patients received EGFR-TKI therapy as the initial therapy; some patients received EGFR-TKI therapy as second- or third-line treatment in this study. In addition, some patients received both gefitinib and erlotinib therapy.

There are several limitations associated with this study. One limitation associated with this study is the retrospective study design. Although the indications and therapeutic strategies for recurrent disease were generally examined by the cancer board of our department, not all patients received treatment according to the same standard. Secondly, post-recurrence survival may be regulated not only by the initial therapy but also by second- or third-line therapy. Thirdly, the patients who received EGFR-TKI therapy included the patients who received gefitinib therapy, erlotinib therapy and both gefitinib and erlotinib therapy. Based on the number and variety of cases, we were unable to demonstrate the outcomes according to each drug. Despite these limitations, this study evaluated the influence of the EGFR mutation status and outcome of EGFR-TKI therapy in 280 recurrent NSCLC cases; therefore, these results reflect the actual clinical outcomes of recurrent NSCLC.

In conclusion, the EGFR mutation status, ECOG PS, brain metastasis and number of recurrent foci were found to be associated with post-recurrence survival in patients with NSCLC. The patients with an EGFR mutation-positive status received much greater survival benefits from EGFR-TKI therapy. In addition, patients may experience adverse effects if the EGFR mutation status is unknown; therefore, it is essential to identify the EGFR status in order to assess the therapeutic strategy for recurrent NSCLC.

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ORIGINAL ARTICLE

The presence of air bronchogram is a novel predictor of negative nodal involvement in radiologically pure-solid lung cancer†

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Abstract

OBJECTIVES: Phase III trials regarding the feasibility of segmentectomy for lung cancer ≤2 cm in size are now underway in Japan and the USA. However, despite their small size, lung cancers that show a pure-solid appearance on thin-section computed tomograpy (CT) are considered to be invasive with a high frequency of nodal involvement.

METHODS: Between 2008 and 2011, 556 clinical Stage IA lung cancer patients underwent pulmonary resection. For all patients, the findings obtained by preoperative thin-section CT were reviewed and the maximum standardized uptake value (SUVmax) on positron emission tomography was recorded. Several clinicopathological features were investigated to identify predictors of nodal metastasis using multivariate analyses.

RESULTS: One hundred and eighty-four clinical Stage IA lung cancer patients showed a pure-solid appearance on thin-section CT. Among them, air bronchogram was found radiologically in 58 (32%) patients. Nodal involvement was observed in 10 (17%) patients with air bronchogram, compared with 43 (34%) without air bronchogram, in clinical Stage IA pure-solid lung cancer. A multivariate analysis revealed that air bronchogram, clinical T1a and SUVmax were significant predictors of postoperative nodal involvement ($P < 0.01$, <0.01, and 0.03, respectively). Furthermore, nodal metastasis was never seen in patients with clinical T1a pure-solid lung cancers who had both air bronchogram and low SUVmax.

CONCLUSIONS: The presence of air bronchogram was a novel predictor of negative nodal involvement in clinical Stage IA pure-solid lung cancer. Segmentectomy with thorough lymph node dissection is a feasible option for these patients despite a pure-solid appearance.

Keywords: Air bronchogram • Pure-solid nodule • Prognosis • Lymph node metastasis

INTRODUCTION

Lung cancers that show a wide area of ground-grass opacity (GGO) are considered to have a good prognosis and in most cases their pathological features are minimally invasive [1, 2]. Recently, the indication for limited surgery has been extended to very early lung cancers that are located peripherally and show a GGO appearance on thin-section computed tomography (CT) scan [3–7]. While there has been considerable discussion on limited surgical resection for lung cancer with a GGO appearance, there have been few studies on limited surgery for lung cancer with a solid appearance on thin-section CT scan, i.e. invasive lung cancer. Intentional segmentectomy is now indicated for part-solid or pure-solid lung cancers 2 cm or less in size in both Japan [8] and the USA [9]. However, postoperative nodal involvement is found in ~20% of cases, even in clinical Stage IA disease [10], and invasive lung cancer can be associated with occult lymph node metastasis, which would result in incomplete resection and loco-regional failure by the indication of limited surgical resection. Furthermore, postoperative nodal involvement is often found in patients with radiologically pure-solid lung cancer [11]. Thus, pure-solid lung cancer is considered to be highly invasive and is in a different category among lung cancers with a solid appearance on thin-section CT scan.

Thus, there is still some controversy regarding the use of limited surgical resection for pure-solid tumours because of the high frequency of lymph node involvement. On the other hand, limited surgery such as segmentectomy is becoming increasingly important as an option for resectable small lung cancer with N0 status [12, 13]. For the more precise application of limited surgical resection, preoperative diagnosis for predicting invasive lung cancer is warranted through the classification of these pure-solid tumours into several subgroups. In the current retrospective study, we focused on the radiological findings of pure-solid lung cancer, especially with regard to air bronchogram on thin-section CT scan, and tried to determine criteria for identifying candidates for limited surgical resection for small-sized tumours.

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MATERIALS AND METHODS

This protocol was approved by the ethics committee at our institute. All patients provided their written informed consent before trial enrolment.

Between January 2008 and December 2011, 556 clinical Stage IA lung cancer patients underwent pulmonary resection at our institute. For all patients, the findings of preoperative computed tomography were reviewed by the authors (A.H., T.M. and K.S.). A contrast-enhanced CT scan was performed to evaluate the entire lung for preoperative staging. The size of the tumours was determined preoperatively based on the findings of thin-section CT scan. In addition, all tumours were subsequently evaluated to estimate the extent of GGO with thin-section CT scan with 2 mm collimation. The lung was photographed with a window level of −500 to −700 H and a window depth of 1000–2000 H as a lung window. The solid component was defined as an area of increased opacification that completely obscured the underlying vascular markings. GGO was defined as an area of a slight, homogeneous increase in density that did not obscure the underlying vascular markings. In the current study, a radiological pure-solid tumour was defined as a lung tumour that only showed consolidation without GGO on thin-section CT, i.e. the ratio of the maximum diameter of consolidation to the maximum tumour diameter (consolidation/tumour ratio, C/T ratio) was equal to 1.0. Air bronchogram was a radiological finding on thin-section CT scan that was defined as an air-filled bronchus surrounded by fluid-filled airspaces in the primary tumour. Typical images of pure-solid lung cancer with air bronchogram are shown in Fig. 1.

There were 184 patients with clinical Stage IA lung cancer with a pure-solid appearance on thin-section CT. All patients were evaluated by positron emission tomography (PET) and the maximum standardized uptake value (SUVmax) was recorded. Regarding the operation, a major lung dissection with systemic lymph node dissection was warranted for a pure-solid tumour in our institute, whereas intentional segmentectomy is now indicated for part-solid or pure-solid lung cancers 2 cm or smaller according to the Japan Clinical Oncology Group (JCOG 0802 [8]). Non-anatomical wedge resection was performed for a few elderly patients or for patients with a high cardiopulmonary risk.

The medical record of each patient was reviewed with regard to gender, sex, pack-year smoking, clinical T-status (c-T1a vs c-T1b), pleural involvement, presence of air bronchogram in the tumour, serum carcinoembryonic antigen level (ng/ml, CEA) and SUVmax on PET. The relationships between these factors and postoperative nodal status were investigated to identify significant predictors in clinical Stage IA pure-solid lung cancer. Fisher's exact test or χ^2 test was used to compare two factors. Univariate and multivariate analyses were used to identify the clinical factors that predicted nodal involvement in clinical Stage IA pure-solid lung cancer. Multivariate analysis was performed by logistic regression analysis using SPSS Statistics 20 (SPSS, Inc.). Forward and backward stepwise procedures were used to determine the combination of factors that were essential for predicting the prognosis. Hosmer–Lemeshow test for a logistic regression analysis was used to assess overall model fit and precision. Reported continuous data were shown with mean and standard deviation (SD) for normality. Statistical analysis was considered to be significant when the probability value was <0.05.

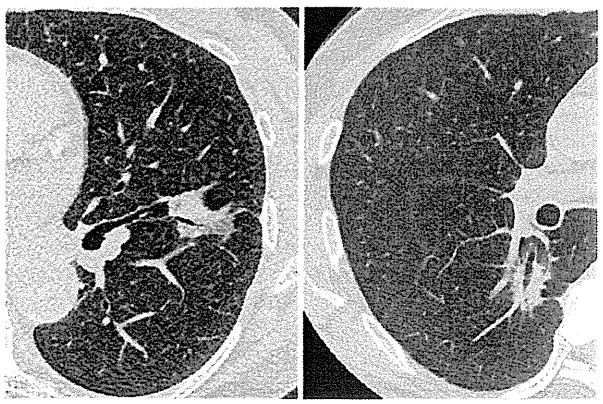

Figure 1: Typical images of pure-solid lung cancer with air bronchogram. An air-filled bronchus is surrounded by a lung tumour that only shows consolidation without ground-grass opacity on thin-section CT scan.

RESULTS

Among 184 eligible pure-solid lung cancers, 102 patients were men and 72 were women. Patients ranged in age from 35 to 89 years, with an average of 67 years. Among them, air bronchogram was found radiologically in 58 (32%) patients. The relationships between several clinical factors and nodal involvement in patients with clinical Stage IA pure-solid lung cancer are summarized in Table 1. Postoperative nodal metastasis was found in 10 (17%) patients with air bronchogram and in 43 (34%) without air bronchogram in clinical Stage IA pure-solid lung cancer.

The relationships between the status of air bronchogram, the mode of surgical resection and the pathological aspects are presented in Table 2. With regard to patients with air bronchogram, standard lobectomy was performed in 51 (88%) patients (6 in N1 station and 3 in N2 station), segmentectomy in 3 (5%) (nodal metastasis was not found) and non-anatomical wedge resection in 4 (7%) (1 in N2 station). One hundred and two (81%) patients without air bronchogram underwent standard lobectomy (15 in N1 station and 25 in N2 station), 12 (9.5%) underwent segmentectomy (2 in N1 station and 1 in N2 station) and 12 (9.5%) underwent non-anatomical wedge resection.

According to a multivariate analysis in patients with clinical Stage IA pure-solid lung cancer, the following factors significantly predicted lymph node metastasis: the presence of air bronchogram, maximum tumour dimension (mean and SD; 15.4 ± 3.4 mm) and SUVmax level (mean and SD; 4.7 ± 3.2) ($P < 0.01$, <0.01 and 0.03, respectively; Table 3). The result of the Hosmer–Lemeshow test was 0.290, which revealed the reliability of our model.

Based on these results, among patients with clinical T1a disease, there were 29 patients with a pure-solid lung cancer with air bronchogram, including 2 (7%) with postoperative nodal involvement. By combining these predictors, we identified subgroups that showed various frequencies of nodal involvement among clinical T1a pure-solid lung cancer (Table 4). Patients with clinical T1a pure-solid lung cancers who had both air bronchogram and SUVmax of ≥2.5 never showed nodal involvement. On the other hand, among patients with clinical T1a pure-solid lung cancer with neither of these predictors, >30% showed pathological nodal involvement. This new radiological sign as a potential predictor for negative nodal involvement indicated several accuracies as the following number; sensitivity = 16%, specificity = 100%, positive predictive value = 100% and negative predictive value = 16%.

Table 1: Results of a univariate analysis for predictors of nodal involvement in patients with clinical Stage IA pure-solid lung cancer

Clinical factors	Number of patients	Number of patients with nodal involvement (%)	*P*-value*
Total	184	53 (29)	
Gender			
Male	112	36 (32)	0.21
Female	72	17 (24)	
Age (years)			
>70	78	16 (21)	0.03
≤70	106	37 (35)	
Pack-year smoking			
>20	100	28 (28)	0.79
≤20	84	25 (30)	
Clinical T-status			
c-T1a	102	14 (14)	<0.01
c-T1b	82	39 (48)	
Pleural involvement			
Absent	107	31 (29)	0.95
Present	77	22 (29)	
Air bronchogram			
Absent	126	43 (34)	0.02
Present	58	10 (17)	
CEA (ng/ml)			
≤3	92	26 (28)	0.87
>3	92	27 (29)	
SUVmax			
≤2.5	42	4 (10)	<0.01
>2.5	142	49 (35)	

CEA: carcinoembryonic antigen; SUVmax: maximum standardized uptake value.
*P-value in χ^2 test or Fisher's exact test.

Table 2: Relationships between the status of air bronchogram, the mode of resection and pathological aspects among clinical Stage IA pure-solid lung cancer patients

	No. of patients with air bronchogram	No. of patients without air bronchogram
Total number of patients	58	126
Operative mode		
Wedge resection	4	12
Segmentectomy	3	12
Lobectomy	51	102
Lymph node dissection		
None	3	13
Hilar only	10	14
Mediastinal/Hilar	45	99
Nodal involvement		
N0	48	83
N1	6	14
N2	4	29
Pathology		
Adenocarcinoma	47	83
Adeno-squamous cell carcinoma	2	2
Squamous cell carcinoma	9	29
Others	0	11

Table 3: Results of a multivariate analysis for predictors of nodal involvement in patients with clinical Stage IA pure-solid lung cancer

Variable	Odds ratio	95% Confidence interval	*P*-value*
Air bronchogram	0.28	0.11–0.71	<0.01
Maximum tumour dimension	8.92	3.78–21.88	<0.01
SUVmax	3.81	1.12–12.82	0.03

SUVmax: maximum standardized uptake value.
*P-value in logistic regression analysis.

Table 4: Probability of the presence of nodal involvement in patients with clinical T1a pure-solid lung cancer

Subgroups	Number of patients	Number of patients with nodal involvement (%)	*P*-value*
Total clinical T1a disease	102	14 (14)	
Presence of air bronchogram and SUVmax ≤2.5			
with both factors	14	0 (0)	0.03
with either factors	41	3 (7)	
with neither factors	47	11 (23)	

SUVmax: maximum standardized uptake value.
*P-value in χ^2 test.

DISCUSSION

Important prospective studies are now underway in Japan and the USA, which consist of Phase III trials regarding the feasibility of limited resection for clinical T1a non-small-cell lung cancer (NSCLC) with a radiologically part-solid or pure-solid appearance. If the prognosis of patients who undergo limited surgery such as segmentectomy is equivalent to those who undergo lobectomy, the standard treatment procedure for resectable lung cancer may change based on the results of Lung Cancer Study Group [14]. Owing to the improvements in and widespread use of CT scan for detecting small lung cancer [15], segmentectomy is of greater importance as an option for resectable small lung cancer with N0 status [12, 13]. In contrast, the greatest concern regarding the indication for limited surgery in patients with solid lung cancer is a potential risk for postoperative nodal metastasis, despite their small size. Historically, lymph node metastasis is found in ~15% of small lung cancers 2.0 cm or less in size. However, pathological nodal metastasis is frequently observed, especially in patients with pure-solid compared with those with part-solid tumours on thin-section CT scan [5, 11]. Furthermore, invasive lung cancer could be associated with occult lymph node metastasis, which would result in incomplete resection following limited surgical resection [16, 17]. Therefore, limited surgical resection should be applied with great caution for pure-solid tumours.

Air bronchogram is a radiological finding in which an air-filled bronchus is surrounded by fluid-filled airspaces. Several authors have confirmed the significance of the presence of air bronchogram in the primary nodules, as a predictor of pathological N0 status [7, 11, 18]. However, an intratumoural air bronchogram is mostly identified in areas with a slight, homogeneous increase in density on thin-section CT scan, such as a GGO lesion. This indicates that the main tumour structure is preserved by the alveolar and bronchiole space, which is due to a lepidic growth pattern [1]. This pattern is a radiological feature of minimally invasive lung cancer. On the other hand, the prognostic significance of the presence of air bronchogram in pure-solid lung cancer has not yet been evaluated. However, the radiological presence of air bronchogram might be useful for predicting a negative lymph node in pure-solid lung cancer, which may help to identify patients who are candidates for limited surgical resection. Thus, in the current retrospective study, we focused on the invasiveness of pure-solid lung cancer with air bronchogram from the perspective of lymph node metastasis.

In this study, a multivariate analysis revealed that the presence of air bronchogram, maximum tumour dimension and SUVmax level were significant predictors of postoperative lymph node metastasis. Furthermore, when we combined the radiological findings and the SUVmax level in 102 clinical T1a pure-solid lung cancers, 30.6% of patients with both the absence of air bronchogram and a high SUVmax showed postoperative nodal involvement, whereas none of the patients with both the presence of air bronchogram and low SUVmax showed nodal metastasis. Our studies indicate that lobectomy with a radical mediastinal lymphadenectomy should not be denied for patients with clinical Stage IA pure-solid lung cancer with a good lung function even in the presence of air bronchogram, because of their high probability of lymph node metastasis (17%) in our study. According to these results, however, the combination of the presence of air bronchogram and a low SUVmax level may be an alternative new radiological finding that is associated with a good prognosis in clinical T1a pure-solid lung cancer.

Thus, we would like to suggest that major lung resection with mediastinal lymph node dissection should be, in principle, the standard treatment for tumours that show a pure-solid appearance on thin-section CT scan. With regard to the appropriate surgical strategy for clinical T1a NSCLC with a radiologically part-solid or pure-solid appearance, the final results of the JCOG [8] and CALGB [9] trials should help thoracic surgeons decide whether or not to apply limited surgery for patients who are at low risk. However, our results indicate that the further classification of small-sized lung cancers with a pure-solid appearance is warranted to determine the optimal indications for limited surgical resection. The combination of the presence of air bronchogram and a low SUVmax level was shown to be significantly effective for predicting node-negative clinical T1a pure-solid lung cancers. Segmentectomy with a thorough lymph node dissection may be a feasible option for these patients, even for those with a pure-solid appearance.

This study was limited by a short median follow-up period, and thus, further investigations are warranted.

In conclusion, the combination of the presence of air bronchogram and a low SUVmax level was shown to be useful for predicting negative nodal involvement in clinical T1a pure-solid lung cancer. With regard to the efficacy of limited surgical resection for small lung cancers, any definitive conclusions should be based on the results of the Phase III trials JCOG.0802 and CALGB-140503.

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Sublobar Resection for Lung Adenocarcinoma Meeting Node-Negative Criteria on Preoperative Imaging

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Background. This study evaluated the usefulness of sublobar resection for patients with clinical stage IA lung adenocarcinoma that met our proposed node-negative criteria: solid tumor size of less than 0.8 cm on high-resolution computed tomography or maximum standardized uptake value of less than 1.5 on [18F]-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography.

Methods. A multicenter database of 618 patients with completely resected clinical stage IA lung adenocarcinoma who underwent preoperative high-resolution computed tomography and [18F]-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography was used to evaluate the surgical results of sublobar resection for patients who met our node-negative criteria.

Results. No patient who met the node-negative criteria had any pathological lymph node metastasis. Recurrence-free survival (RFS) and overall survival (OS) rates at 5 years were significantly higher for patients who met the node-negative criteria (RFS: 96.6%; OS: 95.9%) than for patients who did not (RFS: 75.5%, $p < 0.0001$; OS: 83.1%, $p < 0.0001$). Among patients who met the node-negative criteria, RFS and OS rates at 5 years were not significantly different between those who underwent lobectomy (RFS: 96.0%; OS: 95.9%) and those who underwent sublobar resection (RFS: 97.2%, $p = 0.94$; OS: 95.9%, $p = 0.98$). Of 264 patients with T1b (2-cm to 3-cm) tumors, 106 (40.2%) met the node-negative criteria.

Conclusions. Sublobar resection without systematic nodal dissection is feasible for clinical stage IA lung adenocarcinoma that meets the above-mentioned node-negative criteria. Even a T1b tumor, which is generally unsuitable for intentional sublobar resection, can be a candidate for sublobar resection if it meets these node-negative criteria.

(Ann Thorac Surg 2014;97:1701–7)

Early-stage lung cancer, particularly lung adenocarcinoma, is now frequently being detected because of advanced radiographic techniques, such as high-resolution computed tomography (HRCT), and the widespread use of low-dose helical CT for tumor screening [1–3]. In a prospective randomized controlled study, the Lung Cancer Study Group reported that the outcomes of limited resections, such as segmentectomy and wedge resection, were inferior to those of standard lobectomy in patients with clinical T1 node-negative (N0) M0 non-small cell lung cancer (NSCLC) [4]. However, several studies have demonstrated the usefulness of sublobar resection for peripheral small-sized NSCLC [3, 5–10].

Theoretically, true N0 lung cancer can be treated by sublobar resection without nodal dissection when surgical margins are adequate. We previously reported that preoperative HRCT and [18F]-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography/computed tomography (PET/CT) were useful for predicting N0 clinical stage IA lung adenocarcinoma [11].

The objective of this study was to evaluate the usefulness of sublobar resection for clinical stage IA lung adenocarcinoma that met our previously proposed N0 criteria: solid tumor size of less than 0.8 cm on HRCT or a maximum standardized uptake value (SUVmax) of less than 1.5 on FDG-PET/CT [11].

Patients and Methods

Patients

Between August 1, 2005, and June 30, 2010, we enrolled 618 patients with clinical T1 N0 M0 stage IA lung adenocarcinoma from 4 institutions in Japan (Hiroshima University, Kanagawa Cancer Center, Cancer Institute Hospital, and Hyogo Cancer Center). For this study, we retrospectively analyzed the data for all 618 patients in

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Abbreviations and Acronyms

CI	= confidence interval
CT	= computed tomography
F	= female
FDG	= [18F]-fluoro-2-deoxy-D-glucose
HR	= hazard ratio
HRCT	= high-resolution computed tomography
IRB	= Institutional Review Board
LI	= lymphatic invasion
LN	= lymph node
LNM	= lymph node metastasis
M	= male
N0	= node-negative
NSCLC	= non-small cell lung cancer
OS	= overall survival
PET	= positron emission tomography
PI	= pleural invasion
Pt	= patient
RFS	= recurrence-free survival
SUVmax	= maximum standardized uptake value
VI	= vascular invasion

this multicenter database. The database included patients who underwent preoperative staging using HRCT and FDG-PET/CT, followed by curative resection without neoadjuvant chemotherapy or radiotherapy, with a definitive histopathologic diagnosis of lung adenocarcinoma. Excluded were those with incompletely resected tumors (R1 or R2) and those with synchronous multiple tumors or previous lung operations. This database has been prospectively collected and maintained.

HRCT and FDG-PET/CT, followed by curative R0 resection, had been performed for all patients who were staged according to the TNM Classification of Malignant Tumours, 7th Edition [12]. Mediastinoscopy and endobronchial ultrasonography were not routinely performed because all patients had undergone preoperative HRCT and FDG-PET/CT. HRCT revealed less than 1-cm enlargement of mediastinal or hilar lymph nodes and FDG-PET revealed a SUVmax of less than 1.5 in these lymph nodes.

Segmentectomy was considered for patients with clinical stage IA tumors that could be completely resected with ample surgical margins. No lymph node metastasis was intraoperatively confirmed on rapid frozen sections for enlarged lymph nodes or lymph nodes that were suspected with disease in the thoracic cavity. In cases of apparent or suspected nodal metastasis, lobectomy was chosen. Systematic lymphadenectomy, including hilar and mediastinal node dissection, was performed during segmentectomy but not during wedge resection. Therefore, wedge resection was performed for tumors, of which a ground glass opacity component accounted for great majority on HRCT. All patients who had pathologically diagnosed lymph node metastases received four cycles of platinum-based chemotherapy after the operation. None of the study patients received adjuvant radiotherapy.

Patients were divided into two groups. One group included patients who met the N0 criteria of solid tumor size of less than 0.8 cm on HRCT or a SUVmax of less than 1.5 on FDG-PET/CT [11]. The other group included patients who did not meet these N0 criteria.

This multicenter study was approved by the Institutional Review Boards (IRBs) of Hiroshima University Hospital (IRB No. EKI-644), Kanagawa Cancer Center (IRB No. KEN-31), Cancer Institute Hospital (IRB No. 2008-1018), and Hyogo Cancer Center (IRB No. H20-RK-15). All IRBs waived the requirement for informed consent from individual patients for this retrospective review of a prospective database.

HRCT Acquisition

Chest images were acquired with 16-row multidetector CT independently of subsequent FDG-PET/CT examinations. For high-resolution tumor images, the following parameters were used: 120 kVp; 200 mA; 1- to 2-mm section thickness; 512- × 512-pixel resolution; 0.5- to 1.0-second scanning time; a high-spatial reconstruction algorithm with a 20-cm field of view; and mediastinal (level: 40 HU; width: 400 HU) and lung (level: −600 HU; width: 1,600 HU) window settings. Ground glass opacity was defined as a misty increase in lung attenuation that did not obscure underlying vascular markings. We defined solid tumor size as the maximum dimension of the solid component in the lung windows, excluding the ground glass opacity [13]. Radiologists from each participating institution reviewed the CT scans and determined the tumor sizes.

FDG-PET/CT Acquisition

Patients were instructed to fast for more than 4 hours before intravenous injection of 74 to 370 MBq of FDG, which was followed by a relaxation period of at least 1 hour before FDG-PET/CT scanning. Blood glucose levels were determined before the tracer injection to confirm a level of less than 150 mg/dL. Patients with blood glucose levels of 150 mg/dL or more were excluded from PET/CT imaging. For imaging, we used a Discovery ST (GE Healthcare, Little Chalfont, UK), Aquiduo (Toshiba Medical Systems Corp, Tochigi, Japan), or Biograph Sensation16 (Siemens Healthcare, Erlangen, Germany) integrated 3-dimensional PET/CT scanner.

Following a standard protocol, low-dose, nonenhanced CT images (2- to 4-mm section thickness) for attenuation correction and localization of lesions identified by PET were obtained from the head to the pelvic floor of each patient. Immediately after CT, PET covered the same axial field of view for 2 to 4 minutes per table position, depending on the condition of the patient and scanner performance.

An iterative algorithm with CT-derived attenuation correction was used to reconstruct all PET images with a 50-cm field of view. An anthropomorphic body phantom (NEMA NU2-2001; Data Spectrum Corp, Hillsborough, NC) was used to minimize variations in SUVs among the institutions. A calibration factor was evaluated by dividing the actual SUV by the gauged mean SUV in the

phantom background to decrease interinstitutional SUV inconsistencies. The final SUV used here is referred to as the revised maximum SUVmax. Radiologists from each institution determined the original SUVmax values.

Follow-Up Evaluations

All patients who underwent lung resection were followed up from the day of the operation. Postoperative follow-up procedures for the first 2 years included physical examination and chest roentgenography every 3 months and chest and abdominal CT examinations every 6 months. Subsequently, physical examination and chest roentgenography were performed every 6 months and chest CT examination was performed every year.

Statistical Analysis

Results are given as numbers (%) or medians, unless otherwise stated. A χ^2 test was used to compare frequencies for categoric variables. The Fisher exact test was used when sample sizes were small. Recurrence-free survival (RFS) was defined as the time from the date of the operation until the first event (relapse or death from any cause) or the last follow-up. Overall survival (OS) was defined as the time from the date of the operation until death from any cause or the last follow-up. The Kaplan-Meier method was used to analyze RFS and OS durations, and a log-rank test was used to compare differences in RFS and OS. We performed a Cox proportional hazards model to determine whether age (continuous), sex, solid tumor size (continuous), SUVmax (continuous), or surgical procedure influenced RFS. We only used preoperative potential confounding factors as variables because postoperative factors would never influence the decision for surgical procedure. SPSS 10.5 software (SPSS Inc, Chicago, IL) was used for statistical analysis. The level of statistical significance was set at a p value of less than 0.05.

Table 1. Clinicopathologic Features of Patients Who Did and Did Not Meet the Node-Negative Criteria

Variables[a]	Solid Tumor Size ≥0.8 cm and SUVmax ≥1.5 (n = 293)	Solid Tumor Size <0.8 cm or SUVmax <1.5 (n = 325)	p Value
Age, y	67.0 (37–84)	65 (31–89)	0.04
Male sex	137 (46.8)	135 (41.5)	
Whole tumor size (cm)	2.2 (0.8–3.0)	1.8 (0.6–3.0)	<0.001
Solid tumor size (cm)	1.8 (1.0–3.0)	0.4 (0–3.0)	<0.001
Clinical T			<0.001
T1a	135 (46.1)	219 (67.4)	
T1b	158 (53.9)	106 (32.6)	
SUVmax	3.0 (1.5–17.0)	0.9 (0–9.8)	<0.001
Adenocarcinoma in situ	5 (1.7)	92 (28.3)	<0.001
Procedure			<0.001
Lobectomy	246 (84.0)	137 (42.2)	
Sublobar resection	47 (16.0)	188 (57.8)	
Segmentectomy[b]	23 (7.8)	75 (23.1)	
Wedge resection	24 (8.2)	113 (34.8)	
Lymphatic invasion	87 (29.7)	5 (1.5)	<0.001
Vascular invasion	101 (34.5)	5 (1.5)	<0.001
Pleural invasion	62 (21.2)	5 (1.5)	<0.001
Lymph node metastasis	45 (15.4)	0 (0)	<0.001
N1	24 (8.2)	0 (0)	
N2	21 (7.2)	0 (0)	
Recurrence	57 (19.5)	2 (0.6)	<0.001

[a] Categoric data are shown as number (%) and continuous data as median (range). [b] Details of segmentectomy were right S1 in 4, S2 in 12, S3 in 3, S6 in 23, S8 in 5, S7 + 8 in 1, S8 + 9 in 3, S7 + 8 + 9 + 10 in 1, left S1 + 2 in 7, S3 in 3, S1 + 2 + 3 in 10, S1 + 2 + 3c in 1, S4 in 2, S5 in 1, S4 + 5 in 7, S6 in 10, S8 in 1, S9 in 3, and S6 + 8 + 9 + 10 in 1.

SUVmax = maximum standardized uptake value.

Results

The characteristics of the 325 patients who met our N0 criteria and the 293 patients who did not are summarized in Table 1. There were no 30-day postoperative deaths in this study population. The median follow-up period of censored patients after the operation was 42.9 months. The mean follow-up period after lobectomy and segmentectomy were 43.3 months ± 15.6 and 40.4 ± 14.7 months in the N0 criteria group ($p = 0.10$) and 43.8 ± 16.8 months and 40.1 ± 19.3 months in the non-N0 criteria group ($p = 0.39$), respectively. There were significant differences between the two groups with regard to age, whole tumor size, solid tumor size, clinical T factor, SUVmax, surgical procedure, pathologic invasiveness (lymphatic, vascular, and pleural invasion), lymph node metastasis, and recurrence.

Patients who met the N0 criteria had significantly fewer pathologically invasive tumors and underwent sublobar resection. Lymph node metastases were found in 45 of the 293 patients (15.4%) who did not meet the N0 criteria. Of 45 patients with lymph node metastasis, 1 was N2 after sublobar resection (S6 segmentectomy), 24 were N1 after lobectomy, and 20 were N2 after lobectomy. Two patients who met the N0 criteria had tumor recurrences (Table 2). One was a 57-year-old woman with a solid tumor size of 1.3 cm and an SUVmax of 1.2. Although she had undergone standard lobectomy and had no lymph node metastasis, mediastinal lymph node recurrence subsequently developed. The other patient was a 59-year-old man with a solid tumor size of 1.8 cm and an SUVmax of 1.4. He had undergone wedge resection without lymph node dissection, and multiple lung metastases without lymph node recurrence subsequently developed.

The 5-year RFS rate (96.6%) was significantly better for patients who met the N0 criteria than for patients who did not (75.5%, $p < 0.0001$; Fig 1A). The 5-year OS rate (95.9%) was also significantly better for patients who met the N0 criteria than for patients who did not (83.1%, $p < 0.0001$; Fig 1B).

Among the patients who met the N0 criteria, no significant difference was noted in the 5-year RFS rate

Table 2. Patients Who Met the Node-Negative Criteria and Developed Recurrences

Pt	Age	Sex	Whole Tumor Size	Solid Tumor Size	SUVmax	Procedure	LI	VI	PI	LNM	Recurrence Site	Outcome
1	57	F	1.4 cm	1.3 cm	1.2	Lobectomy	1	0	0	0	Mediastinal LN	24 m, dead
2	59	M	1.8 cm	1.8 cm	1.4	Wedge resection	0	0	0	0	Multiple lung	48.8 m, dead

F = female; LN = lymph node; LI = lymphatic invasion; LNM = lymph node metastasis; M = male; PI = pleural invasion; Pt = patient; SUVmax = maximum standardized uptake value; VI = vascular invasion.

between those who underwent lobectomy (96.0%) and those who underwent sublobar resection (97.2%, $p = 0.94$; Fig 2A). Similarly, the 5-year OS rate was not significantly different between patients who underwent lobectomy (95.9%) and those who underwent sublobar resection (95.9%, $p = 0.98$; Fig 2B). Of 164 patients with T1b tumors, 106 (40.2%) met the N0 criteria (Table 3). These patients rarely had pathologic invasiveness, and no recurrences developed.

In patients who did not meet the N0 criteria, the 5-year RFS rate was 63.9% for those who underwent segmentectomy and 77.7% for those who underwent lobectomy; this difference was not statistically significant ($p = 0.058$; Fig 2C). The 5-year OS rate for patients who underwent lobectomy (82.8%) and those who underwent sublobar resection (85.2%) was also not significantly different ($p = 0.69$; Fig 2D).

Multivariate Cox analysis including the preoperative factors and surgical procedures revealed that solid tumor size and SUVmax were independent prognostic factors for RFS, whereas age, sex, and surgical procedure were not (Table 4). In clinical T1b patients, SUVmax was an independent prognostic factor for RFS, whereas surgical procedure was not (Table 5).

Comment

The purpose of the current study was to assess the usefulness of sublobar resection for clinical stage IA lung adenocarcinoma that met our proposed N0 criteria. Patients who met our N0 criteria had fewer pathologically invasive tumors and fewer recurrences compared with those who did not meet these criteria. These results were consistent with those of our previous report [11].

Recurrences developed in 2 patients in this study who met the N0 criteria. Mediastinal lymph node recurrence developed in 1 patient after standard lobectomy, whereas multiple lung metastases without lymph node involvement after wedge resection without lymph node dissection were found in the other patient. We assumed that these patients would have had recurrences even if they had undergone standard surgical procedures.

Patients who met our N0 criteria had significantly better prognoses compared with those who did not. Therefore, clinical stage IA lung adenocarcinoma could be divided into two groups with different malignant behaviors and prognoses using solid tumor size on HRCT and SUVmax on FDG-PET/CT. These findings support our previous results that solid tumor size on HRCT and SUVmax on FDG-PET/CT were predictors of pathologic tumor invasiveness, lymph node metastasis, and prognosis [11, 13].

Among the patients who met the N0 criteria, we compared 5-year RFS and OS rates between those who underwent lobectomy and those who underwent sublobar resection. Patients who underwent sublobar resection had excellent prognoses, without any significant differences in RFS and OS rates compared with those

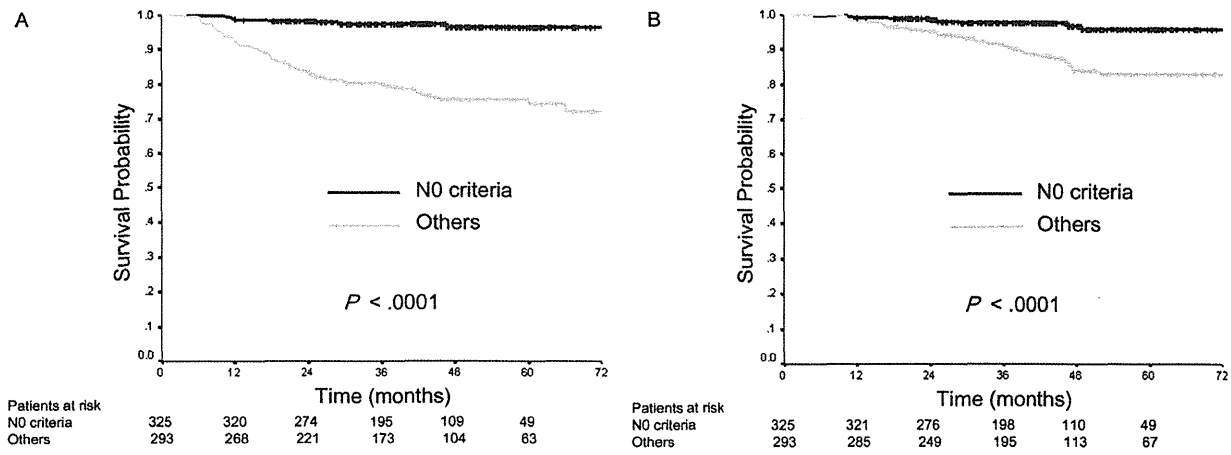

Fig 1. Recurrence-free survival (RFS) and overall survival (OS) curves are shown for patients who met the node-negative (N0) criteria (blue lines) and those who did not (yellow lines). (A) RFS at 5 years was significantly different between patients who met the N0 criteria (96.6%) and those who did not (75.5%, $p < 0.0001$). (B) OS at 5 years was significantly different between patients who met the N0 criteria (95.9%) and those who did not (83.1%, $p < 0.0001$).

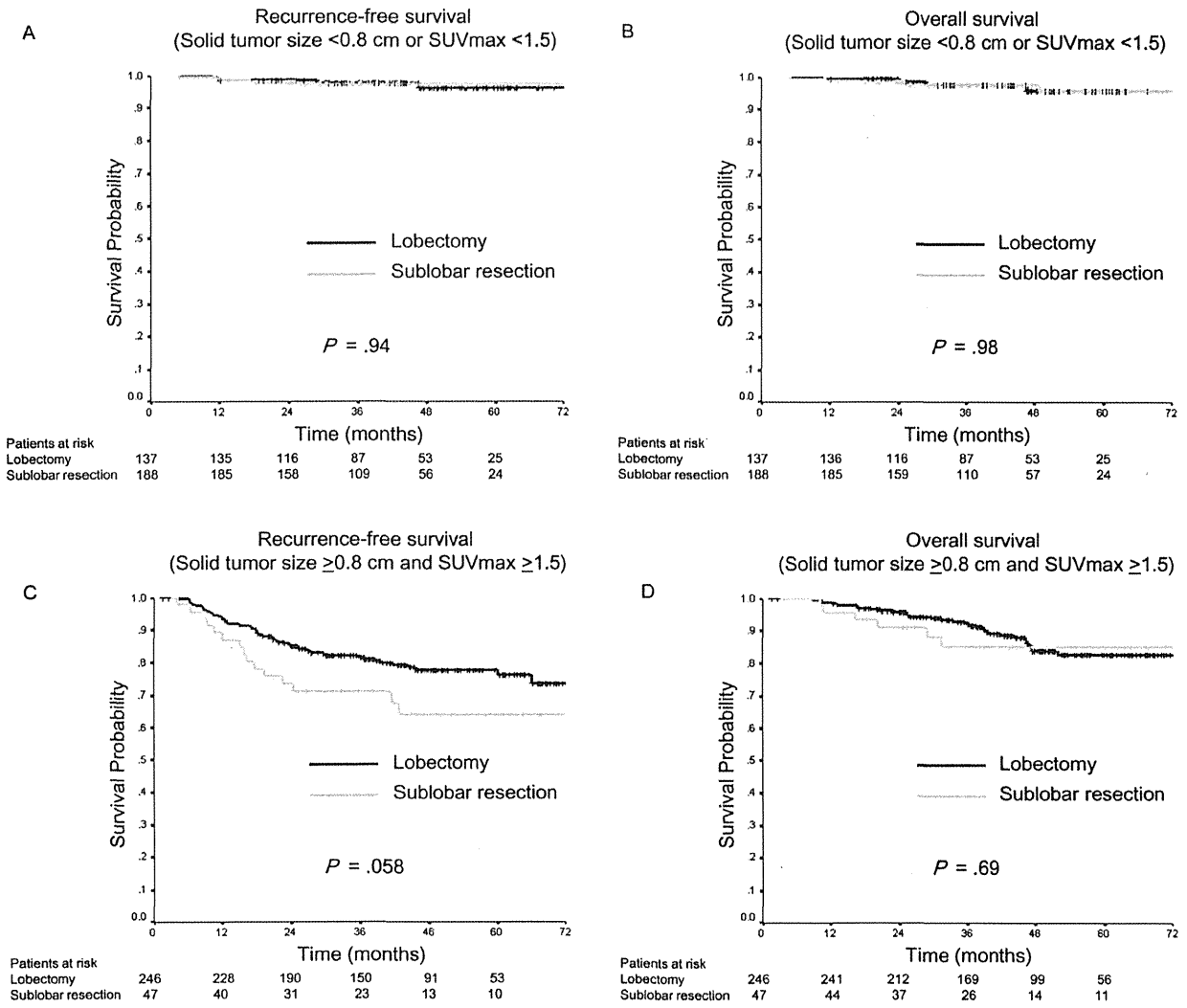

Fig 2. Recurrence-free survival (RFS) and overall survival (OS) curves are shown for patients who underwent lobectomy (blue line) or sublobar resection (yellow line) on the basis of the node-negative (N0) criteria. (A) For the group that met the N0 criteria, the RFS rate at 5 years was not significantly different between patients who underwent lobectomy (96.0%) and those who underwent sublobar resection (97.2%, p = 0.94). (B) For the group that met the N0 criteria, the OS rate at 5 years was not significantly different between patients who underwent lobectomy (95.9%) and those who underwent sublobar resection (95.9%, p = 0.98). (C) For the group that did not meet the N0 criteria, patients who underwent sublobar resection tended to have a worse RFS rate at 5 years (63.9%) than patients who underwent lobectomy (77.7%, p = 0.058). (D) For the group that did not meet the N0 criteria, there was no significant difference in the OS rate at 5 years between patients who underwent lobectomy (82.8%) and those who underwent sublobar resection (85.2%, p = 0.69). (SUVmax = maximum standard uptake value.)

who underwent lobectomy. For this study, we included segmentectomy and wedge resection as sublobar resections.

Actually, segmentectomy and wedge resection are considerably different procedures. The former can be used to approach hilar lymph nodes, whereas the latter cannot. However, patients who met our N0 criteria were considered not to have lymph node metastasis; therefore, systematic lymph node dissection did not appear to be necessary. Both procedures can be used for patients with solid tumor size of less than 0.8 cm on HRCT or a SUVmax of less than 1.5 on FDG-PET/CT. We should consider the surgical margin, and not lymph node dissection, when selecting the surgical procedure for patients with clinical stage IA lung adenocarcinomas that meet these N0 criteria.

Interestingly, approximately 40% of clinical T1b (2 to 3 cm) tumors in this study met the N0 criteria. Most research done in this area has generally not included patients with tumor sizes exceeding 2 cm for sublobar resection [3, 5–8]. However, these patients had T1b tumors with considerably low malignant potentials, and no recurrence developed. Therefore, even patients with T1b tumors that meet these N0 criteria can be candidates for

Table 3. Characteristics of Patients With Clinical T1b Tumors That Met the Node-Negative Criteria

Variables[a]	Solid Tumor Size <0.8 cm or SUVmax <1.5 (n = 106)
Age, y	67.5 (33–89)
Male sex	48 (45.3)
Whole tumor size, cm	2.4 (2.1–3.0)
Solid tumor size, cm	0.6 (0–2.5)
SUVmax	1.0 (0–4.1)
Adenocarcinoma in situ	19 (17.9)
Procedure	
Lobectomy	67 (63.2)
Sublobar resection	39 (36.8)
Segmentectomy	22 (20.8)
Wedge resection	17 (16.0)
Lymphatic invasion	2 (1.9)
Vascular invasion	2 (1.9)
Pleural invasion	2 (1.9)
Lymph node metastasis	0 (0)
Recurrence	0 (0)

[a] Categoric data are shown as number (%) and continuous data as median (range).

SUVmax = maximum standardized uptake value.

sublobar resection if there are sufficient surgical margins. Cox proportional hazards model in this subpopulation also supported the use of sublobar resection. To achieve complete resection with adequate margins, we recommend segmentectomy, but not wedge resection, for T1b tumors meeting these N0 criteria, because providing an adequate margin for T1b tumors by wedge resection is difficult. The extent of resection should be chosen according to tumor size and location, and procedures that can lead to local recurrence must be avoided.

A benefit of sublobar resection is preservation of lung function [3, 14, 15]. In addition, sublobar resection provides outcomes that are equivalent to those of lobectomy for patients selected on the basis of HRCT and FDG-PET/CT findings; therefore, this can be a suitable procedure for these patients. However, 47 of 293 patients who did not meet the N0 criteria and could have possibly had lymph node metastasis underwent sublobar resection. The RFS rate for patients who underwent sublobar resection appeared to be worse than that for patients who underwent lobectomy, although the results were not significantly different ($p = 0.058$). Among 47 patients in the sublobar resection group, 24 (51%) underwent wedge resection. Therefore, patients who do not meet the N0 criteria (solid tumor size >0.8 cm and SUVmax >1.5) should be treated with segmentectomy or lobectomy with systematic hilar and mediastinal lymph node dissection, not wedge resection, because they may have LN metastasis. If segmentectomy is applied to patients who do not meet the N0 criteria, intraoperative lymph node examinations using frozen sections are mandatory. When lymph node metastasis is detected intraoperatively, the procedure should be converted to a lobectomy.

Table 4. Multivariate Cox Analysis for Recurrence-Free Survival (All Patients)

Variables	HR (95% CI)	*p* Value
Age	1.02 (0.99–1.04)	0.24
Sex (male)	1.06 (0.67–1.68)	0.80
Solid tumor size (cm)	2.04 (1.47–2.81)	<0.001
SUVmax	1.15 (1.07–1.24)	<0.001
Procedure (lobectomy)	0.64 (0.35–1.18)	0.15

CI = confidence interval; HR = hazard ratio; SUVmax = maximum standardized uptake value.

Table 5. Multivariate Cox Analysis for Recurrence-Free Survival (Clinical T1b Patients)

Variables	HR (95% CI)	*p* Value
Age	1.02 (0.98–1.06)	0.40
Sex (male)	1.43 (0.75–2.73)	0.28
Solid tumor size (cm)	1.44 (0.88–2.36)	0.14
SUVmax	1.25 (1.12–1.39)	<0.001
Procedure (lobectomy)	0.83 (0.29–2.34)	0.72

CI = confidence interval; HR = hazard ratio; SUVmax = maximum standardized uptake value.

A strength of this study was that HRCT and FDG-PET/CT were performed for all patients and could be used to analyze the details of tumor morphology and glucose metabolism. In addition, SUVmax on FDG-PET/CT is a known prognostic factor for NSCLC, particularly adenocarcinoma [11, 13, 16–22]. Furthermore, we used an anthropomorphic body phantom to minimize interinstitutional SUV variability, which is a major limitation of multicenter PET studies.

Although this was a retrospective study, our updated database included a large number of patients with moderate follow-up periods. This allowed us to validate our N0 criteria and conclude that sublobar resection was useful for patients who met these criteria. Longer follow-up periods will be needed to ensure that these results are reliable.

This study had several limitations. Because this was a retrospective study, patients who underwent sublobar resection were possibly highly selected. In addition, preoperatively verifying the histologic origin of a tumor, particularly small tumors, is sometimes difficult. The lack of data on comorbid conditions and lung function also limited the definitive conclusion that sublobar resection is not less effective than lobectomy for clinical stage IA lung adenocarcinoma. A prospective study to assess the prognostic significance of sublobar resection for patients who meet our proposed N0 criteria is warranted.

In conclusion, we demonstrated that sublobar resection was feasible for patients with clinical stage IA lung adenocarcinomas that met our proposed N0 criteria of solid tumor size of less than 0.8 cm on HRCT or a SUVmax of less than 1.5 on FDG-PET/CT, with a survival rate equivalent to that associated with standard lobectomy. Even a T1b tumor, which is generally unsuitable for

intentional sublobar resection, can be a candidate for sublobar resection if it meets these N0 criteria and has adequate surgical margins.

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High-Speed 3-Dimensional Imaging in Robot-Assisted Thoracic Surgical Procedures

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We used a high-speed 3-dimensional (3D) image analysis system (SYNAPSE VINCENT, Fujifilm Corp, Tokyo, Japan) to determine the best positioning of robotic arms and instruments preoperatively. The da Vinci S (Intuitive Surgical Inc, Sunnyvale, CA) was easily set up accurately and rapidly for this operation. Preoperative simulation and intraoperative navigation using the SYNAPSE VINCENT for robot-assisted thoracic operations enabled efficient planning of the operation settings. The SYNAPSE VINCENT can detect the tumor location and depict surrounding tissues quickly, accurately, and safely. This system is also excellent for navigational and educational use.

(Ann Thorac Surg 2014;97:2182–4)

FEATURE ARTICLES

We previously reported on the importance of appropriate settings in robot-assisted thoracic surgical procedures, because no target is located in the same location within the thoracic cavity [1, 2]. Moreover, once all the da Vinci S (Intuitive Surgical, Inc, Sunnyvale, CA) devices and equipment are positioned, it is difficult to reset the da Vinci S after the operator starts manipulation through the operator console. In this case, a high-speed 3-dimensional (3D) image analysis system, the SYNAPSE VINCENT (Fujifilm Corp, Tokyo, Japan), was used to determine the best positioning of robot arms and instruments preoperatively based on experience with more than 100 video-assisted thoracic operations. Moreover, this system can detect the tumor location and depict surrounding tissues—even 1-mm vessels—quickly, accurately, and safely. An incision for the 3D camera and 2 other incisions are made at the appropriate points according to the SYNAPSE VINCENT analysis. The best angulation of the instrument arms of the da Vinci S are also determined by the same analysis. All computed tomography (CT) must satisfy several conditions necessary to analyze images by the SYNAPSE VINCENT. First, all images are to be taken by multislice CT at more than 64 lines; second, all images are taken at a slice interval thickness of 1.25 mm; third, all image data are saved as digital imaging and communication in medicine (DICOM) image files; and fourth, all images are to be taken using contrast media. The SYNAPSE VINCENT also provides more information concerning tumor size and shape and also whether the tumor invades surrounding tissue and the extent of airway and vessel involvement.

A 38-year-old woman had a posterior mediastinal tumor that appeared spindle-shaped at the upper level of the first to third thoracic vertebrae. The SYNAPSE VINCENT was used to define the tumor together with the surrounding anatomic information and determine the appropriate setting of the da Vinci S and the best positioning of the instrument ports. For the computed tomographic scan, the patient was placed in the same position as projected for the operation. The SYNAPSE VINCENT depicts the tumor and all other anatomic information quickly. Details of thorax, ribs, and virtual imaging of the robot arm directions and placement of the surgical ports are shown in Fig 1. Details of the tumor and surrounding vessels after removal of the image of the rib cage are shown in Fig 2. The direction of the da Vinci S, 3D camera setting, and positioning of arms No. 1 and No. 2 for the clinical operation were determined by

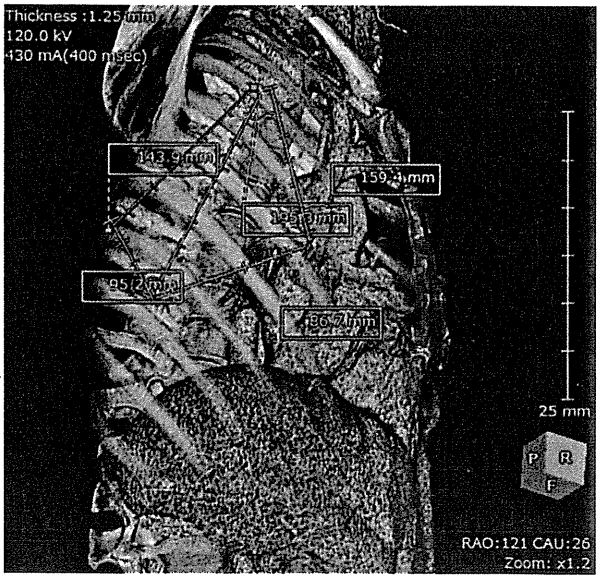

Fig 1. The figures were depicted by the SYNAPSE VINCENT, which showed the tumor (yellow) located in the upper area in the right side of the thorax. Green points on the surface of the patient and lines show the appropriate approaches for the instrument ports and angles of the arms of the da Vinci S and distance of each interval.

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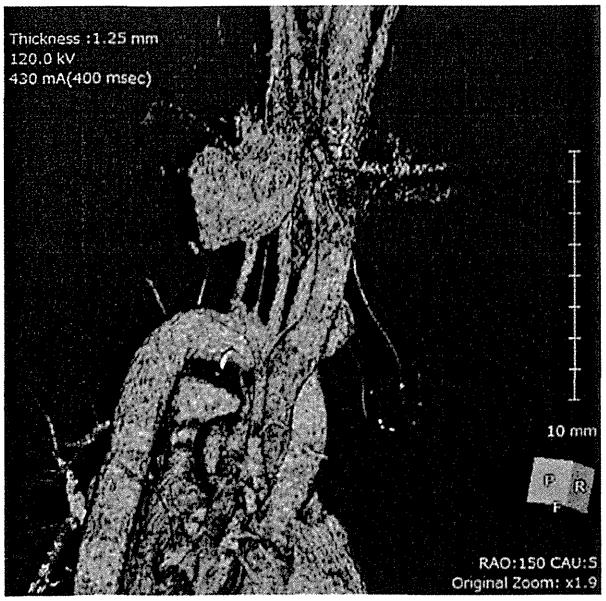

Fig 2. Details of the tumor and surrounding vessels after removal of the image of the rib cage.

preoperative simulation using the SYNAPSE VINCENT (Fig 3). The da Vinci S was rolled in from the 1 o'clock direction, as shown in Fig 3. The patient was placed in a semisupine position. The 3D camera port was placed in the area of the sixth intercostal space at the anterior axillary line. Arms No. 1 and No. 2 and the accessory port were placed in the area of the fifth intercostal space at the anterior axillary line, the sixth intercostal space at the posterior axillary line, and the seventh intercostal space at the anterior axillary line, respectively. Fig 1 shows the 3D anatomic structure of the patient, the suitable points for each instrument port, and the intervals between each point. The distances from the tumor to the point of the instrument port of arms No. 1 and No. 2 and the 3D camera were 143.9 mm, 159.4 mm, and 195.3 mm, respectively. The distances from the 3D camera to the points of the instrument port of arms No. 1 and No. 2 were 95.2 mm and 86.7 mm, respectively.

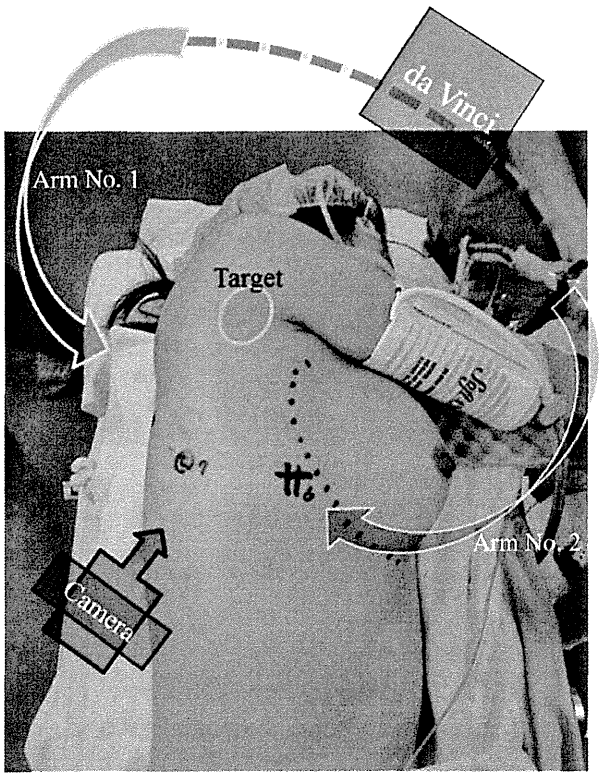

Fig 3. The da Vinci S was rolled in from the 1 o'clock direction, with the patient located between arms No. 1 and No. 2.

The da Vinci S was set up accurately and rapidly for this operation (about 10 minutes until the robot roll-in). The total operation time was 270 minutes, the robot set-up time was 21 minutes, and the console time (the robot working time) was 132 minutes. The amount of bleeding was 167 mL, and the drainage time was 2 days after the operation. The patient had no complications, and slight pain on the visual analogue scale (range 0–10) was a maximum of 1 at the time of discharge from the hospital. The pathologic report revealed a schwannoma (85 × 42 × 20 mm) with no malignancy.

Comment

Robotic operations using the da Vinci S has been approved in various specialties. However, thoracic tumors can be located at various sites in individual cases. In particular, the crucial factors for successful procedures in robot-assisted thoracic operations are the selection of the appropriate placement and the angle of instrument ports selected individually in relation to the target and patient position, which varies according to the tumor location [1, 2]. The distance separating each instrument port is at least 8 cm to prevent interference from other arms. Furthermore, the distance separating each instrument port from the target is at least 10 to 20 cm to secure a sufficient working space within the thoracic cavity.

The recent development of the SYNAPSE VINCENT raises the issue of whether it can yield comparable results in speed and precision. Mochizuki and colleagues [3] and Ikeda and associates [4] reported the feasibility and safety of the SYNAPSE VINCENT in performing useful preoperative simulation and navigation of surgical procedures [5]. It is safer, more precise, and less invasive for the patient, and it is easy to construct an image, depending on the purpose, in 5 to 10 minutes using the SYNAPSE VINCENT. Moreover, if the lesion is in the parenchyma, it helps to perform simulation with virtual skeletal subtraction to estimate potential lesion movement. It also helps to remember that even in such cases, most vascular structures will not move significantly. Because the angle of the 3D image made by the SYNAPSE VINCENT can be changed freely on a personal computer, an angle image similar to the

operation field in the surgical procedure could easily be obtained as a simulation image. Constructed images are displayed in the operating room on a monitor, which can be used for deciding surgical strategy and for navigation during intraoperative surgical manipulation.

Preoperative simulation using the SYNAPSE VINCENT also reduces the surgeon's stress levels, particularly when highly skilled techniques are needed to operate on lesions in difficult to reach and widely spaced areas of the thoracic cavity. This task, including both preoperative simulation and intraoperative navigation, could lead to greater safety and precision in operative settings and manipulation by creating the appropriate port positioning and direction of the instrument arms. These technologic instruments should be helpful for robot-assisted thoracic operations by thoracic surgeons and are also excellent devices for educational training.

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FEATURE ARTICLES

Treatment of Giant Pharyngoesophageal Diverticulum by Video-Assisted Thoracoscopy

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A 67-year-old woman presented with a giant pharyngoesophageal diverticulum (Zenker's diverticulum) that extended deep into the chest. Surgery, using either an open or endoscopic approach, was difficult. We stapled the common wall between the diverticulum and the esophagus using video-assisted thoracoscopic surgery. The patient exhibited good anatomic and functional results at 6 months' follow-up.

(Ann Thorac Surg 2014;97:2184–6)

Pharyngoesophageal diverticulum (Zenker's diverticulum) is a protrusion of pharyngeal mucosa between fibers of the lower pharyngeal constrictor and cricopharyngeal muscles. Treatment of massive Zenker's diverticulum is a challenge. Open surgical approaches require extensive dissection of the diverticulum, which greatly increases the morbidity and mortality rate. Endoscopic surgery, however, can leave an incomplete common wall transection, leading to persistent dysphagia and vomiting. We report a case of an elderly patient with a giant Zenker's diverticulum successfully treated with video-assisted thoracoscopic surgery.

A 67-year-old woman presented with a sore throat and vomiting for the previous 6 months. She also had progressive dysphagia (for both solid and liquid foods) with weight loss for the previous 6 years. The results of a routine physical examination were unremarkable. A barium swallow test showed significant retention of barium in a massive Zenker's diverticulum reaching the carina (10.0 × 6.0 cm), with minimal conduction of barium into the distal esophageal lumen (Fig 1A). A computed tomographic scan revealed a right-sided large pouch with an air-fluid level. The trachea was deviated anteriorly. Profound stenosis of the esophagus was also noted. An upper gastrointestinal endoscopy revealed a pharyngeal

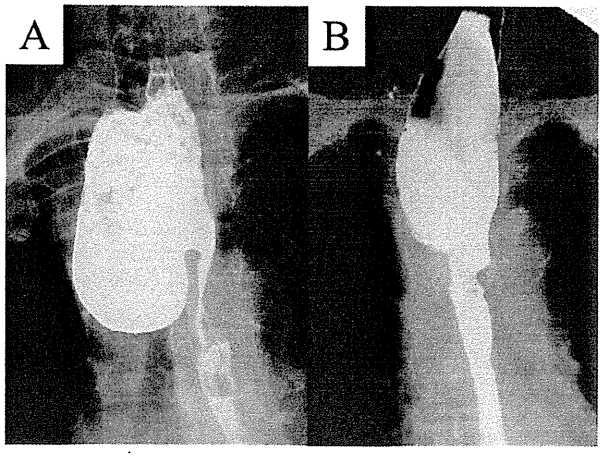

Fig 1. Preoperative and postoperative barium swallow radiographs. (A) Preoperative barium swallow radiograph shows significant retention of barium in a massive Zenker's diverticulum, reaching the carina (10.0 × 6.0 cm), with minimal conduction of barium into the distal esophageal lumen. (B) Postoperative barium swallow radiograph demonstrates free flow of barium into the esophagus and shrinkage of the hypopharyngeal dilatation.

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A single-arm confirmatory study of amrubicin therapy in patients with refractory small-cell lung cancer: Japan Clinical Oncology Group Study (JCOG0901)☆

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ABSTRACT

Objectives: We conducted an open-label, multicenter, single-arm study to confirm the efficacy and safety of amrubicin (AMR), a topoisomerase II inhibitor, for treating refractory small-cell lung cancer (SCLC).
Patients and methods: Patients with chemotherapy-refractory SCLC received 40 mg/m^2 AMR for 3 consecutive days, every 21 days. The primary endpoint was the overall response rate (ORR) and the secondary endpoints were progression-free survival (PFS), overall survival (OS), and safety.
Results: Between November 2009 and February 2011, 82 patients were enrolled. Each patient received a median of four treatment cycles (range, 1–22 cycles). ORR was 32.9% [$P < 0.0001$ by the exact binomial test for the null hypothesis that ORR $\leq$ 10%; 95% confidence interval (CI), 22.9–44.2%]. The median PFS and OS periods were 3.5 months (95% CI, 3.0–4.3 months) and 8.9 months (95% CI, 7.6–11.3 months), respectively. Significant differences in ORR (21.4% *v* 45.0%; $P = 0.034$), PFS (median, 2.9 *v* 5.1 months; $P = 0.0009$), and OS (median, 7.9 *v* 13.1 months; $P = 0.0128$) were observed between patients previously treated with etoposide and others. Neutropenia was the most common grade 3 or 4 adverse events (93.9%), and febrile neutropenia developed in 26.8% patients. No treatment-related death occurred.
Conclusions: AMR monotherapy can be considered an effective and safe treatment option for refractory SCLC. Previous chemotherapy with etoposide may influence AMR efficacy.

1. Introduction

Small-cell lung cancer (SCLC) is the most rapidly growing lung cancer subtype and patient prognosis is extremely poor [1]. Although most SCLC patients respond to initial treatment, long-term survival is low. Unfortunately, disease progression or relapse occurs in almost all advanced-stage SCLC patients and in the majority of early-stage SCLC patients [2–6]. Response to subsequent chemotherapy depends on responsiveness to previous induction

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chemotherapy and the interval between cessation of initial therapy and disease progression [7,8].

Overall response rates (ORRs) of 21–38% and median overall survival (OS) of 6.9–11.7 months were reported in chemotherapy-sensitive SCLC patients after treatment with topotecan, a topoisomerase I inhibitor [8,9]. A previous randomized study demonstrated similar efficacy and improved tolerability of topotecan compared with cyclophosphamide, doxorubicin, and vincristine [10]. Topotecan is also considered as a treatment option for chemotherapy-refractory SCLC; however, low ORRs (0–11%) and OS (median, 4.7–5.4 months) have been reported [8,9,11]. Thus, a standard chemotherapy for the treatment of refractory SCLC has not yet been established. However, effective treatment must be developed to improve prognosis for SCLC patients.

Amrubicin (AMR), a fully synthetic 9-aminoanthracycline, is metabolized in the body to the active metabolite amrubicinol, which has higher antitumor activity than AMR. Both AMR and amrubicinol, which are topoisomerase II inhibitors, exhibit antitumor activities against various human tumors in xenograft models and have shown no risk of typical anthracycline cardiotoxicity [12]. In subgroup analyses of small phase II studies, AMR showed promising activity in patients with refractory SCLC with ORR of 17–50% and median OS of 5.3–10.3 months [9,13].

Accordingly, the results of previous studies indicated that AMR may be useful for treating refractory SCLC. Therefore, we conducted this study to confirm the efficacy and safety of AMR, a topoisomerase II inhibitor, for treating refractory SCLC. A phase III trial was preferred to evaluate the effectiveness of AMR therapy; however, other than AMR therapy, there was no promising treatment under development for refractory SCLC at that time. As second-best evidence that was not from a randomized controlled trial, we designed a nonrandomized single-arm confirmatory study to evaluate whether AMR therapy can be considered as a standard treatment for refractory SCLC.

2. Patients and methods

2.1. Study design

This was an open-label, multicenter, single-arm confirmatory study involving 25 institutions in Japan. The study protocol was approved by the Japan Clinical Oncology Group (JCOG) Protocol Review Committee and the institutional review board of each participating institution.

2.2. Eligibility criteria

Patients were required to have histologically or cytologically documented SCLC, and were refractory to treatment with one or two previous chemotherapy regimens, at least one of which was platinum based. Refractory disease was defined as no response to previous chemotherapy, disease progression on chemotherapy, or disease progression <90 days of completing previous chemotherapy after confirming a complete response (CR) or partial response (PR). Other inclusion criteria included age of 20–74 years, Eastern Cooperative Oncology Group performance status of 0–1, measurable disease, no history of chemotherapy with AMR, no history of surgery for SCLC, no thoracic radiation therapy ≤4 weeks before registration, adequate baseline organ function [leukocyte count ≥ 3000/mm^3, absolute neutrophil count ≥ 1500/mm^3, hemoglobin ≥ 9.0 g/dL, platelet count ≥ 100,000/mm^3, total bilirubin ≤ 2.0 mg/dL, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels ≤ 100 IU/L, serum creatinine level ≤ 2.0 mg/dL, PaO_2 under room air ≥ 60 mmHg, and electrocardiographic findings within normal range]. Written informed consent was obtained from all patients. Patients were ineligible if they had active concomitant malignancy, massive pleural or pericardial effusion, symptomatic brain metastasis, or severe comorbidities such as active infections, uncontrolled hypertension, severe heart disease, uncontrolled diabetes mellitus, bowel obstruction, psychiatric disease, severe emphysema, interstitial pneumonia, or pulmonary fibrosis. Patients having systemic steroid medication and pregnant or breast feeding women were also excluded.

2.3. Treatment

Treatment was started within 1 week after enrollment in the study. Patients received AMR at 40 mg/m^2/day for 3 consecutive days, every 21 days. The treatment was repeated until disease progression, intolerable toxicity, or patient refusal. The dose of AMR was decreased to 35 mg/m^2/day if any of the following were observed during the previous course: leukocyte count <1000/mm^3, platelet count <20,000/mm^3, grade 3 febrile neutropenia, or grade 3 nonhematological toxicity (except nausea, anorexia, weight loss, creatinine, hyponatremia, hyperglycemia or alopecia). A second dose reduction to 30 mg/m^2/day was made in subsequent cycles on the basis of the same criteria. In cases of grade 4 nonhematological toxicity or continued toxicity that would have required a third dose reduction, the protocol treatment was terminated.

Patients received full supportive care as required, including transfusion of blood products. The protocol specified that granulocyte colony-stimulating factor (G-CSF) should be used in accordance with the national health insurance coverage of Japan, indications for G-CSF administration were as follows: (a) when fever (in principal over 38 °C) was observed with a neutrophil count of ≤1000/mm^3; (b) when a neutrophil count of 500/mm^3 was observed; (c) during the previous course, if fever (in principal over 38 C) with a neutrophil count of ≤1000/mm^3 was observed, or if a neutrophil count of 500/mm^3 was observed, then after completing the same chemotherapy, if a neutrophil count of ≤1000/mm^3 was observed. There was no restriction for subsequent chemotherapy after disease progression in this study.

2.4. Evaluation

The Response Evaluation Criteria in Solid Tumors guidelines (ver. 1.0) was used to evaluate tumor response [14]. Computed tomography was performed at baseline and at least every two cycles. Confirmation of a CR or PR was required at least 4 weeks after the first documentation of a response. Independent review of tumor response was performed for patients with any extent of tumor shrinkage. Three reviewers, including a diagnostic radiologist, were assigned as an independent review panel. Adverse events were recorded and graded using the Common Terminology Criteria for Adverse Events (ver. 3.0). Evaluation of cardiotoxicity was performed as needed, as judged by the physician.

2.5. Study endpoints and statistical analysis

The primary endpoint in this study was ORR, which was calculated as confirmed response (CR + PR) according to independent assessments. We believe that tumor shrinkage is essential to improve prognosis for refractory SCLC. Furthermore, previous studies for refractory SCLC showed large variations in survival times [8,9,11,13]. Because ORR with slight variation was considered a hard endpoint, we used ORR as the primary endpoint. As secondary endpoints, we evaluated progression-free survival (PFS) and OS as effectiveness endpoints and the incidence of an adverse event as a safety endpoint. We hypothesized that if the ORR of AMR therapy was high enough compared with that of topotecan therapy, AMR

could be considered as a standard treatment option. The sample size was set as $N = 80$ to achieve a power of at least 80% with a one-sided alpha of 0.05, and expected and threshold values for the primary endpoint of 20% and 10%, respectively. Survival was estimated using the Kaplan–Meier method and subgroups were compared using the log-rank test.

For AMR therapy to be considered as a standard option for patients with refractory SCLC, its safety and survival should also be equal or superior to those of topotecan therapy. According to the results of previous topotecan studies [8,9,11], anticipated values were 2.0–3.0 months for median PFS and 5.0–7.5 months for median OS, and a proportion of treatment-related deaths (≤5%) was also anticipated. The Fisher's exact test was used to compare categorical data. All analyses were performed using SAS release 9.1 statistical software (SAS Institute, Cary, NC, USA).

3. Results

3.1. Patient characteristics

From November 2009 to February 2011, a total of 82 patients (17 women and 65 men; median age, 66 years; age range, 44–74 years) from 25 Japanese institutions were enrolled in this study. All 82 patients were eligible for analysis of the efficacy and safety of AMR. Patient characteristics are listed in Table 1. All 82 patients received prior platinum-based chemotherapy, including pretreatment with irinotecan-containing chemotherapy regimens ($n = 47$, 57.3%) and etoposide-containing chemotherapy regimens ($n = 42$, 51.2%). Thirteen of these patients had received thoracic radiation therapy concurrently or sequentially with chemotherapy.

Each patient received a median of four AMR treatment cycles (range, 1–22 cycles), and 18 (22.0%) had a cumulative AMR doses exceeding 750 mg/m^2. Reasons for off-protocol included disease progression ($n = 67$), unacceptable toxicity ($n = 8$), and patient refusal possibly related to adverse events ($n = 7$). AMR dose reduction was required in 31 patients (37.8%), and the dose was decreased by two levels in seven patients (8.5%).

Table 1
Patient characteristics ($N = 82$).

Characteristics	Patients	
	n	%
Age (years)		
Median	66	
Range	44–74	
Gender		
Female	17	20.7
Male	65	79.3
ECOG performance status		
0	34	41.5
1	48	58.5
Disease extent at entry		
Limited disease	6	7.3
Extensive disease	76	92.7
No. of prior chemotherapy regimens		
1	72	87.8
2	10	12.2
Prior chemotherapy regimen (multiple choices)		
Cisplatin-containing	62	75.6
Carboplatin-containing	26	31.7
Cisplatin and carboplatin-containing	6	7.3
Irinotecan-containing	47	57.3
Etoposide-containing	42	51.2
Topotecan-containing	3	3.7
Response to prior chemotherapy		
Complete response	3	3.7
Partial response	58	70.7
Stable disease	4	4.9
Progressive disease	17	20.7
History of thoracic radiation therapy		
No	69	84.1
Yes	13	15.9

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

Table 2
Response to amrubicin in the intent-to-treat population.

Response	Number of patients	%
CR	2	2.4
PR	25	30.5
SD	37	45.1
PD	16	19.5
Not evaluable	2	2.4
Overall response rate (CR + PR)	27	32.9
95% CI[a]		22.9–44.2

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; CI, confidence interval.
[a] Calculated by the exact method.

3.2. Response

Independent reviews of tumor response were performed for 39 patients with any extent of tumor shrinkage. Among the total study population, CR was achieved in two patients (2.4%), PR in 25 (30.5%), stable disease (SD) in 37 (45.1%) after two courses, and progressive disease (PD) in 16 (19.5%). The response was not evaluable in two patients (2.4%) as a result of early termination of the treatment protocol. One patient refused further treatment after one cycle of AMR therapy, and the other terminated therapy because of poor performance status. Thus, for AMR therapy, an ORR of 32.9% was observed in our study population ($P < 0.0001$ by the exact binomial test for the null hypothesis that ORR ≤10%; 95% CI, 22.9–44.2%) (Table 2).

In a subset analysis of response to AMR, ORR was lower in patients treated with etoposide than in others (21.4% *v* 45.0%, respectively; $P = 0.034$) (Table 3). No remarkable difference in ORR was observed according to demographic characteristics [age,

Table 3
Subset analysis of response to amrubicin.

Characteristics	Number of patients	Response rate (%)	*P*
Age (years)			
44–70	61	32.8	1.00
≥71	21	33.3	
Gender			
Female	17	47.1	0.25
Male	65	29.2	
ECOG performance status			
0	34	35.3	0.81
1	48	31.3	
Disease extent at entry			
Limited disease	6	16.7	0.66
Extensive disease	76	34.2	
No. of prior chemotherapy regimens			
1	72	36.1	0.15
2	10	10.0	
Prior treatment with irinotecan			
No	35	25.7	0.25
Yes	47	38.3	
Prior treatment with etoposide			
No	40	45.0	0.034
Yes	42	21.4	
Response to prior chemotherapy			
CR/PR	61	36.1	0.42
SD/PD	21	23.8	
History of thoracic radiation therapy			
No	69	33.3	1.00
Yes	13	30.8	

Abbreviations: ECOG, Eastern Cooperative Oncology Group; CR, complete response; PR, partial response; SD, stable disease; PD progressive disease.

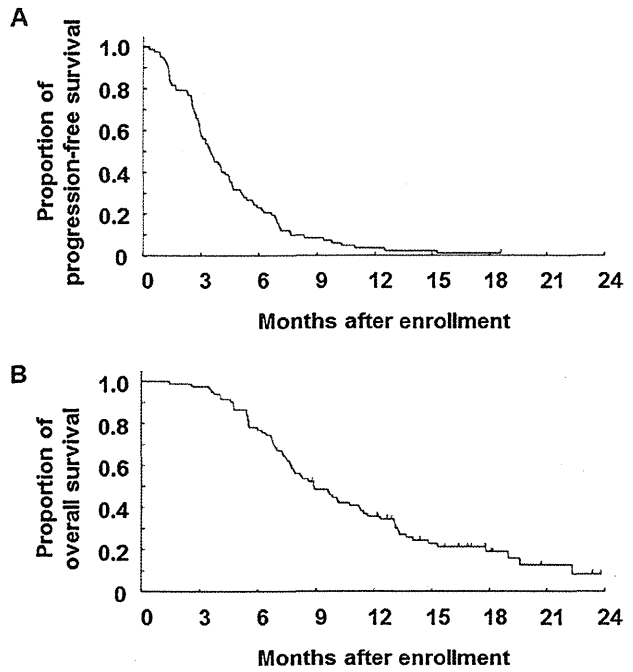

Fig. 1. (A) Progression-free survival and (B) overall survival of patients treated with amrubicin ($n=82$).

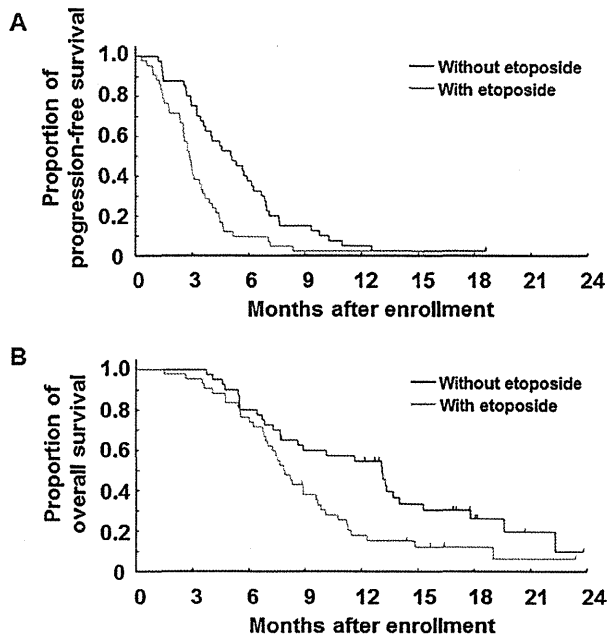

Fig. 2. (A) Progression-free survival and (B) overall survival in patients previously treated with etoposide ($n=42$) and those not treated with etoposide ($n=40$).

gender, performance status, disease extent at entry, number of prior chemotherapy regimens, prior treatment with irinotecan, response to prior chemotherapy (CR/PR *v* SD/PD), or history of thoracic radiation therapy].

3.3. Survival

At the cutoff date for data collection, the median follow-up time was 8.8 months in all registered patients (range, 1.5–23.8 months). Of the 82 patients, 81 (98.8%) were observed until disease progression and 66 (80.5%) until death. The median PFS for all 82 patients was 3.5 months (95% CI, 3.0–4.3 months) and the PFS at 6 months was 23.2% (95% CI, 14.7–32.7%; Fig. 1A). The median OS for all 82 patients was 8.9 months (95% CI, 7.6–11.3 months) and the 1-year survival was 35.7% (95% CI, 25.4–46.1%; Fig. 1B).

PFS was shorter in patients previously treated with etoposide than in others (median, 2.9 *v* 5.1 months; hazard ratio, 2.11; 95% CI, 1.35–3.30; $P=0.0009$; Fig. 2A), as was OS (median, 7.9 *v* 13.1 months; hazard ratio, 1.86; 95% CI, 1.13–3.06; $P=0.0128$; Fig. 2B).

3.4. Safety

The most common adverse events were hematological toxicities, including grade-3 or -4 neutropenia (93.9%), leukopenia (85.4%), anemia (25.6%), and thrombocytopenia (20.7%; Table 4). Grade-3 febrile neutropenia developed in 22 patients (26.8%). Nonhematological toxicities were generally mild and no evidence of cardiotoxicity of AMR was found in this study (Table 4). Pneumonitis was observed in nine patients (grade 4, $n=1$; grade 3, $n=2$; grade 2, $n=3$; and grade 1, $n=3$), and seven (grade 4, $n=1$; grade 3, $n=2$; grade 2, $n=2$; and grade 1, $n=2$) discontinued treatment because of unacceptable toxicity levels. The incidence rate of pneumonitis was higher in patients with history of thoracic radiation therapy than in others (38.5% *v* 5.8%, respectively), but one grade 4 pneumonitis case was observed in a patient without a history of thoracic radiation therapy.

Table 4
Grade 3 or 4 adverse events in patients treated with amrubicin ($N=82$) (CTCAE v3.0).

Adverse event	Grade 3		Grade 4		≥Grade 3	
	n	%	*n*	%	*n*	%
Leukopenia	48	58.5	22	26.8	70	85.4
Anemia	19	23.2	2	2.4	21	25.6
Thrombocytopenia	12	14.6	5	6.1	17	20.7
Neutropenia	18	22.0	59	72.0	77	93.9
Febrile neutropenia	22	26.8	0	0.0	22	26.8
Hyperglycemia	11	16.4	0	0.0	11	16.4
Hyponatremia	9	11.0	4	4.9	13	15.9
Infection	5	6.1	1	1.2	6	7.3
Dyspnea	3	3.7	1	1.2	4	4.9
Elevated ALT level	4	4.9	0	0.0	4	4.9
Elevated AST level	3	3.7	0	0.0	3	3.7
Anorexia	3	3.7	0	0.0	3	3.7
Pneumonitis	2	2.4	1	1.2	3	3.7
Fatigue	1	1.2	0	0.0	1	1.2
Weight loss	1	1.2	0	0.0	1	1.2
Nausea	1	1.2	0	0.0	1	1.2
Sensory neuropathy	1	1.2	0	0.0	1	1.2

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events.

G-CSF was administered to 51 (62.2%) patients and blood transfusions were necessary in 9 (11.0%). No treatment-related death was observed in this study.

4. Discussion

This single-arm confirmatory study was conducted to confirm the efficacy and safety of AMR in patients with refractory SCLC. In the present study, the primary endpoint was the ORR, which was 32.9%. This data supported the result that the ORR of AMR therapy was significantly better than that of topotecan therapy, in accordance with that previously reported in a randomized phase II study by Inoue et al. [9]. A possible limitation of this study is related to its design, which was not a randomized phase III study, but rather a nonrandomized single-arm confirmatory study. Although there was potential for selection bias as a result of this study design, ORR

was sufficiently higher than that for topotecan therapy in previous studies [8,11]. The secondary endpoints, PFS and OS, were also favorable, and no treatment-related deaths occurred in this study. On the basis of these results, we conclude that AMR monotherapy is suitable as an effective and safe treatment option for refractory SCLC.

Jotte et al. [15] reported the results of a randomized phase III trial of AMR versus topotecan as second-line treatment for SCLC. The study randomized 637 patients in a 2:1 ratio for treatment with AMR ($n = 424$) or topotecan ($n = 213$). Treatment with AMR and topotecan showed similar OS periods (median, 7.5 *v* 7.8 months; hazard ratio for death, 0.880; 95% CI, 0.733–1.057; $P = 0.17$); however, higher ORRs (31.1% *v* 16.9%; $P = 0.0001$) and PFS periods (median, 4.1 *v* 3.5 months; hazard ratio for death or disease progression, 0.802; 95% CI, 0.667–0.965; $P = 0.0182$) were found with AMR therapy, and toxicity levels were more acceptable than those with topotecan therapy. Furthermore, in a subset analysis of 295 patients with refractory SCLC, AMR therapy demonstrated a modest improvement in OS (median, 6.2 *v* 5.7 months; hazard ratio for death, 0.766; 95% CI, 0.589–0.997; $P = 0.0469$). These results support our assertion that AMR monotherapy is a reasonable treatment option for patients with refractory SCLC.

In this study, a subgroup analysis revealed that prior treatment with etoposide, a topoisomerase II inhibitor, was associated with a poorer response to AMR and poor survival. Ettinger et al. [16] reported the results of a phase II study of AMR as a second-line therapy for patients with platinum-refractory SCLC. In total, 75 American and European patients were enrolled, of whom, 67 (89.3%) were pretreated with a chemotherapy regimen including etoposide. The confirmed ORR of AMR therapy was 21.3% (95% CI, 12.7–32.3%) and the median PFS was 3.2 months (95% CI, 2.4–4.0 months). These efficacy data are similar to those of the patients previously treated with etoposide in the present Japanese study. Therefore, previous chemotherapy with etoposide, but not ethnic differences, may have influenced the efficacy of AMR therapy. Preclinical studies [17–20] have suggested that treatment with topoisomerase I inhibitors results in downregulation of the topoisomerase I target and reciprocal upregulation of topoisomerase II, thereby causing hypersensitivity to topoisomerase II inhibitors. Conversely, treatment with topoisomerase II inhibitors results in downregulation of topoisomerase II and upregulation of topoisomerase I. These results may explain why prior treatment with etoposide was associated with a lower response to AMR therapy in the present study.

Although etoposide plus cisplatin (EP) is considered the standard first-line chemotherapy for patients with extensive-stage SCLC in Western countries, irinotecan, a topoisomerase I inhibitor, plus cisplatin (IP) is generally used for Japanese patients, which is based on the results of a previous phase III study comparing IP with EP for extensive-stage SCLC (JCOG9511) [2]. AMR may also play an important role in the treatment of refractory SCLC, especially for patients previously treated with IP. In a recent Japanese phase III study comparing AMR plus cisplatin (AP) with IP for the treatment of extensive-stage SCLC (JCOG0509) [21], similar PFS periods were found for AP and IP (median, 5.1 *v* 5.7 months), but AP was inferior to IP in terms of OS (median, 15.3 *v* 18.0 months). Over 90% patients in both groups received subsequent chemotherapy. The most commonly administered drugs after the termination of treatment were topotecan in the AP group and AMR in the IP group. Subsequent chemotherapy with AMR may have contributed to the longer OS period in the IP group.

The most common severe toxicity associated with AMR therapy in the present study was myelosuppression in the form of neutropenia. No treatment-related death was observed, which was probably because of the reasonable protocol-specified dose reductions and/or treatment delays. However, patients experienced febrile neutropenia more frequently in the present study (26.8%) than in previous studies (5.0–13.8%) [9,13,16]. According to the guidelines of the American Society of Clinical Oncology, prophylactic G-CSF use is clinically effective when the risk of febrile neutropenia is 20% [22]. To decrease the incidence of febrile neutropenia in patients treated with AMR for refractory SCLC, aggressive treatment of myelosuppression, including prophylactic G-CSF use, should be considered. Nonhematological toxicity was generally mild, but the treatment was terminated in eight patients (9.8%) because of unacceptable toxicity levels, including pneumonitis in seven. Although no death was associated with pneumonitis in the present study, careful monitoring for the development of pneumonitis is necessary. Similar to previous studies [9,13,16], no evidence of anthracycline-induced cardiotoxicity was found.

In conclusion, AMR monotherapy for refractory SCLC showed a favorable tumor response, prolonged survival, and acceptable toxicity, especially in patients not previously treated with etoposide. Therefore, AMR monotherapy presents a standard treatment option for refractory SCLC.

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Clinical trial registration: UMIN000002763 (http://www.umin.ac.jp/ctr/).

Conflict of interest statement

The authors report no conflicts of interest that could inappropriately influence this work.

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