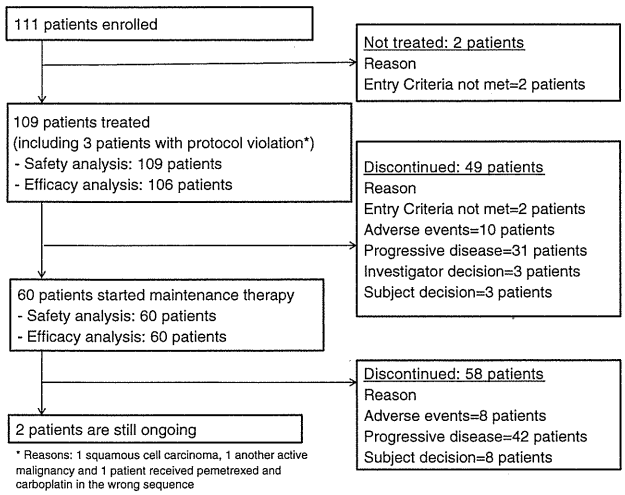

Fig. 1 Patient disposition

adenocarcinoma histology (97.2 %) and stage IV disease (66.1 %).

Treatment delivery

Patients received a median of 5 cycles (range: 1–30) of treatment in the entire study period, with 75 patients (68.8 %) completing at least 4 cycles. After completion of 4 cycles of carboplatin and pemetrexed combination therapy, 60 patients (55.0 %) continued pemetrexed monotherapy with a median of 4 cycles (range: 1–26) in the maintenance period. The remaining 15 patients did not receive pemetrexed maintenance therapy due to disease progression (8 cases), adverse events (4 cases), investigator decision (2 cases), or patient decision (1 case).

Overall, 30 patients (27.5 %) out of 109 experienced dose reductions, and 66 patients (60.6 %) experienced dose delay due to adverse events, mainly due to myelosuppression. Among the 60 patients in the maintenance period, 10 patients (16.7 %) had a dose reduction, and 33 patients (55.0 %) had a dose delay due to toxicities.

Table 1 Patient characteristics

Characteristics	*N*=109	%
Age (yr)		
Median	63	–
Range (min, max)	38–78	–
Gender (*n*)		
Male	69	63.3
Female	40	36.7
Performance status (*n*)		
0	37	33.9
1	72	66.1
Disease stage (*n*)		
IIIB	33	30.3
IV	72	66.1
Recurrence	4	3.7
Histology (*n*)		
Adenocarcinoma[a]	106	97.2
Large cell lung carcinoma	3	2.8
EGFR mutation status (*n*)		
Positive	24	22.0
Negative	63	57.8
Unknown	3	2.8
Not done	19	17.4

[a] One patient's tumor was reclassified as squamous cell carcinoma after study entry, and the examination of *EGFR* gene type was not done

Efficacy

Out of 109 patients, 106 were evaluable for efficacy analysis. Three patients were excluded for the following reasons: revised diagnosis of squamous cell carcinoma during the study (1 patient), diagnosis of another active malignancy (1 patient), and delivery of pemetrexed and carboplatin in the wrong sequence during the initial combination period (1 patient). There were 38 partial responses and no complete responses, yielding an ORR of 35.8 % (95 % CI: 26.8 %–45.7 %) (Table 2). Forty-one patients (38.7 %) had stable disease, yielding an overall DCR (CR + PR + SD) of 74.5 % (95 % CI: 65.1 %–82.5 %) (Table 2). At the median follow-up period of 18.5 months (range: 2.1–24.4 months), the median PFS and OS were 5.7 months (95 % CI: 4.4–7.3 months) and 20.2 months (95 % CI: 16.7 months–not calculable), respectively (Table 2 and Fig. 2).

Among 60 patients who received continuation maintenance with pemetrexed, the median PFS from the beginning of induction treatment was 7.5 months (95 % CI: 6.5–8.3 months); median OS was not calculable, with a 1-year survival rate of 89.7 %. In the 46 patients who discontinued study treatment before receiving pemetrexed maintenance, on the other hand, the median PFS was 2.8 months (95 % CI: 2.2–3.0 months), median OS was 8.6 months (95 % CI: 5.7–14.3 months) and 1-year survival rate was 46.8 %.

Sub-group analysis: *EGFR* mutation status

In the present study, *EGFR* mutation status was evaluated in 85 (80 %) of 106 patients evaluable for efficacy; 24 patients harbored an activating *EGFR* gene mutation, whereas 61 patients were *EGFR* wild-type. We prospectively performed subgroup analysis of efficacy according to *EGFR* mutation status. The ORR in the patients with and without *EGFR* mutations were 37.5 % (95 % CI: 18.8 %–59.4 %) and 36.1 % (95 % CI: 24.2 %–49.4 %), respectively (Table 2). The median PFS was 5.7 months (95 % CI: 5.2–7.2 months)

Table 2 Treatment outcome

		EGFR mutation	
Entire period	Total (*N*=106)	Positive (*N*=24)	Negative (*N*=61)
Median PFS, mo	5.7	5.7	6.9
95 % CI	4.4–7.3	5.2–7.2	4.3–7.8
Median OS, mo	20.2	Not calculable	20.2
95 % CI	16.7–Not calculable	20.2–Not calculable	14.2–Not calculable
Overall best response, *n* (%)			
Complete response	0 (0.0)	0 (0.0)	0 (0.0)
Partial response	38 (35.8)	9 (37.5)	22 (36.1)
Stable disease	41 (38.7)	8 (33.3)	27 (44.3)
Progressive disease	20 (18.9)	3 (12.5)	10 (16.4)
Not evaluable	7 (6.6)	4 (16.7)	2 (3.3)
Overall response rate, *n* (%)	38 (35.8)	9 (37.5)	22 (36.1)
95 % CI	26.8–45.7	18.8–59.4	24.2–49.4
Disease control rate, *n* (%)	79 (74.5)	17 (70.8)	49 (80.3)
95 % CI	65.1–82.5	48.9–87.4	68.2–89.4

CI confidence interval, *PFS* progression-free survival, *mo* month(s), *OS* overall survival

for *EGFR* mutation-positive patients and 6.9 months (95 % CI: 4.3–7.8 months) for *EGFR* wild-type patients (Table 2). At the time of analysis, the median OS was not calculable for *EGFR* mutation-positive patients, but 1-year survival rate was 95.7 %; the median OS of patients with *EGFR* wild-type tumors was 20.2 months (95 %CI: 14.2 months-not calculable) with a 1-year survival rate of 68.1 % (Table 2 and Fig. 3a). In *EGFR* wild-type patients, the median OS of those who were treated with pemetrexed continuation maintenance (*n*=37) was notably longer compared with that of 24 patients who did not continue pemetrexed maintenance, whereas OS results in the patients who harbored *EGFR* activating mutation were similar among those with (*n*=14) or without (*n*=10) maintenance therapy using pemetrexed (Fig. 3b).

Safety

All 109 patients who received the initial combination therapy were assessable for safety analysis. The major adverse events for each treatment period (entire, initial combination, and maintenance periods) are shown in Table 3. Hematologic toxicities reaching ≥ grade 3 were neutropenia (56.0 %), thrombocytopenia (41.3 %), anemia (29.4 %), and leukopenia (22.0 %). Nonhematologic toxicities observed in more than half of patients included appetite loss (75.2 %), nausea (74.3 %), fatigue (67.9 %), and ALT increased (51.4 %), but the incidence of toxicities of grade 3 or higher was less than 10 %. The majority of adverse events were observed during the initial 4 cycles of pemetrexed and carboplatin combination therapy. Common toxicities ≥ grade 3 observed in the maintenance period were similar to those observed during the initial combination treatment period, including neutropenia (38.3 %), thrombocytopenia (16.7 %), leukopenia (11.7 %), and anemia (10.0 %). Newly emerged or deteriorated toxicities during maintenance periods were rarely observed. No treatment-related deaths were reported in this study.

Discussion

This was a prospective, multicenter clinical study of first-line combination therapy with pemetrexed and carboplatin followed by maintenance therapy with pemetrexed in chemo-naive patients with advanced nonsquamous NSCLC. This regimen achieved a response rate of 35.8 %, median PFS of 5.7 months, and median OS of 20.2 months. Although the lower limit of one-sided 95 % CI of PFS seen in this trial (4.4 months) did not exceed the prior assumption of a median PFS of 5.0 months, the survival results were striking. Since patients with *EGFR*-mutation positive advanced NSCLC had dramatically improved survival outcomes following treatment with *EGFR* tyrosine kinase inhibitors, the proportion of such patients in this trial may have had an impact on this favorable survival outcome [10–14]. However, the median OS of 20.2 months in 61 *EGFR* wild-type patients was much longer than expected [13], which was still encouraging.

Our study also confirmed findings from an earlier phase II study which showed excellent tolerability of the pemetrexed/carboplatin combination as a first-line chemotherapy [20]. Similarly, our study supported both the safety of

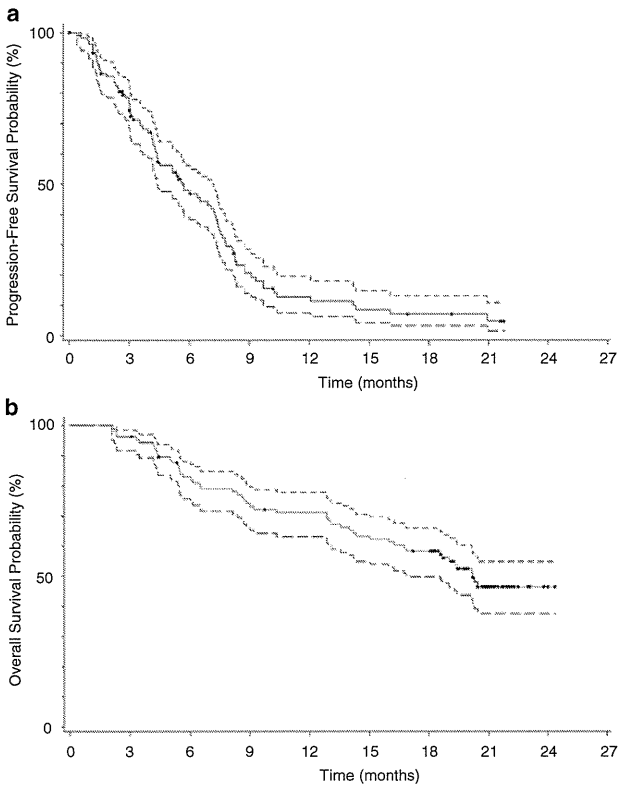

Fig. 2 **a.** Kaplan-Meier curves for progression-free survival curve (*solid line*) with 95 % confidence band (*dashed lines*). **b.** Kaplan-Meier curves for overall survival curve (*solid line*) with 95 % confidence band (*dashed lines*)

pemetrexed and carboplatin as an initial therapy for advanced nonsquamous non-small-cell lung cancer, and also the feasibility of pemetrexed as a maintenance therapy in these patients. The most common hematologic toxicity reaching grades 3 or 4 was neutropenia, but febrile neutropenia occurred in only 1 case. Grade 3 or 4 thrombocytopenia was also frequently observed and 7.3 % of patients received platelet transfusion. However, this condition was considered manageable without any severe bleeding events. There was also no increase in the incidence of hematologic toxicities associated with continuation maintenance with pemetrexed. With regard to nonhematologic toxicity, there were no grade 3 or 4 toxicities encountered in >10 % of patients throughout the study treatment. No unexpected toxicities were observed.

Pemetrexed is used in the maintenance setting for advanced nonsquamous NSCLC, following the results of the PARAMOUNT study, in which continuation maintenance therapy with pemetrexed following induction therapy with pemetrexed/cisplatin resulted in significantly improved PFS and OS [18, 21]. In the present study, the favorable tolerability profile of pemetrexed maintenance after induction of pemetrexed/carboplatin is reflected in the observation that 55 % of patients were able to continue on pemetrexed monotherapy with a median of 4 cycles. The median PFS of 7.5 months from the beginning of induction treatment in 60 patients who received maintenance therapy with pemetrexed is consistent with the finding of the PARAMOUNT study where a median PFS of 6.9 months was achieved by continuation maintenance with pemetrexed [18]. Although there are limitations when comparing results from different studies, these data suggest that pemetrexed continuation maintenance therapy is effective whether cisplatin or carboplatin is used for the induction chemotherapy. In our ad-hoc exploratory analyses, *EGFR* wild-type patients who continued with pemetrexed as a maintenance therapy demonstrated marked OS compared with those who did not receive maintenance therapy, whereas there was no obvious difference in OS of 24 *EGFR*-mutation positive patients, regardless of maintenance treatment. Given that most these patients (10 of 14 patients with pemetrexed maintenance, 9 of 10 patients without maintenance) received gefitinib or erlotinib as poststudy treatment, a good outcome could have been achieved in patients harboring the targetable oncogenic gene alterations by subsequent treatment with these active therapies, even though they did not continue pemetrexed maintenance. Although this study was not a

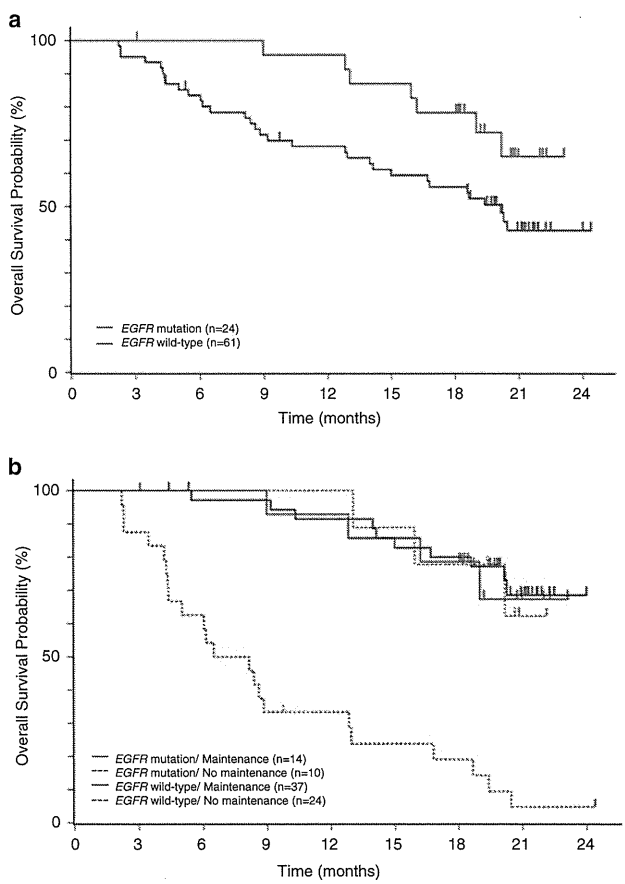

Fig. 3 **a.** Overall survival by EGFR mutation status. **b.** Overall survival by EGFR mutation status and maintenance-treated status

Table 3 Toxicity by treatment period

	Entire period (*N*=109)			Initial combination period (*N*=109)			Maintenance period (*N*=60)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Hematologic	*n*(%)	*n*(%)	*n* (%)	*n*(%)	*n* (%)	*n* (%)	*n* (%)	*n*(%)	*n* (%)
Leukopenia	83 (76.1)	24 (22.0)	–	82 (75.2)	23 (21.1)	–	43 (71.7)	7 (11.7)	–
Neutropenia	86 (78.9)	47 (43.1)	15 (13.8)	84 (77.1)	45 (41.3)	14 (12.8)	44 (73.3)	21 (35.0)	3 (5.0)
Thrombocytopenia	94 (86.2)	30 (27.5)	15 (13.8)	94 (86.2)	30 (27.5)	15 (13.8)	40 (66.7)	10 (16.7)	–
Anemia	98 (89.9)	32 (29.4)	2 (1.8)	98 (89.9)	31 (28.4)	2 (1.8)	52 (86.7)	8 (13.3)	–
	Any Grade	Grade ≥3		Any Grade	Grade ≥3		Any Grade	Grade ≥ 3	
Non-hematologic	*n* (%)	*n* (%)		*n* (%)	*n* (%)		*n* (%)	*n* (%)	
Appetite loss	82 (75.2)	6 (5.5)		81 (74.3)	6 (5.5)		21 (35.0)	–	
Nausea	81 (74.3)	1 (0.9)		80 (73.4)	1 (0.9)		21 (35.0)	–	
Vomiting	42 (38.5)	3 (2.8)		42 (38.5)	3 (2.8)		4 (6.7)	–	
Fatigue	74 (67.9)	2 (1.8)		69 (63.3)	2 (1.8)		33 (55.0)	–	
Rash	32 (29.4)	1 (0.9)		29 (26.6)	1 (0.9)		6 (10.0)	–	
Fever	22 (20.2)	1 (0.9)		20 (18.3)	1 (0.9)		3 (5.0)	–	
Alopecia	8 (7.3)	–		8 (7.3)	–		3 (5.0)	–	
Neuropathy	10 (9.2)	–		7 (6.4)	–		5 (8.3)	–	
ALT increased	56 (51.4)	7 (6.4)		49 (45.0)	5 (4.6)		30 (50.0)	3 (5.0)	
AST increased	55 (50.5)	2 (1.8)		43 (39.4)	1 (0.9)		34 (56.7)	1 (1.7)	

ALT alanine aminotransferase, *AST* aspartate aminotransferase

randomized trial, these results may stimulate further interest in the clinically relevant efficacy of pemetrexed maintenance in *EGFR* wild-type patients for whom the limited therapeutic options exist.

In conclusion, this study regimen of pemetrexed/carboplatin followed by pemetrexed maintenance is feasible and effective as a first-line treatment for advanced nonsquamous NSCLC patients. Our findings have strengthened the rationale for the ongoing randomized phase III trial comparing this regimen with the carboplatin, paclitaxel and bevacizumab combination in patients with advanced, nonsquamous NSCLC [22].

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Disclosure of potential conflicts of interest Keisuke Aoe, Nobuyuki Yamamoto, Naoyuki Nogami, Terufumi Kato and Kazuhiko Nakagawa received honoraria from Eli Lilly Japan K.K. Immediate family of Terufumi Kato is currently employed by Eli Lilly Japan K.K. Naoto Yoshizuka, Risa Sekiguchi and Kazuhiro Kiyosawa are currently employed by Eli Lilly Japan K.K. Other authors declare no conflicts of interest.

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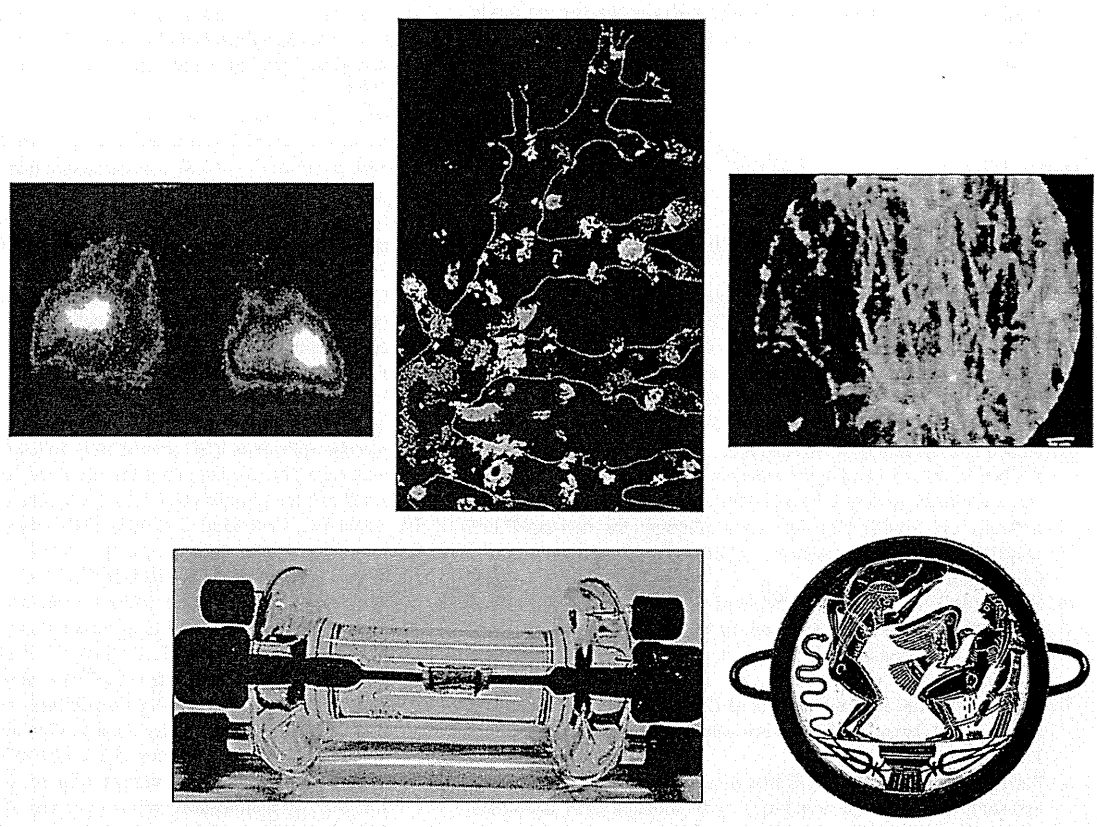

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Rapid On-Site Cytologic Evaluation during Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration for Diagnosing Lung Cancer: A Randomized Study

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Key Words
Bronchoscopy · Diagnosis · Mediastinal lymph nodes · Staging

Abstract
Background: Although rapid on-site cytologic evaluation (ROSE) is widely used during endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA), its role remains unclear. ***Objectives:*** The purpose of the present study was to evaluate the efficacy of ROSE during EBUS-TBNA in the diagnosis of lung cancer. ***Methods:*** One hundred and twenty patients highly suspected of having lung cancer who had hilar/mediastinal lymphadenopathy or a tumor adjacent to the central airway were enrolled in this study and randomized to undergo EBUS-TBNA with or without ROSE. ***Results:*** Twelve patients with visible endobronchial lesions were excluded in the analysis. Thus, a total of 108 patients (55 in the ROSE group, 53 in the non-ROSE group) were analyzed. Additional procedures including EBUS-TBNA for lesions other than the main target lesion and/or transbronchial biopsy in the same setting were performed in 11% of patients in the ROSE group and 57% in the non-ROSE group ($p < 0.001$). Mean puncture number was significantly lower in the ROSE group (2.2 vs. 3.1 punctures, $p < 0.001$), and mean bronchoscopy time was similar between both groups (22.3 vs. 22.1 min, $p = 0.95$). The sensitivity and accuracy for diagnosing lung cancer were 88 and 89% in the ROSE group, and 86 and 89% in the non-ROSE group, respectively. No complications were associated with the procedures. ***Conclusions:*** ROSE during EBUS-TBNA is associated with a significantly lower need for additional bronchoscopic procedures and puncture number.

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Introduction

Transbronchial needle aspiration (TBNA) is a well-established procedure for evaluating lesions adjacent to the central airway. Since the development of TBNA with a flexible bronchoscope in the late 1970s [1], the procedure has been improved with various techniques or devices to increase the diagnostic accuracy. Rapid on-site

Preliminary data were previously presented with slides at ERS 2012 Annual Meeting in Vienna. Trial Registration: UMIN-Clinical Trials Registry; Identifier: UMIN0000001334, http://www.umin.ac.jp/ctr/index.htm.

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cytologic evaluation (ROSE) during TBNA has been suggested as one such way. It has been reported to be effective, as it increases the diagnostic yield [2, 3], decreases the number of needle passes [4, 5], obviates the need for additional diagnostic procedures [4–7], reduces the complication rate of bronchoscopy [5] and reduces the cost [6]. Although its role is controversial [8], many investigators recommend the use of ROSE during TBNA [9, 10].

Development of an endobronchial ultrasound (EBUS) bronchoscope has enabled 'real-time' TBNA by confirming the position of the needle tip under EBUS imaging during the TBNA procedure, allowing for a more highly accurate TBNA procedure than by the conventional TBNA. Although EBUS-guided TBNA (EBUS-TBNA) is a relatively new procedure, many studies have reported its usefulness for hilar/mediastinal explorations [11–13], and it has been rapidly popularized. Many bronchoscopists use ROSE routinely during EBUS-TBNA as well as conventional TBNA in the current clinical practice [12, 13], and some authors recommend the use of ROSE during EBUS-TBNA [14]. However, no prospective comparative studies focused on the utility of ROSE during EBUS-TBNA have been reported, and so its role has remained unclear. We conducted this prospective randomized study to further clarify the role of ROSE during EBUS-TBNA in the diagnosis of lung cancer. The primary endpoint was the frequency with which additional bronchoscopic procedures can be eliminated in the same setting. Secondary endpoints were the diagnostic accuracy of EBUS-TBNA for lung cancer, the diagnostic yield of EBUS-TBNA, number of needle passes, time of the procedures, and the frequency of complications.

Patients and Methods

Patients

We carried out a prospective study which was approved by the institutional review board of Nagoya Medical Center (identifier: 2008-175) and registered with the UMIN-Clinical Trials Registry (identifier: UMIN000001334). Included in this study were 120 patients suspected of having lung cancer along with metastatic lymph nodes or tumors, 10 mm or greater in the shortest diameter on chest computed tomography, all of which were easily accessible with EBUS-TBNA. All patients with lung cancer diagnosed pathologically prior to bronchoscopy were excluded. Patients who had obviously bronchoscopically visible endobronchial lesions were also excluded. Randomization for EBUS-TBNA with or without ROSE was performed by minimization with stratification factors including lymph node location (subcarinal lymph node vs. other), lymph node size (20 mm or greater vs. less than 20 mm) and examiner experience (staff pulmonologists vs. pulmonary residents 5 years or less after receiving their MD). All patients provided their written informed consent.

Procedures

Bronchoscopic procedures were performed under local anesthesia with lidocaine and conscious sedation with intravenous midazolam by staff pulmonologists or supervised pulmonary residents. EBUS-TBNA was performed in the same manner we previously described [15, 16]. After insertion of the EBUS bronchoscope (BF-UC260F-OL8; Olympus, Tokyo, Japan) into the trachea directly or through an endotracheal tube, a balloon attached on the transducer was inflated with saline solution. The balloon was then brought into contact with the airway wall and moved in all directions to identify the lesions for sampling. When the target lesion was visualized by EBUS, a 21- or 22-gauge needle was passed through the working channel of the bronchoscope, which was then advanced through the tracheobronchial wall into the lesion under real-time EBUS visualization. After stylet removal, suction was applied using a syringe while manipulating the needle back and forth within the lesion. After the sampling, the suction was released slowly and the needle was retracted.

The specimen collected in the lumen of the needle was first pushed out with the central stylet and then blown by air with a syringe onto a glass slide. The visible tissue fragment on the glass slide was then collected and transferred into numbered separate containers filled with formalin for histologic examination. The remaining specimen on the glass slide was smeared with another glass slide, then the residual specimen stored at the lumen of the needle and catheter was then washed and flushed into saline for culture [15–17]. In patients assigned to the ROSE group, one glass slide was used for ROSE and another was submitted for permanent cytologic examination with Papanicolaou stain. For ROSE, a cytotechnologist evaluated the cell material of the air-dried smears on-site with a quick staining method (Diff-Quik; Kokusaishiyaku, Kobe, Japan). Additional passes were made after the ROSE result was identified. The decision as to termination or additional samplings was made by the examiner based on the ROSE results. In patients assigned to the non-ROSE group, all smeared cytologic specimens were fixed in 95% alcohol for cytologic examination. Three punctures were defined as a standard number in the study protocol, and additional punctures or additional bronchoscopic procedures such as EBUS-TBNA for other lesions or transbronchial biopsy (TBB) for peripheral pulmonary lesions were performed if the examiner considered it necessary. The location of the lymph node examined [18], the number of punctures and the time of the procedure were recorded.

Diagnosis

Each histologic and cytologic specimen was interpreted separately by an experienced pathologist. 'Suspicious' findings were regarded as negative in our analysis. The final diagnoses were established by pathological evidence from biopsy (e.g. bronchoscopic, radiological or surgical procedures), microbiological analysis or clinical follow-up. Benign diagnoses for patients without a definitive diagnosis by EBUS-TBNA were confirmed by radiological size stability and clinical compatibility during the follow-up period for at least 6 months after bronchoscopy.

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Table 1. Characteristics of patients and lesions

Characteristics	ROSE	Non-ROSE	p value
Patients	55	53	
Male/female	44/11	39/14	0.50
Age, years	68.0±7.5 (51–84)	66.5±10.8 (34–84)	0.39
Smoking history			
Never-/ex-/current-smoker	9/18/28	4/20/29	0.37
Lesion size			
Mean, mm (range)	25.4±11.7 (10–60)	23.4±10.6 (10–67)	0.35
<20/≥20 mm	18/37	20/33	0.69
Location of lesion targeted			
2R	5	3	
2L	1	0	
3p	1	5	
4R	22	15	0.2
4L	1	3	
7	13	16	0.44
10R	1	2	
10L	2	2	
11R	6	5	0.8
11L	3	0	
12R	0	1	
Central parenchyma	0	1	
Lesions other than the main target lesion ≥10 mm accessible by EBUS-TBNA			
With/without	39/16	36/17	0.83
Side of suspected primary lesion			
Right/left	42/13	38/15	0.58
Primary disease			
Benign/malignant	2/53	7/46	0.09
Primary lung cancer/others	51/4	43/10	0.09
Bronchoscopy			
Initial bronchoscopy/previous nondiagnostic bronchoscopy	44/11	37/16	0.27
Examiner			
Staff pulmonologist/resident	50/5	49/4	1

Data are presented as n or means ± SD (range).

Statistical Analysis

Based on our own experience, we estimated that 33% of patients in the ROSE group and 75% of those in the non-ROSE group would have to undergo additional procedures. Demonstration of superiority with a statistical power of 90% at a two-sided significance level of 0.05 would require 66 patients. We considered that about 50% of the endoscopically visible lesions would be excluded from the analysis, and thus enrolled a total of around 120 patients with 60 in each group.

Means and percentages were presented as appropriate. Diagnostic yields, diagnostic sensitivity, specificity, positive predictive value, negative predictive value and accuracy were calculated using the standard definitions on a per-patient basis. Dichotomous variables were analyzed using Pearson's χ^2 test or Fisher's exact test, and continuous variables were analyzed using Student's t test. Statistical analyses were performed using a statistical software program (PASW Statistics 18; SPSS Inc, Chicago, Ill., USA). Results were considered statistically significant when the p value was less than or equal to 0.05.

Results

Patients and Lesions

Between August 2008 and April 2011, a total of 120 patients were enrolled in this study and randomized to undergo EBUS-TBNA with or without ROSE. Twelve patients with a bronchoscopically visible endobronchial lesion were excluded from the analysis. Thus, a total of 108 patients (55 patients in ROSE group, 53 patients in non-ROSE group) were included in this analysis. Characteristics of patients and lesions in each group were summarized in table 1. There was no statistically significant difference in the baseline characteristics between the groups.

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Table 2. Procedural details

Variables	ROSE (n = 55)	Non-ROSE (n = 53)	p value
Mean puncture number for main target lesion	2.2±0.9 (1–6)	3.1±0.4 (3–5)	<0.001
Additional procedures	6	30	<0.001
EBUS-TBNA for other lesions	2	26	
TBB for peripheral lesions	4	3	
EBUS-TBNA for other lesions and TBB for peripheral lesions	0	1	
Sole diagnosis provided by additional procedures	0	3	
Bronchoscopy time, min	22.3±15.9 (9–94)	22.1±7.7 (11–56)	0.95

Data are presented as n or means ± SD (range).

Table 3. Final diagnosis and EBUS-TBNA results

EBUS-TBNA findings	Patients (final diagnosis), n			
	ROSE (n = 55)		Non-ROSE (n = 53)	
Malignant				
Primary lung cancer				
Adenocarcinoma	10		14	
Squamous cell carcinoma	15		7	
Large cell carcinoma	1		0	
Non-small cell carcinoma	3		3	
Small cell carcinoma	16		13[a]	
Metastatic carcinoma	0		1	(renal cell carcinoma)
Malignant lymphoma	1		0	
Mediastinal tumor	0		1	(germ cell tumor)
Benign				
Epithelioid cell granuloma with/without necrosis	1	(1 tuberculosis)	1	(1 unspecified)
Nondiagnostic				
Epithelioid cell granuloma[b]	1	(1 lung cancer)	1	(1 lung cancer)
Nonrepresentative samples	7	(5 lung cancers, 1 amyloid tumor, 1 atypical carcinoid)	12	(5 lung cancers, 1 mediastinal cancer, 1 granuloma, 1 abscess, 4 unchanged with 8–30 months of follow-up)

[a] One was diagnosed by EBUS-TBNA for second target lesion. [b] Sarcoidal reaction.

Comparison of Procedures

Procedural details in each group are summarized in table 2. Punctures for the main target lesion were significantly fewer in the ROSE group than in the non-ROSE group (mean: 2.2 vs. 3.1 punctures, $p < 0.001$). In the ROSE group, 6 of 55 patients (11%) underwent additional procedures (2 EBUS-TBNA for other lesions, 4 TBB) in the same setting according to the negative result of ROSE, while in the non-ROSE group, 30 of 53 patients (57%) underwent additional procedures (26 EBUS-TBNA for other lesions, 3 TBB, 1 both EBUS-TBNA and TBB; $p < 0.001$). Of the 30 patients who underwent additional procedures in the non-ROSE group, 3 (10%) were diagnosed solely by the additional procedures. Mean bronchoscopy time was similar in each group (mean: 22.3 vs. 22.1 min, $p = 0.95$).

Diagnostic Performance

Pathological results of EBUS-TBNA and the final diagnosis per-patient basis are detailed in table 3. Two patients with a final diagnosis of lung cancer were given a histological diagnosis of epithelioid cell granuloma by EBUS-TBNA, which was suggested to be a sarcoidal reaction. The overall diagnostic yield of EBUS-TBNA in the ROSE-group and the non-ROSE group was 85% (47 of 55) and 75% (40 of 53), respectively ($p = 0.23$).

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Table 4. Diagnostic value of EBUS-TBNA for lung cancer

	ROSE (n = 55)	Non-ROSE (n = 53)
Sensitivity	88	86
Specificity	100	100
Positive predictive value	100	100
Negative predictive value	40	63
Accuracy[a]	89	89

Data are presented as %. [a] $p = 0.95$ using χ^2 test.

The diagnostic accuracies of EBUS-TBNA in the diagnosis of lung cancer are shown in table 4. Of the 82 patients with lung cancer diagnosed by EBUS-TBNA, a positive EBUS-TBNA result was obtained from N3 lymph nodes in 11 patients, N2 lymph nodes in 59 patients, N1 lymph nodes in 11 patients and parenchyma in 1 patient.

Accuracy of ROSE

The diagnostic accuracy of ROSE as positive or negative in the diagnosis of malignancy for the final pathological diagnosis on per-lesion bases was calculated. Two false-positive cases and 2 false-negative cases resulted. The sensitivity, specificity, positive predictive value, negative predictive value and accuracy were 96, 78, 96, 78 and 93%, respectively.

Safety

No complication was observed to be associated with bronchoscopy.

Discussion

To our knowledge, this is the first randomized study on the effect of ROSE during EBUS-TBNA in the diagnosis of lung cancer. This study demonstrated that during EBUS-TBNA ROSE reduced the puncture number or obviated the need for additional bronchoscopic procedures, but it was not associated with the total bronchoscopy time. We could not demonstrate differences in diagnostic accuracy or complication rate in this small study. Our study showed the usefulness of EBUS-TBNA as the initial diagnostic test for the pathological confirmation of lung cancer as well.

ROSE feeds back valuable information to the examiner on the adequacy of cytologic samples at the time of needle aspiration procedures, which indicates whether the procedure should be repeated or not. In conventional TBNA, many investigators have reported the usefulness of ROSE, but the role is controversial [8, 9]. For example, several authors have reported that ROSE increases the diagnostic yield [2, 3]. The examiner can modify the technique by changing the puncture site, puncture depth or angle based on the ROSE results, which might increase the diagnostic yield. The results of recent randomized studies contradicted the diagnostic efficacy of ROSE during conventional TBNA [5, 7]. In a randomized study including 168 patients, Trisolini et al. [5] demonstrated no significant difference between TBNA with and without ROSE in terms of diagnostic yield or sample adequacy. In addition, procedure time on TBNA with ROSE was significantly longer than TBNA without ROSE due to processing, and careful review of the slides despite the use of ROSE was associated with fewer biopsy sites. The same investigators noted that the benefit of ROSE during TBNA was avoidance of additional biopsy which was associated with complications. Yarmus et al. [7] also found similar results in their randomized study of 68 patients.

The value of ROSE during EBUS-TBNA may be smaller than that during conventional TBNA in terms of diagnostic yield because of the high diagnostic yields of EBUS-TBNA regardless of using ROSE. In fact, it was reported that 7 aspirates maximized the yield of conventional TBNA for the diagnosis and staging of lung cancer [19], while a study [20] concerning EBUS-TBNA demonstrated that 3 aspirates per lesion were sufficient to obtain optimal results for the staging of lung cancer. The result may suggest that the optimal yield is obtained by 3 aspirates regardless of using ROSE. Griffin et al. [21] also found that ROSE during EBUS-TBNA did not increase the diagnostic yield in their retrospective study. They also reported that ROSE during EBUS-TBNA did not decrease the number of lesions sampled per patient. To the contrary, our study demonstrated that during EBUS-TBNA ROSE reduced the puncture number per lesion or the number of lesions aspirated. In our clinical practice without ROSE, we prefer performing EBUS-TBNA for plural lesions to performing EBUS-TBNA for a single lesion to increase the diagnostic yield if there are multiple evaluable lesions [16]. If we use ROSE, we can judge the necessity of further needle passes or diagnostic procedures from the ROSE results. In our study, EBUS-TBNA for multiple lesions was performed in only 5% of patients with enlarged evaluable lesions other than the main target lesion in the ROSE group, against 75% of patients in the non-ROSE group. However, the clinical benefit might be limited. EBUS-TBNA is extremely safe, so the additional punctures can be performed without additional compli-

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cations. In addition, ROSE could not shorten the bronchoscopy time because preparing and reviewing slides for ROSE took time.

Our study demonstrated the usefulness of EBUS-TBNA as the initial diagnostic test for lung cancer as well. Diagnosis of lung cancer as well as its staging is one of the common indications for EBUS-TBNA. We often encounter patients with a small peripheral primary lung cancer with bulky mediastinal lesions. In addition, some lung cancers, especially small cell lung cancers, present mediastinal masses without a distinct primary parenchymal lesion [22]. Furthermore, the result of EBUS-TBNA plays an important role not only for the diagnosis but also the mediastinal staging. Surgical resection is not the treatment of choice for most patients with the positive result of N3 lymph nodes, N2 lymph nodes or N1 lymph nodes in small cell lung cancer. While many investigators have reported the accuracy of EBUS-TBNA for the staging of lung cancer [11, 12], little has been reported on the role of the procedure in the diagnosis of lung cancer. Lee et al. [22] retrospectively evaluated the diagnostic accuracy of EBUS-TBNA for lung cancer. They reported excellent accuracy and sensitivity of 98 and 97%, respectively. Our study again demonstrated the high accuracy of EBUS-TBNA in the diagnosis of lung cancer with or without ROSE. Despite the high accuracy, we must carefully interpret the pathological findings of epithelioid cell granulomas. In our study, sarcoidal reaction at the target lesion was found in one patient with lung cancer in each group. It may be difficult to distinguish between sarcoidosis and sarcoidal reaction from only pathological samples. If a specimen is obtained with a sarcoid-like appearance from enlarged lymph node in patients with suspected lung cancer, another biopsy for the primary lesion should be performed.

The limitation of our study was that the primary endpoint was the frequency for eliminating the need for additional bronchoscopic procedures, but not the diagnostic sensitivity for lung cancer. Therefore, our study is clearly too small to compare the diagnostic yield of EBUS-TBNA with and without ROSE. At the time of making our study protocol, we expected the difference between the diagnostic accuracy of EBUS-TBNA with and without ROSE would be quite small, so the power calculation for demonstrating diagnostic superiority of EBUS-TBNA with ROSE seemed to be unrealistic. In fact, one review article [12], which analyzed 1,299 patients who underwent EBUS-TBNA for mediastinal staging of lung cancer, reported the pooled sensitivity of EBUS-TBNA with or without ROSE to be 0.97 and 0.92. However, the statistically significant difference could not be demonstrated even in such a large population. To show the diagnostic superiority of EBUS-TBNA with ROSE, thousands of patients in each arm would be required. In our study, although ROSE provided little clinical benefit in patients with high prevalence and probability, it might be useful in other populations. For staging purposes, the preprobability of metastasis may be lower, and thus more lymph nodes should be examined. In addition, the instantaneous results of ROSE during EBUS-TBNA in the staging of lung cancer have been reported to be useful for the decision-making following surgical resection [23]. More detailed elucidation of the role of ROSE during EBUS-TBNA in patients with lung cancer for staging purposes may be warranted in a further study.

In conclusion, ROSE during EBUS-TBNA in the initial diagnosis of lung cancer can reduce the puncture number or eliminate the need for additional bronchoscopic procedures.

Financial Disclosure and Conflict of Interest Statement

The authors have no conflicts of interest to disclose.

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CHEST

Original Research

PULMONARY PROCEDURES

New Dedicated Bifurcated Silicone Stent Placement for Stenosis Around the Primary Right Carina

Masahide Oki, MD, FCCP; and Hideo Saka, MD, FCCP

Background: **Silicone stenting has been widely used to palliate respiratory symptoms in patients suffering from airway stenosis. Although many types and shapes of stents have been developed, there is no ideal stent for stenosis around the carina between the bronchus to the right upper lobe and the bronchus intermedius (primary right carina). The purpose of this study was to evaluate the feasibility, efficacy, and safety of a new silicone stent designed for treating airway stenosis around the primary right carina.**

Methods: **We recruited 16 patients with suspected stenosis around the primary right carina. Ten of the patients met the inclusion criteria for inserting the study stent. All stenting procedures were performed with a rigid and flexible bronchoscope under general anesthesia.**

Results: **The study stent could be mounted successfully on the primary right carina in all 10 patients. Five patients underwent stenting using only the new stent, and the other five underwent stenting with it on the primary right carina and a silicone Y stent on the main carina. The dyspnea index improved in eight of the 10 patients, including one who was mechanically ventilated. Early complications developed in three patients (temporary pneumonia in two and retention of secretions in one), and late complications occurred in two patients (granuloma formation in one and hemoptysis in one).**

Conclusions: **Stent placement with the new silicone stent designed to fit on the primary right carina is feasible, effective, and acceptably safe.**

Trial registry: **UMIN-Clinical Trials Registry; No.: UMIN000001776; URL: www.umin.ac.jp/ctr**

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Central airway obstruction often leads to severe symptoms such as dyspnea or suffocation, and so immediate and appropriate treatment is necessary. Bronchoscopic treatment of central airway stenosis, such as using argon plasma coagulation, electrocautery, a cryoprobe, or a high-pressure balloon, has become widespread, and its usefulness has been well established.[1-4] However, the effects are often temporary, so stent implantation is often performed to maintain the reestablished airway patency. Of the currently available two main types of airway stents, made of either silicone or metal,[1-4] silicone stents have been widely used for both malignant and benign airway stenosis, because of some advantages over metallic stents: easy removal or replacement, easy adjustment of the length by cutting with scissors, lower costs, less frequent granulation tissue formation, and durability. Silicone stents that require a rigid bronchoscope for insertion have generally been placed into the airway within easy reach, including into the trachea, the right main stem bronchus, the left main stem bronchus, and the bronchus intermedius. The right upper lobe bronchus usually branches off at sharp angles from the right main stem bronchus, and it is barely accessible using a rigid bronchoscope. Therefore, there has not been ideal stenting to maintain the patency of the right upper lobe bronchus.

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Several investigators have reported the usefulness of stenting using silicone Y stents for stenosis around the carina between the bronchus to the right upper lobe and the bronchus intermedius (primary right carina).[5-9] However, the main carinal angle is different from the angle of the primary right carina in some patients, so the limbs of the Y stent analogous to the main carinal angle may not fit the primary right carina. In addition, commercially available Y stents designed for placement in the trachea may be too large to place in the right main stem bronchus. Thus, dedicated bifurcated stents with exclusive limb angles or sizes would be needed for more ideal stenting. The purpose of this study was to evaluate the feasibility, efficacy, and safety of a new silicone stent designed for the treatment of airway stenosis around the primary right carina.

Materials and Methods

Patients and Methods

We carried out a prospective preliminary study at Nagoya Medical Center. This study was approved by the institutional review board of Nagoya Medical Center (identifier: 2009-254) and was registered with the University Hospital Medical Information Network-Clinical Trials Registry (No.: UMIN000001776) before its start. From July 2009 to August 2011, 16 patients with airway stenosis around the primary right carina requiring stent placement to maintain airway patency were enrolled in this study. Patients were excluded if they were not expected to be palliated by using the study stent because of the narrowing of the peripheral airway, including the segmental bronchi of the right upper, middle, or lower lobe. Patients with large bronchi, who were expected to do better with commercially available tracheal Y stents, were also excluded. Six patients were judged to meet such exclusion criteria during the stenting procedure, and, thus, no attempt was made to insert the study stent. The remaining 10 patients, for whom the study stent insertion was attempted, were analyzed. Written informed consent was obtained from all patients.

Procedures

The prototype silicone stent (Novatech) (Fig 1), which was designed to adapt to the primary right carina, was used. The outer diameters of the study stent limb for the right main stem bronchus, bronchus intermedius, and right upper lobe bronchus were 13 mm, 10 mm, and 9 mm, respectively. Stent placement was performed using a rigid and flexible bronchoscope under general anesthesia. After the stenotic lesion was examined by a rigid or flexible bronchoscope,[10] the airway lumen was then reestablished by bronchoscopic procedures combining argon plasma coagulation, electrocautery, cryorecanalization, balloon dilatation, or rigid bronchoscopic debulking. If there was no patency of the distal airway, the study stent was not inserted, and instead, the treatment deemed appropriate in clinical practice was given. After that, the diameter and length of the stenotic airway were measured using a flexible bronchoscope, a balloon-type endobronchial ultrasound probe, and a preprocedural chest CT scan, as we described previously.[5] If the study stent was judged appropriate for insertion, it was cut to the length measured.

The study stent was placed on the primary right carina using either the pushing or the pulling methods.[11]

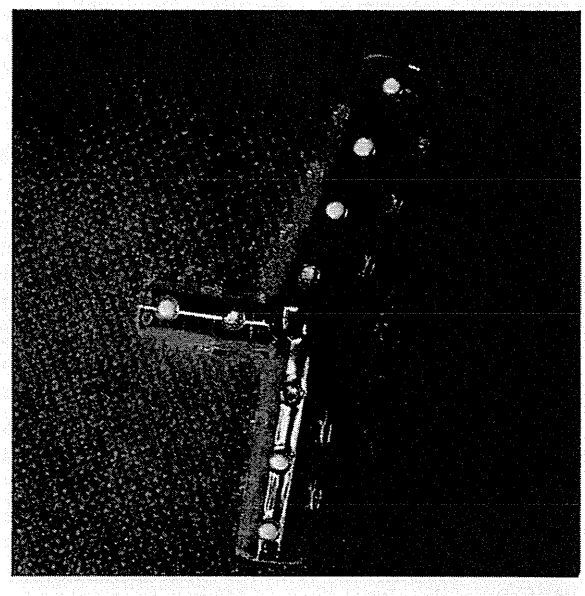

Figure 1. Dedicated bifurcated silicone stent for the stenosis around the primary right carina.

Pushing method: Using a stent introducer system, the study stent was inserted into the right main stem bronchus just above the primary right carina. The stent was then grasped with a rigid forceps and pushed so that the peripheral limbs of the stent saddled the primary right carina.

Pulling method: Before stent insertion, the limb of the study stent for the right upper lobe bronchus was cut shorter than the limb for the bronchus intermedius. The rigid bronchoscope was advanced as far as possible toward the bronchus intermedius, and the stent was then pushed out from the stent introducer into the bronchus intermedius. After that, the stent was grasped with the rigid forceps and carefully withdrawn until a limb slipped into the right upper lobe bronchus. Finally, the stent was pushed to fit on the primary right carina.

If the lesion could not be maintained with only the study stent (eg, extensive stenosis including trachea or left main stem bronchus), we inserted additional stents with the technique described previously.[7,8] If the primary physician judged it necessary, antibiotics were given after the stenting. Nebulization using acetylcysteine to prevent mucus retention was performed, as well as the usual silicone stenting.

Assessments

The primary end point was feasibility and the secondary end points were the efficacy and safety of the novel silicone stent designed for the treatment of airway stenosis around the primary right carina. The feasibility of the study stent placement (number of cases with successful stent placement/number of cases in which the study stent insertion was attempted), changes in pulmonary function before and after stenting, changes in the dyspnea index before and after stenting, and frequency of adverse events were analyzed. Pulmonary function testing and dyspnea index grading, which have been used to assess the efficacy of stenting,[12-16] were performed within 48 h before stenting and within 1 week after. Grading of the dyspnea index was assessed by fact finding on the spot, as follows: grade 0, asymptomatic while climbing stairs; grade 1, symptomatic while climbing stairs; grade 2, symptomatic after walking 100 m on flat ground; grade 3, symptomatic with the least effort (eg, talking, getting dressed); and grade 4, symptomatic

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in bed, at rest. The follow-up of clinical course or prognosis was conducted to the degree possible. If adverse events occurred, the details were recorded, and all events were assessed as to whether they were related to the study procedures.

RESULTS

Patients and Procedures

A total of 10 patients (five men and five women; mean age 65 years, range 46-80 years) underwent stenting using the study stent. The details are shown in Table 1. All patients had a malignant disease: lung cancer in five, breast cancer in one, colon cancer in one, esophageal cancer in one, malignant lymphoma in one, and malignant fibrous histiocytoma in one. The study stent could be placed on the primary right carina in all patients (100%). Five patients underwent stenting using only the study stent (Figs 2-4), and the other five underwent stenting using the study stent and other stents (Y stent on the main carina in four, Y stent on the main carina and straight stent in the left main stem bronchus in one, Fig 5). Median survival after the procedure at the time of data collection was 198 days (range, 13-836 days).

Efficacy

Details of the effectiveness before and after stenting are shown in Table 2. Pulmonary function testing before and after stenting could be performed in eight patients; it could not be performed in one patient who was mechanically ventilated and another who developed severe myelosuppression due to prior chemotherapy. FEV_1 and/or FVC improved in six of eight patients (75%).

Safety

No complications occurred during the actual stenting procedures. Early complications occurred in three patients (pneumonia in two and retention of secretions in one). One patient with malignant fibrous histiocytoma, who underwent stenting with the combination of the study stent and the Y stent, suffered from pneumonia in the right upper lobe lung. The other patient with lung cancer, who also underwent stent placement using both the study stent and the Y stent, developed pneumonia in the left lung. These patients received IV antibiotic therapy, and the pneumonias resolved immediately. One patient with breast cancer who presented with superior vena cava syndrome and right pleural effusion suffered from retention of secretions. Specific therapy (eg, bronchoscopy) other than nebulization was not performed until the stent removal because of the tumor response to radiation therapy 63 days after stent placement.

Late complications were observed in two patients. One patient underwent additional stenting because

Table 1—*Patient Characteristics and Procedural Details*

Patient No.	Age, y	Sex	Disease	Stent Placement	Stent Length,* mm	Bronchoscopic Recanalization Before Stenting	Stents Other Than Study Stent	Stent Removal	Complications	Survival, d
1	80	F	Colon cancer	Achieved	20×10×20	APC, elecrocautery	None	No	None	75
2	69	M	Esophageal cancer	Achieved	15×15×13	Ballooning	None	No	Granuloma formation	426
3	74	F	Breast cancer	Achieved	25×11×13	None	None	63 d after stenting because of effective radiotherapy	Retention of secretions	836
4	53	M	Lung cancer (adeno)	Achieved	20×9×13	Ballooning	None	No	None	797[b]
5	61	F	Lung cancer (adeno)	Achieved	20×5×15	None	Y on main carina	No	None	197
6	73	F	Malignant lymphoma	Achieved	20×7×17	Ballooning	Y on main carina, straight in LMSB	No	None	13
7	46	M	Lung cancer (adeno)	Achieved	10×7×17	None	Y on main carina	No	Pneumonia	115
8	49	M	Lung cancer (squamous)	Achieved	20×9×11	APC, cryotherapy	Y on main carina	No	None	199
9	77	F	Malignant fibrous histiocytoma	Achieved	20×10×13	APC, cryotherapy	Y on main carina	No	Pneumonia	290
10	70	M	Lung cancer (squamous)	Achieved	20×8×10	None	None	No	Hemoptysis	55

adeno = adenocarcinoma; APC = argon plasma coagulation; F = female; LMSB = left main stem bronchus; M = male.
*Data are presented as stent limb length of left main stem bronchus × lingular segment of left upper lobe bronchus × left lower lobe bronchus.
[b]Survival at the time of data collection.

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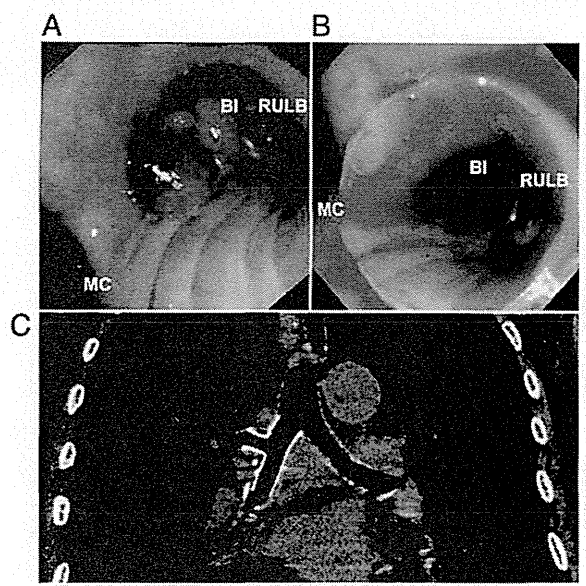

FIGURE 2. Bronchoscopic views and CT image of patient 1 in Tables 1 and 2. A, Bronchoscopic view before stent placement, showing the right main stem bronchus and the BI invaded by colon cancer. B, Bronchoscopic view after stent placement on the primary right carina. C, CT image after stent placement on the primary right carina. BI = bronchus intermedius; MC = main carina; RULB = right upper lobe bronchus.

of the progression of esophageal cancer 230 days after stenting. During the procedure, mild granulation tissue at the right upper lobe bronchus was observed and treated with argon plasma coagulation. Another patient developed hemoptysis and died 55 days after stenting. The patient had experienced hemoptysis before stenting, so it may have been related to the progression of squamous cell lung cancer.

DISCUSSION

Stenting has been widely performed to maintain airway patency in patients suffering from central airway stenosis or obstruction caused by various benign

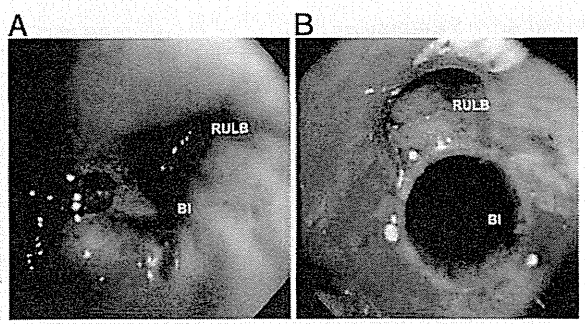

FIGURE 3. Bronchoscopic views of patient 2 in Tables 1 and 2. A, Bronchoscopic view before stent placement, showing the orifice of the RULB and the BI obstructed by esophageal cancer. B, Bronchoscopic view after stent placement on the primary right carina. See Figure 2 legend for expansion of abbreviations.

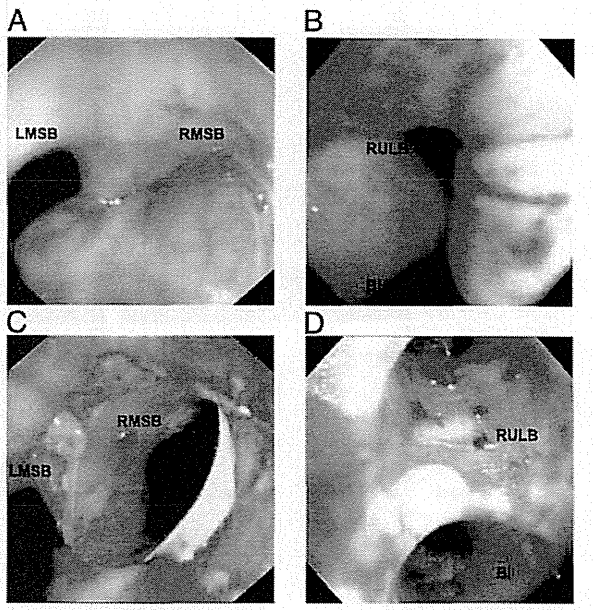

FIGURE 4. Bronchoscopic views of patient 4 in Tables 1 and 2. A, Bronchoscopic view before stent placement, showing the RMSB compressed by lung cancer (adenocarcinoma). B, Bronchoscopy revealing stenotic bronchi around the primary right carina. C and D, Bronchoscopic views after stent placement on the primary right carina. LMSB = left main stem bronchus; RMSB = right main stem bronchus. See Figure 2 legend for expansion of other abbreviations.

or malignant diseases. We often encounter patients with stenosis of the right upper lobe bronchus, which could lead to atelectasis or obstructive pneumonia. Although many types and shapes of stents have been developed,[17-21] there is no ideal stent for the stenotic airway around the primary right carina to facilitate ventilation and the clearance of secretions from the right upper lobe lung. Several investigators have introduced a "window" method, using a fenestrated silicone[22] or metallic[23] stent toward the right upper lobe bronchus to ventilate. Certainly, the window punched out in the stent wall, which is located at the orifice of the right upper lobe bronchus, makes ventilation and expectoration possible. However, it is useless in maintaining the airway patency or in preventing restenosis of the right upper lobe bronchus. In addition, tumor or granulation tissue is likely to extend into and obstruct the window immediately. Furthermore, the location of the window is likely to move from the orifice of the right upper lobe bronchus, because migration of straight stents occurs frequently. In the past few years, a method using a silicone Y stent to straddle the primary right carina was reported.[5-9] This method has overcome the drawbacks of the "window" method, and is quite effective in certain cases. However, commercially available Y stents are designed to fit the airway around the main carina, but not the sizes and limb angles in some patients. Some investigators[24]

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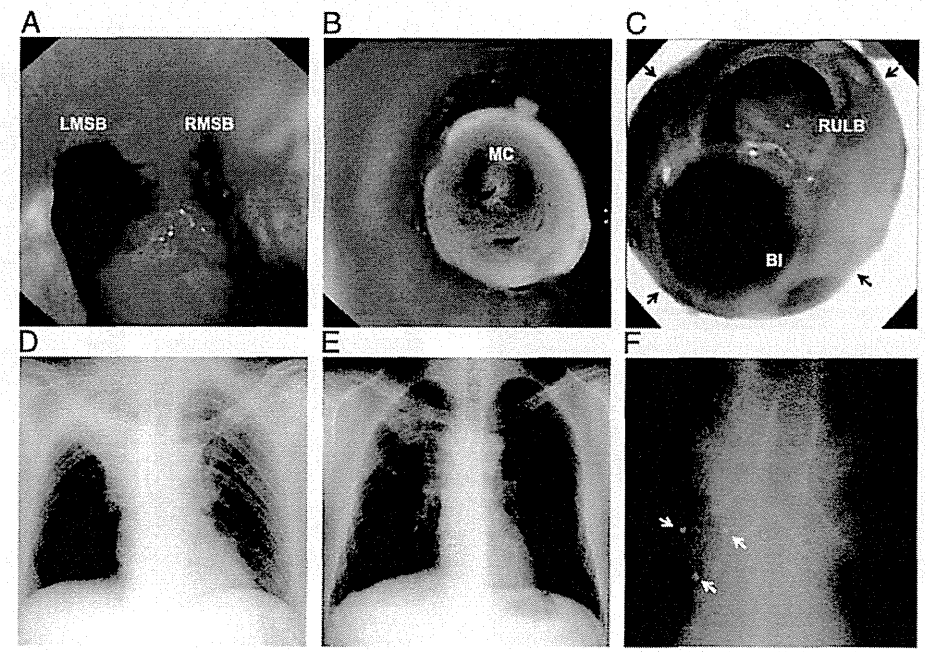

FIGURE 5. Bronchoscopic views and chest roentgenograms of patient 8 in Tables 1 and 2. A, Bronchoscopic view before stent placement, showing the trachea and the RMSB invaded by lung cancer (squamous cell carcinoma). B, Bronchoscopic view of additional radiopaque Y stent on the main carina. C, Bronchoscopic view of the primary right carina after stent placement. The right main bronchial limb (arrows) of the additional Y stent was inserted into the right main stem bronchial limb of the study stent. D, Chest roentgenogram before stent placement, showing atelectasis of the right upper lobe lung. E and F, Chest roentgenograms after stent placement. Radiopaque studs (arrows) of the study stent and a Y stent can be seen. See Figure 2 and 4 legends for expansion of other abbreviations.

have reported the usefulness of a Montgomery T-tube in place of a stent for the primary right carinal stenosis, because the rectangular limb of a Montgomery T-tube resembles the primary right carinal angle. However, its drawback is anatomic; the diameter of the right main stem bronchus is different from that of the bronchus intermedius.

Our study demonstrated that the new bifurcated silicone stent could be placed on the primary carina and fit well; it could be successfully placed on the primary right carina in all patients with the "pushing" or "pulling" method, the techniques for inserting a Y stent on the main carina.[11] Thus, the study stent can be inserted by a physician familiar with Y stent placement. Although our study was designed to assess only the effectiveness just after the procedure, stenting with the study stent achieved good clinical efficacy. The dyspnea index improved immediately in eight of the 10 patients, and the pulmonary function test improved in all but two patients who suffered pneumonia or mucus retention at the time of the evaluation. The two patients who developed pneumonia

Table 2—*Efficacy Before and After Stenting*

Patient No.	Dyspnea Index[a] Before (After) Stenting	Supplemental O_2 Before (After) Stenting, L/m	FEV_1 Before (After) Stenting, mL	FVC Before (After) Stenting, mL
1	2 (1)	0 (0)	1,090 (1,370)	1,380 (1,790)
2	2 (0)	2 (0)	1,260 (2,650)	1,700 (3,630)
3	3 (2)	0 (0)	1,850 (1,210)	2,830 (2,280)
4	2 (2)	0 (0)	1,380 (1,700)	2,760 (3,020)
5	4 (2)	4 (0)	750 (1,630)	1,050 (2,150)
6	4 (3)	1 (1)	N/A	N/A
7	1 (1)	0 (0)	1,560 (1,080)	1,750 (1,750)
8	4 (1)	MV (0)	N/A	N/A
9	2 (1)	0 (0)	1,040 (1,390)	1,540 (1,410)
10	2 (1)	0 (0)	1,710 (1,790)	2,050 (2,410)

MV = mechanical ventilation; N/A = not available; O_2 = oxygen.

[a]Dyspnea index: 0, asymptomatic while climbing stairs; 1, symptomatic while climbing stairs; 2, symptomatic after walking 100 m on flat ground; 3, symptomatic with the least effort (e.g. talking, getting dressed); 4, symptomatic in bed, at rest.

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had extensive stenotic lesions, so they underwent stenting with a combination of the study stent and a Y stent. The tracheal limbs of the Y stents used in these patients (50 mm and 35 mm) were somewhat longer than the tracheal limb of the Y stent used in patients who previously underwent stent placement with a combination of the two Y stents in our institution (median, 20 mm; range, 15-30 mm).[8] The pneumonias resolved immediately with antibiotic treatment, with no relapse. However, stent length should be minimized while covering the whole stenotic region to prevent mucus retention or pneumonia.

A limitation of the current preliminary study is that its team has extensive practical experience in performing stenting procedures. All stenting procedures were performed by one of the current authors with > 10 years of experience in stenting procedures, who was familiar with Y stent placement on the main carina and/or the primary right carina. To insert this stent, a certain amount of experience and skill is needed. Other limitations are the small sample size and use of a single stent of one size. Larger studies with different-sized stents are warranted.

Conclusions

Our findings suggest that placement of this new silicone stent designed to fit on the primary right carina is feasible, effective, and acceptably safe.

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Author contributions: Dr Oki had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Dr Oki: contributed to the new stent design, study design, subject recruitment, performance of stenting procedures, data analysis, data interpretation, preparation of the manuscript, and approval of the final manuscript.
Dr Saka: contributed to the new stent design, study design, subject recruitment, performance of stenting procedures, data analysis, data interpretation, preparation of the manuscript, and approval of the final manuscript.
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Other contributions: The prototype bifurcated silicone stents (a total of 10 stents) were provided to the authors by Novatech, La Ciotat, France. This work was performed at Nagoya Medical Center, Nagoya, Japan.

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Transesophageal Bronchoscopic Ultrasound-Guided Fine Needle Aspiration for Diagnosis of Sarcoidosis

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Key Words
Endobronchial ultrasound · Endoscopic ultrasound · Sarcoidosis · Transbronchial needle aspiration · Endoscopic ultrasound with bronchoscope-guided fine needle aspiration · Bronchoscopy

Abstract
Background: Several studies have reported that specimens from mediastinal lesions located adjacent to the esophagus can be sampled using an ultrasound bronchoscope instead of an ultrasound endoscope. ***Objectives:*** The aim of this study was to evaluate the diagnostic utility of transesophageal bronchoscopic ultrasound-guided fine needle aspiration using an ultrasound bronchoscope in patients with stage I/II sarcoidosis. ***Methods:*** Thirty-three patients suspected of having stage I/II sarcoidosis were included in this prospective study. Needle aspiration through the esophagus using an ultrasound bronchoscope was performed for hilar and/or mediastinal lymph nodes. The final diagnosis of sarcoidosis was based on clinicoradiological compatibility and pathological findings. ***Results:*** A total of 62 lymph nodes with a mean shortest diameter of 13.6 mm were examined. Of the 33 patients enrolled, 29 were given a final diagnosis of sarcoidosis. Four of the residual patients had other diseases (1 lung cancer, 1 tuberculosis, 2 non-specific lymphadenitis). Transesophageal bronchoscopic ultrasound-guided fine needle aspiration showed noncaseating epithelioid cell granulomas in 25 of 29 patients (86%; 95% confidence interval 73–100) with the final diagnosis of sarcoidosis. No complications were observed. ***Conclusions:*** Transesophageal bronchoscopic ultrasound-guided fine needle aspiration is feasible, safe and accurate for the diagnosis of stage I/II sarcoidosis.
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Introduction

Sarcoidosis is a multisystem granulomatous disease of unknown etiology. We commonly encounter patients with the disease in our daily clinical practice. Sarcoidosis often presents characteristic clinical and radiological pictures, and thus, the clinical diagnosis is highly reliable.

Preliminary data were previously presented at the CHEST 2011 annual meeting (trial registration: UMIN-Clinical Trials Registry; identifier: UMIN0000002883; http://www.umin.ac.jp/ctr/index.htm).

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