Although PFS following first-line chemotherapy has not been validated as a surrogate endpoint for OS, post-progression survival (PPS) has been shown to be strongly associated with OS after first-line chemotherapy for advanced NSCLC.[11,12] Furthermore, it has been suggested that OS can be approximated as the sum of PPS and PFS.[3] Very few novel anticancer drugs have become available for extensive SCLC, and the relationship between PPS and OS in extensive SCLC remains unclear.

At the level of the individual patient, it is of interest to assess the effect of therapy administered after disease progression on survival. The validation of surrogate measures for OS after first-line therapy in individual patients with advanced NSCLC has been reported previously.[13] Further, the surrogate endpoint sometimes does not reflect the primary endpoint. The significance of PPS in SCLC also remains unclear at the level of the individual patient. Therefore, it is important to establish whether PFS, PPS, or tumor response could be valid surrogate endpoints for OS after first-line therapy in patients with extensive SCLC using individual-level data.

The first-line treatment of choice in extensive-stage SCLC remains 4 to 6 cycles of platinum combination chemotherapy.[1] Although many patients initially achieve clinical remission or disease control with first-line chemotherapy, most subsequently experience disease progression and eventually die of extensive SCLC. We examined first-line cisplatin and irinotecan combination chemotherapy because it is considered the standard first-line chemotherapy in these cases.[1] Previously, in a phase 3 study of extensive SCLC, first-line chemotherapy with irinotecan plus cisplatin was found to be more effective than etoposide/cisplatin (median survival of 12.8 months versus 9.4 months, $p = 0.002$).[14] The MST of patients with extensive SCLC was approximately 1 year. For extensive SCLC patients, OS is shorter and options for subsequent chemotherapy are limited.

In the present study, we analyzed the relationships of PFS, PPS, and tumor response with OS in patients with extensive SCLC at the individual level. The patients recruited to this study had only a limited number of options for subsequent-line chemotherapy. We also explored the prognostic value of baseline and tumor characteristics for PPS.

Methods

Patients

Between September 2002 and November 2012, 60 patients with extensive SCLC were treated with cisplatin and irinotecan as first-line chemotherapy and were enrolled in this study. The tumor response was not evaluated in 10 cases, and PFS data were censored in one case. These 11 patients were excluded from the analyses to maintain uniformity in patient background characteristics. Thus, data from 49 patients were analyzed. The study protocol was approved by the Institutional Review Board of Shizuoka Cancer Center (#.25-J91-25-1-3).

The patients in this study were treated with cisplatin (60 $mg \cdot m^{-2} \cdot day^{-1}$ for 1 day, followed by a pause of 28 days) and irinotecan (60 $mg \cdot m^{-2} \cdot day^{-1}$ on days 1, 8, and 15, followed by a pause of 28 days). This cycle was repeated every 28 days for a maximum of six courses.

The best overall response and maximum tumor shrinkage were recorded as tumor responses. Radiographic tumor responses were evaluated according to the Response Evaluation Criteria In Solid Tumors, ver. 1.1[15]: Complete response (CR), disappearance of all target lesions; partial response (PR), at least a 30% decrease in the sum of the target lesion diameters with the summed baseline diameters as a reference; progressive disease (PD), at least a 20% increase in the sum of the target lesion diameters with the smallest sum observed during the study serving as reference; and stable disease (SD), insufficient shrinkage to qualify as PR and insufficient expansion to qualify as PD. PFS was calculated from the start of treatment to the date of PD or death from any cause. OS was recorded from the first day of treatment until death or was censored on the date of the last follow-up consultation. PPS was recorded as the time from tumor progression until death or was censored on the date of the last follow-up consultation. In this study, we defined treatment-free interval (TFI) as the period from the date of completion of first-line treatment to the first relapse. When prophylactic cranial irradiation (PCI) was performed as first-line treatment, the date of completion was defined as the last day of these treatments. We defined sensitive relapse as TFI $\geq$ 90 days, based on the definition in several previous trials.[16,17]

Statistical analyses

To examine whether PFS, PPS, or tumor shrinkage was correlated with OS, we used Spearman rank correlation analysis and linear regression analysis. In order to identify possible prognostic factors for PPS, the proportional hazards model with a stepwise regression procedure was applied. Hazard ratios (HR) and 95% confidence intervals (CI) were estimated using this model. Because the HR is defined for a 1-unit difference, some factors were converted to an appropriately scaled unit. PPS values were compared using the log-rank test. A P value of ≤ 0.05 was considered significant for all tests. The two-tailed significance level was also set at 0.05. All statistical analyses were performed using JMP version 9.0 for Windows (SAS Institute, Cary, NC, USA).

Results

Patient characteristics and treatment efficacy

Of the 49 patients included in the analyses, 43 patients died; the median follow-up time was 14.0 months (range, 0.7-36.8 months). The characteristics of the 49 patients (median age, 63 years; range, 43-75 years) included in the present study are shown in Table 1. Target lesions were not evaluated in one of the cases. One, 38, 5, and 4 patients showed CR, PR, SD, and PD, respectively. The response rate was 79.6% and the disease control rate was 91.8%.

After progressing past first-line chemotherapy, 5 of the 49 patients did not receive further chemotherapy. The other 44 patients received subsequent chemotherapy after completing their first-line chemotherapy. Among the 49 patients, the median number of follow-up therapeutic regimens was 2 (range, 0-5 regimens). The chemotherapy regimens employed, after progressing past the first-line chemotherapy regimen, are shown in Table 2. Amrubicin was the most common second-line chemotherapy agent, and paclitaxel was the most common third-line chemotherapy agent.

The median PFS and OS were 5.5 months and 13.9 months, respectively [Figure 1a, 1b].

Table 1: Baseline patient characteristics

Characteristic	
Gender	
Male/female	44/5
Median age at treatment (years)	63 (43-75)
Performance Status (PS)	
0/1/≥2	13/32/4
Histology	
Small cell carcinoma/others	49/0
Stage	
IIIB/IV	0/49
Number of first-line chemotherapy courses	
1/2/3/4/5/6	1/4/3/38/2/1
Median (range)	4 (1-6)
Number of regimens after progression following first-line chemotherapy	
0/1/2/3/4/5	5/18/13/8/3/2
Median (range)	2 (0-5)
Median sum of target lesion diameters [mm] (range)	112 (29-287)
Prophylactic cranial irradiation	
Yes/No	3/46
Median treatment-free interval [days] (range)	68 (29-287)

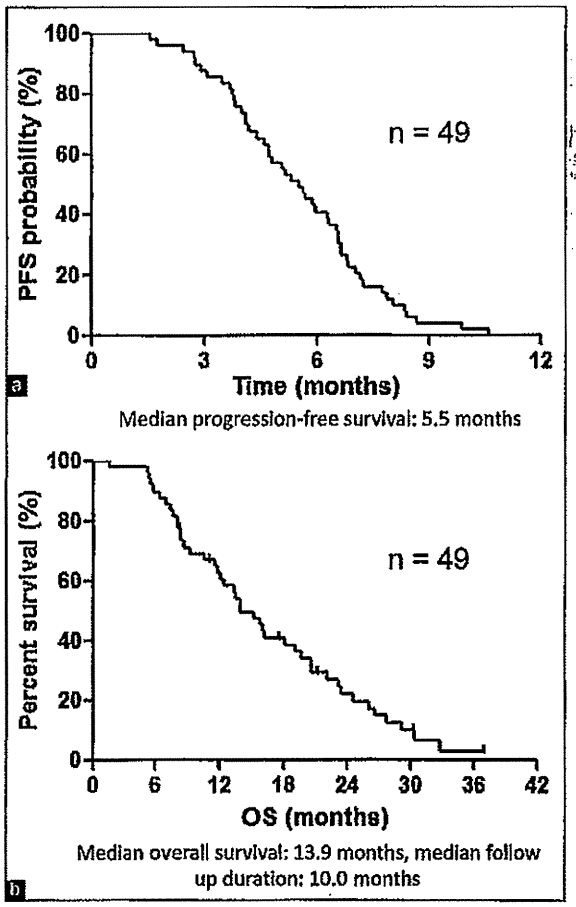

Figure 1: (a) Kaplan-Meier plots showing progression-free survival (PFS) (b) Kaplan-Meier plots showing overall survival (OS)

Relationship between OS and PFS, PPS, and tumor shrinkage

The relationship between OS and PFS, PPS, and tumor shrinkage is shown in Figure 2a, 2b, and 2c, respectively. PPS

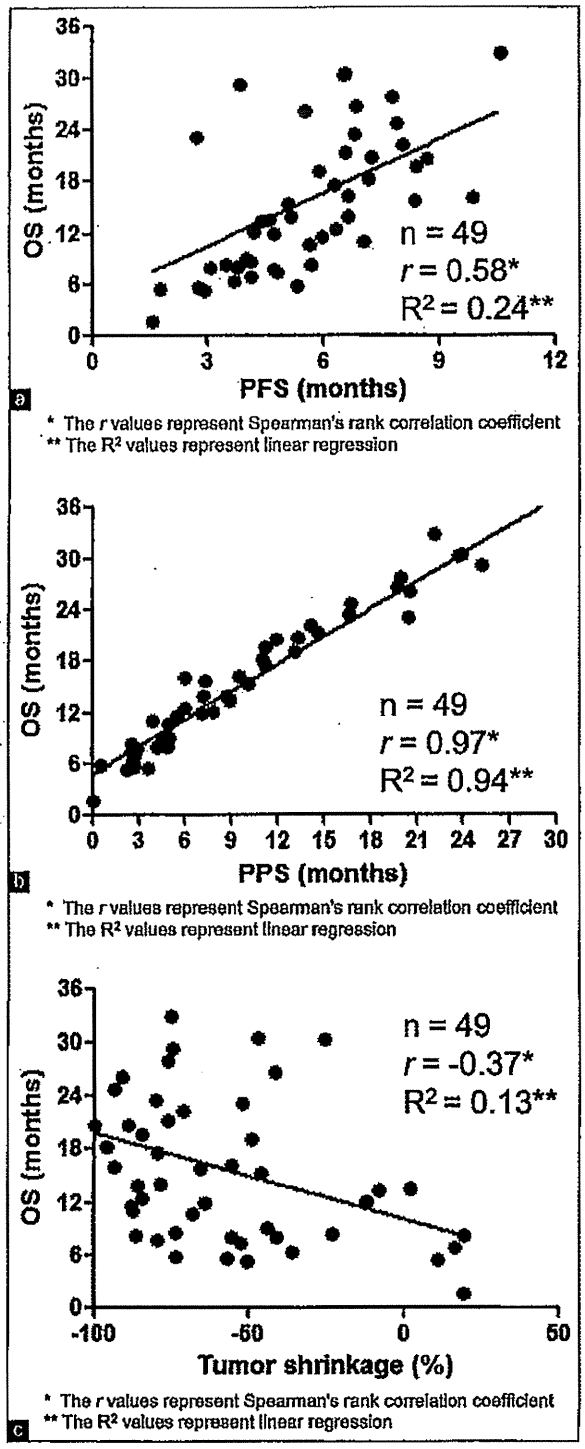

Figure 2: (a) Correlation between overall survival (OS) and progression-free survival (PFS) (b) Correlation between overall survival (OS) and post-progression survival (PPS) (c) Correlation between overall survival (OS) and tumor shrinkage

was strongly associated with OS ($r = 0.97$, $p < 0.05$, $R^2 = 0.94$), based on Spearman's rank correlation coefficient and linear regression, whereas PFS was moderately correlated with OS ($r = 0.58$, $p < 0.05$, $R^2 = 0.24$). Furthermore, tumor shrinkage was only weakly correlated with OS ($r = 0.37$, $p < 0.05$, $R^2 = 0.13$).

Factors affecting post-progression survival

PPS was strongly associated with OS. Therefore, the association between PPS and various clinical factors was assessed. In the univariate analysis [Table 3], PS at the end of first-line treatment, at the beginning of second-line treatment, and TFI (≥90/<90 days) as well as the best response at first-line treatment, the best response from the second-line treatment, and the number of regimens employed after progression beyond first-line chemotherapy were found to be associated with PPS ($p < 0.05$). Next, a multivariate analysis for PPS was conducted [Table 4]. This revealed that the best response after second-line treatment (non-PD/PD), and the number of regimens employed after progression following first-line chemotherapy were significantly associated with PPS ($p \leq 0.05$). The log-rank tests confirmed that PPS was significantly associated with the best response at second-line treatment (non-PD/PD), and the number of regimens employed ($p < 0.05$; Figure 3a and 3b). Based on the best response at second-line treatment, patients with non-PD had a median PPS of 13.1 months, which was longer than that of their counterparts, who had a median PD of 7.2 months (log-rank, $p = 0.05$; Figure 3a). According to the number of regimens employed after progression following first-line chemotherapy, the median PPS for those who were not administered additional regimens was 3.5 months; with 1 additional regimen, the median PPS was 5.5 months; and with ≥2 regimens, the median PPS was 14.1 months, (log-rank test, $p < 0.01$; Figure 3b). These results remained consistent after adjustment using the Cox proportional hazards models [Table 4].

Discussion

We examined the relationships of OS with PFS, PPS, and tumor shrinkage at the individual level in patients with extensive small cell lung cancer. PPS was strongly associated with OS, whereas PFS and tumor shrinkage were moderately and weakly correlated with OS, respectively. In addition, the best response to second-line treatment (non-PD vs. PD), and the number of regimens employed after progression following first-line chemotherapy, independently affected PPS.

Table 2: Chemotherapy regimens employed after progression following first-line chemotherapy

	Second-line	≥Third-line	Total
CDDP+Irinotecan re-challenge	3	1	4
CDDP+VP16	2	1	3
CBDCA+VP16	2	4	6
CBDCA+PTX	0	3	3
Amrubicin	27	10	37
Topotecan	3	4	7
Paclitaxel	3	12	15
Irinotecan	0	2	2
Gemcitabine	3	7	10
Others	1	1	2

The validity of surrogate endpoints has been previously determined through meta-analyses.[18,19] In recent years,

Table 3: Univariate Cox regression analysis of baseline patient characteristics for post-progression survival

Factors	Post-progression survival		
	Hazard ratio	95% CI	*p* value
Gender	1.06	0.42-3.56	0.907
Age (years) at the beginning of first-line treatment	0.97	0.93-1.02	0.341
PS at the beginning of first-line treatment	1.20	0.70-2.05	0.490
Number of courses of first-line treatment administered	0.67	0.46-1.02	0.066
Sum of target lesion diameters	1.00	0.99-1.00	0.102
Best response at first-line treatment			
PR/non-PR	0.65	0.31-1.53	0.306
Non-PD/PD	0.22	0.08-0.77	0.021
PS at the end of first-line treatment	4.45	2.22-9.36	<0.001
Prophylactic cranial irradiation	0.81	0.28-3.39	0.738
Treatment-free interval (≥90/<90 days)	2.07	1.10-4.66	0.023
Age at the beginning of second-line treatment	0.96	0.92-1.01	0.196
PS at the beginning of second-line treatment	2.04	1.26-3.32	0.003
Best response following second-line treatment			
PR/non-PR	0.82	0.34-1.73	0.627
Non-PD/PD	0.48	0.24-0.92	0.028
Number of regimens after progression beyond first-line chemotherapy	0.50	0.35-0.70	<0.001

95% CI = 95% Confidence interval, PS = Performance status, PR = Partial response, PD = Progressive disease

Table 4: Multivariate Cox regression analysis of performance status (PS) at the end of first-line treatment, PS at the beginning of second-line treatment, best response at first-line treatment, best response at second-line treatment, and number of regimens employed after progression beyond first-line chemotherapy for post-progression survival

Factors	Post-progression survival		
	Hazard ratio	95% CI	*p* value
PS at the end of first-line treatment	1.81	0.60-6.10	0.29
PS at the beginning of second-line treatment	1.00	0.44-2.10	0.99
Best response at first-line treatment			
Non-PD/PD	0.50	0.14-2.34	0.34
Best response at second-line treatment			
Non-PD/PD	0.49	0.23-1.00	0.05
Number of regimens employed after progression beyond first-line chemotherapy	0.61	0.41-0.86	<0.01

95% CI = 95% Confidence interval, PD = Progressive disease

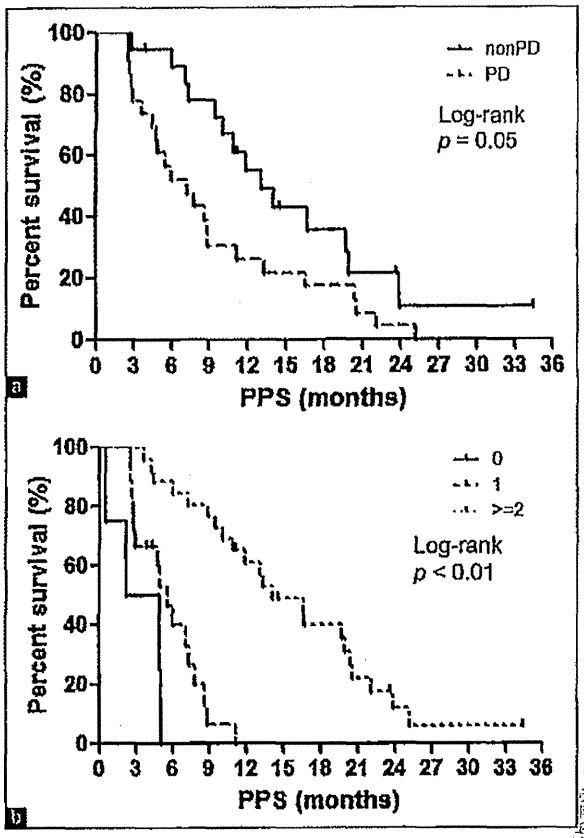

Figure 3: (a)Kaplan-Meier plots showing post-progression survival (PPS), according to the best response following second-line treatment Non-progressive disease (non-PD), median = 13.1 months; progressive disease (PD), median = 7.1 months. (b) Kaplan-Meier plots showing post-progression survival (PPS), according to the number of regimens after progression No further regimen, median = 3.5 months; 1 regimen, median = 5.5 months; 2 regimens, median = 14.1 months

biostatisticians have proposed a wide variety of measures for validating surrogate endpoints.[20,21] Although PFS is a potential surrogate endpoint for OS in extensive stage SCLC[22], its validity remains controversial. Broglio *et al.* recently focused on PPS, which they termed survival post progression (defined as OS minus PFS), in a hypothetical clinical trial setting under the assumption that treatment affected PFS but not PPS.[3] Recently, PPS was found to be strongly associated with OS after first-line chemotherapy for advanced NSCLC in a clinical trial[11,12], and we have previously reported the significance of PPS for advanced NSCLC based on an analysis of individual patients.[13]

In contrast with the findings of a previous study[22], we did not observe that PFS was a surrogate endpoint for OS in extensive stage SCLC, although PPS was not evaluated in the previous study. We analyzed our results pertaining to first-line therapy, which suggested that PFS and tumor response did not adequately reflect OS in such settings. We found that PFS was much shorter than PPS, and thus, PPS was closely related to OS — the relationship was linear. The fact that PPS accounted for the majority of OS suggests that the chemotherapy used was not sufficiently effective for PFS to be a significant component of OS. Thus, in clinical trials with patients expected to have a short PFS after first-line chemotherapy, for example those with extensive SCLC, as was the case in our study, factors that affect PPS need to be considered.

Based on trial-level data for advanced NSCLC, a long PPS is associated with a good PS and the use of first-line monotherapy with a molecular targeted agent.[11] Studies based on individual advanced NSCLC patients revealed that a long PPS was associated with the PS at the beginning of second-line treatment, the best response after second-line treatment (non-PD/PD), and the number of regimens employed after disease progression following first-line chemotherapy.[13] To date, however, no predictive factors for PPS in cases of extensive SCLC have been identified. We studied the prognostic value of baseline factors for PPS in individual patients. We found that the best response after second-line treatment, and the number of regimens employed after progression following first-line chemotherapy were strongly associated with PPS. Moreover, we confirmed the significance of these relationships using log-rank tests. Our findings suggest that patients for whom the disease has been controlled with second-line treatment achieve prolonged PPS after progression following first-line chemotherapy. These patients are also likely to be able to continue chemotherapy and achieve prolonged PPS, which is associated with a longer OS. The number of treatment regimens used after progression following first-line chemotherapy probably reflects the increasing number of available drugs, such as amrubicin, paclitaxel, and topotecan, which are available as second- or third-line chemotherapy for extensive SCLC. In fact, a number of different agents were used to treat our patients, as shown in Table 2.

This study has several limitations. First, the sample size was small. However, because relatively few extensive SCLC patients are treated with first-line cisplatin and irinotecan at our institution, this limitation is difficult to overcome, especially as the patients needed to have similar background characteristics. Nevertheless, our institution treats the relatively largest number of such cases, and the practice policy is largely unified simply because this is a single institution. There is of course some bias, but understanding the nature of this bias ensures that the results are still meaningful. In a future study, we will include a larger patient cohort, and more detailed examination is warranted. Second, we could not thoroughly evaluate treatments after progression following second-line chemotherapy, although only a few patients received third-line or subsequent chemotherapy. Third, the date on which a response was recorded was decided by each physician, which might have introduced variance in the PFS and tumor response rate. Fourth, chemotherapy regimens differ between Japan and the USA. In Japan, based on the results of a Japanese phase III trial[14], standard first-line chemotherapy for extensive SCLC currently is cisplatin combined with irinotecan. This combination is also described in the National Comprehensive Cancer Network guidelines as a suitable treatment option. Amrubicin is an effective second-line chemotherapy drug in a number of cancers including SCLC. In a phase III trial, it resulted in a significantly improved response rate compared to topotecan and also improved survival, especially in the subgroup of refractory patients.[23] On the basis of this trial,

amrubicin is now the standard second-line chemotherapy agent for extensive SCLC in Japan.

In conclusion, using individual patient data, PFS and tumor response were not found to be ideal surrogates for OS in patients with extensive SCLC who had limited options for subsequent chemotherapy. However, in these patients, PPS, rather than PFS, was strongly associated with OS. In addition, the best response after second-line treatment (non-PD/PD), and the number of regimens employed after disease progression following first-line chemotherapy were prognostic factors for PPS. Thus, the treatment course after progression following first-line chemotherapy greatly influences OS. We believe these findings justify further study to validate PPS as a surrogate marker of OS in patients with extensive SCLC.

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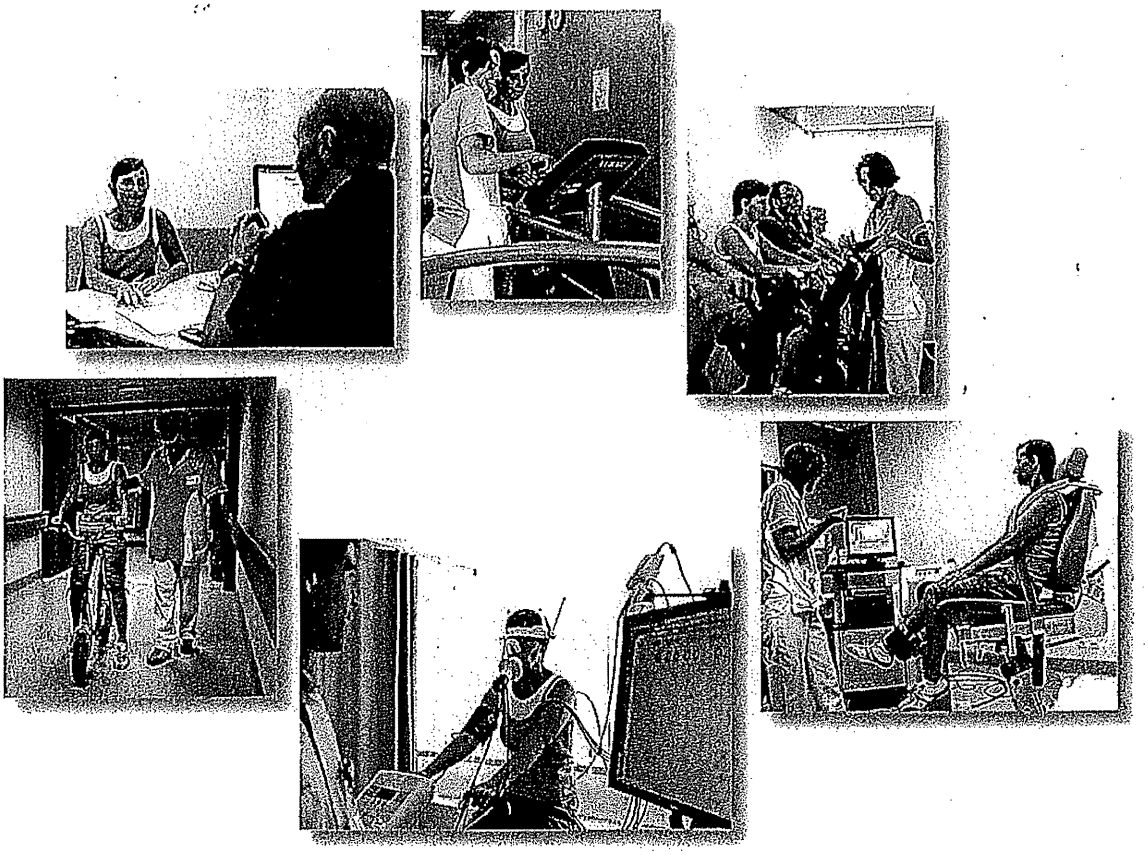

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Feasibility and Accuracy of Molecular Testing in Specimens Obtained with Small Biopsy Forceps: Comparison with the Results of Surgical Specimens

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Key Words
Bronchoscopy · Ultrathin bronchoscopy · Genotyping · *EGFR* · *KRAS* · *ALK* · Endobronchial ultrasound

Abstract
Background: During bronchoscopy, small biopsy forceps are increasingly used for the diagnosis of peripheral pulmonary lesions. However, it is unclear whether the formalin-fixed paraffin-embedded specimens sampled with the small biopsy forceps are suitable for the determination of genotypes which become indispensable for the management decision regarding patients with non-small cell lung cancer. ***Objectives:*** The aim of this study was to evaluate the feasibility and accuracy of molecular testing in the specimens obtained with 1.5-mm small biopsy forceps. ***Methods:*** We examined specimens in 91 patients, who were enrolled in our previous 3 studies on the usefulness of thin bronchoscopes and given a diagnosis of non-small cell lung cancer by bronchoscopy with the 1.5-mm biopsy forceps, and then underwent surgical resection. An experienced pathologist examined paraffin-embedded specimens obtained by bronchoscopic biopsy or surgical resection in a blind fashion on epidermal growth factor receptor *(EGFR)* mutations, anaplastic lymphoma kinase *(ALK)* rearrangements and *KRAS* mutations. ***Results:*** Twenty-five (27%), 2 (2%) and 5 (5%) patients had an *EGFR* mutation, *ALK* rearrangement and *KRAS* mutation, respectively, based on the results in surgical specimens. *EGFR*, *ALK* and *KRAS* testing with bronchoscopic specimens was feasible in 82 (90%), 86 (95%) and 83 (91%) patients, respectively. If molecular testing was feasible, the accuracy of *EGFR*, *ALK* and *KRAS* testing with bronchoscopic specimens for the results with surgical specimens was 98, 100 and 98%, respectively. ***Conclusion:*** The results of molecular testing in the formalin-fixed paraffin-embedded specimens obtained with the small forceps, in which the genotype could be evaluated, correlated well with those in surgically resected specimens.

Introduction

Bronchoscopy has been widely used for the diagnosis of peripheral pulmonary lesions; however, the diagnostic yield of conventional bronchoscopy for peripheral pulmonary lesions, particularly small lesions, has not been satisfactory [1, 2]. Recent modifications of this procedure using some new devices, such as endobronchial ultrasound [3–12], thin bronchoscopes [8, 11, 13], navigation

Preliminary data were previously presented at the ATS 2013 Annual Meeting in Philadelphia, Pa., USA.

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devices [3, 4, 6, 7, 10], or a guide sheath [3–5, 7, 9, 10], dramatically increased the diagnostic yield of bronchoscopy, and seem to be reasonable as a first diagnostic test in terms of accuracy and safety [1, 2]. Traditionally, bronchoscopes with a 2.0-mm working channel have been considered standard, and so 1.8- or 1.9-mm biopsy forceps which are available for the 2.0-mm working channel have been most widely used [14]. On the other hand, several investigators reported the usefulness of a thin guide sheath for the 2.0-mm working channel [3–5, 7, 9–12] or thin bronchoscopes with a 1.7-mm working channel [8, 11, 13]. The standard-sized biopsy forceps are not available for such modified bronchoscopy, and so 1.5-mm biopsy forceps have been used. The small biopsy forceps are now commercially available and increasingly used in clinical practice. Although the size of samples obtained with the forceps is relatively small, many investigators have reported its good ability to sample tissues for definitive diagnosis [3–5, 7–13].

Recent advancement in the field of genomics has enabled the development of some useful molecular targets such as epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors or anaplastic lymphoma kinase (ALK) inhibitors. *EGFR* mutations and *ALK* rearrangements have been demonstrated to be a reliable predictive biomarker of the efficacy of the EGFR-tyrosine kinase inhibitors and ALK inhibitors, respectively [15–18]. Thus, the determination of genotypes has become indispensable for the management decision in patients with non-small cell lung cancer (NSCLC) who might potentially benefit from these molecular targets. As a consequence, the diagnosis of NSCLC should include genotyping as well as subtype classification [1, 14, 19–22]. Although various bronchoscopic specimens are available for genotyping [23–30], formalin-fixed paraffin-embedded specimens have been most widely employed in clinical practice because of their easy use, long-time storage and low costs [14]. Although the feasibility and reliability of genotyping in formalin-fixed paraffin-embedded bronchoscopic specimens obtained with standard-size forceps are well-established [23], it remains unclear whether the specimens sampled with the small biopsy forceps are suitable for genotyping. As a consequence, the clinical use of the small biopsy forceps in place of the standard-sized biopsy forceps during bronchoscopy has not yet been justified. The aim of this study was to evaluate the feasibility and accuracy of genotyping in the relatively small specimens obtained with the 1.5-mm small biopsy forceps by comparing large surgical specimens.

Patients and Methods

Patients

We reviewed our previous 3 studies [8, 11, 13] conducted from 2005 to 2009, which evaluated the diagnostic yield of thin bronchoscopy or bronchoscopy with a thin guide sheath for peripheral pulmonary lesions. In those studies, 1.5-mm small biopsy forceps (FB-32D/XBO1–951/FB-233D; Olympus; Tokyo, Japan) were used for sampling specimens. Of the 372 patients analyzed in those studies, 94 were given a diagnosis of NSCLC by bronchoscopy and underwent surgical resection. Informed consent was obtained from live patients, and 3 patients refused to participate in this study. Thus, a total of 91 patients were enrolled and analyzed. The institutional review board of Nagoya Medical Center approved this study (identifier: 2011-482).

Molecular Testing

At the Department of Pathology, Nagoya Medical Center, six 4-μm-thick unstained sections from bronchoscopic biopsy and corresponding surgical specimens were prepared, and were sent to the Molecular Pathology Laboratory of the Aichi Cancer Center Hospital. Because this study was conducted simulating the routine diagnosis, individual samples were processed as usual. The unstained slides, of which identification numbers were randomly labeled, were submitted to the pathologists. Although the specimens could be differentiated as to whether they were obtained by surgery or bronchoscopy, the correspondences between surgical and bronchoscopic specimens were completely blinded. After confirmation of tumor cell contents on re-sectioned slides for molecular testing, genotypes of *EGFR*, *KRAS* and *ALK* were assessed. For *EGFR* mutation, the Cycleave polymerase chain reaction (PCR) technique and fragment analysis were used for the detection of *EGFR* L858R and exon 19 deletion, respectively, as described previously [31]. Similarly, *KRAS* mutation was analyzed by the Cycleave PCR technique. *ALK* gene rearrangements were screened with immunohistochemistry using sensitive *ALK* antibody (clone 5A4, Santa Cruz, Calif., USA) and the EnVision FLEX+ detection system (Dako, Copenhagen, Denmark). When positive or equivocal results were obtained with the immunohistochemistry, further confirmatory fluorescent in situ hybridization was carried out using an *ALK* break-apart probe (Vysis LSI ALK Dual Color, Break Apart Rearrangement Probe; Abbott Molecular, Abbott Park, Ill., USA) as previously described [32, 33].

Results

Patients

Bronchoscopic specimens and surgical specimens from a total of 91 Japanese patients (63 males and 28 females; median age 65; range 25–83 years) were retrospectively evaluated. Sixty-four patients had adenocarcinoma, 21 had squamous cell carcinoma, 3 had large cell carcinoma, 2 had a combination of adenocarcinoma and squamous cell carcinoma, and 1 had a combination of small cell carcinoma and adenocarcinoma. The median lesion size in the longest diameter on CT was 28 mm (range

Table 1. Results of EGFR testing

Variable	Type of specimens	
	bronchoscopic specimens	surgical specimens
Specimens examined	86	91
Specimens with *EGFR* mutations	21	25
Fragment analysis		
Exon 19	13	15
Wild type	71	75
No PCR amplification	2	1
Cycleave PCR		
L858R	8	10
Wild type	74	81
No PCR amplification	4	0

Data are presented as number.

Table 2. Results of ALK testing

Variable	Type of specimens	
	bronchoscopic specimens	surgical specimens
Specimens examined	86	91
Specimens with *ALK* rearrangements	2	2
IHC		
Positive	2	2
Equivocal	1	2
Negative	83	87
FISH (for IHC positive or equivocal cases)		
Positive	2	2
Negative	1	2

Data are presented as number. IHC = Immunohistochemistry; FISH = fluorescent in situ hybridization.

11–65 min). Routine hematoxylin and eosin stain had been performed, followed by further immunohistochemical stains for definitive diagnosis in bronchoscopic specimens at the time of diagnosis in 20 of 91 (22%) patients. After NSCLC was diagnosed with bronchoscopic biopsy using a 1.5-mm biopsy forceps, 77 patients underwent lobectomy, 9 segmentectomy, and 5 wedge resection. The pathological tumor and nodal stages based on the surgical procedures were as follows: T1 in 33, T2 in 40, T3 in 16 and T4 in 2; N0 in 52, N1 in 18, N2 in 12 and no nodal dissection or sampling in 9.

Re-Evaluation of Sectioned Slides for Molecular Testing

All specimens essentially contained tumor cells diagnosed as cancer, but tumor cells might have disappeared with slides re-sectioned for molecular analysis. Therefore, we checked and confirmed sufficient contents of tumor cells for molecular testing in 86 of 91 (95%) biopsy specimens, and all (100%) surgical specimens.

Mutations

Results of *EGFR* mutation detection are shown in table 1. *EGFR* mutations were detected in the surgical specimens in 25 patients (27%; exon 19 in 15 patients and L858R in 10 patients). Of the 25 patients, *EGFR* mutation could not be detected in the bronchoscopic specimens in 4 patients including 2 without analysis of mutations because of specimens with no tumor cells; thus, *EGFR* mutations were detected in the bronchoscopic specimens in 21 (23%) patients. All patients with *EGFR* mutations had adenocarcinoma. In the surgical specimens, PCR amplification failed in one patient, and so gene analysis for both exon 19 and L858R was feasible in 90 of 91 patients (99%). In the bronchoscopic specimens, gene analysis was feasible in 82 (excluding no tumor cells in 5 and no PCR amplification with either fragment analysis or Cycleave PCR technique in 4) of 91 patients (89%). In 81 patients in whom gene analysis with both bronchoscopic and surgical specimens was feasible, the sensitivity, specificity and accuracy for detection of *EGFR* mutations with bronchoscopic specimens based on the results with surgical specimens was 91, 100 and 98%, respectively.

Results of *ALK* gene rearrangement detection are shown in table 2. *ALK* rearrangements were detected in the surgical specimens in 2 patients (2%), which corresponded to the results in the bronchoscopic specimens. The 2 patients had adenocarcinoma. The feasibility of *ALK* testing was 100% (all 91 patients) in surgical specimens and 95% (86 of 91 patients) in bronchoscopic specimens. In patients in whom *ALK* testing was feasible, the accuracy of *ALK* testing in the bronchoscopic specimens was 100%.

Results of *KRAS* mutation detection are shown in table 3. *KRAS* mutations were detected in the surgical specimens in 5 patients (5%; G12 mutation in 5 patients). The analysis with bronchoscopic specimens proved *KRAS* negative in 1 of the 5 *KRAS*-positive patients in surgical specimens. In addition, *KRAS* testing with bronchoscopic specimens resulted in *KRAS* positive in 1 patient who was judged as *KRAS* negative in the testing with the surgical specimens (fig. 1). All but 1 *KRAS*-positive patient with squamous cell carcinoma

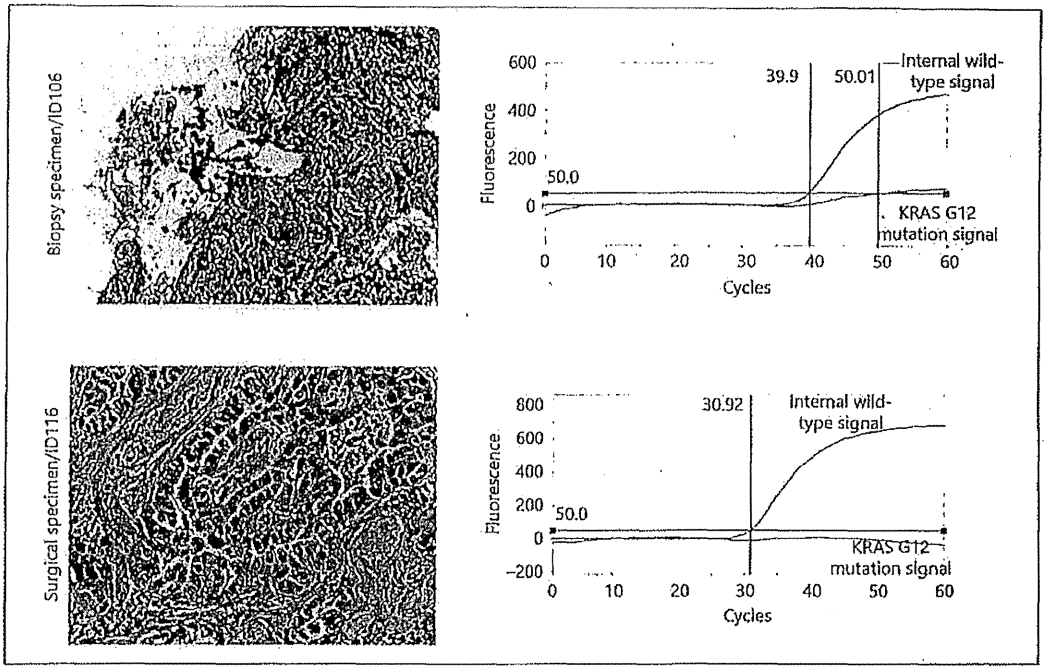

Fig. 1. Bronchoscopic and surgical specimens in a patient showed discordant results in *KRAS* mutation. A few adenocarcinoma cells were clustered in the bronchoscopic specimen (upper left), appearing to be degenerative. Hematoxylin and eosin staining. ×200, original magnification. The result of *KRAS* mutation assay (upper right) showed a slight increase in the *KRAS* G12 mutation signal that reached the cutoff value of 50 fluorescence intensity. In contrast, the surgical specimen had a sufficient number of tumor cells (lower left). Hematoxylin and eosin staining. ×200, original magnification. The same specimen had no increase in the signal of KRAS G12 mutation (lower right).

Table 3. Results of KRAS testing

Variable	Type of specimens	
	bronchoscopic specimens	surgical specimens
Specimens examined	86	91
Specimens with *KRAS* mutations	5[a]	5
Cycleave PCR		
G12	5	5
Wild type	78	85
No PCR amplification	3	1

Data are presented as number. [a] Suspected false-positive result in 1.

had adenocarcinoma. Testing for *KRAS* mutations with surgical specimens and bronchoscopic specimens was feasible in 90 of 91 (99%) patients and 83 of 91 (91%) patients, respectively. In 82 patients in whom gene analyses with both bronchoscopic specimens and surgical specimens were feasible, the sensitivity, specificity and accuracy of *KRAS* mutation analysis with bronchoscopic specimens based on the results with surgical specimens were 80, 99 and 98%, respectively.

A flow chart of patients for molecular testing is shown in figure 2.

Finally, a total of 13 patients had incorrect results with bronchoscopic specimens (no tumor cells in 5, no PCR amplification for either genotyping in 4, and a false-positive or false-negative result of genotypes based on the results with surgical specimens in 4). Thus, molecular testing using bronchoscopic specimens could be correctly performed in 78 of 91 (86%) patients (bronchoscopic specimens: 78 of 91 vs. surgical specimens: 90 of 91, p = 0.001, Fisher's exact test). Immunohistochemical stains with bronchoscopic specimens had been performed at the time of diagnosis in 14 of 78 (18%) patients with concordant results with surgical specimens and 6 of 13 (46%) patients with infeasible molecular testing or discordant results with surgical specimens (p = 0.03, Fisher's exact test).

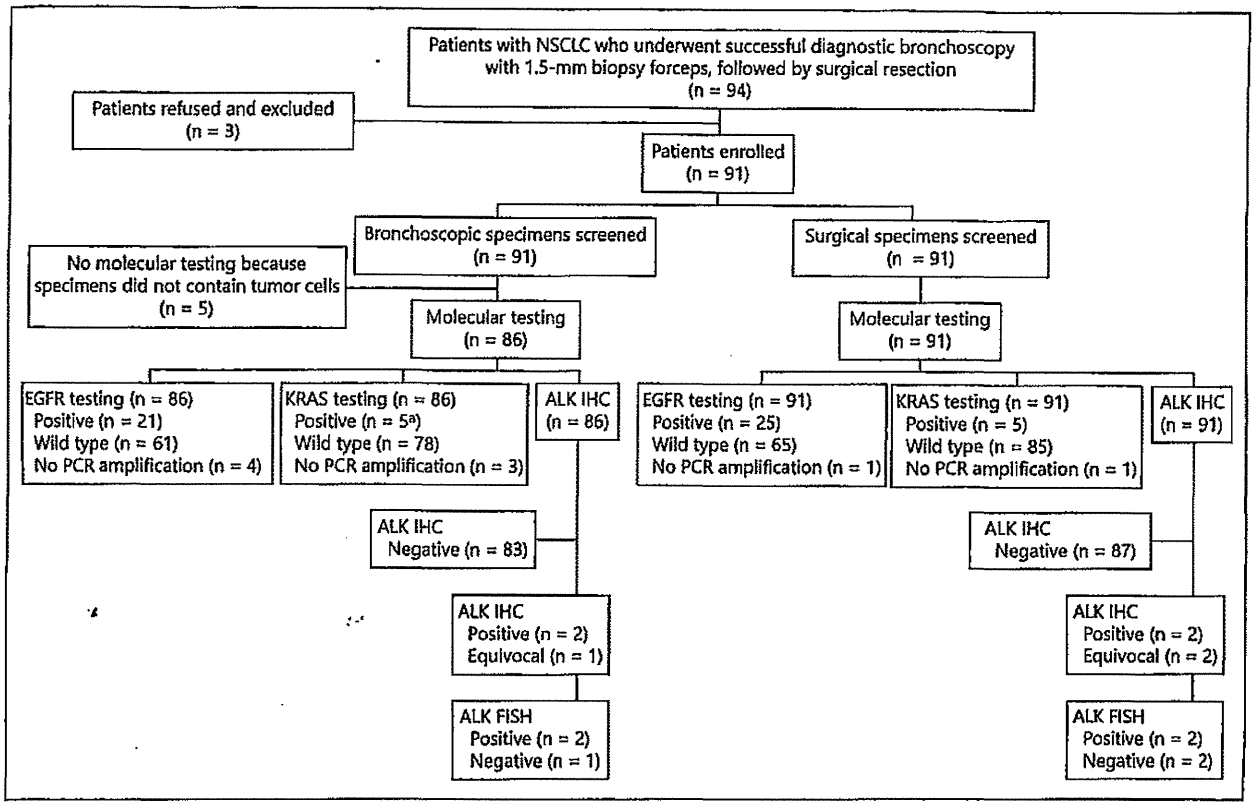

Fig. 2. A flow chart of patients for molecular testing. [a] One suspected false-positive result is included. FISH = Fluorescence in situ hybridization; IHC = immunohistochemistry.

The results of 6 patients with positive but discordant results of genotypes between bronchoscopic and surgical specimens are summarized in table 4.

Discussion

In this study, we investigated the feasibility and accuracy of genotyping within the limited size of specimens obtained with the 1.5-mm biopsy forceps by comparing surgical specimens. Our study demonstrated the high feasibility of approximately 90% for genotyping in the specimens obtained with the small biopsy forceps notwithstanding the use of samples which had been preserved for several years. In addition, the results of genotypes in the specimens, which could be examined for the genotypes, correlated well with the results from large specimens obtained with surgical resection. To our knowledge, this is the first study to evaluate the feasibility and accuracy of genotyping in the samples obtained with the small forceps.

Discovery of driver mutations such as *EGFR*, *ALK* and *KRAS* in the specimens from patients with NSCLC has revolutionized the management of NSCLC, especially adenocarcinoma. *EGFR* mutations have been proved to be a reliable predictive biomarker of both progression-free survival as well as tumor response to treatment with EGFR-tyrosine kinase inhibitors [15–17]. Similarly, *ALK* rearrangements are associated with progression-free survival and tumor response to treatment with ALK inhibitors [18]. In contrast to these molecular abnormalities, the clinical value of knowing *KRAS* mutations is still limited since the targeted therapies are still not available, although some promising agents which inhibit part of the *KRAS* pathway are now being investigated [22, 34]. A recent molecular testing guideline recommended *EGFR* mutation testing or suggested *ALK* rearrangement testing at the time of diagnosis in patients with advanced-stage disease who are suitable for therapy [22]. Moreover, even in patients with early-stage disease, the *EGFR* mutation or *ALK* rearrangement testing at diagnosis is encouraged.

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Table 4. Cases with discordant genotypes between bronchoscopic and surgical specimens

No.	Sex	Age, years	Histology	Mutation	Type of specimens		Interpretation of results in bronchoscopic specimens
					bronchoscopic specimens	surgical specimens	
1	F	80	ADC	*EGFR* (exon 19)	not examined	positive	no tumor cells
2	M	62	ADC	*EGFR* (exon 19)	not examined	positive	no tumor cells
3	F	55	ADC	*EGFR* (L858R)	negative	positive	false-negative result for few tumor cells
4	F	65	ADC	*EGFR* (L858R)	negative	positive	false-negative result for small ratio of tumor cells to non-tumor cells
5	M	75	ADC	*KRAS* (G12)	negative	positive	false-negative result for few tumor cells
6	M	61	ADC	*KRAS* (G12)	positive	negative	false-positive result for equivocal fluorescence intensity in bronchoscopic specimen

ADC = Adenocarcinoma.

as the results may provide some benefits in terms of portability [22]. Thus, not only high yield for definitive diagnosis but also high feasibility and reliability for molecular testing is indispensable as a first diagnostic test. Nowadays, numerous types of cytologic and histologic samples can be used for molecular testing [35]. Above all, formalin-fixed paraffin-embedded samples, as we used in this study, have been most widely used for molecular testing as they have numerous advantages such as ease of use, long-time storage and low costs [14]. In fact, we used paraffin-embedded specimens preserved for more than 2 years without any special storage techniques. The feasibility of molecular testing in long-time stored specimens seems to be very important because new driver mutation genes and targeted therapies are developing one after another. The feasibility and reliability of molecular testing using bronchoscopic specimens such as specimens obtained with aspiration standard biopsy forceps or aspiration needles are well established [35]. Our study further demonstrated the usefulness of relatively smaller bronchoscopic specimens with fewer tumor cells obtained by small biopsy forceps for molecular testing.

In this study, 5 patients failed genotyping with bronchoscopic specimens due to an insufficient number of tumor cells. Although we regularly biopsied 8–10 tissue samples in individual patients [8, 11, 13], the specimens in the 5 patients only had a few tumor cells that did not allow molecular testing. Resectioning of the tissue blocks could waste the tissues, and might reduce a number of tumor cells in some instances. Because diagnostic hematoxylin and eosin staining slides are made of unstained slides, preparation of additional unstained slides might serve to increase the feasibility. Therefore, it might be an alternative way to submit the specimens with ordering simultaneous histological diagnosis and molecular testing, based on the potential benefit of molecular testing. In terms of PCR failure, it is well known that the PCR based on formalin-fixed paraffin-embedded samples is affected by fixation time, fixation solution, and the duration of ischemic time and tissue processing techniques including decalcification using strong acids [14, 21, 22, 29]. In fact, the surgical specimen in the patient showing PCR failure contained the costal bone where the tumor cells invaded, suggesting that the tissues were treated with decalcification solution. In the case of bronchoscopic specimens, inadequate fixation duration might cause PCR failure. Because biopsied tissues are usually tiny in contrast to the surgical specimens, the fixation that is optimized for surgical specimens could be too long for biopsy specimens. Careful management according to the sample size might be needed [14, 19–22].

As shown in table 4, the result of genotyping in the surgical specimens and bronchoscopic specimens was discordant in 6 patients. *EGFR* mutations in the bronchoscopic specimens were not analyzed in 2 patients as the specimens did not contain tumor cells. Two patients (1 *KRAS*-negative patient and 1 *EGFR*-negative patient in the bronchoscopic specimens but positive in surgical specimens) had bronchoscopic specimens with few tumor cells in which the mutated signal might be below the detection threshold for mutations. As shown in figure 1, 1 patient with bronchoscopic specimens with a slight increase in fluorescence intensity was judged as *KRAS* positive; however, this result was regarded as false-positive from the negative result in surgical specimens. The re-

maining patient was judged as *EGFR* negative in bronchoscopic specimens with a sufficient amount of tumor cells. Although the reason is unclear, this might be due to the small ratio of tumor cells to nontumor cells. Mutant DNA needs to comprise approximately 1% of the total DNA using DNA-based assays to detect mutations [36]. If the specimen contains a high percentage of nontumor cells, false-negative results may occur, even in specimens with a sufficient amount of tumor cells [37]. Certainly, the number of tumor cells would be associated with the success/failure of molecular testing. Folch et al. [28] compared the amount of tumor cells in the cell block specimens sampled by endobronchial ultrasound-transbronchial needle aspiration between the molecular testing failure group and the success group, and found that a specimen with less than 100 tumor cells per slide was associated with the failure of molecular testing. However, the detection threshold varies according to the detection methods. Actually, a clear positive reaction in a single cell is considered to be positive with *ALK* immunohistochemistry. Interpretation of the negative mutation results in specimens with few tumor cells, so the small ratio of tumor cells to nontumor cells or equivocal results of molecular testing demands great caution. Molecular pathologists should alert the attending physicians about the quality of the molecular testing so as not to cause false-negative or false-positive results.

In conclusion, bronchoscopic specimens obtained by the small biopsy forceps are feasible for genotyping of NSCLC in most cases. The results in the bronchoscopic specimens, in which the genotype could be evaluated, correlated well with those in surgically resected specimens. The clinical use of the small biopsy forceps during bronchoscopy can therefore be justified in terms of high feasibility and accuracy for molecular testing.

Financial Disclosure and Conflicts of Interest

None of the authors has any conflict of interest to disclose.

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Review

Current status and future perspectives of cooperative study groups for lung cancer in Japan

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ABSTRACT

The performance of scientifically and ethically valid prospective clinical trials is the only means by which to obtain reliable clinical evidence that can improve clinical practice and thus the outcome of patients with lung cancer. The efficacy of treatment for advanced lung cancer remains limited; many cooperative study groups for lung cancer have been established in Japan since 1990s, and they have completed several landmark investigator-initiated clinical trials. This review highlights eight active Japanese cooperative study groups for lung cancer and summarizes their achievements made through clinical trials. In addition to their benefits, the existence of multiple study groups for a single disease such as lung cancer presents several challenges including the provision of infrastructure to ensure the scientific integrity of trial results, the unnecessary duplication of effort and the wasting of limited resources, and the accrual and completion of large-scale phase III trials in the shortest possible time. Collaboration among Japanese cooperative groups has recently increased in order to overcome these challenges. Although institutional barriers to the performance of such large intergroup trials remain, further harmonization and collaboration among cooperative groups will be vital in allowing Japanese investigators to make further important contributions for the development of new lung cancer therapies.

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Abbreviations: JCOG, Japan Clinical Oncology Group; SCLC, small cell lung cancer; ED, extensive disease; OS, overall survival; WJOG, West Japan Oncology Group; NSCLC, non-small-cell lung cancer; EGFR, epidermal growth factor receptor; PFS, progression-free survival; TKI, tyrosine kinase inhibitor; OLCSG, Okayama Lung Cancer Study Group; TCOG, Tokyo Cooperative Oncology Group; NPO, nonprofit organization; NEJSG, North East Japan Study Group; CJLSG, Central Japan Lung Study Group; TORG, Thoracic Oncology Research Group; LOGiK, Lung Oncology Group in Kyushu

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1. Introduction

Lung cancer is the most common cause of death from cancer in Japan, being responsible for more than 70,000 deaths annually. Most individuals with lung cancer are already at an advanced stage of the disease at the time of diagnosis. Chemotherapy is the mainstay of treatment for such patients, but their median survival time is limited to ~15 months [1,2]. The development of new treatment strategies to improve the clinical outcome of individuals with this challenging disease is thus a priority.

The establishment of more effective treatments for advanced lung cancer requires the performance of scientifically and ethically valid prospective multicenter clinical trials. The first professional cooperative study group for lung cancer research in Japan was the Japan Clinical Oncology Group (JCOG), which was formed in 1990. Several other cooperative study groups for lung cancer were subsequently established to promote and support multicenter clinical trials of new treatments for this disease. Recently, the "Study for Enhancement of Quality and Efficiency of Cancer Therapeutic Development Research via Collaboration among Cooperative Groups and Designated Cancer Care Hospitals" was established to enhance collaboration of eight selected Japanese cooperative groups for lung cancer. It is supported by the National and Cancer Research Development Fund (26-A-22) and is chaired by Haruhiko Fukuda and Nobuyuki Yamamoto. For this review, we collected information about eight cooperative study groups by direct interviews. This review describes the current status and future challenges of investigator-initiated clinical trials for lung cancer.

2. Clinical Trial Groups in Japan

2.1. *Japan Clinical Oncology Group*

The Japan Clinical Oncology Group (JCOG) was launched in 1990 as a cooperative study group to perform multicenter clinical trials for cancer in Japan (Fig. 1, Table 1). It remains the only Japanese cooperative group supported primarily by a governmental research fund. Staff at the headquarters of JCOG, which includes a Data Center (director, Haruhiko Fukuda) and an Operations Office (director, Kenichi Nakamura), work closely with individual investigators to support the operational aspects of clinical trials. They thus provide help with protocol development, patient registration, reporting of adverse events, data management, and statistical analysis as well as perform regular (twice a year) central monitoring and site visit audits.

The individual study groups of JCOG are currently divided into 16 categories on the basis of specific tumor type or treatment modality. Among them, the Lung Cancer Study Group (LCSG) consists of 38 institutions distributed throughout the country and has conducted several practice-changing clinical trials, in particular for small cell lung cancer (SCLC). The first chair of LCSG was Nagahiro Saijo (1982–2002), who was succeeded by Tomohide Tamura (2002–2014) and then by Yuichiro Ohe (elected in 2014). One of the landmark trials performed by LCSG was a randomized phase III trial comparing cisplatin plus irinotecan with cisplatin plus etoposide (the standard treatment at the time) in chemotherapy-naïve patients with extensive disease (ED)-stage SCLC (JCOG9511) [3]. The trial was terminated early because the planned interim analysis showed a highly significant improvement in overall survival (OS) for patients treated with cisplatin plus irinotecan compared with those who received cisplatin plus etoposide. Although two subsequent large phase III trials in the United States failed to show a significant difference in OS between these two regimens, cisplatin plus irinotecan is now considered the standard regimen for previously untreated patients with ED-SCLC in Japan.

The number of elderly SCLC patients continues to rise with the growing geriatric population, with ~50% of individuals with SCLC now 70 years of age or older. JCOG performed a phase III trial comparing split doses of cisplatin (25 mg/m^2, days 1–3) plus etoposide (80 mg/m^2, days 1–3) (SPE regimen) with carboplatin (area under the curve=5, day 1) plus etoposide (80 mg/m^2, days 1–3) (CE regimen) in elderly (>70 years of age) or high-risk patients with ED-SCLC (JCOG9702) [4]. Although thrombocytopenia of grade 3 or 4 occurred more frequently in the CE arm than in the SPE arm (56% versus 14%, $P<0.01$), both regimens were found to be feasible and active, yielding a median OS of ~10 months. On the basis of the results of this phase III study, the CE regimen is now commonly used for elderly untreated patients with ED-SCLC. JCOG has recently initiated a randomized phase III trial comparing carboplatin plus irinotecan with the CE regimen for elderly (≥70 years) chemotherapy-naïve patients with ED-SCLC (JCOG1201) (Fig. 2A).

2.2. *West Japan Oncology Group*

The West Japan Thoracic Oncology Group (WJTOG) was established in 1992 as an expert group specific for lung cancer (Table 1). It was initially named the West Japan Lung Cancer Study Group, and it subsequently became the West Japan Oncology Group (WJOG) after joining gastrointestinal and breast

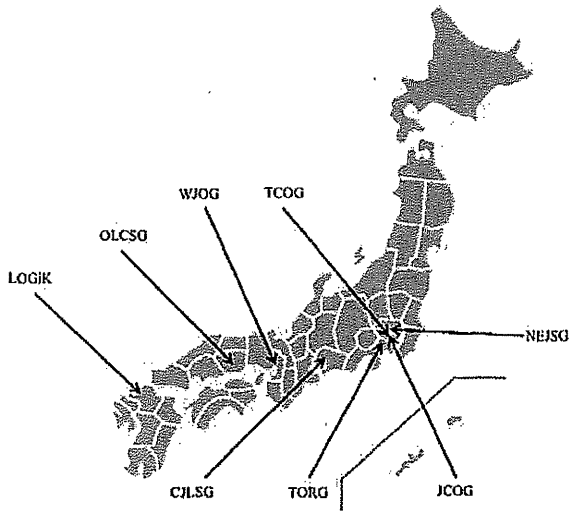

Fig. 1 – Cooperative study groups for lung cancer in Japan.

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Table 1 – Characteristics of the clinical study groups for lung cancer in Japan.

Group	Year established	Chairman	Number of facilities	Allowance for personal membership	Number of members	Data center	Financial resource	Phase III studies	References
JCOG	1990	Yuichiro Ohe	38	+	4600	+	A	+	[3,4]
WJOG	1992	Yoichi Nakanishi	187	+	1000	+	A, C, D, E	+	[1,5,6]
OLCSG	1995	Katsuyuki Kiura	20	+	110	−	D	+	[7]
TCOG	2001	Minoru Kurihara	37	+	77	−	C, D, E	+	[8,9]
GILSG	2003	Hiroshi Saito	30	+	100	−	A, B, C, D	−	[10–12]
TORG	2004	Koshiro Watanabe	52	+	90	+	C, D	−	[13–16]
LOGIK	2004	Hiroshi Semba	89	+	322	−	F	−	[17,18]
NEJSG	2006	Toshihiro Nukiwa	108	+	20	−	A, C, D	+	[19–21]

A: National grant, B: Other grant, C: Donation, D: Membership fee, E: Consigned research fund, F: Clinical Research Support Center Kyushu.
Japan Clinical Oncology Group, JCOG; West Japan Oncology Group, WJOG; Okayama Lung Cancer Study Group, OLCSG; Tokyo Cooperative Oncology Group, TCOG; Central Japan Lung Study Group, GILSG; Thoracic Oncology Research Group, TORG; Lung Oncology Group in Kyushu, LOGIK; North East Japan Study Group, NEJSG.

cancer groups in the late 2000s. Hiroshi Ariyoshi, the original chair of WJTOG, was succeeded in 2004 by Masahiro Fukuoka, who in turn was succeeded in 2009 by Yoichi Nakanishi. The missions of WJOG are to carry out clinical trials and to educate oncologists and patients with regard to appropriate cancer treatments and clinical studies. The data center was initially set up in 1998 at Kinki University Faculty of Medicine under the direction of Kazuhiko Nakagawa, and it subsequently relocated to Namba, Osaka, in 2004 (Fig. 1). At present, the WJOG Data Center is staffed by eight data managers led by Shinichiro Nakamura and ensures the adequacy, integrity, and quality of the data for patients enrolled in clinical trials. A total of 187 institutions across the country participate in clinical lung cancer research performed by WJOG.

WJTOG performed a multicenter, randomized, open-label, phase III trial (WJTOG3405) of first-line treatment with gefitinib versus cisplatin plus docetaxel in patients with advanced non-small-cell lung cancer (NSCLC) positive for activating mutations of the epidermal growth factor receptor (EGFR) gene [5]. The study demonstrated the superiority of gefitinib over cisplatin plus docetaxel in terms of its primary end point of progression-free survival (PFS). This was the first published report establishing the proof of concept that molecularly targeted agents are far more effective than conventional chemotherapy when administered to the appropriate genetically defined patient population. WJOG is currently conducting a phase III trial for patients with completely resected EGFR mutation-positive NSCLC of p-stage II or III. In this trial (WJOG6410L), patients are randomized to receive gefitinib (250 mg/day, 2 years) or cisplatin plus vinorelbine (four cycles), and the primary end point is disease-free survival.

WJOG also has two ongoing phase III trials of continuation maintenance therapy for advanced NSCLC. In WJOG5610L, patients with advanced nonsquamous NSCLC negative for EGFR mutations are initially treated with the combination of pemetrexed, carboplatin, and bevacizumab (Fig. 2B). Those individuals who complete four cycles of this treatment without disease progression are then randomized to receive bevacizumab alone or bevacizumab plus pemetrexed, with the goal of identifying an optimal maintenance regimen that improves OS. WJOG recently completed a multicenter randomized phase III study comparing carboplatin plus S-1 with carboplatin plus paclitaxel as a first-line treatment in patients with advanced NSCLC [1]. The primary objective of this Lung Cancer Evaluation of TS-1 (LETS) study—determination of the non-inferiority of carboplatin and S-1 compared with carboplatin and paclitaxel in terms of OS—was met. On the basis of the trial results, the Japanese guidelines for lung cancer treatment were updated to include carboplatin plus S-1 as one of the standard platinum-based regimens for first-line treatment of advanced NSCLC. Subsequent survival analysis according to histological subtype of NSCLC revealed that carboplatin plus S-1 showed a tendency to improve OS, with a 3.4-month increase in median OS compared with carboplatin plus paclitaxel (14.0 months versus 10.6 months; hazard ratio of 0.713 and 95% confidence interval of 0.476–1.068), for patients with squamous NSCLC [6]. This outcome is of particular interest because of the limited therapeutic options available for this patient population compared with patients with nonsquamous cell carcinoma. On the basis of

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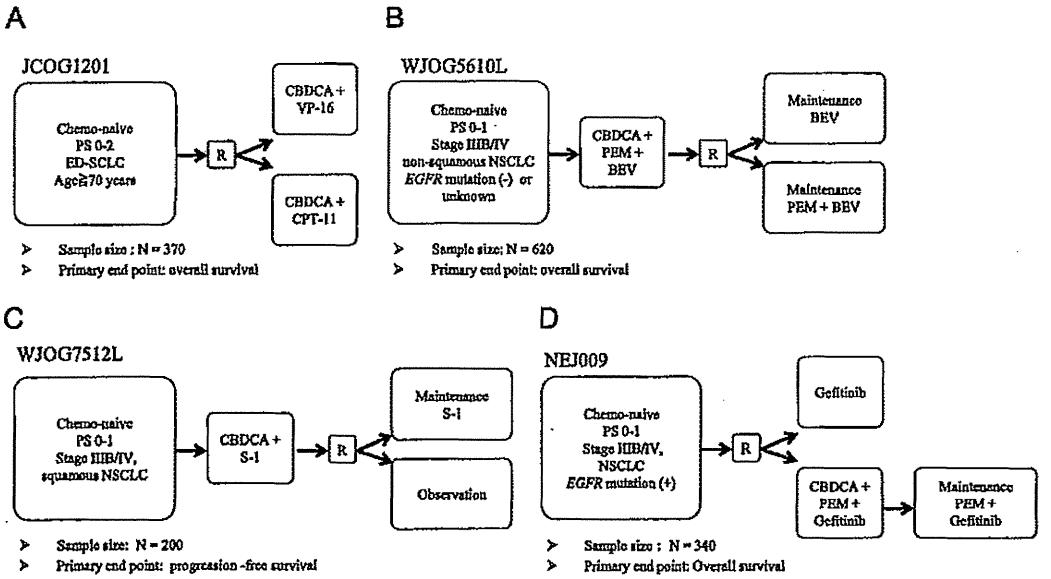

Fig. 2 – Ongoing phase III trials for advanced lung cancer in Japan. (A) JCOG1201. (B) WJOG5610L. (C) WJOG7512L. (D) NEJ009. Abbreviations: PS, performance status; R, randomization; CBDCA, carboplatin; VP-16, etoposide; CPT-11, irinotecan; PEM, pemetrexed; BEV, bevacizumab.

these results, WJOG is now conducting a randomized phase III trial for squamous NSCLC (WJOG7512L) (Fig. 2C), in which patients treated with four cycles of carboplatin plus S-1 are randomized to receive single-agent S-1 maintenance therapy or observation. Depending on the outcome, this would be the first study to establish the benefit of maintenance therapy for patients with squamous NSCLC.

Collaboration with JCOG is also an important activity of WJOG. JCOG1210/WJOG7813L, a randomized phase III trial comparing single-agent docetaxel with pemetrexed plus carboplatin followed by pemetrexed maintenance for elderly (≥75 years) individuals with nonsquamous NSCLC, is ongoing (Fig. 3A).

2.3. *Okayama Lung Cancer Study Group*

The Okayama Lung Cancer Study Group (OLCSG) was founded in 1995 to conduct multi-institutional clinical trials and now consists of 20 institutions in the Chugoku and Shikoku districts affiliated with the former Second Department of Internal Medicine at Okayama University Medical School (Table 1). During the last two decades, the group has published more than 20 research studies, some of which have been included in meta-analyses of prophylactic cranial irradiation in patients with SCLC and of thoracic irradiation and chemotherapy in those with limited disease SCLC. More recently, OLCSG performed a phase III trial of cisplatin, docetaxel, and concurrent thoracic irradiation in patients with locally advanced NSCLC (OLCSG 0007), the results of which informed the Japanese guidelines for the treatment of NSCLC [7]. The data for OLCSG 0007 were managed at Okayama University and Aichi Cancer Center Research Institute, whereas the statistical analysis was performed at the latter institution. OLCSG has not outsourced data management to an independent external data center, but it is now planning to do so for better quality assurance.

Over the last decade, substantial progress has been made in the development of genotype-based targeted therapies for advanced NSCLC. The discovery of somatic mutations in the tyrosine kinase domain of the EGFR and of the association of such mutations with a high response rate to EGFR tyrosine kinase inhibitors (EGFR-TKIs) such as gefitinib and erlotinib has had a profound impact on the treatment of metastatic NSCLC. This molecular basis for therapy selection may also be applicable to patients with locally advanced NSCLC, for whom targeted therapies remained to be established. OLCSG and LOGiK (see Section 2.7) are now conducting an intergroup trial to evaluate induction therapy with single-agent gefitinib followed by cisplatin, docetaxel, and concurrent thoracic irradiation for patients with EGFR mutation-positive locally advanced NSCLC (Fig. 3B).

2.4. *Tokyo Cooperative Oncology Group (TCOG)*

The Tokyo Cooperative Oncology Group (TCOG) was established in 1972 for the purpose of performing multi-institutional cooperative clinical trials of treatments for inoperable cancers of various organs, with Kiyoji Kimura (a former vice director of National Cancer Center Hospital) as its first organizer (Table 1). Its early research results with N1-(2-tetrahydrofuryl)-5-fluorouracil (FT-207) in 1974 and with 5-fluorouracil (5-FU) in 1975 led to the approval of these agents for clinical use in Japan. On the basis of its active clinical studies and continuing educational activities including monthly medical conferences and annual summer seminars, the group was certified as a nonprofit organization (NPO) by the Tokyo Metropolitan Government in 2001. The first leaders included Hisanobu Niitani as president and five other directors.

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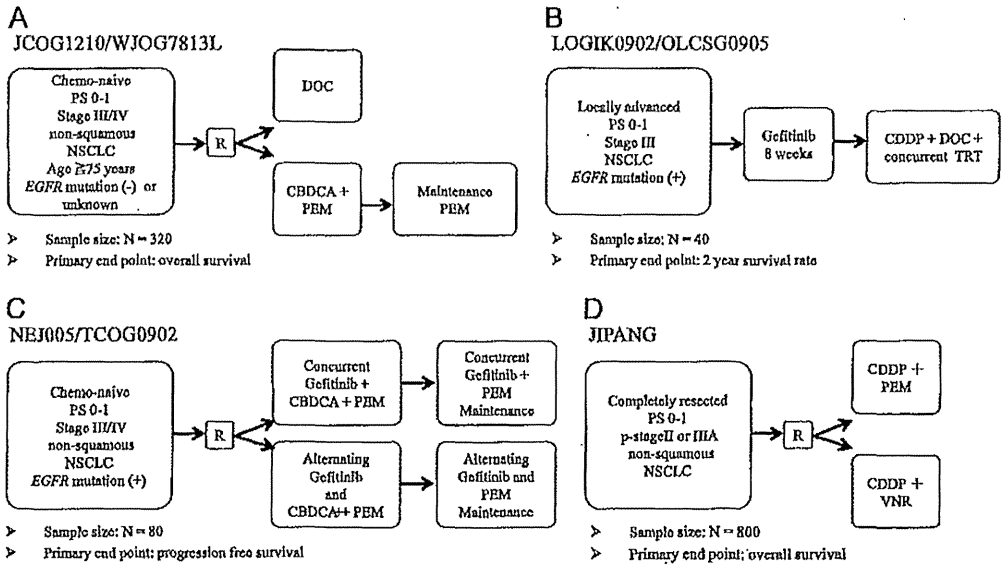

Fig. 3 – Recent intergroup trials for lung cancer in Japan. (A) JCOG1210/WJOG7813L. (B) LOGIK0902/OLCSG0905. (C) NEJ005/TCOG0902. (D) JIPANG. Abbreviations: PS, performance status; R, randomization; DOC, docetaxel; CBDCA, carboplatin; PEM, pemetrexed; TRT, thoracic radiotherapy; p-stage, pathological stage; CDDP, cisplatin; VNR, vinorelbine.

TCOG now consists of 37 institutions and is currently conducting clinical trials mostly in thoracic and gastrointestinal oncology. It has a clinical trial registration center and six committees for academic planning, clinical trial planning, clinical trial evaluation, overall trial monitoring, data and safety monitoring, and statistical analysis. For phase I and II studies, data management is carried out by the clinical trial registration center, and statistical considerations and analysis are the responsibility of the principal investigators with voluntary consultation of the statistical analysis committee. Because of a shortage of human resources, however, data management and statistical analysis for phase III studies are largely outsourced. TCOG has held monthly conferences for the past 33 years with ~70 participants at each meeting and annual summer seminars for the past 14 years with ~500 multidisciplinary team professionals in attendance. It has published >30 research articles on clinical trials in Japanese or English, which were accompanied by presentations at various medical conferences including those of the Japan Society of Clinical Oncology, American Society of Clinical Oncology, and European Society for Medical Oncology [8,9]. Since 2006, TCOG has also cooperated with the North East Japan Study Group (NEJSG, see Section 2.8) on lung cancer trials, with more than seven trials to date (Fig. 3C).

2.5. *Central Japan Lung Study Group*

The Central Japan Lung Study Group (CJLSG) was established in 2003 as an NPO to promote the prevention and diagnosis of, the performance of clinical trials for, and education about respiratory diseases (Table 1). The first chairperson of the group was Kaoru Shimokata. CJLSG consists of 30 facilities located mainly in central Japan, and most of its members are medical doctors who work in regional or university hospitals. CJLSG is supported by member fees and donations, and it holds educational seminars on several aspects of respiratory medicine including clinical trials, bronchoscopy, and clinical statistics for young doctors.

CJLSG has published the results of several clinical trials in international scientific journals [10–12] and is currently conducting 14 trials related to pneumonia, molecular biology, supportive care, and chemotherapy in lung cancer patients. CJLSG is now planning PREDICT1, a prospective observational survey of predictors of responses based on the analysis of blood samples for chemotherapy with carboplatin plus pemetrexed in patients with nonsquamous NSCLC.

2.6. *Thoracic Oncology Research Group*

The Thoracic Oncology Research Group (TORG) was founded as an NPO in 2004 (Table 1). It currently consists of 52 collaborative institutions, and it is chaired by Koshiro Watanabe; the TORG has published four studies to date [13–16]. The TORG data center promotes quality control of clinical trials by contributing to patient registration, data collection and management, and central monitoring. The monitoring reports are submitted to and reviewed by an independent monitoring committee and study investigators on a semiannual basis. Interim analysis is performed when a preplanned number of patients have been enrolled during the study period. In addition, TORG has taken appropriate advice from several biostatisticians when conducting new clinical trials or analyzing trial data.

TORG has seven and 11 trials in accrual and follow-up phases, respectively. Although TORG has no experience in conducting large-scale randomized trials, three studies have registered 100 or more patients. The policies of TORG are to initiate

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