showed that female ever-smoker exhibited inverse relationship between age and *EGFR* mutation that seemed to be discrepant with other population.

In addition, among ever-smoking male, although the age-related trend of increasing *EGFR* mutation is observed, this trend is weaker than that of never-smokers as mentioned above. One of possible explanations for these results is that smoking induces other causative alterations for lung cancer and relative rate of *EGFR* mutation among lung cancer patients is lower than smoker. Thus, the impact of age that is one of possible surrogate of smoking dose is not stronger than among never-smoker patients. Regarding the difference between male and female in ever-smokers, female is supposed to be more susceptible to tobacco carcinogens than male [24,25]. Thus, smoking effect may overcome the age related trend of increasing *EGFR* mutation among female smoker. Further validation in other large-scaled study is mandatory.

In conclusion, we proved that *EGFR* mutation occurred cumulatively with age in both male and female among never smokers. This indicates possible existence of unidentified internal/external factors related to aging inducing *EGFR* mutated lung cancer warranting further studies.

Conflict of interest statement

None declared.

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ORIGINAL ARTICLE - THORACIC

Induction chemoradiotherapy is superior to induction chemotherapy for the survival of non-small-cell lung cancer patients with pathological mediastinal lymph node metastasis

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Abstract

OBJECTIVES: The purpose of this study was to compare the clinical outcomes of induction chemoradiotherapy and chemotherapy and to identify the prognostic factors for non-small-cell lung cancer patients with mediastinal lymph node metastasis who were treated with induction therapy.

METHODS: Between August 1995 and December 2010, 50 non-small-cell lung cancer patients with pathological mediastinal lymph node metastasis were scheduled to receive induction therapy followed by surgery. Irinotecan plus cisplatin was used for induction chemotherapy from June 1995 to April 1999, and docetaxel plus cisplatin with concurrent radiation at a dose of 40–46 Gy has been used for induction chemoradiotherapy since May 1999.

RESULTS: Thirty-five patients were treated with induction chemoradiotherapy and 15 were treated with induction chemotherapy. For the entire population, the 3-year and 5-year overall survival rates were 64.1 and 53.9%, respectively, and the 1-year and 2-year disease-free survival rates were 70.0 and 53.1%, respectively. Among the clinicopathological factors, the chemoradiotherapy group exhibited longer overall survival and disease-free survival than the chemotherapy group (overall survival, $P = 0.0020$; disease-free survival, $P = 0.015$). Pathological downstaging was also significantly associated with favorable overall survival ($P = 0.0042$) and disease-free survival ($P = 0.021$). A multivariate analysis showed that chemoradiotherapy ($P = 0.0099$) and pathological downstaging ($P = 0.039$) were independent prognostic factors.

CONCLUSIONS: Our results indicated that induction chemoradiotherapy was superior to induction chemotherapy with regard to the outcome of non-small-cell lung cancer patients with mediastinal lymph node metastasis.

Keywords: Lung cancer • Induction therapy • Chemoradiotherapy • Chemotherapy

INTRODUCTION

Surgical resection is the first therapeutic option for the control of local disease in patients with non-small-cell lung cancer (NSCLC). Locally advanced disease status is associated with a possibility of micrometastasis to distant sites, which is often the cause of disease recurrence, typically resulting in a poor outcome. In this situation, surgery does not contribute to a disease cure. Mediastinal lymph node metastasis of NSCLC without clinical distant metastasis is one of the categories of locally advanced disease for which the prognosis remains unsatisfactory. NSCLC patients with mediastinal lymph node metastasis form a heterogeneous population, ranging from unresectable N stage with a tumor mass that was either not discrete or unmeasurable to resectable N stage with a single node with a short-axis diameter of 1 cm on a transverse computer tomography (CT) scan image [1]. Thus, the clinical manifestations and treatment option for N2 disease also exhibit substantial heterogeneity. Indeed, numerous clinical trials including various combinations of chemotherapy with or without radiotherapy followed by surgery or definitive chemoradiotherapy have been adapted to establish an appropriate strategy for patients with mediastinal lymph node metastasis [2–8]. The two recent studies failed to demonstrate a benefit from the addition of surgery in the entire population [2–8]. However, in the subset analysis of the intergroup trial 0139 for patients who underwent a lobectomy vs a matched subset undergoing chemoradiotherapy, the surgical group showed a significantly more favorable survival rate. This

result strongly suggests the possible advantage of surgical resection after induction chemoradiotherapy for a select population of patients with N2 disease [2–8]. Regarding the comparison between induction chemoradiotherapy and chemotherapy, no prospective randomized studies have been reported. As retrospective study, only Higgins and colleagues reported the outcome: induction chemoradiotherapy was associated with a higher rate of mediastinal downstaging but not an improvement in overall survival (OS) [9].

We have been using cisplatin-based induction therapy for the treatment of NSCLC patients with locally advanced diseases such as N2/3 and T3/4 diseases since 1995 [10–13]. In this study, we compared the clinical outcome of induction chemoradiotherapy and chemotherapy and investigated prognostic factors for NSCLC patients with mediastinal lymph node metastasis who were treated with induction therapy.

MATERIAL AND METHODS

Patient selection and evaluation

Between July 1995 and December 2010, a total of 86 NSCLC patients with clinical N2/3 disease were scheduled for treatment with induction therapy followed by surgery at Okayama University Hospital. Mediastinal lymph node metastasis was pathologically confirmed in 50 patients prior to induction therapy and they were the subjects of this study. Thirty-six patients who were not examined for mediastinal nodal metastasis were excluded from this study to avoid including false positive N2/3 cases. Among 50 patients, the outcome of 37 patients was reported in our previous reports and they were prospectively treated with induction chemotherapy and chemoradiotherapy [10, 11]. Briefly, previously untreated NSCLC patients with pathologically confirmed mediastinal nodal metastasis were eligible for enrollment in those studies. Patient information was shared at a meeting among pulmonary oncologists, radiation oncologists and general thoracic surgeons to determine whether induction therapy was indicated for the treatment of individual patients with locally advanced NSCLC. When mediastinal lymph node metastasis was suspected based on the findings of a chest CT or an 18-fluoro-2-deoxyglucose (FDG) positron emission tomography (PET)/CT scan, a cervical mediastinoscopy or endobronchial ultrasound-guided transbronchial biopsy (EBUS) was performed to evaluate stations 2, 4 and 7. An anterior mediastinoscopy was also performed when metastasis was suspected at stations 5 or 6.

The patient inclusion criteria were an age of 75 years or younger, an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1 [14], and adequate organ functional reserves, as described previously [10, 11]. Written informed consent was obtained from all the patients. The study protocol was approved by the Institutional Review Board/Ethical Committee of Okayama University. The disease stage was evaluated using chest radiography, enhanced chest and abdominal CT scans, including the adrenal glands, enhanced brain magnetic resonance imaging (MRI), a radionuclide bone scan or an FDG PET/CT scan and bronchoscopy. The International Association of the Study of Lung Cancer TNM staging system for NSCLC, seventh edition, was used to determine the disease staging and nodal location [15].

Treatment plans

The details of the treatment regimens were described in our previous study [10, 11]. Irinotecan plus cisplatin was used for induction chemotherapy from June 1995 to April 1999, and docetaxel plus cisplatin with concurrent radiation at a dose of 40 Gy (1999–2000)–46 Gy (2000–10) has been used for induction chemoradiotherapy since May 1999. Following the induction therapy, patient response was evaluated based on a chest radiograph and CT scans. Patients without progressive disease were, in principle, scheduled to undergo surgery within 6 weeks of the completion of the induction therapy, as described previously. Briefly, the surgical procedure was determined based on the disease extent before induction treatment. While a posterolateral thoracotomy was used as the basic approach, a median sternotomy was applied for patients with contralateral mediastinal lymph node metastasis or when great vessels, such as the main pulmonary artery, needed to be secured for a safe resection. A lobectomy with mediastinal lymph nodal dissection was basically the resection of first choice; however, a bilobectomy or pneumonectomy was performed in cases requiring these procedures because of disease extension [12]. A sleeve resection was preferred to avoid a pneumonectomy, if appropriate. A complete ipsilateral superior mediastinal and subcarinal lymphadenectomy was performed in all cases. For patients with primary lower lobe lesions, stations 8 and 9 lymph nodes were also resected. Patients with primary left pulmonary lesions also underwent the resection of stations 5 and 6 lymph nodes. The bronchial stump was covered with pericardial fat tissue or pedicled intercostal muscle. When a sleeve resection was performed, the greater omentum was, in principle, used to wrap the anastomosis. Post-operative adjuvant treatment was left to the physician's discretion.

Survival and statistical analysis

After completion of scheduled therapy, chest and abdominal CT and enhanced brain MRI were repeated every 3 months for at least 2 years. During 3–5 years after completion, chest and abdominal CT and enhanced brain MRI were repeated every 6 months. A radionuclide bone scan or PET-CT was performed if necessary. After 5 years, chest X-ray was repeated every year and further image analyses were performed if necessary. The OS and the disease-free survival (DFS) were calculated from the date of initiation of induction therapy until the date of death or the last follow-up for OS and until confirmed disease recurrence or death for DFS. The survival curve was calculated by the Kaplan–Meier method and the difference between groups was compared with the log-rank test. A multivariate analysis was performed using the Cox proportional hazard model. Fisher's exact tests were applied to examine differences in categorical factors across groups. All data were analyzed using JMP® 9.0.0 Program for Windows (SAS Institute Inc., Cary, NC, USA). All statistical tests were two-sided and probability values <0.05 were defined as being statistically significant.

RESULTS

Patient characteristics

Fifty NSCLC patients with pathological mediastinal lymph node metastasis were the subjects of this study. Thirty-five patients

Table 1: Patient characteristics

Characteristics	Total	ChRT	ChT	*P*-value
Median and range of age (years)	59.8 (31–74)	59 (31–74)	59 (34–74)	
Sex				
Male	37	24	13	0.29
Female	13	11	2	
Histological subtypes				
Adenocarcinoma	26	18	8	0.9
Squamous cell carcinoma	18	14	4	
Adenosquamous carcinoma	2	1	1	
Large cell carcinoma	4	2	2	
Stage				
IIIA	45	30	15	0.3
T1N2M0	9	6	3	
T2N2M0	29	19	10	
T3N2M0	7	5	2	
IIIB	5	5	0	
T2N3M0	2	2	0	
T4N2M0	3	3	0	
Pulmonary resection[a]				
Lobectomy	33	25	8	0.079
Sleeve lobectomy	5	4	1	
Bilobectomy	7	4	3	
Right pneumonectomy	2	0	2	
Left pneumonectomy	2	1	1	

ChRT: chemoradiotherapy; ChT: chemotherapy.
[a]Pulmonary resection (pneumonectomy vs others).

were treated with induction chemoradiotherapy and 15 were treated with induction chemotherapy. The patient characteristics were as shown in Table 1. The median patient age was 59 years (range: 31–74 years). There were 37 men and 13 women in the series. The histological subtype was adenocarcinoma in 26 patients, squamous cell carcinoma in 18, large cell carcinoma in 4 and adenosquamous carcinoma in 2. Forty-five patients had stage IIIA disease, and 5 had stage IIIB disease. Forty-six patients underwent a mediastinoscopy, and 4 underwent an endobronchial EBUS. Patients who had bulky or extra-nodal N3 diseases were not enrolled. There was no significant difference in clinicopathological factors between the chemoradiotherapy group and chemotherapy group (Table 1).

Induction therapy

In the chemotherapy group, 11 patients (73.3%) completed induction chemotherapy without dose modification. Four patients (27.7%) required dose modification, consisting of 2 patients with completion of the scheduled therapy with dose modification and two with a modified scheduled therapy in which each patient skipped once or twice. In 35 chemoradiotherapy patients, 13 (37.1%) completed the planned full-dose induction chemotherapy with radiation at a dose of 46 Gy (12 patients) and 40 Gy (1 patient). Eleven patients (31.4%) completed the planned dose modified induction chemotherapy with radiation at a dose of 46 Gy (9 patients), 42 Gy (1 patient) and 32 Gy (1 patient). Eleven patients (31.4%) received the modified induction chemotherapy with single omission (9 patients; 7 with a 46 Gy radiation) or double omission (2 patients with a 46 Gy radiation) of drug administration.

Surgery, pathological response and postoperative adjuvant therapy

The median time from the end of induction therapy until surgery was 35 days (range: 25–59 days). Surgical resection was performed in 49 patients. The surgical procedures in the chemoradiotherapy group included a lobectomy in 25 patients, a sleeve lobectomy in 4, a bilobectomy in 4 and a left pneumonectomy in 1. Those in the chemotherapy group included a lobectomy in 8 patients, a sleeve lobectomy in 1, a bilobectomy in 3, a right pneumonectomy in 2 and a left pneumonectomy in 1. One patient in the chemoradiotherapy group did not undergo surgery because of severe congestive heart failure. Regarding resectability, 1 of the 34 patients in the chemoradiotherapy group exhibited incomplete tumor resection with pleural dissemination. Four of the 15 patients in the chemotherapy group exhibited incomplete tumor resection with mediastinal lymph node invasion to the paratracheal region and superior vena cava [10]. The rate of incomplete resection was significantly higher in the chemotherapy group than in the chemoradiotherapy group ($P = 0.026$).

The pathological responsiveness of the resected specimens was estimated. In the chemoradiotherapy group, pathological downstaging and pathological complete response were confirmed in 16 (45.7%) and 7 (20.6%) of the 34 patients, respectively. In the chemotherapy group, 2 (13.3%) and 1 (6.7%) of the 15 patients exhibited pathological downstaging and pathological complete response, respectively. The rate of pathological downstaging was significantly higher in the chemoradiotherapy group than in the chemotherapy group ($P = 0.021$). In the chemoradiotherapy group, 2 patients with N2 disease at the start of induction chemoradiotherapy exhibited N3 disease upon pathological examination of the resected specimens. Of the 49

patients who underwent surgical resection, 14 of the 34 chemoradiotherapy patients and 13 of the 15 chemotherapy patients received post-operative adjuvant therapy.

Post-operative adjuvant therapy was performed in 14 patients in the chemoradiotherapy group and 13 patients in the chemotherapy group. The content of adjuvant therapy of chemoradiotherapy group consisted of docetaxel plus cisplatin in 9 patients, irinotecan plus cisplatin in 3 patients, gemcitabine plus cisplatin in 1 patient and gemcitabine plus carboplatin in 1 patient. That of chemotherapy group consisted of irinotecan plus cisplatin in 8 patients, radiation therapy to a total dose of 50 Gy in 5 patients.

Pattern of relapse

At the time of the final data analysis in February 2012, the median follow-up period for the surviving patients was 5.9 years, ranging from 1.2 to 12.6 years. Twenty-eight patients (56.0%) were alive. Disease relapse had occurred in 26 patients, consisting of only distant relapse in 14 (chemoradiotherapy group, 10 patients; chemotherapy group, 4 patients), only loco-regional relapse in 7 (chemoradiotherapy group, 2 patients; chemotherapy group, 5 patients) and both distant and loco-regional relapse in 5 (chemoradiotherapy group, 2 patients; chemotherapy group, 3 patients) at the time of the initial diagnosis of relapse. The rate of local relapse was significantly higher in the chemotherapy group than in the chemoradiotherapy group (4 [11.4%] of 35 cases vs 7 [46.7%] of 15 cases; $P = 0.010$). Total distant relapse occurred in 12 (34.3%) of the 35 patients in the chemoradiotherapy group and 7 (46.7%) of the 15 patients in the chemotherapy group, with no significant difference observed between the groups.

Survival

For the entire population, the 3-year and 5-year OS rates were 64.1 and 53.9%, respectively, and the 1-year and 2-year DFS rates were 70.0 and 53.1%, respectively. While no deaths directly related to induction therapy or surgery occurred, one chemotherapy patient who underwent a right pneumonectomy but ended up with an incomplete resection died of radiation pneumonitis during the post-operative radiotherapy period. The survival curves for the chemoradiotherapy and chemotherapy groups are shown in Fig. 1. Significant differences in OS ($P = 0.0020$) and DFS ($P = 0.015$) were noted between the chemoradiotherapy and chemotherapy groups. Furthermore, patients with pathological mediastinal downstaging after induction therapy had a significantly longer OS ($P = 0.0042$) and DFS ($P = 0.021$) than those without pathological mediastinal downstaging (Fig. 2; Table 2). Patients with pathological complete response tended to show a longer OS than those without pathological complete response ($P = 0.092$). In DFS, pathological

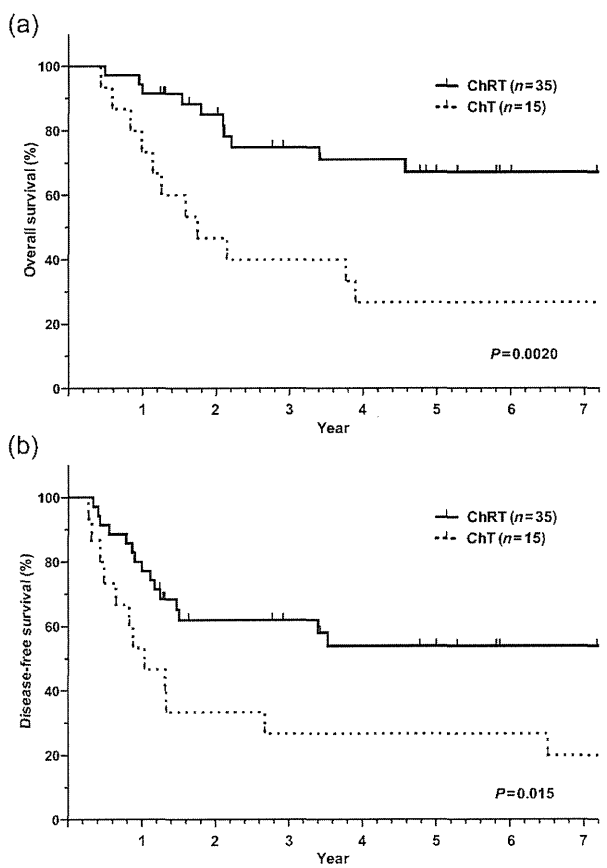

Figure 1: Survival curves stratified by induction therapy. (**a**) Overall survival; (**b**) disease-free survival. ChRT: chemoradiotherapy; ChT: chemotherapy.

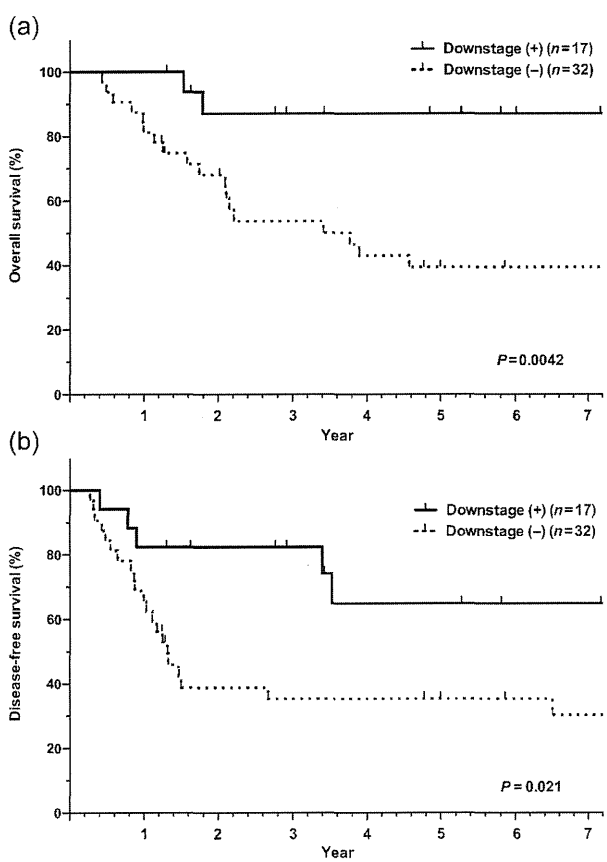

Figure 2: Survival curves stratified by pathological downstaging. (**a**) Overall survival; (**b**) disease-free survival.

Table 2: Overall survival and disease-free survival rates according to clinicopathological factors

Variables	*N*	OS			DFS		
		3-year (%)	5-year (%)	*P*	1-year (%)	2-year (%)	*P*
Induction therapy							
ChRT	35	74.8	67.1	0.0020	77.1	61.9	0.015
ChT	15	40	26.7		53.3	33.3	
Mediastinal downstage							
(+)	18	87.1	87.1	0.0042	82.4	82.4	0.021
(−)	31	53.7	39.4		65.6	38.8	
Sex							
Male	37	60.9	51.9	0.58	73.0	53.6	0.99
Female	13	75.2	60.2		61.5	53.9	
Histology							
AD	26	67.2	51.7	0.99	73.1	47.8	0.42
Non-AD	24	60.8	55.7		66.7	58.3	
Pulmonary resection							
Lobectomy	38	68	53.9	0.46	73.7	53.7	0.81
Others	11	54.6	54.6		63.6	54.6	
pCR							
(+)	8	85.7	85.7	0.092	87.5	87.5	0.034
(−)	41	61.4	49.7		68.3	47.8	

ChRT: chemoradiotherapy; ChT: chemoradiotherapy; AD: adenocarcinoma; pCR: pathological complete response; *P*-value was calculated by log-rank test.

Table 3: Multivariate analysis using Cox proportional hazard model

Variables	Overall survival			Disease-free survival		
	HR	95% CI	*P*	HR	95% CI	*P*
Induction ChRT vs ChT	0.31	0.13–0.75	0.0099	0.43	0.20–0.97	0.042
Mediastinal downstaging (+) vs (−)	0.19	0.010–0.94	0.039	0.61	0.18–1.64	0.35
pCR (+) vs (−)	1	0.039–25.4	1	0.25	0.012–1.7	0.17

ChRT: chemoradiotherapy; ChT: chemotherapy; HR: hazard ratio; CI: confidence interval; pCR: pathological complete response.

complete response was significantly associated with favorable DFS ($P = 0.034$). Among the other factors that were examined (sex, histology and extent of pulmonary resection), no significant factors related to a favorable outcome were observed except pathological complete responders (OS, $P = 0.092$ and DFS, $P = 0.034$; Table 2). Adjuvant therapy after surgery did not affect the outcome of the patients.

A multivariate analysis of all the patients considering induction therapy, pathological downstaging and pathological complete response showed that induction chemoradiotherapy and pathological downstaging were independent factors of favorable OS (chemoradiotherapy, $P = 0.0099$ and pathological downstaging, $P = 0.039$; Table 3). In addition, only induction chemoradiotherapy was an independent factor of favorable DFS ($P = 0.042$).

DISCUSSION

In our study, induction chemoradiotherapy and the downstaging of mediastinal lymph node metastasis were independent prognostic factors for N2/3 NSCLC patients who were treated with induction therapy. Our results indicated that induction chemoradiotherapy was associated with a significantly longer survival period than induction chemotherapy. The poor prognosis of patients receiving induction chemotherapy is thought to be due to the high rate of local recurrence, including the macroscopically incomplete resection of metastatic mediastinal lymph nodes. Indeed, the rationale for induction treatment in patients with locally advanced disease is to facilitate a complete surgical resection by reducing the quantity of cancer cells in the primary tumor and metastatic regional nodes and to eradicate possible micrometastases [16]. Patients with mediastinal lymph node metastasis, especially those with extra-nodal invasion, have a risk of incomplete resection, and induction chemoradiotherapy can prevent the survival of residual tumor cells near the resected margin, compared with chemotherapy. These facts strongly suggest that powerful induction therapy for local control may lead to an improvement in the prognosis of NSCLC patients with mediastinal lymph node metastasis. The absence of residual tumor cells obtained by the high pathological complete