TABLE 1. Characteristics of Patients Screened for *EML4-ALK*

No.	Age (years)	Sex	Histology	Procedure	Smoking status	*EML4-ALK*
1	63	F	Ad	TLB	Never	Negative
2	62	M	Ad	TBLB	Current	Negative
3	74	M	Ad	TLB	Current	Negative
4	71	M	Ad	TBLB	Current	Negative
5	63	F	Ad	TBLB	Never	Variant 1
6	75	M	Ad	TBLB	Former	Negative
7	59	M	Ad	Needle biopsy	Current	Negative
8	85	M	Ad	TBLB	Current	Negative
9	73	F	Ad	Lymph node biopsy	Never	Negative
10	68	F	Ad	TBLB	Current	Negative
11	65	M	Ad	TBLB	Current	Variant 1
12	57	M	Ad	TBLB	Current	Negative
13	68	F	Ad	TLB	Never	Negative
14	73	M	Ad	TBLB	Former	Negative
15	67	F	Ad	TBLB	Never	Negative
16	67	M	Ad	TBLB	Former	Negative
17	57	M	Ad	TBLB	Former	Negative
18	56	M	Large	TBLB	Current	Negative
19	65	M	Ad	TBLB	Current	Negative
20	60	M	Ad	TBLB	Current	Variant 1

Ad, adenocarcinoma; Large, large cell carcinoma; TLB, thoracoscopic lung biopsy; TBLB, transbronchial lung biopsy.

We therefore examined the sensitivity of our assay for detection of these variants. Samples containing 1000, 100, 10, or 1 copy of plasmid DNA [pcDNA3.1(+) for variants 1, 3a, or 3b] and 1 ng of normal human genomic DNA (Promega, Madison, WI) were prepared by 10-fold serial dilution. MS spectra revealed a clear peak at the expected size for variants 1, 3a, or 3b in all samples, including those containing only one copy of the variant DNA (Fig. 3*A*). We also examined assay sensitivity when the samples were diluted with pCR2.1 containing *ALK* cDNA (pCR2.1-alk). Samples containing 1000, 100, 10, or 1 copy of the variant plasmids were thus diluted with 10 pg (~2 × 10^6 copies) of pCR2.1-alk. A clear peak at the expected size was again detected in all the samples including those containing only one copy of the variant DNA (Fig. 3*B*). These results therefore suggested that the sensitivity of the assay for the detection of *EML4-ALK* variants is high.

Detection of *EML4-ALK* Variants in FFPE Samples

We next evaluated the ability of our assay to detect *EML4-ALK* variants in three surgically resected FFPE samples of NSCLC shown to be positive for *ALK* rearrangements by FISH analysis (Fig. 4*A*). The primary PCR products for the assay were also analyzed by gel electrophoresis, with the expected sizes of the amplification products being 115, 103, and 119 bp for variants 1, 3a, and 3b, respectively. Bands corresponding to *EML4-ALK* variant 1 (case 2), variant 3a (cases 1 and 3), and variant 3b (case 3) were detected (Fig. 4*B*). Similarly, we detected MS peaks corresponding to *EML4-ALK* variant 1 and to variants 3a or 3b in case 2 and in cases 1 and 3, respectively (Fig. 4*C*). The presence of *EML4-ALK* variants in these three cases was confirmed by subcloning and sequencing of PCR products (Fig. 4*D*). We further analyzed several NSCLC specimens shown to be negative for *EML4-ALK* by FISH analysis; no mass peaks for *EML4-ALK* variants were detected by the MassARRAY assay (data not shown). These results thus suggested that the MassARRAY assay is able to detect *EML4-ALK* variants in FFPE samples.

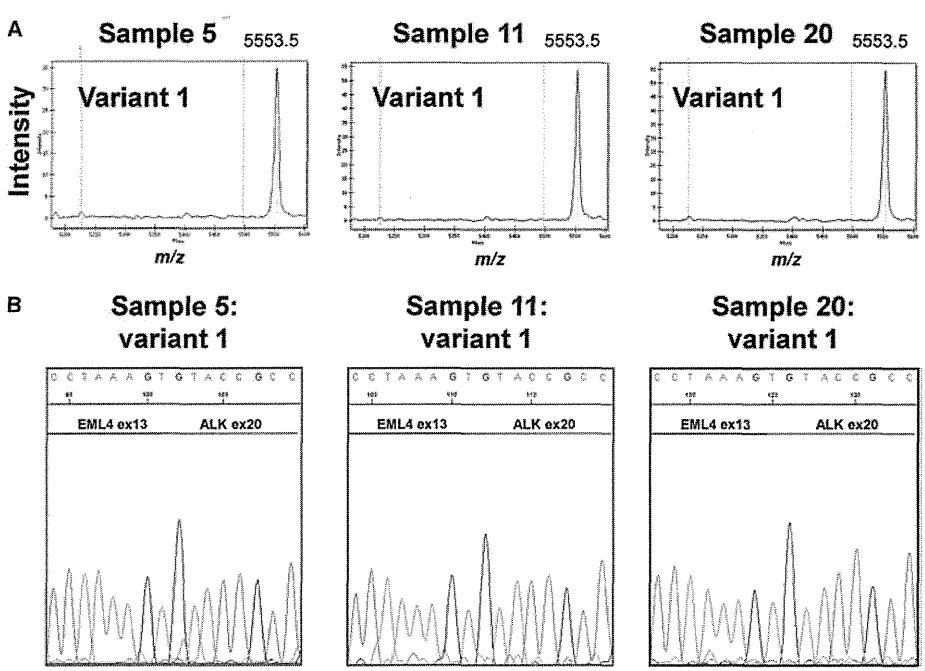

FIGURE 5. Detection of *EML4-ALK* in formalin-fixed, paraffin-embedded samples of non–small cell lung cancer obtained by transbronchial lung biopsy. (*A*) Representative spectra of *EML4-ALK*–positive samples. The experiments were repeated twice with identical results. (*B*) The polymerase chain reaction products from (*A*) were subcloned and sequenced.

Screening for *EML4-ALK* Variants in FFPE Biopsy Samples of Advanced NSCLC

Molecular analysis of biopsy samples from patients with advanced NSCLC is often difficult because of the small amount of tissue available. We therefore examined the feasibility of detection of *EML4-ALK* variants with the MassARRAY assay in FFPE biopsy specimens obtained from 20 patients with advanced NSCLC, the characteristics of whom are shown in Table 1. Three specimens (samples 5, 11, and 20) were found to be positive for variant 1 of *EML4-ALK*, with none of the other variants being detected (Fig. 5*A*). The presence of *EML4-ALK* variant 1 in these three cases was confirmed by subcloning and sequencing of PCR products (Fig. 5*B*). We also performed FISH analysis on the 20 FFPE specimens. Of the three *EML4-ALK*–positive cases detected by the MassARRAY assay, two (samples 5 and 20) were positive by FISH whereas the third (sample 11) could not be evaluated because of poor tissue quality (data not shown). None of the cases that tested negative by the MassARRAY assay was positive by FISH. These results thus suggested that our assay is effective for *EML4-ALK* screening with FFPE biopsy specimens of advanced NSCLC.

DISCUSSION

We have developed a MassARRAY assay for screening of *EML4-ALK* in FFPE samples of NSCLC tissue. This novel assay is capable of detecting nine different *EML4-ALK* variants with a high sensitivity.

Dual-color split-signal FISH analysis has been considered the gold standard in screening for *ALK* rearrangement. However, given that *EML4* and *ALK* loci are located in relatively close proximity on chromosome 2p, the detection of the *EML4-ALK* fusion gene on the basis of the gap between the probes is sometimes difficult. The identification and counting of signals on tissue sections is impeded by factors such as cutting artifacts and nuclear overlap related to the thickness and homogeneity of the tissue sections and the size of the nuclei. The MassARRAY system is a nucleic acid analysis platform which utilizes a three-step process composed of PCR amplification, single-base primer extension, and MALDI–TOF MS analysis. The presence of *EML4-ALK* in our MassARRAY assay is detected on the basis of the presence of products of predicted mass.

The amount of tumor tissue available for molecular analysis is often limited in patients with advanced NSCLC. Furthermore, RNA extracted from FFPE samples is highly degraded and less amenable to RT-PCR analysis compared with that isolated from nonfixed, freshly frozen tissue. We succeeded in amplifying *EML4-ALK* cDNA by PCR from FFPE tissue with primers designed to yield short amplicons (70–130 bp). The design of such short amplicons can also be applied to quantitative PCR systems such as amplification-refractory mutation system for allele-specific PCR assays. In our system, PCR amplification was performed with a high number of cycles (45 cycles), and increased accumulation of PCR products conferred higher sensitivity. We tested 20 FFPE biopsy samples from patients with NSCLC with our assay and detected a clear mass peak for *EML4-ALK* variant 1 in 3 of these samples, each of which was confirmed positive for this variant by subcloning and sequencing of the PCR products. In contrast to FISH, our assay is able to distinguish between the different *EML4-ALK* variants in a small amount of FFPE NSCLC tissue, and it should prove to be a useful tool for the detection of *EML4-ALK* variants in diagnostic testing for this fusion gene.

ACKNOWLEDGMENTS

Supported by the Third-Term Comprehensive 10-Year Strategy for Cancer Control of the Ministry of Education, Culture, Sports, Science, and Technology of Japan as well as by Health and Labor Scientific Research Grants [20-9].

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Successful Long-Term Treatment With Pemetrexed of NSCLC Associated With *EML4-ALK* and Low Thymidylate Synthase Expression

Masayuki Takeda,[1] Isamu Okamoto,[1] Kazuko Sakai,[2] Kaoru Tanaka,[1] Masaaki Terashima,[1] Kazuto Nishio,[2] Kazuhiko Nakagawa[1]

Clinical Practice Points

- The discovery of an *EML4-ALK* rearrangement led to a new direction in research for molecular targeted therapy in non–small-cell lung cancer (NSCLC).
- Recent retrospective studies have suggested that *EML4-ALK*–positive patients may have a superior progression-free survival (PFS) with treatment using pemetrexed-based therapies; however, the underlying biological mechanism is unclear.
- We report a patient with NSCLC positive for the *EML4-ALK* fusion gene who benefited from treatment with pemetrexed plus carboplatin over a period of 15 months.
- Immunohistochemical analysis revealed a low level of intratumoral thymidylate synthase (TS) expression, suggesting that such a low expression level for this target of pemetrexed may have contributed to the long-term response to pemetrexed-based chemotherapy.
- Further studies are warranted to investigate predictive values of intratumoral TS levels in *EML4-ALK*–positive patients.

Clinical Lung Cancer, Vol. 13, No. 2, 157-9
Keywords: *EML4-ALK*, NSCLC, Pemetrexed, Predictive marker, Thymidylate synthase

Introduction

Fusion between echinoderm microtubule-associated protein-like 4 (*EML4*) and anaplastic lymphoma kinase (*ALK*) genes has recently been identified in non–small cell lung cancer (NSCLC). The dual MET-ALK inhibitor crizotinib has shown promising activity in patients whose tumors harbor this oncogene,[1] but it has remained unclear whether such patients manifest similar sensitivity to cytotoxic chemotherapy. Two recent retrospective studies have suggested that *EML4-ALK*–positive patients may have a superior progression-free survival (PFS) with treatment using pemetrexed-based therapies.[2,3] We now report a case of *EML4-ALK*–positive NSCLC that showed long-term benefit from treatment with pemetrexed plus carboplatin.

A 62-year-old woman, an asymptomatic nonsmoker, was admitted to our hospital after the detection of an abnormal shadow on a chest roentgenogram. A chest computed tomographic scan revealed a solitary spiculated lesion in the right upper lung lobe associated with pleural effusion suggestive of pleural dissemination (Figure 1A). A biopsy specimen obtained by video-assisted thoracoscopic surgery yielded a pathologic diagnosis of pleural dissemination of a signet-ring adenocarcinoma (Figure 1C). Mutation analysis showed that the tumor was wild type for the epidermal growth factor receptor (*EGFR*) gene. Fluorescence in situ hybridization (FISH) analysis with break-apart probes for *ALK* revealed the presence of an *ALK* rearrangement (Figure 1D), and subsequent reverse transcription and polymerase chain reaction (PCR) analysis confirmed the presence of *EML4-ALK* fusion transcript variant 1 (Figure 1E). As a first-line treatment, pemetrexed plus carboplatin were chosen for the following reasons. Pemetrexed is active in the nonsquamous NSCLC histologic type, and carboplatin-based regimens have been preferred over cisplatin regimens because they are less toxic and more convenient to administer in the outpatient treatment setting. The treatment consisted of pemetrexed 500 mg/m^2 and carboplatin area under the curve (AUC) 6 every 21 days for 4 cycles followed by maintenance pemetrexed 500 mg/m^2 on day 1 of a 21-day cycle. A computed tomographic scan revealed 33% shrinkage of tumor, which was categorized as a partial response according to Response

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Submitted: Sept 5, 2011; Revised: Sept 19, 2011; Accepted: Sept 24, 2011

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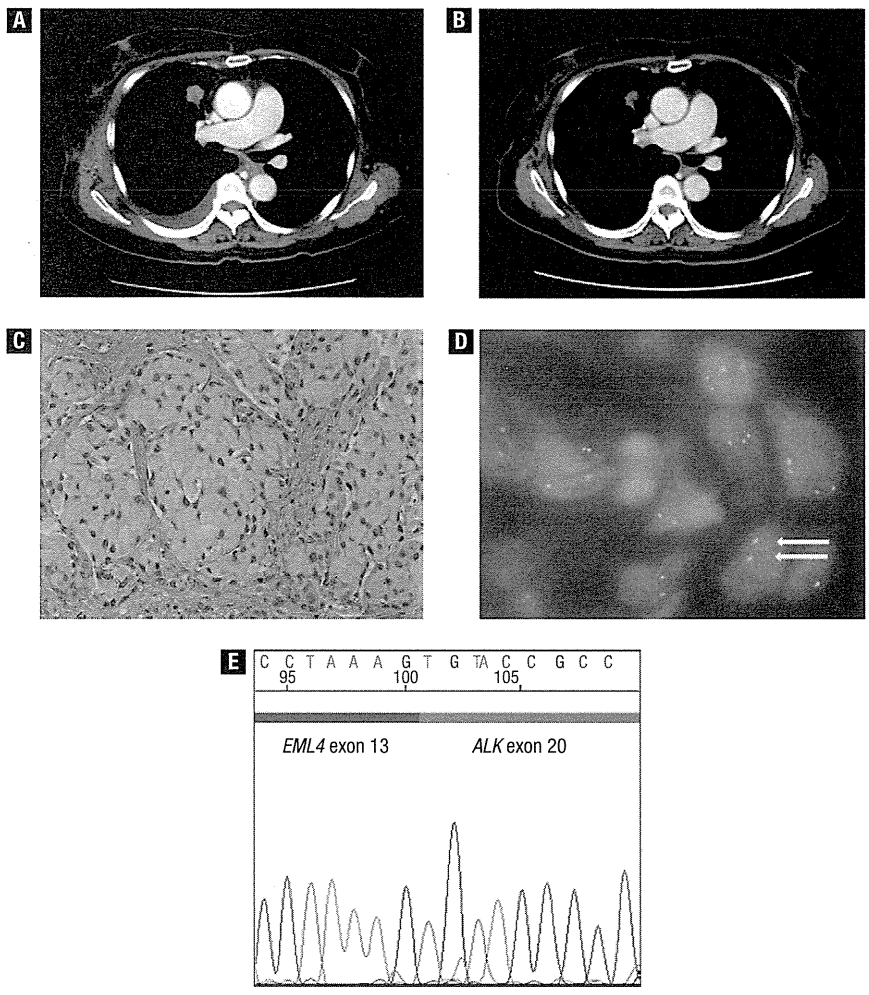
1525-7304/$ - see frontmatter
doi: 10.1016/j.cllc.2011.09.003

Figure 1 Chest Computed Tomographic Scans of the Patient Before (A) and 14 Months After (B) Initiation of Treatment With Pemetrexed and Carboplatin. Pathologic Analysis of a Biopsy Specimen Revealed Cancer Cells With Signet-Ring Cell Features (Hematoxylin-Eosin; Original Magnification, ×200). (C) Fluorescence in Situ Hybridization (FISH) Analysis Revealed a Split of Red and Green Probes that Flank the *ALK* Translocation Site (Yellow Arrows) (D). The Translocation was Confirmed to Be *EML4-ALK* Variant 1 by Direct Sequencing of Real-Time Polymerase Chain Reaction (PCR) Products (E)



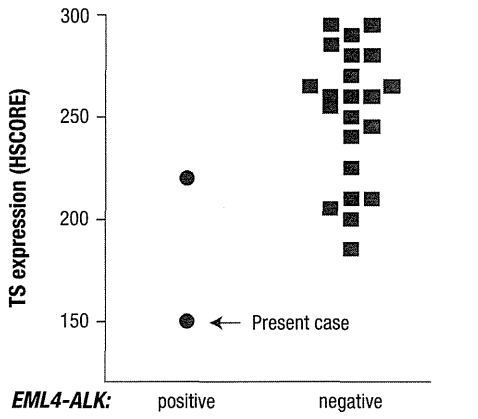
Evaluation Criteria in Solid Tumors (RECIST) 1.1. A total of 20 treatment cycles (16 maintenance cycles) had been administered over 15 months at the time of this writing, with no evidence of severe adverse events or disease progression (Figure 1B).

Discussion

The *EML4-ALK* fusion gene has recently been identified in a subset of NSCLC tumors, being detected most often in never-smokers and associated with distinct pathologic features such as signet-ring cell adenocarcinoma. ALK inhibitors have shown marked clinical efficacy in NSCLC patients harboring *EML4-ALK*,[1] but it has remained unclear whether such patients will manifest similar sensitivity to platinum-based combination chemotherapy compared with patients whose tumors are negative for *EML4-ALK*.

Preliminary data from a small number of patients who were retrospectively identified as harboring *EML4-ALK* suggest that *EML4-ALK*–positive tumors treated with platinum-based chemotherapy show a response similar to that of tumors without *EML4-ALK* or *EGFR* mutations.[4] However, 2 recent studies have suggested that *EML4-ALK*–positive patients may have a superior PFS when treated with pemetrexed-based therapies compared with patients with other molecularly defined subtypes of NSCLC,[2,3] although the reason for this difference is not known. A semiquantitative immunohistochemical analysis of the expression of thymidylate synthase (TS), a target

Figure 2 Relation Between Thymidylate Synthase (TS) Expression Level (HSCORE) and *EML4-ALK* Status in 24 NSCLC Specimens from Patients Treated With Pemetrexed Combined With Platinum Agents. TS Expression Levels in *EML4-ALK*–Positive Tumors (HSCOREs of 150 and 220) Were Lower Than All or Most of Those in *EML4-ALK*–Negative Tumors (HSCORE Range, 185-295)



enzyme of pemetrexed, in tumor biopsy specimens from 24 consecutive patients with NSCLC treated with pemetrexed combined with platinum agents revealed that patients with a low level of TS expression had a significantly longer PFS than did those with a high level of TS expression.[5] Additional analysis has now revealed that *EML4-ALK* (the 2 most common variants, variant 1 and variant 3a) was present in 2 of these 24 patients, including the present case (Figure 2). Moreover the lowest level of TS expression was observed in our patient, who harbored the *EML4-ALK* variant 1. Given the importance of a low level of TS expression for increased sensitivity to pemetrexed-based regimens, the low TS expression level of the proband may have contributed to the long-term efficacy of pemetrexed. The other patient harboring *EML4-ALK* (variant 3a) manifested a moderate level of TS expression but had early disease progression after 1 cycle of treatment. Whether a low level of TS expression is associated with *EML4-ALK*–positive NSCLC and confers an improved response to TS-targeting agents such as pemetrexed in such patients remains to be determined. TS-targeting agents such as pemetrexed may offer new ways of increasing antitumor potency in *EML4-ALK*-positive NSCLC patients. Further investigations are thus warranted concerning the role of TS in *EML4-ALK*-positive patients.

Conclusion

We report the successful long-term treatment with pemetrexed and carboplatin in a patient with *EML4-ALK*–positive NSCLC. The low TS expression level of the tumor may have contributed to the beneficial outcome of pemetrexed-based chemotherapy.

Disclosure

The authors report that they have no relevant relationships to disclose.

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Randomized Study of Endobronchial Ultrasound-Guided Transbronchial Biopsy

Thin Bronchoscopic Method versus Guide Sheath Method

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Introduction: In endobronchial ultrasound-guided transbronchial biopsy (EBUS-TBB), techniques using a thin bronchoscope or a guide sheath have been proposed for accurate biopsy instrument reinsertion into the bronchial route indicated by a radial ultrasonic probe. The purpose of this study was to compare the diagnostic yields of these techniques for peripheral pulmonary lesions.

Methods: Patients with suspected peripheral pulmonary lesions were included in this prospective, randomized, noninferiority study and assigned to undergo EBUS-TBB under fluoroscopic guidance using a prototype 3.4-mm thin bronchoscope or a 4.0-mm bronchoscope with a guide sheath.

Results: A total of 205 patients were enrolled and randomized, of whom 203 patients (101 thin bronchoscopic method; 102 guide sheath method) were included in the analysis. Diagnostic histologic specimens were obtained in 65% (41% for benign and 75% for malignant lesions) of the thin bronchoscopy group and 62% (25% for benign and 71% for malignant lesions) of the guide sheath group. Diagnostic performance of the thin bronchoscopic method was confirmed to be noninferior to the guide sheath method (difference in diagnostic yields, 3.6%; 90% confidence interval, −7.5 to 14.7%). Mean procedure time was significantly shorter in the thin bronchoscopy group than the guide sheath group (27 versus 33 minutes; $p = 0.002$). Complications including pneumothorax, moderate bleeding, and pneumonia occurred in 5% and 2% in the respective groups ($p = 0.28$).

Conclusions: EBUS-TBB using the thin bronchoscope was noninferior to the guide sheath method for the diagnosis of peripheral pulmonary lesions and was associated with shorter procedural time.

Key Words: Bronchoscopy, Endobronchial ultrasound, Lung cancer, Solitary pulmonary nodule, Thin bronchoscope, Transbronchial biopsy.

(*J Thorac Oncol.* 2012;7: 535–541)

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Disclosure: The prototype thin bronchoscope and the thin ultrasonic probe were generously loaned to the authors by Olympus, Tokyo, Japan. Dr. Oki has received an honorarium for a lecture from Olympus at the Annual Meeting of the Japan Society of Respiratory Endoscopy in May 2010.

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ISSN: 1556-0864/12/0703-0535

Peripheral pulmonary lesions are commonly encountered in our daily practice and require a definitive diagnosis with pathological or microbiological assessment in most cases. For the definitive diagnosis, the transbronchial approach using a flexible bronchoscope under fluoroscopic guidance has been the conventional method and it is still the most popular method. However, the conventional method is no longer a recommended procedure due to its low diagnostic yield.[1,2] Bronchoscopy has evolved considerably during the past decade, and several promising procedures with new devices, such as endobronchial ultrasound (EBUS)[3,4] and navigational bronchoscopy,[5,6] which modified conventional bronchoscopy, have been proposed to improve the diagnostic yield. Above all, EBUS with a radial ultrasonic probe largely improved the results of bronchoscopy, and bronchoscopy with EBUS has been described as an alternative procedure for diagnosing small peripheral pulmonary lesions in a guideline on lung cancer management.[2] Although EBUS-guided transbronchial biopsy (EBUS-TBB) with an ultrasonic probe improved the accuracy of bronchoscopy, it has the methodological limitation that the procedure is not "real-time" ultrasound guidance because the ultrasonic probe must be removed from the bronchoscope to introduce biopsy instruments after the target lesion is localized. The biopsy instrument cannot often be readvanced along the same bronchi into which the ultrasonic probe was inserted. To overcome this limitation, a method using a guide sheath, which acts as an extended working channel beyond the reach of the bronchoscope for repeated biopsy, was developed.[4,7] In fact, this method has been employed in many trials focused on EBUS-TBB.[8]

Recently, thin bronchoscopes, which were compatible with an ultrasonic probe, were developed, and their usefulness for the diagnosis of peripheral pulmonary lesions has been reported.[9] The thin bronchoscopes can be advanced to the more distal bronchi compared with standard-sized bronchoscopes.[10] Theoretically, if the bronchoscope can be advanced close to the lesions, a guide sheath which plays a role as an extended working channel is unnecessary. The aim of this study was to compare the diagnostic yields of EBUS-TBB using the thin bronchoscopic method and the guide sheath method for peripheral pulmonary lesions.

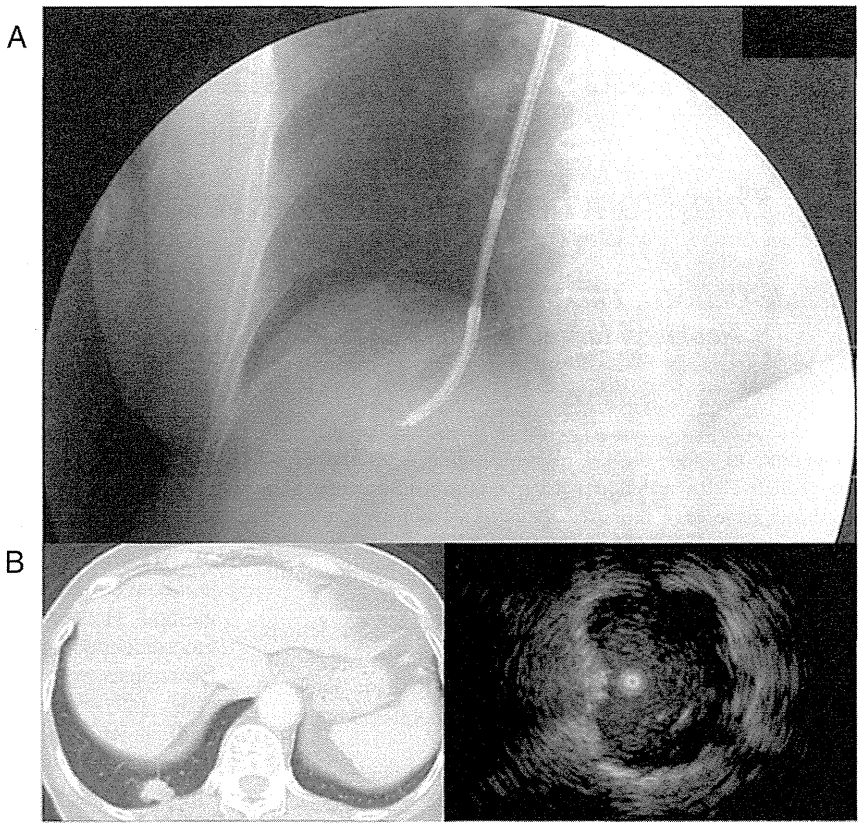

FIGURE 1. Fluoroscopic image of transbronchial biopsy using a thin bronchoscope (*A*), computed tomographic image (*B*), and ultrasonic image of a metastatic colon cancer (adenocarcinoma) examined and diagnosed by endobronchial ultrasound-guided transbronchial biopsy with the thin bronchoscopic method (*C*).

PATIENTS AND METHODS

Patients

Between April 2007 and October 2009, we carried out a prospective study which was approved by the institutional review board of Nagoya Medical Center (identifier: 2006-78) and registered with the UMIN-Clinical Trials Registry (identifier: UMIN000000696). Included in this study were 205 patients with localized peripheral pulmonary lesions, such as a solitary pulmonary nodule (Figures 1*B* and 2*B*), a pulmonary mass, or a localized infiltrate, referred for diagnostic bronchoscopy. Randomization for EBUS-TBB using either the thin bronchoscopic method or the guide sheath method was performed by minimization with stratification factors including lesion size in the longest diameter on chest computed tomography (≥20 versus <20 mm), lesion distance from hilum on computed tomography (central versus intermediate versus peripheral, as classified by Baaklini et al.[1]) and the examiner (staff pulmonologists versus pulmonary residents <6 years after receiving their MD). All patients provided their written informed consent.

Thin Bronchoscopic Method

A prototype hybrid-bronchofibervideoscope (Y-0007; Olympus; Tokyo, Japan, Figure 3*A*) incorporating a charge-coupled device in the control section was used. It has a 3.4-mm distal end diameter, a 1.7-mm working channel diameter, 180° up and 130° down angulation, a 90° field of view, and a 2- to 50-mm depth of field. The bronchoscope allows the use of a 1.5-mm forceps but not a standard 1.8- or 1.9-mm forceps. EBUS procedures were performed with an endoscopic ultrasound center (EU-M30S; Olympus) and a thin ultrasonic probe (UM-S20–17S; Olympus, Figure 3*B*) which is a 20-MHz mechanical radial type ultrasonic probe with an external diameter of 1.4 mm.

Bronchoscopic procedures were performed using conscious sedation with bolus IV midazolam and local anesthesia with lidocaine by staff pulmonologists or supervised pulmonary residents of our institution. As previously described,[9] a 5.0-mm inner diameter endotracheal tube was placed transnasally under thin bronchoscopic control which facilitated repeated insertion and removal of the bronchoscope. After examining the endobronchial region, the thin bronchoscope was advanced toward the bronchus most likely leading to the lesion under direct vision. Then, an ultrasonic probe was passed through the working channel and advanced to the lesion under bronchoscopic control with fluoroscopic visualization. If the lesion surrounding the ultrasonic probe was clearly visualized by EBUS (Figure 1*C*), the bronchus in which the ultrasonic probe passed through could be considered the correct route leading to the target lesion. After determining the leading bronchus, the thin bronchoscope was further advanced as far as possible using the ultrasonic probe as a guide and wedged into the peripheral bronchus. After that, the ultrasonic probe was removed and TBB was per-

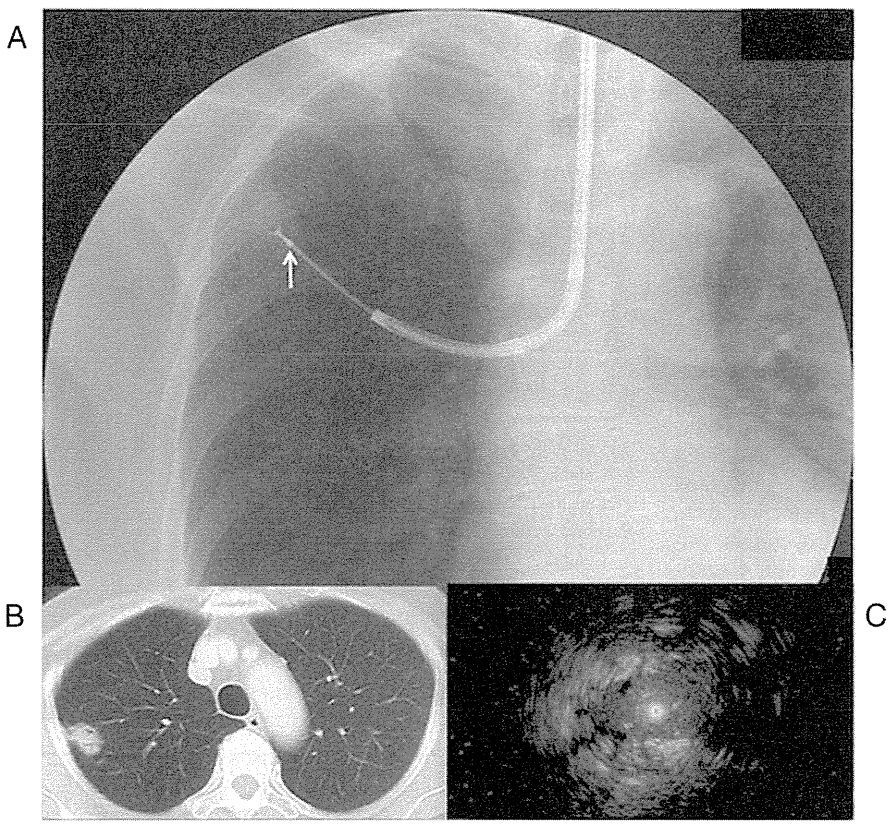

FIGURE 2. Fluoroscopic image of transbronchial biopsy using a guide sheath with a metallic marker (arrow) (*A*), computed tomographic image (*B*), and ultrasonic image of a lung cancer (adenocarcinoma) examined and diagnosed by endobronchial ultrasound-guided transbronchial biopsy with the guide sheath method (*C*).

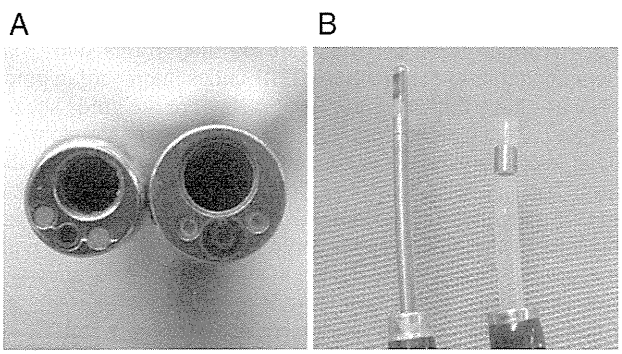

FIGURE 3. A comparison of bronchoscopes. *A*, Tip of the 3.4-mm thin bronchoscope with a 1.7-mm working channel (*left*) and the 4.0-mm bronchoscope with a 2.0-mm working channel (*right*). *B*, A 3.4-mm bronchoscope with a 1.4-mm ultrasonic probe (*left*) and a 4.0-mm bronchoscope with a guide sheath which is compatible with the 1.4-mm ultrasonic probe (*right*).

formed using a 1.5-mm forceps (FB-32D; Olympus) under fluoroscopic guidance (Figure 1*A*). Ten biopsy specimens were taken from each lesion, and each specimen was then transferred into numbered separate containers filled with formalin for histologic examination. After TBB, brushing using a cytology brush (BC-203D-2006; Olympus) was performed twice followed by washing with 10 to 20 ml of saline solution for cytological and microbiological examination. The bronchus level reached with the bronchoscope, the locational relation between the ultrasonic probe and the lesion on an EBUS image, the time of the procedure measured, and degree of bleeding (severe $\geq$60 ml, moderate $\geq$30 ml)[4] were recorded. A chest radiograph was obtained routinely to identify pneumothorax 2 hours after the procedures.

Guide Sheath Method

For bronchoscopy with a guide sheath, a 4.0-mm hybrid-bronchofibervideoscope with a 2.0-mm working channel (P260F; Olympus, Figure 3*A*) and a guide sheath (SG-200C; Olympus, Figure 3*B*) were used. Other instruments including an ultrasonic probe, biopsy forceps, and cytology brush used in the guide sheath method were the same type with the thin bronchoscopic method. EBUS-TBB using the 4.0-mm bronchoscope with a guide sheath was suggested to have better localization yield and diagnostic ability for peripheral pulmonary lesions than EBUS-TBB with the combination of a larger bronchoscope, ultrasonic probe, and guide sheath,[11] and so it was chosen as a comparative procedure. In fact, several investigators[5,7,11–14] reported the usefulness of EBUS-TBB with the guide sheath method using these instruments.

Bronchoscopic procedure was performed similar to thin bronchoscopy, except in the techniques for using a guide sheath. In advance, the ultrasonic probe was inserted into the guide sheath and advanced a few millimeters beyond its distal end. The ultrasonic probe with a guide sheath was then

introduced into the working channel and advanced toward the target lesion with fluoroscopic guidance. If the ultrasonic probe could not be advanced toward the target lesion, a guiding device (CC-6DR-1; Olympus) was introduced into the guide sheath and then advanced while confirming by fluoroscopy as the manner previously described.[4,7] Once the lesion was located by EBUS (Figure 2*C*), the ultrasonic probe was withdrawn from the guide sheath, and biopsies were performed through the guide sheath (Figure 2*A*), followed by brushings and washing.

Diagnosis

Each histologic and cytologic specimen was interpreted separately by an experienced pathologist. "Suspicious" findings were regarded as negative in our analysis. An inconclusive histological diagnosis of nonspecific fibrosis or inflammation was considered to be nondiagnostic. The final diagnoses were established by pathological evidence from biopsy including bronchoscopic or surgical procedures, microbiological analysis, or clinical follow-up. Benign diagnoses, which could not be pathologically or microbiologically diagnosed, were confirmed by radiological size stability and clinical compatibility during the follow-up period for at least 1 year after bronchoscopy.

Data Analysis

This study was designed to compare the diagnostic performance of the thin bronchoscopic method with that of the guide sheath method. The primary end point was the diagnostic yield, while secondary endpoints were safety, the bronchus level reached with the bronchoscopes, visibility on EBUS, and time of the procedure.

Noninferiority of the thin bronchoscopic method was to be concluded if the lower bound of the 90% confidence interval (CI) for the difference in the diagnostic yields exceeded the predetermined noninferiority bound of −10%. Based on the expected diagnostic yield of 65% using the guide sheath method[4,7] and 70% using the thin bronchoscopic method,[9] demonstration of noninferiority with a statistical power of 80% at a one-sided significance level of 0.05 would require 242 patients, and we arranged to enroll 260 patients with 130 in each group to account for dropouts. When the enrolment was closed because the term of the lease of the prototype thin bronchoscope was over, 205 patients were enrolled. Two patients were excluded from the analysis because they had lesions located within the segmental bronchi that were defined as central lesions.[2]

In the description of baseline characteristics of the patients and lesions, procedural details, and complication rate, means and percentages were presented as appropriate. Except for the noninferiority analysis of the primary end point, dichotomous variables were analyzed using Pearson's χ^2 test or Fisher's exact test, and continuous variables were analyzed using Student *t* test. Statistical analyses were performed using a statistical software program (PASW Statistics 18; SPSS Inc., Chicago, IL). Results were considered statistically significant when the *p* value was ≤0.05.

TABLE 1. Characteristics of Patients and Lesions

Characteristics	Thin Bronchoscopic Method	Guide Sheath Method	*p*
No. of patients	101	102	
Male/female	71/30	72/30	0.96
Age, yr	65.6 ± 11.0	67.4 ± 10.2	0.24
Lesion size, mm	30.6 ± 14.7	29.8 ± 13.9	0.70
Median, mm (range)	26 (10–70)	27.5 (10–72)	
<20 mm/≥20 mm	25/76	27/75	0.78
Lesion location by bronchopulmonary segment			
Right upper lobe	41	30	
Right middle lobe	8	11	
Right lower lobe	21	23	0.70
Left upper lobe	15	18	
Lingula	4	5	
Left lower lobe	12	15	
Lesion location from the hilum			
Central/intermediate/peripheral	0/32/69	0/27/75	0.41
Final diagnosis			
Benign/malignant/unknown	22/76/3	20/82/0	0.62
Prevalence of malignancy, %	76	80	
Examiner			
Staff pulmonologist/resident	89/12	92/10	0.63

Data are presented as *N* or mean ± SD unless otherwise stated.

RESULTS

Patients and Lesions

A total of 205 patients were enrolled in this study and randomized to undergo EBUS-TBB under fluoroscopic guidance using the thin bronchoscopic method or the guide sheath method. Two patients (one in each group) with an endobronchial lesion within the segmental bronchus identified with the bronchoscope were excluded from the analysis. Thus, a total of 203 patients with peripheral pulmonary lesions (101 patients with the thin bronchoscopic method, 102 patients with the guide sheath method) were included in this analysis. Characteristics of patients and lesions in each group are summarized in Table 1. There were no statistically significant differences in baseline characteristics between both groups.

Diagnostic Yield

Histological results of EBUS-TBB and the final diagnosis are detailed in Table 2. Patients were given final diagnosis of malignant or benign disease except three patients who did not return to follow-up in the thin bronchoscopy group. Prevalence of malignancy in the thin bronchoscopy group and the guide sheath group was 76% and 80%, respectively ($p = 0.62$).

The diagnostic yields of EBUS-TBB from specific histopathological findings in 203 patients are shown in Table 3. A histologic diagnosis was made in 66 of 101 patients (65%) using EBUS-TBB with the thin bronchoscopic method and in 63 of 102 patients (62%) with the guide sheath method. The difference in diagnostic yields was 3.6%,

TABLE 2. Final Diagnosis and Results of EBUS-TBB

Histologic Findings	No. of Patients (Final Outcomes)	
	Thin Bronchoscopic Method (n = 101)	Guide Sheath Method (n = 102)
Malignant		
Adenocarcinoma	27	35
Squamous cell carcinoma	11	14
Large cell carcinoma	2	1
Non-small cell carcinoma	9	4
Bronchioloalveolar carcinoma	1	
Small cell carcinoma	4	2
Spindle cell sarcoma		1
Metastatic carcinoma	3 (2 colon, 1 rectum)	
Malignant lymphoma		1
Benign		
Epithelioid cell granuloma with necrosis	4 (2 NTM, 2 unspecified)	3 (2 TB, 1 fungus)
Epithelioid cell granuloma without necrosis	1 (1 unspecified)	
Organizing pneumoniia	3	2
Sclerosing hemangioma	1	
Nondiagnostic		
Suspected lung cancer	5 (5 lung cancer)	5 (5 lung cancer)
Nonrepresentative samples	30 (14 lung cancer, 1 TB, 1 NTM, 9 improved, 2 unchanged with 14–23-mo follow-up, 3 no return to follow-up)	34 (19 lung cancer, 1 TB, 1 granuloma, 1 cryptococcosis, 1 abscess, 1 hamartoma, 6 improved, 4 unchanged with 13–27-mo follow-up)

EBUS-TBB, endobronchial ultrasound-guided transbronchial biopsy; NTM, nontuberculous mycobacteriosis; TB, tuberculosis.

TABLE 3. Diagnostic Yield of EBUS-TBB

Variables	No. of Lesions Diagnosed/ Lesions Examined (%)	
	Thin Bronchoscopic Method (n = 101)	Guide Sheath Method (n = 102)
Benign		
<20 mm	2/11 (18)	1/4 (25)
≥20 mm	7/11 (64)	4/16 (25)
Malignant		
<20 mm	8/12 (67)	15/23 (65)
≥20 mm	49/64 (77)	43/59 (73)
Unknown[a]		
<20 mm	0/2 (0)	0
≥20 mm	0/1 (0)	0
Total	66/101 (65)	63/102 (62)

[a]Patients who did not return to follow-up.
EBUS-TBB, endobronchial ultrasound-guided transbronchial biopsy.

with a 90% CI from −7.5 to 14.7%. Noninferiority of the thin bronchoscopic method was thus confirmed by the lower limit of the CI being more than the predetermined margin of −10%.

When divided by the lesion size or type of lesion (benign or malignant), we found no significant differences across diagnostic yields by the lesion size (p = 0.25) or the type of lesion (p = 0.62) in the thin bronchoscopy group versus guide sheath group.

Brushing and/or washing provided diagnosis in two patients with a negative EBUS-TBB result in the thin bronchoscopy group and three patients with a negative EBUS-TBB result in the guide sheath group. Overall diagnostic yields of bronchoscopy in the thin bronchoscopy group and the guide sheath group were 67% (68 of 101 patients) and 65% (66 of 102 patients), respectively (p = 0.67).

Comparison of Procedures

Procedural details in each method are summarized in Table 4. The 3.4-mm thin bronchoscope could reach more distal bronchi compared with the 4.0-mm bronchoscope which was used in the guide sheath method (mean, 4.6 versus 3.9 generations; $p < 0.001$). Localized rates of the target lesion with EBUS were not different in either group (p = 0.67). Mean procedure time was significantly shorter in the thin bronchoscopy group than in the guide sheath group (27 versus 33 minutes; p = 0.002).

Safety

Three pneumothorax, 1 pneumonia, and 1 moderate bleeding cases (5 of 101 patients; 5%) resulted from thin bronchoscopy, while 2 cases (2 of 102 patients; 2%) developed pneumonia after bronchoscopy with the guide sheath method (p = 0.28).

DISCUSSION

In this randomized study, we compared the diagnostic yield of EBUS-TBB using a thin bronchoscope to using a guide sheath for peripheral pulmonary lesions. We showed

TABLE 4. Procedural Details

Variables	Thin Bronchoscopic Method (n = 101)	Guide Sheath Method (n = 102)	p
Bronchus level reached with bronchoscope, generation (median; range)	4.6 ± 1.2 (5; 2–9)	3.9 ± 1.0 (4; 2–6)	<0.001
Location of probe in relation to lesion confirmed by EBUS			
Within lesion	74	70	
Adjacent to lesion	17	18	0.67
Invisible with EBUS	10	14	
Procedural time, min (median; range)	27.4 ± 11.3 (23.5; 12–59.5)	33 ± 13.8 (28; 16–77.5)	0.002

Data are presented as N or mean ± SD (median; range).
EBUS, endobronchial ultrasound.

that the thin bronchoscopic method was noninferior to the guide sheath method for the histological diagnosis of peripheral pulmonary lesions, and the procedure time was significantly shorter in the thin bronchoscopy group.

The addition of endobronchial ultrasound guidance has greatly enhanced the accuracy of bronchoscopy for peripheral pulmonary lesions.[15] Thus, biopsy with a radial ultrasonic probe has been described as only an alternative bronchoscopic procedure for the diagnosis of small peripheral pulmonary lesions in a guideline on lung cancer management.[2] However, this procedure has the potential methodological limitation that it is not "real-time" ultrasound guidance. If once the leading bronchus is identified by EBUS, the ultrasonic probe must be removed from the bronchoscope for biopsy. The biopsy instrument cannot often be reinserted correctly into the target bronchus indicated by EBUS. To reduce the limitation, the employment of the guide sheath to facilitate the transfer of instruments for repeated biopsy was proposed.[4,7] In addition, the combination of a thinner 4.0-mm bronchoscope and/or a guiding device seems to be effective for detecting the lesions. Although no prospective study has focused on EBUS-TBB with or without a guide sheath, many experts have adopted the guide sheath method in their studies.[4,5,7,11–14,16] Although it had readily enabled repeated biopsy, the manipulation of the guide sheath for exploring the peripheral pulmonary lesions, which sometimes needs a guiding device, seems to be more complex than the technique without the guide sheath.[17] The guide sheath with a thin wall tends to bend easily and thus prevents smooth insertion of a biopsy forceps or a cytology brush.

Innovation in technology has permitted the development of some promising bronchoscopes including those with a thinner diameter or larger working channel than the conventional types. Conventional thin bronchoscopes less than 3.9 mm in external diameter equipped with a 1.2-mm working channel,[18,19] and eventually thin bronchoscopes with a 1.7-mm working channel which allow the use of a thin radial ultrasonic probe have recently been developed.[9,10,20] In a former preliminary study,[9] we demonstrated that the diagnostic yield of EBUS-TBB with the thin bronchoscope for peripheral pulmonary lesions with a mean size of 31 mm was 69%. The results of this study are consistent with those of the former preliminary study. The present comparative study showed EBUS-TBB with the thin bronchoscopic method, and the guide sheath method had a similar diagnostic performance for evaluation of peripheral pulmonary lesions.

Thin bronchoscopy and the present guide sheath method have the limitation of the 1.7-mm working channel. First, it limits the size of the biopsy instruments used. However, the results of our study have demonstrated the adequacy of the small forceps for sampling histologic specimens. Actually, many other studies[5,7,9–14,16] using the small forceps have shown field-proven results in terms of diagnostic yield. In addition, the histological specimens allow further diagnostic investigation including immunohistochemical examination. In fact, an immunohistochemical examination using various antibodies, which provides useful information for diagnosing the tumor type or tumor origin, was performed in 26 of 115 patients with a malignant disease diagnosed by EBUS-TBB. In the present investigation, the diagnostic yield of each method for small benign lesions seems to be lower than in other studies. The reasons are unclear but may relate to the prevalence of the nonspecific inflammation. In this study, inconclusive histological results such as nonspecific fibrosis or inflammation were analyzed as nondiagnostic, and a considerable number of cases with suspected inflammation, which was diminished or had disappeared during the clinical follow-up period and seems difficult to diagnose with bronchoscopy, were included as shown in Table 2. Another possible limitation of the 1.7-mm working channel is its poor suction power. Bleeding is one of the well-known and potentially serious complications associated with TBB, and the poor suction power may be disadvantageous for such events. However, biopsy using the small forceps and the technique in which the tip of the thin bronchoscope is wedged into the peripheral bronchi during TBB serve to reduce the risk of a massive hemorrhage. In this study, only a case of moderate bleeding which was resolved without any interventions was observed. Pneumothorax is another well-known complication associated with TBB. In a recent meta-analysis[8] on EBUS-TBB, the occurrence rate was reported to be 1%, ranging from 0 to 5%. Although pneumothorax occurred in 3% of patients in the thin bronchoscopy group, the risk of pneumothorax would not be exceptionally high with thin bronchoscopy. In fact, in our preliminary study[9] on EBUS-TBB with thin bronchoscopy including 74 patients with peripheral pulmonary lesions, no patient developed pneumothorax.

CONCLUSIONS

Our findings suggest that EBUS-TBB using the thin bronchoscope was noninferior to the guide sheath method for the diagnosis of peripheral pulmonary lesions and was associated with shorter procedural time.

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Original Article

A Phase 3 Study of Induction Treatment With Concurrent Chemoradiotherapy Versus Chemotherapy Before Surgery in Patients With Pathologically Confirmed N2 Stage IIIA Nonsmall Cell Lung Cancer (WJTOG9903)

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BACKGROUND: This study sought to ascertain whether induction-concurrent radiotherapy added to chemotherapy could improve the survival of patients undergoing surgery for stage IIIA N2 nonsmall cell lung cancer (NSCLC). **METHODS:** Patients with pathologically proven N2 disease were randomized to receive either induction chemotherapy (docetaxel 60 mg/m^2 and carboplatin AUC [area under the receiver operating characteristic curve] = 5 for 2 cycles) plus concurrent radiation therapy (40 Gy) followed by surgery (CRS arm) or induction chemotherapy followed by surgery (CS arm). They subsequently underwent pulmonary resection when possible. **RESULTS:** Sixty patients were randomly assigned between December 2000 and August 2005. The study was prematurely terminated in January 2006 because of slow accrual. The most common toxicity was grade 3 or 4 leukopenia in 92.9% of patients in the CRS arm and 46.4% in the CS arm. Induction therapy was generally well tolerated, and there were no treatment-related deaths in either arm. Downstaging in the CS arm and CRS arm was 21% and 40%, respectively. The progression-free survival (PFS) and overall survival (OS) in the CS arm were 9.7 months and 29.9 months (PFS, hazard ratio [HR] = 0.68, P = .187), and those in the CRS arm were 12.4 months and 39.6 months (OS, HR = 0.77, P = .397), respectively. The PFS with and without downstaging was 55.0 and 9.4 months, respectively (HR = 3.39, P = .001). The OS with and without downstaging was 63.3 and 29.5 months, respectively (HR = 2.62, P = .021). **CONCLUSIONS:** The addition of radiotherapy to induction chemotherapy conferred better local control without significant adverse events. Tumor downstaging is important for prolonging the OS in patients with stage IIIA (N2) NSCLC. *Cancer* **2012;118:6126-35.** © *2012 American Cancer Society.*

KEYWORDS: induction therapy before surgery, phase 3 study, carboplatin, docetaxel, stage IIIA nonsmall cell lung cancer.

Lung cancer is the leading cause of cancer death in most industrialized countries. Nonsmall cell lung cancer (NSCLC) accounts for approximately 80% of all lung cancers. One-third of patients with NSCLC are found to have locally advanced tumors (stage IIIA or IIIB) at the time of initial diagnosis. Pulmonary resection remains the only accepted mode of therapy and hope for potential cure in patients with early stage I or II NSCLC. However, patients with stage IIIA, N2 disease are at substantial risk of recurrence and death even after complete surgical resection. The resectability of patients with stage III locally advanced lung cancer is only 14% to 20%, and the corresponding 5-year survival rate ranges from

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We thank Shinichiro Nakamura, MD, Naomi Osumi, Kouichi Hosoda, and other staff members of West Japan Thoracic Oncology Group data center for data management.

DOI: 10.1002/cncr.26689, **Received:** April 12, 2011; **Revised:** August 18, 2011; **Accepted:** September 19, 2011, **Published online** June 6, 2012 in Wiley Online Library (wileyonlinelibrary.com)

13% to 36%.[1,2] When pathologic involvement of the mediastinal lymph nodes is documented prior to surgical resection, a high rate of both local and distant failure with resection alone has provided the rationale for a combined modality approach consisting of induction chemotherapy or chemoradiotherapy before surgery. Induction therapy has several theoretical advantages,[3] such as increasing the sensitivity of tumors in early-stage disease, decreasing the tumor volume to enable better local control in subsequent surgery, faster eradication of clinically undetected micrometastatic disease, and better patient tolerance and compliance compared with postsurgery treatments.

With regard to preoperative chemotherapy for stage IIIA lesions with mediastinal lymph node metastasis, 5 randomized clinical trials of induction chemotherapy prior to surgery have been conducted.[4-8] Two of these studies involved small cohorts (n = 60) that included mainly stage IIIA, N2 disease, and showed a significant survival advantage associated with induction chemotherapy compared with surgery alone.[5,6] None of the other trials reported any beneficial outcome for bimodality therapy compared with surgery alone.[4,7,8]

Induction treatment using combined concurrent chemoradiotherapy prior to surgery resulted in NSCLC cure rates of 30% to 40% at 5 years and appeared to improve survival over treatment with surgery alone.[9-11] We conducted a phase 2 trial of induction chemoradiotherapy before surgery in 22 patients with stage IIIA NSCLC who have pathologically proven mediastinal lymph node metastasis.[12] The chemotherapy regimen used was cisplatin and etoposide, and the radiation dosage was 40 Gy. The response rate was 64% and the 5-year survival rate was 41%. Subsequently, we conducted a phase 2 study of induction chemoradiotherapy before surgery in 40 early stage NSCLC (stage IB, II).[13] Carboplatin (AUC = 5), and docetaxel (60 mg/m^2) were administered once every 3 weeks for 2 cycles concurrent with 40 Gy radiation. In patients with no evidence of disease progression, thoracotomy was performed 3 to 5 weeks later. All the patients completed induction chemoradiotherapy, and 39 patients underwent thoracotomy and were completely resected. There were no treatment-related deaths, and estimated 5-year survival was 69.9%. Induction concurrent chemotherapy (carboplatin plus docetaxel) with 40 Gy of thoracic radiotherapy was considered to be feasible and tolerable. Based on the findings of these 2 previous phase 2 trials, we planned a phase 3 study in which patients with pathologically documented stage IIIA (N2) NSCLC were randomized to either an induction chemotherapy followed by surgery (CS) arm, or an induction-concurrent chemoradiotherapy followed by surgery (CRS) arm. The primary endpoint of this trial was the overall survival rate at 5 years.

MATERIALS AND METHODS

Eligibility

The present study was undertaken at multiple academic and community hospitals in Japan. The 6th edition of the TNM staging system was used to stage the lung cancers using a computed tomography (CT) scan of the chest and upper abdomen; bone scan; and CT or magnetic resonance imaging (MRI) scan of the brain. Inclusion criteria were stage IIIA (pN2) disease: T1, T2, or T3 primary NSCLC with pathological proof of N2 disease (from biopsy samples of the ipsilateral mediastinal nodes that were visible on a CT scan). The size of the metastatic mediastinal lymph node was more than 1 cm along the short axis. Patients were assessed together by a thoracic surgeon, a radiation oncologist, and a medical oncologist or pulmonologist to establish whether N2 disease was present to the extent that concurrent chemotherapy and radiotherapy were indicated instead of definitive resection. It was also necessary to determine whether each lesion was potentially resectable. Additional inclusion criteria were measurable disease as defined by the World Health Organization (WHO), an Eastern Cooperative Oncology Group performance status of 0 or 1, and adequate hematologic, hepatic, cardiac, renal (serum creatinine $\leq$ 1.5 mg and creatinine clearance $\geq$ 40 mL/hour), and pulmonary functions (including partial pressure of arterial oxygen [PaO_2] $\geq$ 70 Torr, forced expiratory volume in 1 second [$FEV_{1.0}$] $\geq$ 1.5 L). The exclusion criteria were prior malignancy other than nonmelanoma skin cancer or adequately treated stage I in situ cervical cancer, uncontrolled angina pectoris, a history of congestive heart failure or myocardial infarction within 3 months, pulmonary fibrosis detectable by CT scan, chronic obstructive pulmonary disease ($FEV_{1.0} \leq 65\%$), and greater than 10% weight loss within the previous 6 months.

All patients provided written informed consent after study approval by the institutional review board of each participating center.

Study Design and Treatment

In the current phase 3 multicenter trial, patients were randomly assigned on a 1:1 basis to an induction CS arm or an induction CRS arm (Fig. 1). The patients were then

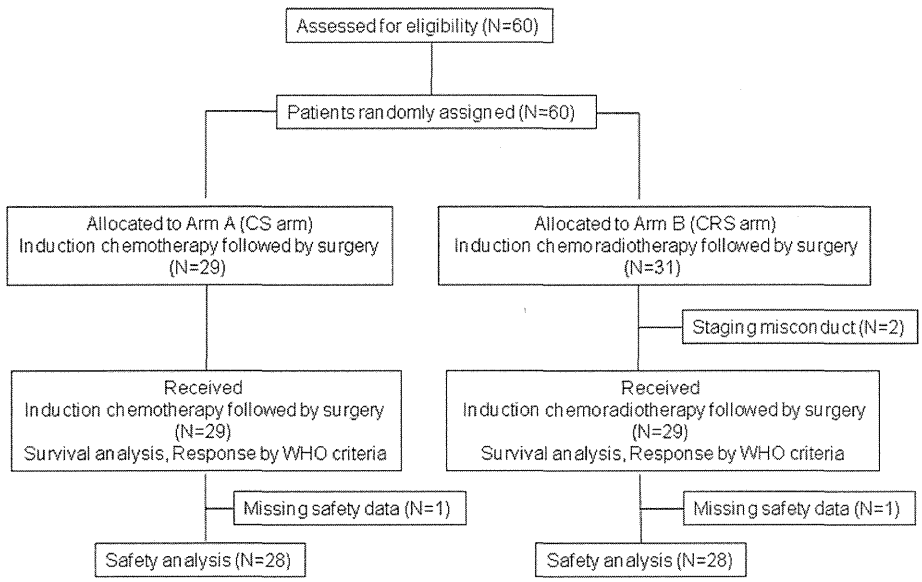

Figure 1. CONSORT diagram is shown for this study. CRS indicates concurrent chemoradiotherapy followed by surgery; CS, chemotherapy followed by surgery; WHO, World Health Organization.

stratified by sex, institution, and number of mediastinal lymph nodes. The induction chemotherapy involved 2 cycles of carboplatin (area under the receiver operating curve [AUC] = 5 on days 1, 22, intravenous infusions) and docetaxel (60 mg/m^2 on days 1, 22, intravenous infusions). Thoracic radiotherapy (40 Gy in 20 fractions of 2 Gy over 4 weeks) was also administered from day 1 in the CRS arm (Fig. 2)

All patients were treated with a linear accelerator photon beam of 6 MV or more. At the commencement of this multi-institutional study, a 3-dimensional (3D) treatment planning system using CT was not available at some of the participating institutions. Hence, 2-dimensional (2D) treatment planning techniques were allowed. Radiation doses were specified at the center of the target volume, and doses were calculated assuming tissue homogeneity without correction for lung tissues. The primary tumor and involved nodal disease received 40 Gy in 2 Gy fractions over 4 weeks via the anterior and posterior opposing portals. Radiation fields included the primary tumor with a margin of at least 1.0 cm, and the ipsilateral hilum and mediastinal nodal areas with a margin of 0.5 to 1.0 cm from the paratracheal lymph nodes (#2) to 4.5 cm below the tracheal bifurcation including subcarinal lymph nodes (#7). The contralateral hilum was not included. The supraclavicular areas were not treated routinely, but the ipsilateral supraclavicular area was treated when the primary tumor was located in the upper lobe.

The patients were reassessed using CT scan plus repeat pulmonary function tests 2 to 4 weeks after completion of the induction therapy. The response to induction was assessed by WHO criteria without the need for a second confirmation of response. If the disease had not progressed and the patient remained medically healthy, a complete surgical resection with a mediastinal lymph node dissection was performed 3 or 4 weeks after the induction therapy was completed. No consolidation chemotherapy was administered after surgery. Dose-reduction guidelines were specified in the protocol for both treatment arms. Patients in the CRS arm who could not be treated surgically within 6 weeks after induction therapy received further radiotherapy of up to 66 Gy in 33 fractions in total. In this boost radiotherapy procedure, the spinal cord was excluded from the radiation fields.

Patients were scheduled for a chest CT scan 4 to 6 weeks after completion of the last chemotherapy cycle and were followed up every 2 months for at least 5 years. During this time, the patients received CT scans of the chest and upper abdomen, CT or MRI scans of the brain, and bone scans every 6 months.

Statistical Methods

Analyses were performed by intention to treat, using only eligible patients. The primary endpoint was the survival rate at 5 years. Overall survival (OS) was defined as the time from randomization to death from any cause.

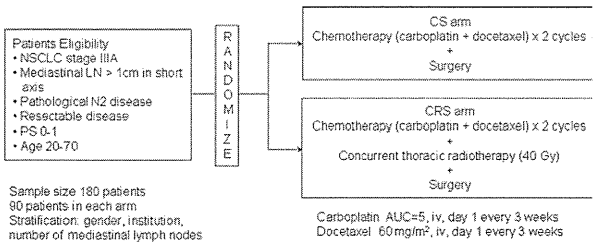

Figure 2. The study schema is shown. AUC, area under the receiver operating characteristic curve; CRS, concurrent chemoradiotherapy followed by surgery; CS, chemotherapy followed by surgery; iv, intravenous; LN, lymph node; NSCLC, nonsmall cell lung cancer; PS, performance status.

Secondary endpoints were the response rate and the toxicity of induction therapy, resectability rate, downstaging rate, death from any cause, operative morbidity, progression-free survival (defined as the time from randomization to disease progression), and patterns of failure. We calculated the sample size assuming a 2-sided log-rank test with a type I error rate of 0.05 and 80% statistical power, and a follow-up of 5 years.

The target sample size was 180 patients to detect a 20% absolute improvement in the CRS arm,[12] assuming 20% 5-year OS in the CS arm. Kaplan-Meier methods were used to estimate the median OS and PFS. The HRs and the 95% confidence intervals (CIs) were estimated using the Cox proportional hazards regression model, and the OS and PFS were analyzed using the log-rank test.

RESULTS

Patient Characteristics

Between December 2000 and August 2005, 60 patients were randomly assigned and 58 patients were treated. The 2 untreated patients (both in the CRS arm) did not satisfy the eligibility criteria and were excluded from the subsequent analyses. Because of the slow patient accrual, this study was terminated at 60 enrollments in accordance with a Data Safety and Monitoring Committee recommendation made in December 2005. Patient characteristics were well-balanced in terms of age, sex, histology, smoking history, and TNM stage. The chemotherapy cycles of induction therapy did not differ between the CS arm (mean 2 ± 0 standard deviation) and the CRS arm (mean 1.9 ± 0.3 standard deviation). Regarding the number of patients possessing multistation mediastinal lymph node metastases, there was no difference between the 2 arms ($P = .297$; Table 1).

Table 1. Patient Demographics

Characteristic	CS	CRS	*P*
Registered patients	29	31	
Median age (range), y	57.0 (36-70)	58.0 (34-69)	.947
Sex (M/F)	19/10	21/10	.855
Histology (adenocarcinoma/squamous carcinoma/other)	16/8/5	23/5/3	.422
Smoker/nonsmoker	22/7	23/8	.881
T 1/2/3	11/14/4	11/18/2	.577
N 0/1/2/3	0/0/29/0	0/0/30/1	.329
Lymph node station (single/multiple)	15/14	11/20	.297
M 0/1	29/0	30/1	1.000
Staging misconduct	0	2	
Survival analysis	29	29	
Missing safety data	1	1	
Safety data analysis	28	28	

Abbreviations: CRS, concurrent chemoradiotherapy followed by surgery; CS, chemotherapy followed by surgery.

The 25 patients (89%) in the CS arm and 20 patients (71%) in the CRS arm completed 2 cycles of chemotherapy at full dose. There was no difference in dose intensity of docetaxel and carboplatin between the 2 arms. Docetaxel dose intensity in each arm was as follows: 1.00 ± 0.00 (CS arm, first course), 0.99 ± 0.04 (CS arm, second course), 1.00 ± 0.00 (CRS arm, first course), 0.94 ± 0.08 (CRS arm, second course). Carboplatin dose intensity in each arm was as follows: 0.97 ± 0.16 (CS arm, first course), 0.95 ± 0.12 (CS arm, second course), 1.00 ± 0.00 (CRS arm, first course), 0.88 ± 0.14 (CRS arm, second course).

In the CRS arm, 28 of 29 patients received 40 Gy of radiation dose as scheduled and the remaining 1 patient received only 34 Gy because of neutropenic fever. A total of 77% of patients underwent 3D treatment planning radiation using computed tomography.

Treatment Efficacy

The tumor response for the induction therapy was 7 PRs, 19 NCs, 2 PDs in the CS arm, and 7 PRs, 19 NCs, 2 PDs in the CRS arm. Overall response rate was 25% in both arms. The number of patients who underwent surgery was 25 of 29 (86.2%) in the CS arm and 26 of 29 (89.7%) in the CRS arm. The reasons for patients not undergoing surgery were PD in 2 patients, no recovery of PS after chemotherapy in 1 patient, and patient refusal in 1 patient in the CS arm, and PD in 2 patients and no recovery from adverse events in 1 patient in the CRS arm. Postprotocol treatment of patients not undergoing surgery was radiotherapy in 2 patients, chemoradiotherapy in 1 patient, and best supportive therapy in 1 patient in the CS arm,

Table 2. Toxicity, From National Cancer Institute Common Toxicity Criteria, Version 2.0

Adverse Event	Chemotherapy + Surgery (n = 28)		Chemoradiotherapy + Surgery (n = 28)		*P*
	Grade 1 + 2	Grade 3 + 4	Grade 1 + 2	Grade 3 + 4	
Nausea	19 (67.9%)	0	21 (75.0%)	3 (10.7%)	.554
Vomiting	2 (7.1%)	0	7 (25.0%)	1 (3.6%)	.036
Fever	5 (17.9%)	0	14 (50.0%)	0	.011
Dyspnea	0	0	1 (3.6%)	0	.313
Infection	2 (7.1%)	2 (7.1%)	4 (14.3%)	1 (3.6%)	.716
Peripheral neuropathy	2 (7.1%)	0	1 (3.6%)	0	.553
Allergic reaction	1 (3.6%)	0	5 (17.9%)	0	.084
Dysphagia	0	0	9 (32.1%)	0	
Leukopenia	12 (42.9%)	13 (46.4%)	2 (7.1%)	26 (92.9%)	.075
Neutropenia	6 (21.4%)	21 (75.0%)	3 (10.7%)	25 (89.3%)	.313
Anemia	25 (89.3%)	0	24 (85.7%)	2 (7.1%)	.639
Thrombocytopenia	12 (42.9%)	0	19 (67.9%)	2 (7.1%)	.014
Increased transaminase	8 (28.6%)	0	12 (42.9%)	1 (3.6%)	.168
Increased creatinine	2 (7.1%)	0	7 (25.0%)	0	.069

and single-agent chemotherapy in 3 patients in the CRS arm. The downstaging rate was 20.8% (5 of 24, missing data 1 patient) in the CS arm and 40.0% (10 of 25, missing data 1 patient) in the CRS arm ($P = .215$). After downstaging, pTNM of patients in the CS arm was pT1N0M0, pT2N0M0, pT3N0M0, pT1N1M0, and pT2N1M0 in 1 patient each. On the contrary, pTNM of patients in CRS arm was T0N0M0 in 3 patients (pathologic complete response), T1N0M0 in 2 patients, T2N0M0 in 4 patients, and T2N1M0 in 1 patient. The surgical procedures used and the number of patients treated were as follows: lobectomy in 20, bilobectomy in 3, wedge resection plus segmentectomy in 1, and pneumonectomy in 1 (the CS arm); lobectomy in 23, bilobectomy in 1, and exploratory thoracotomy in 2 (the CRS arm).

Toxicity

Table 2 summarizes the toxicity characteristics among the treated patients. The most common toxicity was a grade 3 or 4 leukopenia in 26 patients (92.9%) in the CRS arm and 13 patients (46.4%) in the CS arm ($P = .075$). Grade 3 or 4 neutropenia was reported in 25 (89.3%) and 21 (75.0%) patients in the CS arm ($P = .313$). Grade 3 or 4 thrombocytopenia was reported in 2 patients (7.1%) in the CRS arm but was not observed in any patient in the CS arm. Among the nonhematological toxicities, grade 1 or 2 vomiting was reported in 7 (25.0%) cases in the CRS arm and in 2 (7.1%) in the CS arm ($P = .036$). Grade 1 or 2 fever was reported in 15 patients (50.0%) in the CRS arm and 5 (17.9%) in the CS arm ($P = .011$). Grade 1 or 2 dysphagia due to radiation was reported in 9 patients (32.1%) in the CRS arm. Other toxicities during induction therapy did not differ between the arms. No treatment-related deaths were reported throughout the trial in either arm.

Survival and First Relapse Site

Median follow-up times for surviving patients in the CS and CRS arms were 60.7 months (range 1.8 to 86.5 months) and 60.8 months (range 44.5 to 87.5 months), respectively. Progression-free survival (PFS) did not improve in the CRS arm versus the CS arm (median, 12.4 months vs 9.7 months; HR = 0.68 [95% CI = 0.38-1.21], $P = .187$; Fig. 3A). Overall survival (OS) also did not improve in the CRS arm versus the CS arm (median, 39.6 months vs 29.9 months; HR = 0.77 [95% CI = 0.42-1.41], $P = .397$; Fig. 3B). The 3-year survival rates in the CRS and CS arms were 51.7% and 39.3%, and the 3-year PFS rates were 34.5% and 17.9%, respectively. The median OS of patients with and without downstaging in the CRS arm was 72.1 months and 31.2 months, respectively (HR = 4.16 [95% CI = 1.16-14.93], $P = .018$). In the CS arm, these values were 32.6 months and 29.0 months, respectively (HR = 1.47 [95% CI = 0.424-5.09], $P = .542$). Exploratory analyses of all patients from both arms according to mediastinal downstaging showed that patients without downstaging (n = 35) had a median PFS of 9.4 months and a 3-year PFS rate of 14.3% (Fig. 4A). However, patients with downstaging (n = 15) had a significantly longer median PFS of 55.0 months and a 3-year PFS rate of 60.0% (HR = 3.39 [95% CI = 1.54-7.48], $P = .001$). In terms of the OS, patients without downstaging had a median OS of 29.5 months, with a 3-year survival rate of 40.0% (Fig. 4B). In contrast,

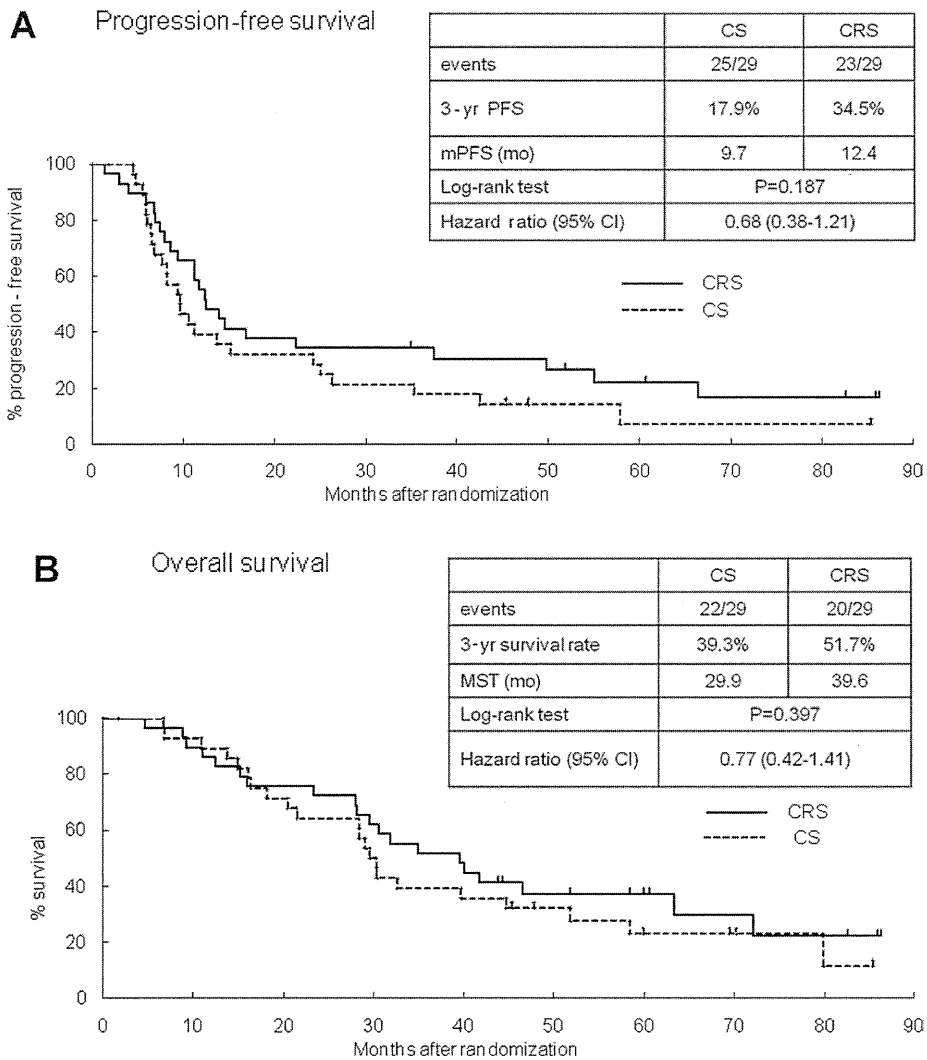

Figure 3. Curves are shown for (A) progression-free survival (PFS) and (B) overall survival analyses. CI, confidence interval; CRS, concurrent chemoradiotherapy followed by surgery; CS, chemotherapy followed by surgery; MST, median survival time.

patients with downstaging had a significantly longer OS of 63.3 months, with a 3-year survival rate of 66.7% (HR = 2.62 [95% CI = 1.12-6.09], $P = .021$).

Relapse was noted in 25 patients out of 28 in the CS arm (missing data 1) and in 24 out of 29 in the CRS arm. Local lymph node relapse in the CS arm and CRS arm occurred in 7 and 5 patients, respectively. Distant relapse occurred in 13 and 15 patients in the CS and CRS arms, respectively. Local and distant relapses occurred in 5 and 4 patients in the CS and CRS arms, respectively (Table 3). It is noteworthy that the brain and lung are the most frequent sites of distant metastasis (21 patients). One notable difference in the relapse pattern was the recurrence in the radiation field of the hilar and mediastinal lymph nodes. This was 41% (12 of 29 patients) in the CS arm, significantly higher than the 17% (5 of 29 patients) found in the CRS arm ($P = .0435$, chi-square test).

DISCUSSION

Our present study focuses on stage IIIA disease with pathologically proven mediastinal lymph node metastasis by investigating whether CRS would confer a better 5-year survival than CS. The observed trend was of a better OS and PFS in the CRS arm than in the CS arm. The median OS in the CRS and CS arms was 39.6 months

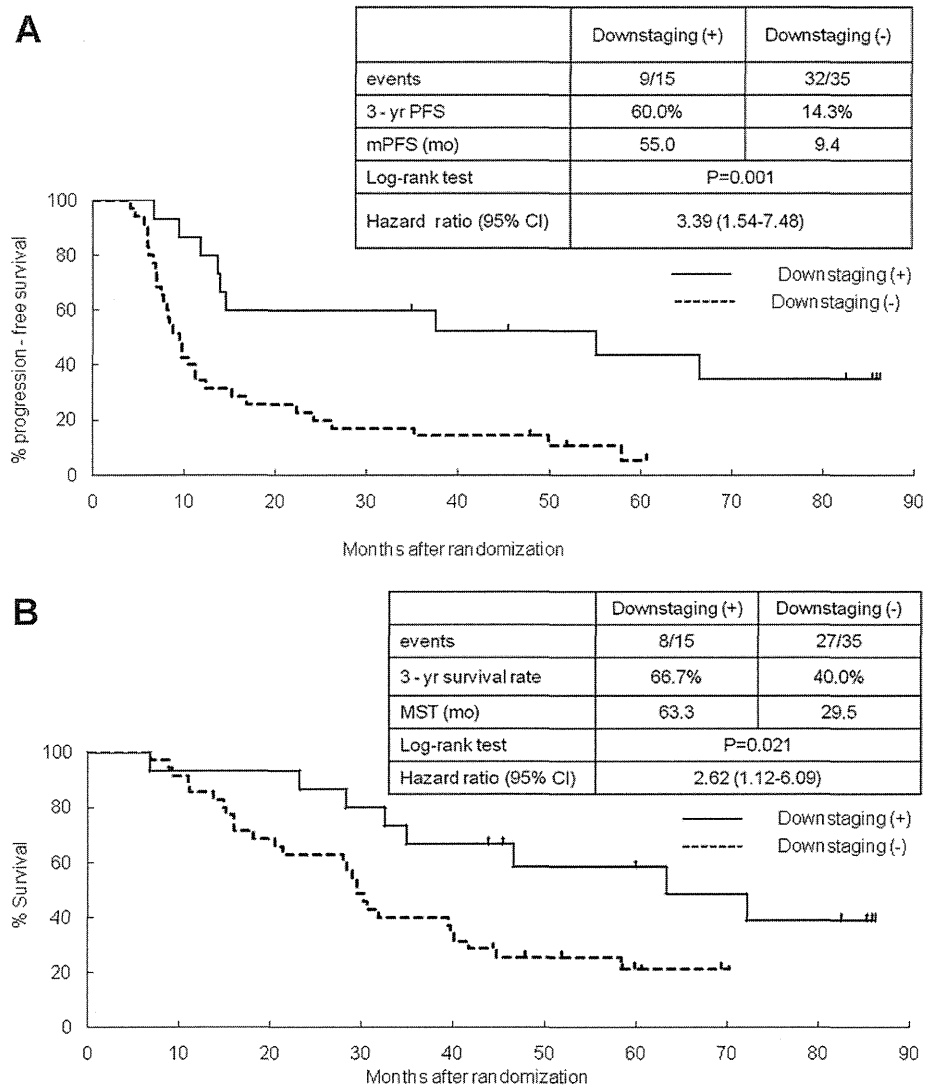

Figure 4. Curves are shown for (A) progression-free survival (PFS) and (B) overall survival of all resected patients according to downstaging. CI indicates confidence interval; CRS, concurrent chemoradiotherapy followed by surgery; CS, chemotherapy followed by surgery; MST, median survival time.

and 29.9 months, respectively. The median PFS in the CRS and CS arms was 12.4 months and 9.7 months, respectively. These differences are not statistically significant due to the small sample size. However, the median OS in the CRS arm in our study is clearly favorable compared with previous reports (13-32 months) in which patients with stage IIIA and IIIB disease were treated with preoperative chemoradiotherapy.[9-12] In particular, Albain et al recently reported a phase 3 study of concurrent chemoradiotherapy with or without surgical resection for stage IIIA, N2 NSCLC.[14] The median OS with and without surgery was 23.6 months and 22.2 months, respectively ($P = .24$) and the median PFS was better in patients with surgery (12.8 months vs 10.5 months, $P = .017$). In further exploratory analysis, the median OS was improved in the surgical group when a lobectomy was performed compared with a matched nonsurgical group (33.6 months vs 21.7 months, $P = .002$). However, the OS for patients in the pneumonectomy subgroup of the surgical cohort was not significantly poorer than that of the matched cohort in the nonsurgical group (18.9 months vs 29.4 months). A randomized study conducted by the German investigators directly compared CS with CRS in patients with stage IIIA-IIIB NSCLC.[15] The interventional-concurrent group

Table 3. First Relapse Site

Relapse Site	CS (n = 25)	CRS (n = 24)
Local	7	5
Hilar/mediastinal lymph node[a]	7	3
Supraclavicular lymph node	1	3
Distant	13	15
Lung	5	11
Bone	3	4
Liver	2	3
Brain	9	9
Para-aortic lymph node	0	2
Others	0	4
Local + distant	5	4
Hilar/mediastinal lymph node[a]	5	2
Supraclavicular lymph node	2	3
Lung	3	2
Bone	1	0
Pericardium	2	0
Brain	1	2
Others	2	0

Abbreviations: CRS, concurrent chemoradiotherapy followed by surgery; CS, chemotherapy followed by surgery.
[a] Recurrence in the radiation field.

was to receive 3 cycles of cisplatin and etoposide, followed by twice-daily radiation (total 45 Gy) with concurrent weekly carboplatin and vindesine, and then surgical resection. The control chemotherapy group was to receive 3 cycles of cisplatin and etoposide followed by surgery and then further radiotherapy. Of 524 eligible patients, 142 of 264 (54%) in the interventional group and 154 of 260 (59%) in the control group underwent surgery; 98 of 264 (37%) and 84 of 260 (32%) underwent complete resection. There was no significant difference according to the treatment group for PFS (intervention group: median 9.5 months vs control group: 10.0 months) or for OS (median 15.7 months vs 17.6 months). This may be due to the fact that they enrolled a substantial proportion of patients with a high disease burden (15% with T4N2 and 22% with T4N3).

Systemic chemotherapy is another neoadjuvant treatment modality that has been administered before surgery. The postsurgery OS in these cases was found to range from 20 to 28.7 months, and the 3-year survival rate ranged from 17% to 45%.[4-8] More recently, van Meerbeeck et al conducted a phase 3 trial that investigated the role of surgery versus radiotherapy after induction chemotherapy in 579 patients with pathologically documented stage IIIA, N2, NSCLC.[16] Patients received 3 cycles of platinum-based chemotherapy, and nonprogressors were then randomized for surgery (n = 164) or thoracic radiotherapy (n = 165). The median and 5-year OS values for patients assigned to the resection group versus the radiotherapy group were 16.4 versus 17.5 months and 15.7% versus 14%, respectively (HR = 1.06 [95% CI = 0.84-1.35]). However, the median OS was poorer than in our present study (39.6 months in the CRS arm) or in the study by Albain et al (23.6 months in chemoradiotherapy in the surgery arm).

The response rate from induction chemoradiotherapy in our study was relatively low (25%) and is poorer than the 59% to 74% reported for other concurrent chemoradiotherapy studies.[9-12] The most likely reason is that the period between induction therapy and surgery in our patients was short and shrinkage could not be confirmed in many cases, which resulted in a low response rate and a high stable disease rate (67.9%). Another possible reason is that in the present study we used a suboptimal preoperative radiation dose schedule (40 Gy in 20 fractions over 4 weeks). A better response rate is typically achieved following a higher radiation dose (45 Gy)[14] or hyperfractionated accelerated irradiation.[9-11,15,17,18] An exploratory analysis showed that the OS of our patients with downstaging (72.1 months) was significantly better than that of patients without downstaging (31.2 months) in the CRS arm ($P = .008$), although this survival benefit in patients with downstaging was not demonstrated in the CS arm ($P = .542$). Although the in-field recurrence was significantly higher in the CS arm compared with the CRS arm, this did not translate to better PFS or OS in the CRS arm because there was no significant difference of distant and distant + local recurrence between the 2 arms (CS vs CRS, 18/28; 64% vs 19/29; 65%). The number of patients having multistation lymph node disease in the CS arm was relatively high (14 of 29, 52%) compared with the CRS arm (11 of 31, 35%). This tendency might have led to low downstaging rate in the CS arm because irradiation has potent local control effect. The high downstaging rate and the absence of treatment-related death in our CRS arm translated into a longer median OS (39.6 months) and higher 3-year survival rate (51.7%). Choi et al[9] conducted a phase 2 study of an induction treatment involving twice-daily radiation and concurrent chemotherapy in 42 patients with stage IIIA NSCLC, and reported that the 5-year survival rate in patients with pathological complete response (79%) was significantly higher ($P = .04$) than that in patients with pN1 (42%) or pN2