(3.9%) were distant. Age, sex, and whole tumor size on HRCT were not significantly different between patients with solid and mixed tumors. Solid tumors were significantly correlated with a large solid component size, a high SUVmax, and the presence of lymphatic, vascular, and pleural invasion and lymph node metastasis ($P < .001$, $P < .001$, $P < .001$, $P < .001$, $P < .001$, $P = .001$, respectively; Table 1).

Local recurrence occurred in 5 patients (3.6%) with solid tumors (1 involving the bronchial stump and 4 involving the mediastinal lymph nodes) and 4 patients (1.3%) with mixed tumors (1 involving the residual lung after segmentectomy and 3 involving the mediastinal lymph nodes). A significant difference in DFS was identified between patients with solid tumors (n = 137; 2-year DFS, 83.1%) and those with mixed tumors (n = 299; 2-year DFS, 94.2%; $P = .0006$; Figure 1, *A*).

After matching for solid component size, there were 97 well-matched solid and mixed tumor pairs. Significant differences were identified in whole tumor size, SUVmax, and lymphatic, vascular, and pleural invasion between the 2 tumor types ($P < .001$, $P < .001$, $P = .008$, $P = .029$, $P = .003$, respectively, Table 2). Solid tumors were significantly correlated with a small whole tumor size, a high SUVmax, and the presence of pathologic invasiveness.

Furthermore, a difference in DFS was identified between patients with solid tumors (n = 97; 2-year DFS, 83.5%) and those with mixed tumors (n = 97; 2-year DFS, 91.8%; Figure 1, *B*) after matching for solid component size.

After matching for SUVmax, there were 96 well-matched solid and mixed tumor pairs. No significant differences in clinical characteristics, except for solid component size, were found between the 2 tumor types (Table 3).

A difference in DFS was identified between patients with solid tumors (n = 96; 2-year DFS, 87.1%) and those with mixed tumors (n = 96; 2-year DFS, 90.4%; Figure 1, *C*) after matching for SUVmax.

After matching for solid component size and SUVmax, there were 79 well-matched solid and mixed tumor pairs. No significant differences in clinical characteristics, except for whole tumor size, were found between the 2 tumor types (Table 4).

Furthermore, there was no difference in DFS between patients with solid tumors (n = 79; 2-year DFS, 87.0%) and patients with mixed tumors (n = 79; 2-year DFS, 83.9%; Figure 1, *D*) after matching for solid component size and SUVmax.

Figure 2 shows examples of solid and mixed tumors with the same solid component size (1.0 cm). Regardless of tumor type, tumors with low SUVmax were not associated with lymphatic invasion, whereas those with high SUVmax were.

TABLE 1. Comparison of solid and mixed tumor characteristics in all cohort patients

	Solid tumors (n = 137)	Mixed tumors (n = 299)	*P*
Age (y)	65.5 ± 10.5	65.7 ± 8.8	.85
Sex			.12
Male	71 (51.8%)	130 (43.5%)	
Female	66 (48.2%)	169 (56.5%)	
Whole tumor size (cm)	2.1 ± 0.6	2.0 ± 0.6	.69
Solid component size (cm)	2.1 ± 0.6	1.1 ± 0.7	<.001
SUVmax	4.9 ± 3.3	2.6 ± 2.9	<.001
Lymphatic invasion			<.001
Negative	89 (65.0%)	270 (90.3%)	
Positive	48 (35.0%)	29 (9.7%)	
Vascular invasion			<.001
Negative	79 (57.7%)	264 (88.3%)	
Positive	58 (42.3%)	35 (11.7%)	
Pleural invasion			<.001
Negative	100 (73.0%)	278 (93.0%)	
Positive	37 (27.0%)	21 (7.0%)	
Lymph node metastasis			<.001
Negative	114 (83.2%)	284 (95.0%)	
Positive	23 (16.8%)	15 (5.0%)	
Procedure			.001
Lobectomy	111 (81.0%)	190 (63.5%)	
Segmentectomy	9 (6.6%)	48 (16.1%)	
Wedge resection	17 (12.4%)	61 (20.4%)	

SUVmax, Maximum standardized uptake value.

DISCUSSION

The present study demonstrated, as expected, that solid tumors were associated with highly malignant variables, such as large solid component size, high SUVmax, and lymphatic, vascular, and pleural invasion and lymph node metastasis in all cohort patients. In addition, patients with solid tumors had worse DFS than those with mixed tumors. A retrospective study has previously shown that pure solid tumors have malignant potential with nodal or pleural involvement and worse DFS compared with predominantly solid tumors with a GGO component.[13] Other studies have also revealed that tumors with a predominant GGO component are less invasive and have a more favorable prognosis in patients with clinical stage IA lung adenocarcinomas.[4,8,14] Our study is consistent with these findings.

With regard to the tumor size on HRCT, solid component size is more useful than whole tumor size for predicting pathologic invasiveness and prognosis. In our previous study, solid component size was found to have a higher predictive value for lymphatic, vascular, and pleural invasion compared with whole tumor size; furthermore, solid component size was an independent prognostic factor for DFS.[6] It was not clear whether mixed tumors and solid tumors have similar malignant behaviors and prognoses when both have the same solid component size on HRCT. Therefore, we conducted a matched analysis to compare solid and mixed tumors after matching for solid component size in both tumor types. Even after matching for solid component

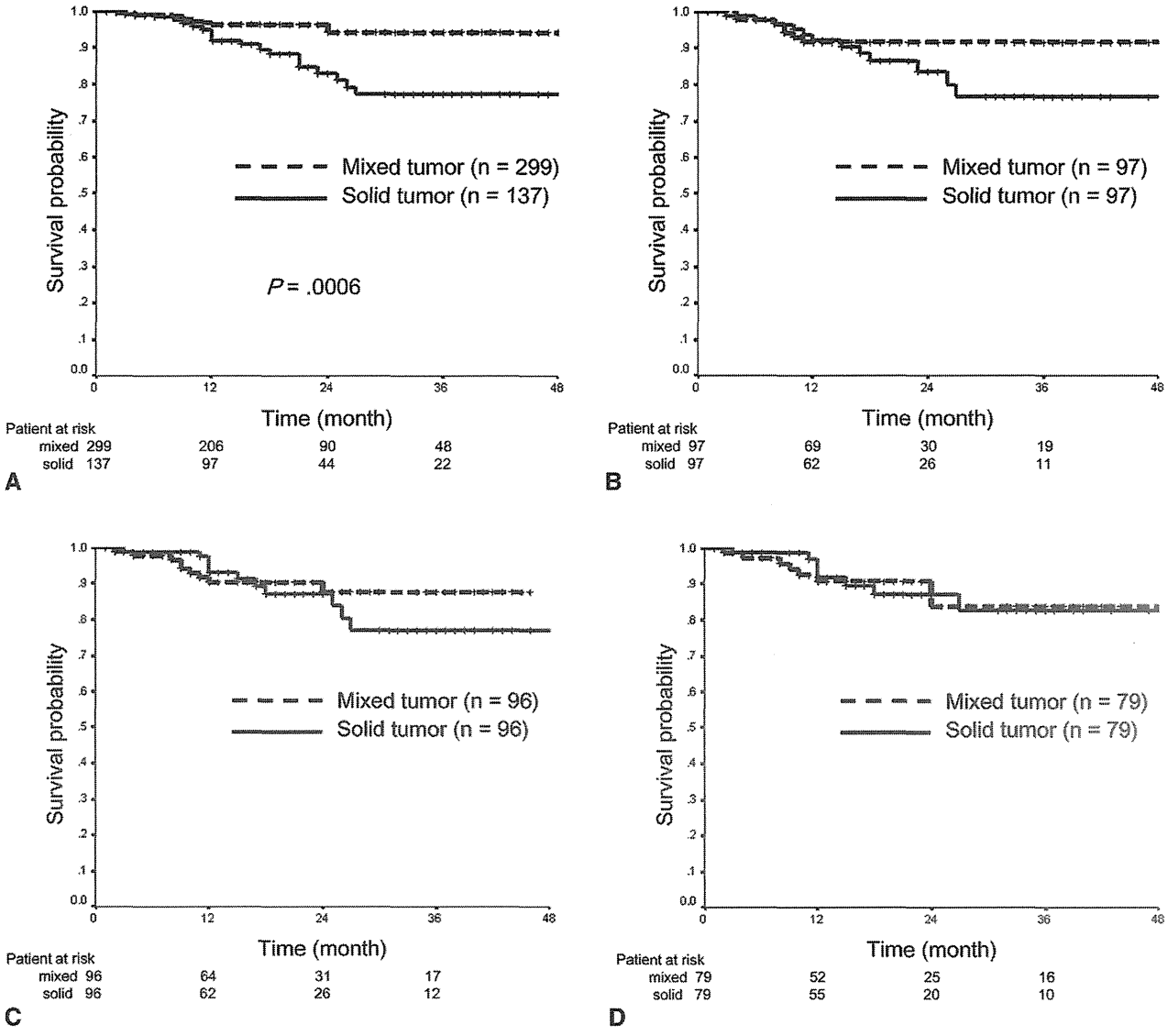

FIGURE 1. DFS curves of patients according to tumor type on HRCT. A, In all cohort patients, 2-year DFS of 94.2% (mean DFS of 47 months; 95% confidence interval [CI], 46-48 months) and 83.1% (mean DFS of 42 months; 95% CI, 39-45 months) were identified for mixed and solid tumors, respectively ($P = .0006$). B, In patients matched for solid component size, 2-year DFS of 91.8% (mean DFS of 46 months; 95% CI, 43-48 months) and 83.5% (mean DFS of 42 months; 95% CI, 38-45 months) were identified for mixed and solid tumors, respectively. C, In patients matched for SUVmax, 2-year DFS of 90.4% (mean DFS of 42 months; 95% CI, 39-44 months) and 87.1% (mean DFS of 42 months; 95% CI, 38-46 months) were detected for mixed and solid tumors, respectively. D, In patients matched for solid component size and SUVmax, 2-year DFS of 83.9% (mean DFS of 43 months; 95% CI, 40-47 months) and 87.0% (mean DFS of 43 months; 95% CI, 40-47 months) were detected for mixed and solid tumors, respectively.

size in both tumor types on HRCT, solid tumors were more frequently correlated with high SUVmax and malignant behavior compared with mixed tumors. In addition, the DFS of patients with solid tumors was worse than that of patients with mixed tumors. This means that solid tumors have more malignant potential than mixed tumors even if both tumor types have the same solid component size on HRCT. This is a new finding. SUVmax on PET/CT is reported to be a predictor of malignant behavior and prognosis in cases of lung adenocarcinomas.[6,11,12,15-17] SUVmax on PET/CT is a preoperative factor, whereas lymphatic, vascular, and pleural invasion are postoperative factors. We have previously reported that SUVmax is a significant predictor of malignant behavior.[6,11,12,16,17]

We experimentally performed a matched analysis to compare solid and mixed tumors after matching for SUVmax. In this matched model, solid tumors and mixed tumors had similar clinical characteristics except solid component size, but there seemed to be a difference in DFS. Although both tumor types have the same SUVmax, solid tumors seem to have a worse potential than mixed tumors.

TABLE 2. Comparison of solid and mixed tumor characteristics in patients matched for solid component size

	Solid tumors (n = 97)	Mixed tumors (n = 97)	*P*
Age (y)	64.9 ± 10.4	66.1 ± 10.0	.63
Sex			.054
Male	50 (51.5%)	36 (37.1%)	
Female	47 (48.5%)	61 (62.9%)	
Whole tumor size (cm)	1.8 ± 0.5	2.3 ± 0.5	<.001
Solid component size (cm)	1.8 ± 0.5	1.8 ± 0.5	N/A
SUVmax	4.8 ± 3.4	3.0 ± 2.5	<.001
Lymphatic invasion			.008
Negative	63 (64.9%)	81 (83.5%)	
Positive	34 (35.1%)	16 (16.5%)	
Vascular invasion			.029
Negative	62 (63.9%)	76 (78.4%)	
Positive	35 (36.1%)	21 (21.6%)	
Pleural invasion			.003
Negative	71 (73.2%)	88 (90.1%)	
Positive	26 (26.8%)	9 (9.9%)	
Lymph node metastasis			.13
Negative	82 (84.5%)	90 (92.8%)	
Positive	15 (15.5%)	7 (7.2%)	
Procedure			.38
Lobectomy	74 (76.3%)	83 (85.6%)	
Segmentectomy	7 (7.2%)	8 (8.2%)	
Wedge resection	16 (16.5%)	6 (6.2%)	

SUVmax, Maximum standardized uptake value; *N/A,* not applicable.

TABLE 3. Comparison of solid and mixed tumor characteristics in patients matched for maximum standardized uptake value

	Solid tumor (n = 96)	Mixed tumor (n = 96)	*P*
Age (y)	65.4 ± 10.4	65.5 ± 9.3	.94
Sex			.26
Male	49	40	
Female	47	56	
Whole tumor size (cm)	2.0 ± 0.6	2.1 ± 0.6	.24
Solid tumor size (cm)	2.0 ± 0.6	1.5 ± 0.7	<.001
SUVmax	4.0 ± 2.6	4.0 ± 2.6	N/A
Lymphatic invasion			.12
Negative	65	74	
Positive	31	22	
Vascular invasion			.47
Negative	62	67	
Positive	34	29	
Pleural invasion			.071
Negative	70	81	
Positive	26	15	
Lymph node metastasis			.54
Negative	80	84	
Positive	16	12	
Procedure			.50
Lobar resection	77	73	
Segmentectomy	6	15	
Wedge resection	13	8	

SUVmax, Maximum standardized uptake value; *N/A,* not applicable.

TABLE 4. Comparison between solid and mixed tumor characteristics in patients matched for solid component size and maximum standardized uptake value

	Solid tumor (n = 79)	Mixed tumor (n = 79)	*P*
Age (y)	64.4 ± 10.7	66.0 ± 8.9	.27
Sex			.62
Male	37 (46.8%)	41 (51.9%)	
Female	42 (53.2%)	38 (48.1%)	
Whole tumor size (cm)	1.8 ± 0.5	2.2 ± 0.5	<.001
Solid component size (cm)	1.8 ± 0.5	1.8 ± 0.5	N/A
SUVmax	3.7 ± 2.4	3.7 ± 2.6	N/A
Lymphatic invasion			.31
Negative	53 (67.1%)	60 (75.9%)	
Positive	26 (32.9%)	19 (24.1%)	
Vascular invasion			1.0
Negative	56 (70.9%)	56 (70.9%)	
Positive	23 (29.1%)	23 (29.1%)	
Pleural invasion			.71
Negative	62 (78.5%)	65 (82.3%)	
Positive	17 (21.5%)	14 (17.7%)	
Lymph node metastasis			.80
Negative	67 (84.8%)	69 (87.3%)	
Positive	12 (15.2%)	10 (12.7%)	
Procedure			.15
Lobar resection	61 (77.2%)	66 (83.5%)	
Segmentectomy	5 (6.3%)	8 (10.1%)	
Wedge resection	13 (16.5%)	5 (6.3%)	

SUVmax, Maximum standardized uptake value; *N/A,* not applicable.

In a next step, we evaluated whether mixed tumors exhibited malignant behavior and prognosis similar to those of solid tumors after matching for solid component size and SUVmax. In this matched model, solid tumors and mixed tumors had similar clinical characteristics and DFS. As shown in Figure 2, tumors with equivalent solid component size and SUVmax had the same malignant behavior (eg, lymphatic invasion), regardless of type. The DFS of patients with solid and mixed tumors was also comparable after matching for solid component size and SUVmax. These findings indicate that solid tumors and mixed tumors show similar biological behavior and prognosis when both have the same solid component size on HRCT and the same SUVmax value on PET/CT. In other words, solid component size on HRCT and SUVmax on PET/CT are important factors for evaluating malignant behavior of clinical stage IA lung adenocarcinomas before surgery, and this is regardless of the GGO proportion. Solid and mixed lung adenocarcinoma tumors with low SUVmax reflect pathologic noninvasiveness and may be good candidates for sublobar resection. We have previously reported, in the same population who were evaluated in the current study, that tumors with SUVmax less than 1.5 were not associated with lymph node metastasis or recurrence,[12,18] and we recommend that individuals with clinical stage IA lung adenocarcinomas with

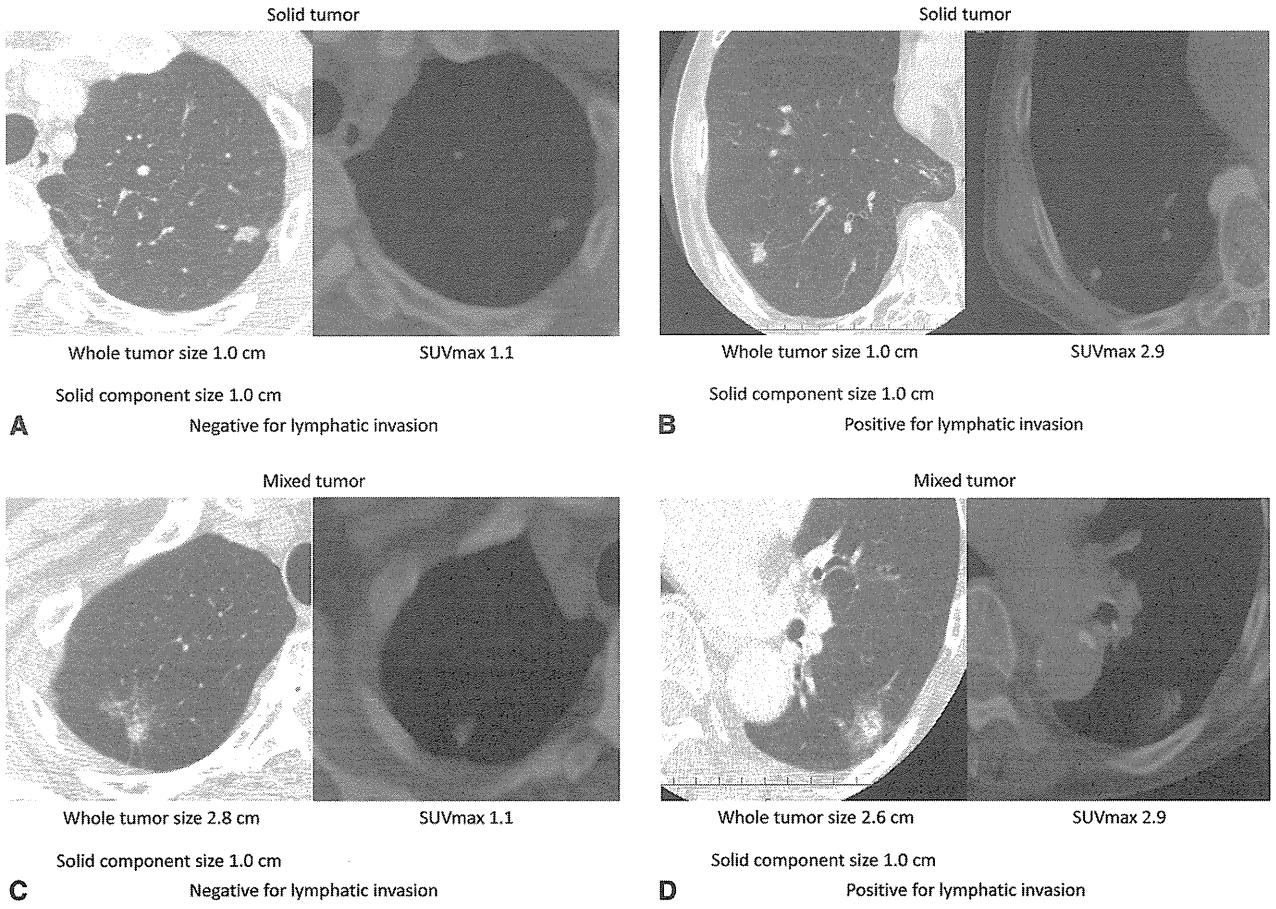

FIGURE 2. Examples of solid and mixed tumors on HRCT. A, Whole tumor size = solid component size: 1.0 cm, SUVmax: 1.1. This solid tumor was negative for lymphatic invasion. B, Whole tumor size = solid component size: 1.0 cm, SUVmax: 2.9. This solid tumor was positive for lymphatic invasion. C, Whole tumor size: 2.8 cm, solid component size: 1.0 cm, SUVmax: 1.1. This mixed tumor was negative for lymphatic invasion. D, Whole tumor size: 2.6 cm, solid component size: 1.0 cm, SUVmax: 2.9. This mixed tumor was positive for lymphatic invasion. *SUVmax,* Maximum standardized uptake value.

SUVmax less than 1.5 should undergo sublobar resection with adequate surgical margins.[18]

One of the strengths of this study is the use of PET/CT in all patients. PET/CT, which is the diagnostic tool of choice for patients with non–small cell lung cancer, improves the sensitivity of preoperative staging and reduces the frequency of futile thoracotomies.[19] In addition, SUVmax on PET/CT is a known prognostic factor for non–small cell lung cancer, especially for adenocarcinoma.[6,11,12,16,17] For patients with clinical stage IA lung adenocarcinoma who do not undergo PET/CT, tumor type (solid or mixed) is an important factor for predicting malignant behavior and prognosis. Because the follow-up period was short in this study, long-term follow-up is needed to confirm the DFS results.

CONCLUSIONS

In cases of clinical stage IA lung adenocarcinoma, solid tumors are more malignant than mixed tumors even after matching for solid component size in both tumor types. However, solid tumors have the same malignant potential and prognosis as mixed tumors when both tumor types are matched for solid component size on HRCT and SUVmax on PET/CT.

References

1. Okada M, Koike T, Higashiyama M, Yamato Y, Kodama K, Tsubota N. Radical sublobar resection for small-sized non-small cell lung cancer: a multicenter study. *J Thorac Cardiovasc Surg*. 2006;132:769-75.
2. Nakayama H, Yamada K, Saito H, Oshita F, Ito H, Kameda Y, et al. Sublobar resection for patients with peripheral small adenocarcinomas of the lung: surgical outcome is associated with features on computed tomographic imaging. *Ann Thorac Surg*. 2007;84:1675-9.
3. National Lung Screening Trial Research Team, Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, Fagerstrom RM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med*. 2011;365:395-409.
4. Nakata M, Saeki H, Takata I, Segawa Y, Mogami H, Mandai K, et al. Focal ground-glass opacity detected by low-dose helical CT. *Chest*. 2002;121:1464-7.
5. Jang HJ, Lee KS, Kwon OJ, Rhee CH, Shim YM, Han J. Bronchioloalveolar carcinoma: focal area of ground-glass attenuation at thin-section CT as an early sign. *Radiology*. 1996;199:485-8.

6. Tsutani Y, Miyata Y, Nakayama H, Okumura S, Adachi S, Yoshimura M, et al. Prognostic significance of using solid versus whole tumor size on high-resolution computed tomography for predicting the pathological malignant grade of tumors in clinical stage IA lung adenocarcinoma: a multicenter study. *J Thorac Cardiovasc Surg*. 2012;143:607-12.
7. Goldstraw P, Crowley J, Chansky K, Giroux DJ, Groome PA, Rami-Porta R, et al. International Association for the Study of Lung Cancer International Staging Committee; Participating Institutions. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of Malignant Tumours. *J Thorac Oncol*. 2007;2:706-14.
8. Suzuki K, Asamura H, Kusumoto M, Kondo H, Tsuchiya R. "Early" peripheral lung cancer: prognostic significance of ground glass opacity on thin-section computed tomographic scan. *Ann Thorac Surg*. 2002;74:1635-9.
9. Nakamura H, Saji H, Ogata A, Saijo T, Okada S, Kato H. Lung cancer patients showing pure ground-glass opacity on computed tomography are good candidates for wedge resection. *Lung Cancer*. 2004;44:61-8.
10. Delbeke D, Coleman RE, Guiberteau MJ, Brown ML, Royal HD, Siegel BA, et al. Procedure guideline for tumor imaging with 18F-FDG PET/CT 1.0. *J Nucl Med*. 2006;47:885-95.
11. Nakayama H, Okumura S, Daisaki H, Kato Y, Uehara H, Adachi S, et al. Value of integrated positron emission tomography revised using a phantom study to evaluate malignancy grade of lung adenocarcinoma. *Cancer*. 2010;116:3170-7.
12. Okada M, Nakayama H, Okumura S, Daisaki H, Adachi S, Yoshimura M, et al. Multicenter analysis of high-resolution computed tomography and positron emission tomography/computed tomography findings to choose therapeutic strategies for clinical stage IA lung adenocarcinoma. *J Thorac Cardiovasc Surg*. 2011;141:1384-91.
13. Inoue M, Minami M, Sawabata N, Utsumi T, Kadota Y, Shigemura N, et al. Clinical outcome of resected solid-type small-sized c-stage IA non-small cell lung cancer. *Eur J Cardiothorac Surg*. 2010;37:1445-9.
14. Suzuki K, Kusumoto M, Watanabe S, Tsuchiya R, Asamura H. Radiologic classification of small adenocarcinoma of the lung: radiologic-pathologic correlation and its prognostic impact. *Ann Thorac Surg*. 2006;81:413-9.
15. Cerfolio RJ, Bryant AS, Ohja B, Bartolucci AA. The maximum standardized uptake values on positron emission tomography of a non-small cell lung cancer predict stage, recurrence, and survival. *J Thorac Cardiovasc Surg*. 2005;130:151-9.
16. Okada M, Tauchi S, Iwanaga K, Mimura T, Kitamura Y, Watanabe H, et al. Associations among bronchioloalveolar carcinoma components, positron emission tomographic and computed tomographic findings, and malignant behavior in small lung adenocarcinomas. *J Thorac Cardiovasc Surg*. 2007;133:1448-54.
17. Tsutani Y, Miyata Y, Misumi K, Ikeda T, Mimura T, Hihara J, et al. Difference in prognostic significance of maximum standardized uptake value on [18F]-fluoro-2-deoxyglucose positron emission tomography between adenocarcinoma and squamous cell carcinoma of the lung. *Jpn J Clin Oncol*. 2011;41:890-6.
18. Tsutani Y, Miyata Y, Nakayama H, Okumura S, Adachi S, Yoshimura M, et al. Prediction of pathological node-negative clinical stage IA lung adenocarcinoma for optimal candidates undergoing sublobar resection. *J Thorac Cardiovasc Surg*. 2012;144:1365-71.
19. Fischer B, Lassen U, Mortensen J, Larsen S, Loft A, Bertelsen A, et al. Preoperative staging of lung cancer with combined PET-CT. *N Engl J Med*. 2009;361:32-9.

CHEST

Original Research

PULMONARY PROCEDURES

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

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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]

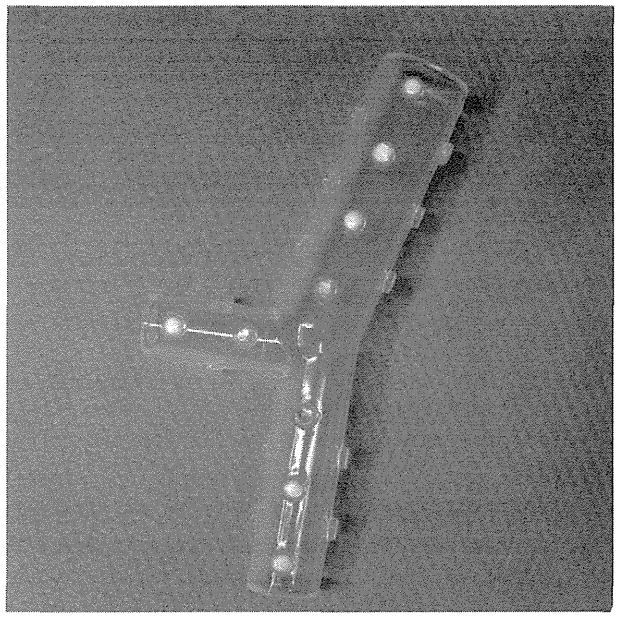

Figure 1. Dedicated bifurcated silicone stent for the stenosis around the primary right carina.

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

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,[a] 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.

[a]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.

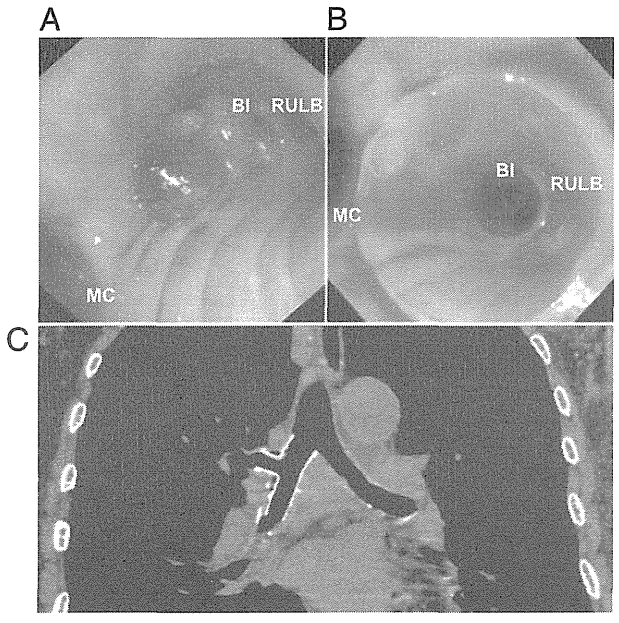

FIGURE 2. Bronchoscopic views and CT image of patient 1 in Tables 1 and 2. A, Bronchoscopic view before stent placement, showing the right main stem bronchus and the BI invaded by colon cancer. B, Bronchoscopic view after stent placement on the primary right carina. C, CT image after stent placement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

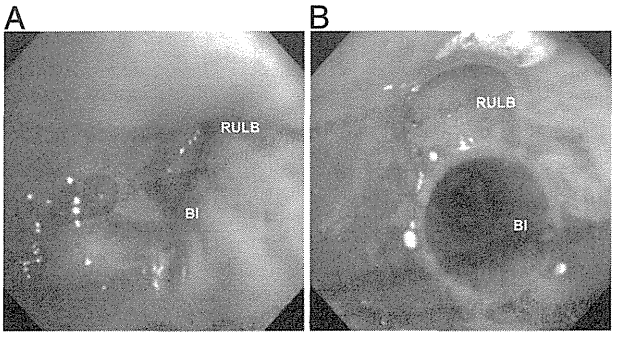

FIGURE 3. Bronchoscopic views of patient 2 in Tables 1 and 2. A, Bronchoscopic view before stent placement, showing the orifice of the RULB and the BI obstructed by esophageal cancer. B, Bronchoscopic view after stent placement on the primary right carina. See Figure 2 legend for expansion of abbreviations.

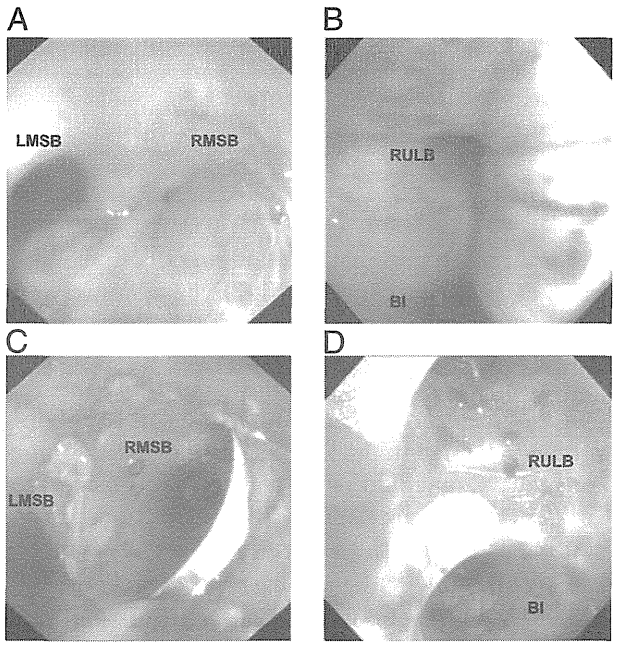

FIGURE 4. Bronchoscopic views of patient 4 in Tables 1 and 2. A, Bronchoscopic view before stent placement, showing the RMSB compressed by lung cancer (adenocarcinoma). B, Bronchoscopy revealing stenotic bronchi around the primary right carina. C and D, Bronchoscopic views after stent placement on the 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]

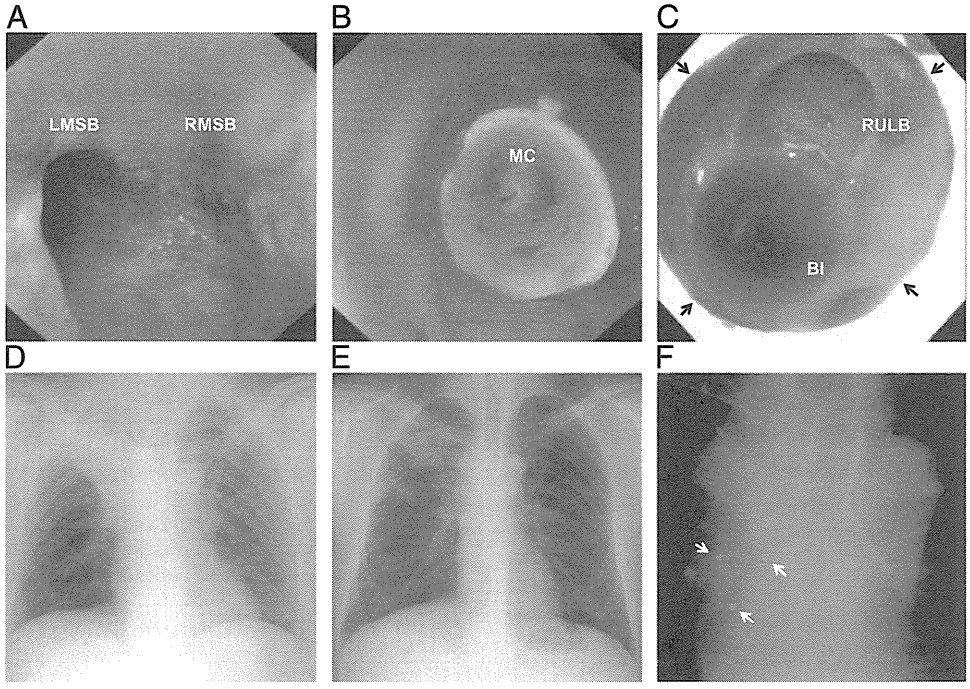

FIGURE 5. Bronchoscopic views and chest roentgenograms of patient 8 in Tables 1 and 2. A, Bronchoscopic view before stent placement, showing the trachea and the RMSB invaded by lung cancer (squamous cell carcinoma). B, Bronchoscopic view of additional radiopaque Y stent on the main carina. C, Bronchoscopic 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.

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.

Acknowledgments

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.

References

1. Bolliger CT, Sutedja TG, Strausz J, Freitag L. Therapeutic bronchoscopy with immediate effect: laser, electrocautery, argon plasma coagulation and stents. *Eur Respir J*. 2006; 27(6):1258-1271.
2. Wahidi MM, Herth FJ, Ernst A. State of the art: interventional pulmonology. *Chest*. 2007;131(1):261-274.
3. Kvale PA, Selecky PA, Prakash UB; American College of Chest Physicians. Palliative care in lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest*. 2007; 132(suppl 3):368S-403S.
4. Du Rand IA, Barber PV, Goldring J, et al; British Thoracic Society Interventional Bronchoscopy Guideline Group. British Thoracic Society guideline for advanced diagnostic and therapeutic flexible bronchoscopy in adults. *Thorax*. 2011;66(suppl 3): iii1-iii21.
5. Oki M, Saka H, Kitagawa C, Kogure Y. Silicone y-stent placement on the carina between bronchus to the right upper lobe and bronchus intermedius. *Ann Thorac Surg*. 2009;87(3):971-974.
6. Shioi R, Yasuo M, Ushiki A, et al. Management of right upper airway patency by a silicon stent in a case of endobronchial metastasis. *Respir Med CME*. 2009;2(7):191-196.
7. Oki M, Saka H, Kitagawa C, et al. Double Y-stent placement for tracheobronchial stenosis. *Respiration*. 2010;79(3):245-249.
8. Oki M, Saka H. Double Y-stenting for tracheobronchial stenosis. *Eur Respir J*. 2012;40(6):1483-1488.
9. Lee HJ, Puchalski J, Sterman DH, et al. Secondary carina Y-stent placement for post-lung-transplant bronchial stenosis. *J Bronchology Interv Pulmonol*. 2012;19(2):109-114.
10. Oki M, Saka H. Thin bronchoscope for evaluating stenotic airways during stenting procedures. *Respiration*. 2011;82(6): 509-514.
11. Dutau H, Toutblanc B, Lamb C, Seijo L. Use of the Dumon Y-stent in the management of malignant disease involving the carina: a retrospective review of 86 patients. *Chest*. 2004; 126(3):951-958.
12. Vergnon JM, Costes F, Bayon MC, Emonot A. Efficacy of tracheal and bronchial stent placement on respiratory functional tests. *Chest*. 1995;107(3):741-746.
13. Monnier P, Mudry A, Stanzel F, et al. The use of the covered Wallstent for the palliative treatment of inoperable tracheobronchial cancers. A prospective, multicenter study. *Chest*. 1996;110(5):1161-1168.
14. Bolliger CT, Heitz M, Hauser R, Probst R, Perruchoud AP. An Airway Wallstent for the treatment of tracheobronchial malignancies. *Thorax*. 1996;51(11):1127-1129.
15. Miyazawa T, Yamakido M, Ikeda S, et al. Implantation of ultraflex nitinol stents in malignant tracheobronchial stenoses. *Chest*. 2000;118(4):959-965.
16. Miyazawa T, Miyazu Y, Iwamoto Y, et al. Stenting at the flow-limiting segment in tracheobronchial stenosis due to lung cancer. *Am J Respir Crit Care Med*. 2004;169(10):1096-1102.
17. Dumon JF. A dedicated tracheobronchial stent. *Chest*. 1990; 97(2):328-332.
18. Dumon JF, Dumon MC. Dumon-Novatech Y-stents: a four-year experience with 50 tracheobronchial tumors involving the carina. *Journal of Bronchology*. 2000;7(1):26-32.
19. Freitag L, Eicker R, Linz B, Greschuchna D. Theoretical and experimental basis for the development of a dynamic airway stent. *Eur Respir J*. 1994;7(11):2038-2045.
20. Noppen M, Meysman M, Claes I, D'Haese J, Vincken W. Screw-thread vs Dumon endoprosthesis in the management of tracheal stenosis. *Chest*. 1999;115(2):532-535.
21. Vergnon JM, Costes F, Polio JC. Efficacy and tolerance of a new silicone stent for the treatment of benign tracheal stenosis: preliminary results. *Chest*. 2000;118(2):422-426.
22. Breen DP, Dutau H. On-site customization of silicone stents: towards optimal palliation of complex airway conditions. *Respiration*. 2009;77(4):447-453.
23. Peled N, Shitrit D, Bendayan D, Kramer MR. Right upper lobe 'window' in right main bronchus stenting. *Eur J Cardiothorac Surg*. 2006;30(4):680-681.
24. Deshmukh V, Zuccatosta L, Sediari M, Mei F, Gasparini S, Salvolini L. Stenting right main bronchus with montgomery T tube for upper lobe ventilation. *J Bronchology Interv Pulmonol*. 2010;17(1):90-92.

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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.

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.

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.

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 ($p = 0.23$).

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-

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.

References

1 Oho K, Kato H, Ogawa I, Hayashi N, Hayata Y: A new needle for transfiberoptic bronchoscopic use. Chest 1979;76:492.
2 Davenport RD: Rapid on-site evaluation of transbronchial aspirates. Chest 1990;98:59–61.
3 Diette GB, White P Jr, Terry P, Jenckes M, Rosenthal D, Rubin HR: Utility of on-site cytopathology assessment for bronchoscopic evaluation of lung masses and adenopathy. Chest 2000;117:1186–1190.
4 Baram D, Garcia RB, Richman PS: Impact of rapid on-site cytologic evaluation during transbronchial needle aspiration. Chest 2005; 128:869–875.
5 Trisolini R, Cancellieri A, Tinelli C, Paioli D, Scudeller L, Casadei GP, Parri SF, Livi V, Bondi A, Boaron M, Patelli M: Rapid on-site evaluation of transbronchial aspirates in the diagnosis of hilar and mediastinal adenopathy: a randomized trial. Chest 2011;139:395–401.
6 Diacon AH, Schuurmans MM, Theron J, Louw M, Wright CA, Brundyn K, Bolliger CT: Utility of rapid on-site evaluation of transbronchial needle aspirates. Respiration 2005; 72:182–188.
7 Yarmus L, Van der Kloot T, Lechtzin N, Napier M, Dressel D, Feller-Kopman D: Randomized prospective trial of the utility of rapid on-site evaluation of transbronchial needle aspirate specimens. J Bronchol Inter Pulmonol 2011;18:121–127.

8 Boyan W: On-site cytopathologic analysis of bronchoscopic needle aspiration: con: on-site analysis is not indicated. J Bronchol 2003;10:152–154.
9 Chin R Jr: On-site cytopathologic analysis of bronchoscopic needle aspiration: pro: on-site analysis is indicated. J Bronchol 2003;10:150–151.
10 Gasparini S: It is time for this 'ROSE' to flower. Respiration 2005;72:129–131.
11 Varela-Lema L, Fernández-Villar A, Ruano-Ravina A: Effectiveness and safety of endobronchial ultrasound-transbronchial needle aspiration: a systematic review. Eur Respir J 2009;33:1156–1164.
12 Gu P, Zhao YZ, Jiang LY, Zhang W, Xin Y, Han BH: Endobronchial ultrasound-guided transbronchial needle aspiration for staging of lung cancer: a systematic review and meta-analysis. Eur J Cancer 2009;45:1389–1396.
13 Ost DE, Ernst A, Lei X, Feller-Kopman D, Eapen GA, Kovitz KL, Herth FJ, Simoff M, AQuIRE Bronchoscopy Registry: Diagnostic yield of endobronchial ultrasound-guided transbronchial needle aspiration: results of the AQuIRE Bronchoscopy Registry. Chest 2011;140:1557–1566.
14 Bulman W, Saqi A, Powell CA: Acquisition and processing of endobronchial ultrasound-guided transbronchial needle aspiration specimens in the era of targeted lung cancer chemotherapy. Am J Respir Crit Care Med 2012;185:606–611.
15 Oki M, Saka H, Kitagawa C, Tanaka S, Shimokata T, Kawata Y, Mori K, Kajikawa S, Ichihara S, Moritani S: Real-time endobronchial ultrasound-guided transbronchial needle aspiration is useful for diagnosing sarcoidosis. Respirology 2007;12:863–868.
16 Oki M, Saka H, Kitagawa C, Kogure Y, Murata N, Ichihara S, Moritani S: Prospective study of endobronchial ultrasound-guided transbronchial needle aspiration of lymph nodes versus transbronchial lung biopsy of lung tissue for diagnosis of sarcoidosis. J Thorac Cardiovasc Surg 2012;143:1324–1329.
17 Oki M, Saka H, Kitagawa C, Kogure Y, Murata N, Adachi T, Ichihara S, Moritani S: Transesophageal bronchoscopic ultrasound-guided fine needle aspiration for diagnosis of sarcoidosis. Respiration 2013;85:137–143.
18 Mountain CF, Dresler CM: Regional lymph node classification for lung cancer staging. Chest 1997;111:1718–1723.
19 Chin R Jr, McCain TW, Lucia MA, Cappellari JO, Adair NE, Lovato JF, Dunagan DP, Brooks MA, Clark HP, Haponik EF: Transbronchial needle aspiration in diagnosing and staging lung cancer: how many aspirates are needed? Am J Respir Crit Care Med 2002;166:377–381.
20 Lee HS, Lee GK, Lee HS, Kim MS, Lee JM, Kim HY, Nam BH, Zo JI, Hwangbo B: Real-time endobronchial ultrasound-guided transbronchial needle aspiration in mediastinal staging of non-small cell lung cancer: how many aspirations per target lymph node station? Chest 2008;134:368–374.
21 Griffin AC, Schwartz LE, Baloch ZW: Utility of on-site evaluation of endobronchial ultrasound-guided transbronchial needle aspiration specimens. Cytojournal 2011;8:20.
22 Lee JE, Kim HY, Lim KY, Lee SH, Lee GK, Lee HS, Hwangbo B: Endobronchial ultrasound-guided transbronchial needle aspiration in the diagnosis of lung cancer. Lung Cancer 2010;70:51–56.
23 Yasufuku K, Pierre A, Darling G, de Perrot M, Waddell T, Johnston M, da Cunha Santos G, Geddie W, Boerner S, Le LW, Keshavjee S: A prospective controlled trial of endobronchial ultrasound-guided transbronchial needle aspiration compared with mediastinoscopy for mediastinal lymph node staging of lung cancer. J Thorac Cardiovasc Surg 2011;142:1393–1400.

Rationale and Design of the Japan Molecular Epidemiology for Lung Cancer Study

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Abstract

We present the rationale for the Japan Molecular Epidemiology for Lung Cancer study designed to elucidate molecular mechanisms of carcinogenesis in smokers and never-smokers with non–small-cell lung cancer. This prospective, ongoing, multicenter study is being conducted nationwide in Japan. Although there is no doubt that active smoking is the major cause of lung cancer, the contribution of other possible factors, including environmental tobacco or wood smoke, human papilloma virus, radon, occupational exposures, and genetic susceptibility, is highly likely, based on studies of never-smokers with non–small-cell lung cancer. Because of the predominance of women in the never-smoker subgroup, the role of female hormones in lung cancer development has also been considered. We hypothesize that driver mutations, which are critical for the development of lung cancer, are triggered by the environmental factors with or without the influence of the hormone. The SWOG-led intergroup molecular epidemiology study S0424 was conducted to focus on these issues by using a detailed questionnaire and specimen collection in statistically significant cohorts of smokers and never-smokers from both sexes. The Japan Molecular Epidemiology for Lung Cancer study follows and extends the S0424 molecular epidemiology concept in principle by using a similar approach that will facilitate future comparisons between the studies but with a greater focus on more recently defined driver mutations and broad genomic sequencing.

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Introduction

Lung cancer is a leading cause of cancer-related morbidity and mortality in the world. Although the disease is predominantly caused by tobacco smoke, approximately 25% of all lung cancers worldwide are not attributable to this etiology. In fact, approximately 30% of Japanese patients with non–small-cell lung cancer (NSCLC) are never-smokers, as observed in a study that consisted of more than 20,000 patients.[1] Lung cancer in never-smokers differs significantly from that of smokers in clinical characteristics and in the distribution of oncogenic abnormalities, and it has been suggested to be a distinct disease.[2]

Although several possible explanations have been proposed, the cause of lung cancer in never-smokers remains unclear. Explanations include environmental tobacco smoke (ETS) exposure,[3] radon,[4] wood smoke,[5] occupational exposure,[6] oncogenic virus,[7,8] genetic change,[9] and sex hormone.[10,11] A Japan Public Health Center–based prospective study showed that, in Japan, second-hand smoke exposure is clearly related to the development of lung adenocarcinoma in never-smokers.[3] The study identified a statistically significant dose-response relationship between the quantity and the intensity of husbands' smoking and their wives' incidence of lung cancer. Our previous study with a detailed questionnaire in a prospective way enhances this finding that the development of epidermal growth factor receptor (*EGFR*) mutations is significantly associated with the dose of ETS exposure in never-smokers.[12] However, there are con-

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flicting data published on the relationship between ETS and *EGFR* mutations in never-smokers with NSCLC. A study from Korea showed opposite results, in which the development of the mutation was inversely proportional to the ETS[13]; although, in the United States, there was no association between them.[14] A study with a well-designed and standardized questionnaire in a larger sample size is required to conclude this issue.

An oncogenic role for the HPV has been widely investigated in NSCLC.[7] Although all the published reports were retrospective analyses with potentially significant limitations and bias, the systematic review nevertheless suggested that the development of lung cancer in Asia can be attributed to some extent to HPV. Moreover, a different detection rate was observed geographically even within east Asia, with a higher rate in the southern area than in the northern regions. There is a substantial need to confirm these findings by using a standardized HPV detection methodology in a prospective study in Japanese patients.

The association between sex and lung cancer carcinogenesis is also an important consideration. Although studies provide conflicting results on the strength of this association, it has been postulated that women are more vulnerable to tobacco smoke–associated carcinogens than men. The large SWOG study S0424 was originally designed to address this issue by using a detailed questionnaire and NSCLC tissue specimens from smoker and never-smoker men and women with newly diagnosed stage I, stage II, or stage III NSCLC,[15] in which polycyclic aromatic hydrocarbons and aromatic amines of DNA adducts are measured to quantitate levels of DNA damage stratified by sex and the smoking status. Cigarette smoke contains a large number of carcinogens, and polycyclic aromatic hydrocarbons and aromatic amines are among the most important contributors to the carcinogenic process. The Japan Molecular Epidemiology for lung cancer (JME) study follows and extends the concept of S0424 by using a similar approach that will allow for direct comparison of data in the future.

Sex hormones, including estrogen and progesterone, have been suggested to play an important role in lung carcinogenesis. Results of epidemiologic studies showed that women were predominant in number in the never-smoking subpopulation. Further, results of large randomized studies suggest that estrogen plus progestin therapy is associated with an increased risk of lung cancer. The prospective Vitamins and Lifestyle Study followed a cohort of more than 36,000 peri- and postmenopausal women during 6 years of follow-up.[16] After adjusting for smoking and other confounding factors, the incidence of lung cancer was increased for those who used estrogen plus progestin. The risk was proportional to the duration of hormone exposure (hazard ratio 1.48 [95% CI, 1.03-2.12] for those with $\geq$10 years of exposure to estrogen plus progestin).

In terms of biologic function, estrogen receptors (ER) are expressed in diverse normal and neoplastic tissues, and mediate growth and maturation of normal tissue. A number of studies have noted expression of ERs in a large portion of lung tumors. In a couple of studies, the development of *EGFR* mutations was significantly associated with expression of ER β in NSCLC surgical specimens.[10,11] There have been no studies that systematically evaluated ER expression in lung cancer and its relationship with genetic mutations or environmental and reproductive risk factors.

Identification of driver mutations in NSCLC has been instrumental in improving treatment strategies. *ALK* (anaplastic lymphoma kinase) gene translocations have been demonstrated to be critical targets and biomarkers for crizotinib efficacy,[17] similar to *EGFR* mutations for gefitinib and erlotinib, and the discovery of other mutations for treatment is ongoing. The Lung Cancer Mutational Consortium in the United States[18] and the Lungscape project in the European Union[19] are currently exploring new molecular targets for treatment in lung cancer. Powerful tools for genome-wide characterization have been developed, including next-generation sequencing, which enables comprehensive examination of somatic mutations associated with carcinogenesis. The Cancer Genome Atlas is an ongoing global project that uses this technology to distill essential driver abnormalities from the background noise.[20] A focus of the JME study is to explore new driver mutations by using advanced technologies and approaches now available with regard to sex of the patient and tobacco smoke exposure. The association between oncogenic abnormality profiles and drug sensitivity and prognosis will also be examined.

In addition, the JME study is designed to investigate the relationship between ethnicity and NSCLC carcinogenesis. It is clear that NSCLCs are different in tumor biology between Caucasian and Asian patients. Gandara et al[21] showed that there was a significant difference in survival and toxicities between the US and the Japanese patients treated with carboplatin and paclitaxel in a "common arm" trial, in which the study design, eligibility criteria, and staging were similar. The median overall survival in the metastatic disease was 12 and 14 months for Japanese patients vs. 9 months for US patients ($P = .0006$).[21] As for *EGFR* mutations, the frequencies appear to be highly distinct; the high detection rate in Asia was reported consistently across publications. Different influences of smoking status on the development of NSCLC also was observed between the United States and Japan in population-based prospective studies. In a comparison of the Japanese cohort with US Cancer Prevention Study II during the same period,[22] Japanese never-smokers had an increased risk of lung cancer, whereas Japanese current smokers were at a lower risk of the cancer compared with those in the United States. To elucidate the mechanistic contributions of ethnic differences, there is a need to collaborate in comprehensive and global approaches for examining development of NSCLC as well as the clinical behavior and outcome.

Objectives

The primary objective of this study is to assess surgical lung specimens from patients with stage I, stage II, stage IIIA, or stage IIIB NSCLC for driver mutations, expression of HER2 and ER α and ER β, the presence of smoking-associated DNA adducts, and evidence of HPV, and to explore new molecular markers by using next-generation sequencing. By using information collected before surgery on patient demographics, smoking history and occupational exposures, carcinogenic mechanisms will be elucidated in never-smokers and ever-smokers. Secondary objectives are to examine whether the relapse rate, disease-free survival, and overall survival time differ among the patients with different mutational