(ii) segmentectomy or lobectomy, (iii) mediastinal/hilar nodal sampling or dissection, (iv) clinical stage IA and (v) maximal tumour dimension of <30 mm. The exclusion criteria included: (i) synchronous or metachronous (within 5 years) malignancy other than carcinoma *in situ* and (2) patients with preoperative treatment such as radiotherapy or chemotherapy. Mediastinal lymph node dissection was performed according to the methods described by Naruke *et al.* [7]. Segmentectomy was performed for patients with tumours that showed pure GGO on thin-section CT or for patients with high risk, such as poor performance in a lung function test.

All patients underwent thin-section thoracic CT scanning before the operation on an X-vision/SP (Toshiba, Tokyo, Japan). A conventional contrast-enhanced CT scan was performed to evaluate the entire lung for preoperative staging. In addition, the main tumour was evaluated preoperatively to estimate the extent of GGO with a thin-section helical CT scan with 2 mm collimation. Images were reconstructed with a field of view of 15–20 cm. The lung was photographed with a window level of −500 to −700 H and a window width of 1000–2000 H as a lung window setting, and with a window level of 30–60 H and a window width of 350–600 H as a mediastinal window setting. The size of primary nodules was determined digitally based on the findings of thin-section CT (2-mm thick). The consolidation component was defined as the area of increased opacification that completely obscured the underlying vascular markings. GGO was defined as the area of a slight, homogeneous increase in density that did not obscure the underlying vascular markings (Fig. 1). In all patients, the time interval between CT scan and surgical intervention was <1 month. The medical record of each patient was examined to determine age, gender, pack-year smoking, preoperative serum carcinoembryonic antigen (CEA) level and histological tumour type. All preoperative radiological findings were reviewed on the lung window on thin-section CT scan by several of the authors (T. M., T.M., A.H., K.S.) and the following factors were evaluated: maximum dimensions of consolidation and the tumour, air bronchogram, pleural indentation and preoperative serum CEA level (Fig. 2). Univariate and multivariate analyses were performed by the logistic regression procedure with Stat Flex ver. 6.0 (Artech Co., Ltd) to determine the relationship between pathological nodal involvement and the above-mentioned clinical and radiological findings. In the multivariate analysis, stepwise procedures were used to determine the predictors for pathological nodal disease. A statistical analysis was considered to be significant when the $P < 0.05$.

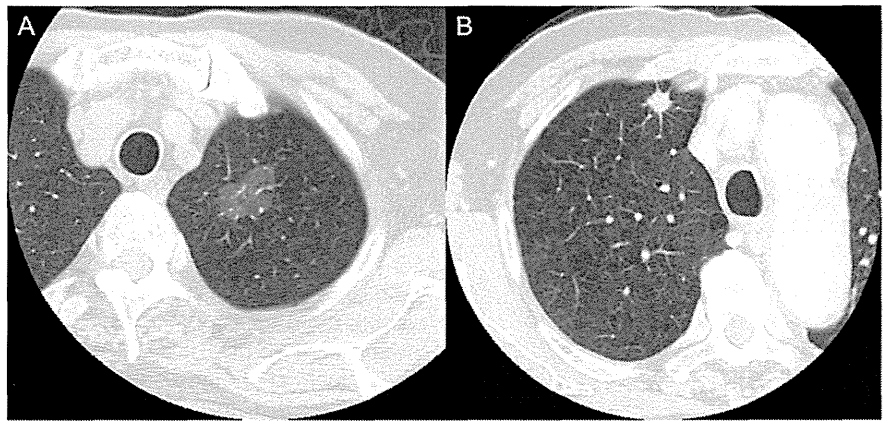

Figure 1: 'GGO' was defined as increasing density in lung attenuation that did not obscure the underlying vascular markings (**A**). 'Consolidation' was defined as increased opacification that completely obscured vascular structures (**B**).

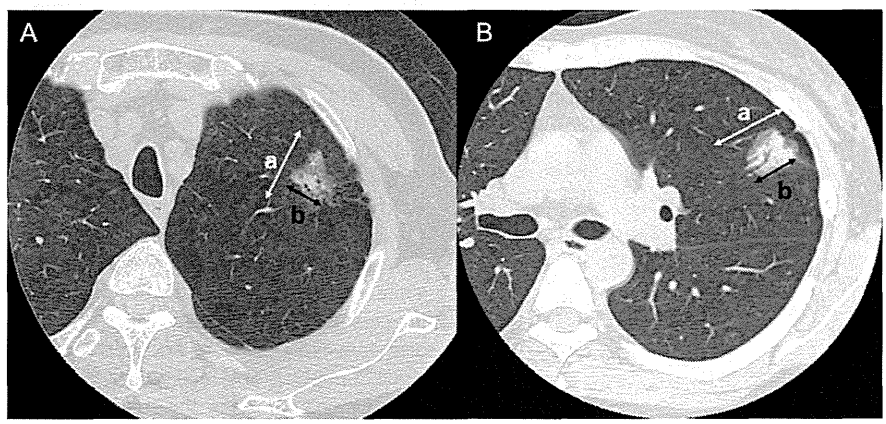

Figure 2: Findings of peripheral lung cancer on thin-section CT (A), (B); a: maximum tumour dimension, b: maximum dimension of consolidation defined as the size of area with increasing density without identifying its structure.

RESULTS

Between January 2004 and January 2011, 749 patients underwent surgery and 398 were found to be eligible. The 200 men and 198 women ranged in age from 30 to 89 years, with a median of 66 years. Pathological nodal involvement was found in 59 (14.8%) patients. Based on a univariate analysis, the maximum dimensions of consolidation and the tumour on thin-section CT, the presence of air bronchogram and the preoperative serum CEA level were significant predictors for nodal involvement ($P < 0.01$, respectively) (Table 1). Among 202 patients with lung cancer showing an air bronchogram on thin-section CT, 13 (6.4%) showed pathological nodal involvement. Among the 30 patients who did not show consolidation on thin-section CT scan, none had lymph node metastasis. If the size of consolidation was 10 mm or less regardless of the presence of air bronchogram, none of the patients had lymph node metastasis. On the other hand, among the patients with pure solid lung cancers, 59 (16.0%) had lymph node metastasis.

The multivariate analysis revealed that the maximum dimension of consolidation and the presence of air bronchogram on thin-section CT scan were significant factors for predicting nodal metastasis (Table 2). Among the patients with pure consolidation lung cancers, i.e. no GGO, and no air bronchogram, 44 (32.6%) showed nodal involvement. In contrast, none of the patients with of 10 mm or less and air bronchogram showed nodal involvement.

We investigated the relationship between nodal involvement and tumour size: the incidence of nodal involvement was 23/235 (9.8%) for tumours <20 mm in size, and 36/163 (22.1%) for tumours 20 mm or more in size. This difference was not statistically significant in a multivariate analysis. Neither was the preoperative serum CEA level significant in the multivariate model.

Table 1: Relationship between clinical features and the presence of pathological N-positive status among all patients with surgically resected lung cancer

Factors	No. of patients	Pathological N-positive (%)	Probability
Total	398	59 (14.8)	
Gender			0.50
Male	200	32 (16.0)	
Female	198	27 (13.6)	
Age			0.121
Range, median	30–89, 66		
Pack-year smoking			0.671
Range, median	0–180, 8.5		
Maximum tumour dimension			0.001*
Range, median	5–30, 20		
≤20 mm	235	23 (9.8)	
>20, ≤30 mm	163	36 (22.1)	
Maximum consolidation dimension			<0.001*
Range, median	0–30, 16		
≤20 mm	299	25 (10.9)	
>20, ≤30 mm	99	34 (34.3)	
Air bronchogram			<0.001*
Positive	202	13 (6.4)	
Negative	196	46 (23.5)	
Pleural indentation			0.329
Positive	201	33 (16.4)	
Negative	197	26 (13.2)	
CEA			0.013*
<3.0	241	27 (11.2)	
≥3.0	157	32 (20.4)	
Histology			0.366
Adenocarcinoma	343	48 (14.0)	
Squamous	38	8 (21.1)	
Other	17	4 (23.5)	

*p value in logistic regression analysis.

Table 2: Multivariate analysis of factors associated with pathological N-positive status among all patients with surgically resected lung cancer

Factors	Odds ratio	95% CI	Probability
Maximum consolidation			
Dimension ≤20 mm or not	8.24	1.81–37.49	0.006*
Air bronchogram			
Presence vs absence	4.69	2.21–9.97	0.007
Maximum tumour			
Dimension ≤20 mm or not	1.49	1.41–5.45	0.402
Preoperative CEA			
<3.0 or not	1.63	0.87–3.06	0.124

DISCUSSION

This is the first retrospective study to demonstrate that the maximum dimension of consolidation is a more suitable prognostic factor than the maximum tumour dimension as a measure of the T factor. Several studies have proved that radiological and pathological prognostic factors, such as GGO and a consolidation, are associated with lymph node metastasis. These investigations claimed that the prognosis of lung adenocarcinoma with a large area of GGO on thin-section CT scan was much better than that of conventional adenocarcinoma of the lung regardless of the maximum tumour dimension [8, 9]. On the other hand, a tumour with more than 50% consolidation component is considered to be 'invasive' carcinoma and could be more likely to show lymph node metastasis [10]. Only a few investigators have attempted to evaluate the extent of consolidation according to its proportion, rather than its maximum dimension [11, 12].

In this study, the maximum dimension of consolidation was a significant predictor of pathological lymph node-positive status in both univariate and multivariate analyses, while the maximum tumour dimension was not significant in a multivariate model. This suggests that the maximum dimension of consolidation may be the most reliable measurement of the T factor for assessing a mixture of consolidation and GGO. Even for small lung cancers, lobectomy has been recommended as a standard procedure, since lymph node metastasis can be found in ~15% of lung cancers <20 mm in size. Recent studies have shown that GGO and consolidation were well correlated with pathological lymph node metastasis and lead to limited surgical resection instead of lobectomy only when the maximum tumour dimension is <20 mm [13, 14]. However, our radiological findings could be used to predict pathological lymph node metastasis, and patients with

tumours of pure GGO, with no solid component and larger than 20 mm in size, would be candidates for limited surgical resection such as segmentectomy with nodal dissection. This information may also be useful for treating early lung cancers, with the advantages of maintained lung function and a reasonable prognosis.

The other significant predictor of pN0 disease was the presence of air bronchogram in the primary nodules. Air bronchogram is a radiographical finding, an air-filled bronchus surrounded by fluid-filled airspaces, and is mostly identified in areas with a slight, homogeneous increase in density on thin-section CT, such as GGO. However, with an increase in density and the solid component of primary nodules, it can be difficult to detect the underlying bronchovascular structure [15]. Disappearance of air bronchogram in the primary nodules shows that consolidation replaced GGO as a main component and its structure collapsed from a lepidic growth pattern [16–18].

One of the major limitations of this study is that few patients with resectable early lung cancer developed recurrence or other medical conditions in this short follow-up period, and we could not evaluate the correlation between the long-term prognosis and radiological findings, such as the maximum dimension of consolidation and the presence of air bronchogram.

In conclusion, this study showed that clinical stage IA lung cancer patients with consolidation had worse outcomes than those without consolidation. The maximum dimension of consolidation was an independent unfavourable prognostic factor, regardless of the maximum tumour dimension. The maximum dimension of consolidation was an upstaging factor for the T classification.

Conflict of interest: none declared.

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ORIGINAL ARTICLE

THORACIC

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.

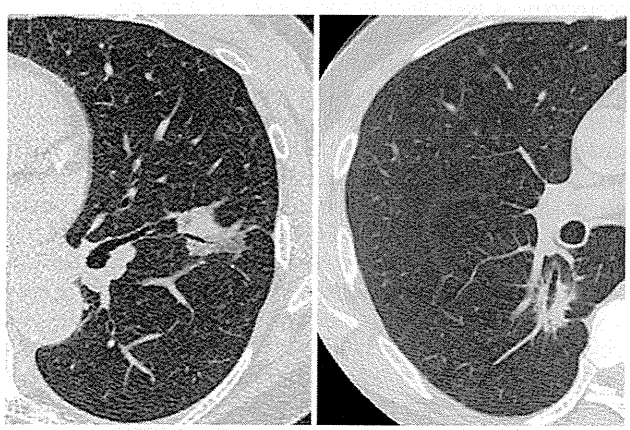

Figure 1: Typical images of pure-solid lung cancer with air bronchogram. An air-filled bronchus is surrounded by a lung tumour that only shows consolidation without ground-grass opacity on thin-section CT scan.

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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ORIGINAL ARTICLE

THORACIC

Time to refine N2 staging? cN2α and cN2β based on local regional involvement provide a more accurate prognosis in surgically treated IIIA non-small-cell lung cancer than N2 alone or the number of node stations involved†

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Abstract

OBJECTIVES: The number of stations of N2 nodes involved has been considered to be one of the most important prognostic factors for lung cancer. However, most reports have dealt with the pathological nodal status rather than with the clinical nodal status. We investigated the relationship between the prognosis and the location of the primary tumour and nodes involved.

METHODS: A retrospective study was conducted in 1257 patients with primary lung cancer, which were resected between 1996 and 2009. Among them, 78 patients (6.2%) had cN2, c-stage IIIA, pN2 and non-small-cell lung cancer. We defined cN2α as only involvement of an upper mediastinal lymph node (UMLN) for a main tumour located in the upper lobe or as that of a lower mediastinal lymph node (LMLN) for a main tumour located in the lower lobe. cN2β was defined as involvement of an LMLN for a main tumour located in the upper lobe with or without metastatic UMLN or as that of a UMLN for a main tumour located in the lower lobe with or without metastatic LMLN. We analysed preoperative clinical factors, as well as overall and disease-free survival.

RESULTS: The overall 5-year survival rate was 30.6%, and the disease-free 5-year survival rate was 22.6%. The disease-free 5-year survival rate for a tumour located in an upper lobe was significantly better than that for a tumour located in a lower lobe (27.9 vs 11.1%, $P = 0.007$). A significant difference in survival was seen between cN2α and cN2β (29.6 vs 0%, $P < 0.001$), but not between cN2 single and multiple (23.4 vs 19.5%, $P = 0.123$). A multivariate analysis with Cox's proportional hazards model revealed that cN2α independently predicted good disease-free survival. The sensitivity, specificity and positive predictive value for pN2 single based on clinical CT findings were 72.7, 48.2 and 35.6%, respectively.

CONCLUSIONS: Clinical mediastinal lymph node status based on the location of the primary tumour and the node involved was an important preoperative prognostic factor. Thus, this factor should be considered when planning and evaluating clinical trials. Another important finding was that clinical single-station N2 is not always pathological single-station N2 disease.

Keywords: Lung cancer • Mediastinal lymph node • Stage IIIA • N2

INTRODUCTION

Generally, chemoradiotherapy is recommended for patients with cN2 stage IIIA non-small-cell lung cancer (NSCLC), because their prognosis is very poor and the presence of mediastinal lymph node metastasis is equivalent to systemic disease. On the other hand, many surgical oncologists have experienced stage IIIA patients who were cured with only surgical resection [1, 2]. Thus, many institutions have reported clinical trials to identify the appropriate treatment and the role of surgery for cN2 stage IIIA NSCLC, but the appropriate treatment strategy is still controversial [3–8]. Of these clinical trials, the large-scale North American Intergroup Trial 0139 noted that surgery after induction chemo-radiotherapy can be beneficial if lobectomy is adequate for complete resection, although overall survival in the tri-modality therapy group was not significantly different from that in the chemo-radiotherapy group [3]. Based on these results, in the American Association of Chest Physicians (ACCP) evidence-based clinical guidelines, chemo-radiotherapy is recommended for patients with cN2 stage IIIA NSCLC and induction therapy followed by surgery is one of the options in a clinical trial [9].

The treatment of stage IIIA NSCLC is still very difficult and controversial because of the large heterogeneity in the pathological

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status and the wide range of overall 5-year survival rate in these patients (from 0 to 36%) despite a prospective multi-institutional trial for patients with the same stage [3–6, 8]. Therefore, stage IIIA NSCLC should be classified into subgroups and some reports have stated that the involvement of multiple mediastinal lymph nodal stations significantly predicts a poor prognosis [10–12]. However, these conclusions about multiple-station N2 were based on the results regarding postoperative pathological lymph node status, and the clinical factors that influence the prognosis in patients with cN2 stage IIIA are unknown. Furthermore, although the ACCP and ESMO guidelines do not address the relation between the location of the primary tumour and the mediastinal nodes involved, we expect that this relation may be closely related to the extent of metastasis, since we identified N2 and N3 in mediastinal lymph nodes [9, 13]. For example N3 disease may be more likely to involve a mediastinal lymph node in station 2R station for primary tumour located at right S10 in terms of the distance between primary tumour and the lymph node involved. Thus, in this study, we examined the number of clinically involved mediastinal lymph node stations and the relationship between the primary tumour and the mediastinal nodes involved to help identify stratification factors regarding the pre-treatment strategy for use in future clinical trials.

MATERIALS AND METHODS

Study population

A retrospective study was conducted in 1257 patients with primary lung cancer, which was resected between January 1996 and December 2009 at our institute. Among these patients, 79 (6.3%) had cN2, c-stage IIIA, pN2 and NSCLC. However, since 1 patient had no information about preoperative radiological findings, 78 (6.2%) were selected. These patients underwent more than lobectomy and radical resection of a mediastinal lymph node. The clinical and pathological stages were determined according to the 7th edition of the Union International Contre le Cancer TNM staging system supported by the International Association for the Study of Lung Cancer (IASLC) [14]. Preoperative staging included computed tomography (CT) of the chest, CT or ultrasonography of the upper abdomen, CT or magnetic resonance imaging (MRI) of the brain, bone scintigraphy in all cases and positron emission tomography (PET)/PET-CT in recent cases. Actually, only 10 patients underwent PET or PET/CT. In this study, a mediastinal lymph node with a short-axis diameter of 10 mm or more was diagnosed as metastasis; we did not refer to PET-CT findings regarding the mediastinal lymph node because the definition of metastasis was unclear and may have been different among institutions or radiologists. In addition, we recommended that patients undergo adjuvant chemotherapy based on platinum doublets, based on consideration of the performance status of patients after the operation.

Classification and definition of N2 status

According to IASLC map [15], we classified metastatic lymph nodes for each station and defined single N2 as only one station with a metastatic mediastinal lymph node and multiple N2 as two or more stations with a metastatic mediastinal lymph node. Furthermore, in this study, N2 lymph nodes were divided into upper and lower mediastinal lymph nodes. The upper mediastinal lymph nodes (UMLN) were #2R and #4R for lung cancer on the right side and #2L, #4L, #5 and #6 for that on the left side and lower mediastinal lymph nodes (LMLN) were #7, #8 and #9 for both sides. We defined cN2α as involvement of a UMLN for a main tumour located in an upper lobe or involvement of an LMLN for a main tumour located in a lower lobe, regardless of whether it was single or multiple N2 disease (Fig. 1A). We defined cN2β as involvement of an LMLN for a main tumour located in an upper lobe with or without metastatic UMLN or involvement of a UMLN for a main tumour located in a lower lobe with or without

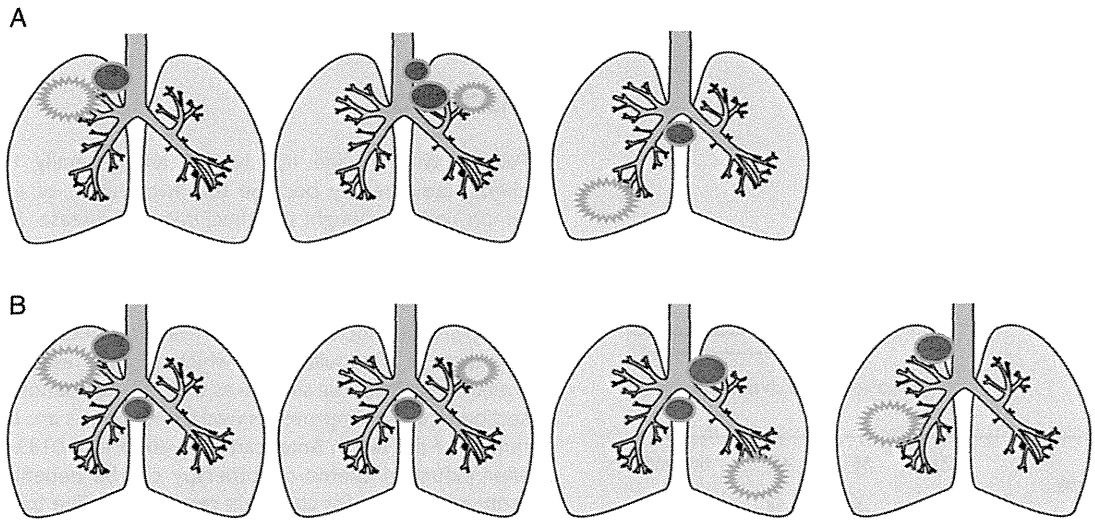

Figure 1: (**A**) We defined cN2α as only involvement of UMLN in NSCLC located in an upper lobe or as that of LMLN in NSCLC located in a lower lobe. (**B**) We defined cN2β as involvement of LMLN in NSCLC located in an upper lobe with or without metastatic UMLN or as that of UMLN in NSCLC located in a lower lobe with or without metastatic LMLN. NSCLC: non-small-cell lung cancer; UMLN: upper mediastinal lymph node; LMLN: lower mediastinal lymph node.

metastatic LMLN regardless of whether it was single or multiple N2 disease (Fig. 1B).

Study design and statistical analysis

We analysed preoperative clinical factors, including gender, age, smoking status, tumour marker (carcinoembryonic antigen), clinical T factor, tumour location (upper or lower lobe and right or left side) and clinical lymph node status (cN2 single or multiple and cN2α or cN2β), and investigated not only overall survival but also disease-free interval, because we considered that the regimens used and the effects of chemotherapy after recurrence could differ over time. The patients were followed up every 3 months after the operation for at least 5 years and underwent CT of the chest and upper abdomen every 6 months and CT or MRI of the brain, bone scintigraphy or PET-CT every year for the first 2 years. Thereafter, they received these scans at least once a year. The day of recurrence was determined by a professor or associate professor of thoracic oncology.

Cumulative survival was estimated with a Kaplan–Meier model. The overall and disease-free survival rates were calculated from the day of the first pulmonary resection. Survival rates were compared with the log-rank test. Univariate analyses were performed by the log-rank test. A probability value of <0.05 was set as the cut-off point for the selection of variables for multivariate analysis. In a multivariate analysis, Cox's proportional hazard model was used to identify prognostic factors. To compare two factors, the χ^2 test or Fisher exact test was used. A *P*-value of <0.05 was accepted as statistically significant. All statistical calculations were performed using the Stat View Version 5.0 statistical software (SAS Institute, Inc., Cary, NC, USA).

RESULTS

Overall survival and patient characteristics

The overall 5-year survival rate was 30.6% (Fig. 2) and the median follow-up was 48.9 months (range, 1–150 months). There were 56 men and 23 women who ranged in age from 33 to 84 years (median 64 years). The incidence of single and multiple cN2 was 57.7% (45 of 78) and 42.3% (33 of 78) and that of single and multiple pN2 was 28.2% (22 of 78) and 71.8% (56 of 78). On the other hand, the rates of cN2α and cN2β were 76.9% (60 of 78) and 23.1% (18 of 78) and that of pN2α and pN2β were 66.7% (52 of 78) and 33.3% (26 of 78), respectively. In the cN2α and cN2β groups, while there was a statistically significant difference between single and multiple cN2 ($P < 0.001$), no significant difference was found between single and multiple pN2 ($P = 0.766$). With regard to surgical procedures, only 6 patients (7.7%) underwent pneumonectomy while most (82.1%) received lobectomy. Four patients (5.1%) had unexpected *P*-stage IV (Table 1): 2 had pleural dissemination, 1 had malignant pericardial effusion and 1 had pleural dissemination and malignant pleural effusion. Twenty-three patients (29.5%) underwent induction or adjuvant chemotherapy.

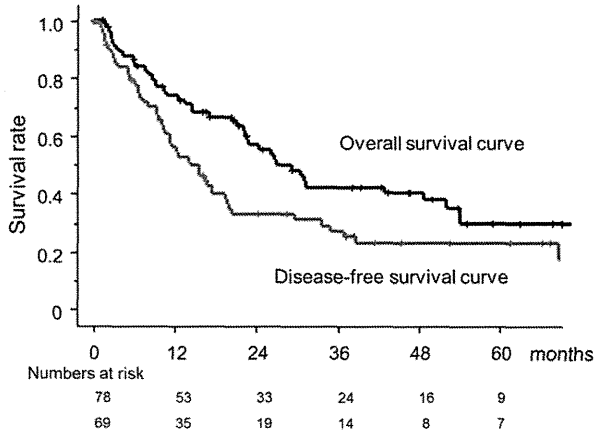

Figure 2: Overall survival and disease-free survival curves for patients with cN2/pN2 who underwent surgical resection.

Disease-free survival analysis

The disease-free 5-year survival rate was 22.6% (Fig. 2). The disease-free 5-year survival rate for tumours located in an upper lobe was significantly better than that for those in a lower lobe (27.9 vs 11.1%, $P = 0.007$). While the difference in survival between cN2α and cN2β was statistically significant (29.6 vs 0%, $P < 0.001$), no significant difference was found between single and multiple cN2 (23.4 vs 19.5%, $P = 0.123$). There were no significant differences among other clinical factors (Table 2). Multivariate analysis with Cox's proportional hazard model revealed that cN2α independently predicted good disease-free survival (Table 3). Figure 3 shows the disease-free survival curves for cN2α and cN2β.

Relationship between clinical and pathological lymph node status

The sensitivity, specificity and positive predictive value for single pN2 based on clinical findings of CT were 72.7, 48.2 and 35.6% (Table 4), respectively. For pN2α, these values were 90.4, 50.0 and 78.3% (Table 1). More than half of single cN2 were multiple pN2.

DISCUSSION

Patients with c-stage IIIA NSCLC are generally treated with chemo-radiotherapy because the involvement of a mediastinal lymph node is thought to reflect systemic disease. Recently, two large-scale trials have suggested that surgical resection for c-stage IIIA NSCLC did not improve overall survival or progression-free survival [3, 4]. Many institutions have been trying tri-modality therapy, which includes surgical resection because they believe that there is a population in which surgical resection improves overall or disease-free survival as well as a population in which resection does not improve survival. These beliefs are based on the finding of the North American Intergroup Trial 0139 that surgery after induction chemo-radiotherapy can be beneficial if lobectomy is adequate for complete resection [3]. The treatment strategy for c-stage IIIA NSCLC remains controversial because of its heterogeneity. The overall 5-year survival rate has a very wide range despite prospective multi-institutional trials and

Table 1: Clinicopathological features of cN2/pN2 patients

Variable	cN2α	N2β	*P*-value[a]
Gender			
Male	45 (75.0%)	10 (55.6%)	0.143
Female	15 (25.0%)	8 (44.4%)	
Age			
Years (median)	65 (33–84)	59 (34–79)	-
Smoking status (pack-year)			
≥40	32 (58.2%)	5 (27.8%)	0.031
<40	23 (41.8%)	13 (72.2%)	
Carcinoembryonic antigen (ng/ml)			
≥3.0	37 (63.8%)	12 (75.0%)	0.554
<3.0	21 (36.2%)	4 (25.0%)	
Clinical T factor			
T1	17 (28.3%)	6 (33.3%)	0.723
T2	33 (55.0%)	8 (44.4%)	
T3	10 (16.7%)	4 (22.3%)	
Clinical lymph node status			
cN2 single	42 (70.0%)	3 (16.7%)	<0.001
cN2 multiple	18 (30.0%)	15 (83.3%)	
Tumour location			
Upper lobe	51 (85.0%)	4 (22.2%)	<0.001
Lower lobe	9 (15.0%)	14 (77.8%)	
Right	38 (63.3%)	11 (61.1%)	>0.999
Left	22 (36.7%)	7 (38.9%)	
Surgical mode			
Lobectomy	51 (85.0%)	13 (72.2%)	0.254
Bilobectomy	6 (10.0%)	2 (11.1%)	
Pneumonectomy	3 (5.0%)	3 (16.7%)	
Histological type			
Adenocarcinoma	39 (65.0%)	13 (72.2%)	0.838
Squamous cell carcinoma	16 (26.7%)	4 (22.2%)	
Others	5 (8.3%)	1 (5.6%)	
Pathological T factor			
T1	12 (20.0%)	7 (38.9%)	0.242
T2	23 (38.3%)	4 (22.2%)	
T3	22 (36.7%)	5 (27.8%)	
T4	3 (5.0%)	2 (11.1%)	
Pathological stage			
IIIA	55 (91.7%)	14 (77.8%)	0.254
IIIB	3 (5.0%)	2 (11.1%)	
IV	2 (3.3%)	2 (11.1%)	
Pathological L/N status			
pN2 single	18 (30.0%)	4 (28.6%)	0.766
pN2 multiple	42 (70.0%)	14 (71.4%)	
pN2α	47 (78.3%)	5 (27.8%)	<0.001
pN2β	13 (21.7%)	13 (72.2%)	
Chemotherapy			
None	44 (73.3%)	10 (58.8%)	0.249
Done	16 (26.7%)	7 (41.2%)	
Induction	2 (3.3%)	1 (5.9%)	
Adjuvant	14 (23.4%)	6 (35.3%)	

[a] χ^2 test or Fisher's exact test.

retrospective large-scale multi-institutional trials for the same stage, for example 0–34% with surgery alone and 10–36% with trimodality therapy (Table 5) [1–8, 10]. In this study, the overall 5-year survival rate was 30.6%, and we think that the population was adequate although it was a retrospective study.

To resolve the problem of heterogeneity in patients with cN2 stage IIIA, it has been suggested that they be classified into subgroups. Patients undergoing surgical resection with pN2 stage IIIA were classified into three or four groups according to whether they were clinically N2 or N0–1 and pathologically whether a single or multiple lymph node levels were involved, and their survival curves were very impressive [10, 12]. Based on these studies, it has been considered that patients with multiple-station N2 stage IIIA NSCLC were not indicated for surgical resection and

Table 2: Prognostic factors of disease-free survival in a univariate analysis

Clinicopathological factors	3-year (%)	5-year (%)	*P*-value[a]
Gender			
Male	26.9	26.9	0.800
Female	26.6	15.9	
Age (years)			
More than 70	44.2	36.8	0.166
70 or less	20.4	17.5	
Smoking status (pack-year)			
≥40	23.2	18.5	0.424
<40	31.8	27.8	
Carcinoembryonic antigen (ng/ml)			
≥3.0	20.9	17.4	0.285
<3.0	33.4	33.4	
Clinical T factor			
T1	30.0	24.0	0.560
T2 or 3	25.0	21.9	
Tumour location			
Upper lobe	33.2	27.9	0.007
Lower lobe	11.1	11.1	
Tumour location			
Right	30.5	23.2	0.708
Left	21.7	21.7	
Clinical lymph node status			
cN2 single	31.5	23.4	0.123
cN2 multiple	19.5	19.5	
Clinical lymph node status			
cN2α	35.1	29.6	<0.001
cN2β	0	0	

[a]Log-rank test.

Table 3: Prognostic factors of disease-free survival in a multivariate analysis

Variables	*Hazard ratio*	*95% CI*	*P*-value[a]
Tumour location: LL (vs UL)	1.477	0.690–3.162	0.316
L/N status: cN2α (vs cN2β)	0.424	0.192–0.937	0.034

[a]Cox's proportional hazard model.
CI: confidence interval; LL: Lower lobe; UL: Upper lobe; L/N: lymph node.

those with single-station N2 stage IIIA NSCLC could be indicated for surgical resection. However, these conclusions could be wrong because whether a patient showed single- or multiple-station N2 in these reports was based on the pathological status after surgical resection. Our study showed that 64.4% of clinical single-station N2 was pathological multiple-station N2. On the other hand, while mediastinoscopy has played an important role in resolving the discrepancy between the clinical mediastinal lymph node status and the pathological status, recently, the involvement of a mediastinal lymph node has been mainly diagnosed using endobronchial ultrasonography (EBUS) based on findings of CT and PET-CT [16]. In practice, it would be difficult to perform a biopsy for all mediastinal lymph node stations in all patients using EBUS.

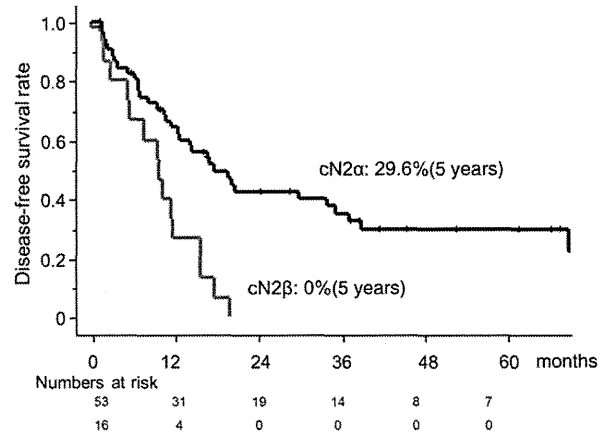

Figure 3: Disease-free survival curve for cN2α and cN2β according to the location of mediastinal lymph node metastasis for each location of the main tumour.

Table 4: Relationship between clinical and pathological lymph node status (N2 single or multiple)

	pN2 single	pN2 multiple	Total
cN2 single	16	29	45
cN2 multiple	6	27	33
Total	22	56	78

Therefore, we should realize that clinical single-station N2 is not always pathological single-station N2.

Our present study revealed the importance of the location of the primary tumour and the nodes involved in patients with clinical stage IIIA NSCLC. The disease-free 5-year survival rate for cN2α was significantly better than that for cN2β (29.6 vs 0%, $P < 0.001$). Some previous reports support our results. First, it was reported that when mediastinal metastasis is limited to upper nodes from an upper-lobe tumour, to lower nodes from a lower-lobe tumour or to aortic nodes from a left upper-lobe tumour, acceptable survival could be expected after radical resection [17]. Second, it has been stated that superior mediastinal metastasis should be recognized as an indicator of a poor prognosis in tumours of both lower lobes [18]. However, these results were based on the pathological status of mediastinal lymph node metastasis after surgical resection. To the best of our knowledge, there has been no previous report on the clinical location of mediastinal lymph node metastasis for each location of the main tumour, such as cN2α or cN2β. However, the present study has some limitations; i.e. the sample size was small and our study was both retrospective and at a single institution. Furthermore, there was a long period of registration: from 1996 to 2009. While a prospective multi-institutional trial would be useful, our results are still valuable since such a trial could be difficult because surgical resection is not currently recommended for cN2 NSCLC.

In conclusion, clinical mediastinal lymph node status based on the location of the primary tumour and the node involved was found to be an important preoperative prognostic factor. Thus, this factor should be taken into consideration when planning and

Table 5: The range of reported survival rate in c-stage IIIA non-small-cell lung cancer

Authors (year)	Phase	Study design	Number	Overall survival (5 years) (%)
Eberhart *et al.* (1998) [7]	II	CT + CRT + S	52	31
Roth *et al.* (1998) [5]	III	Ind. CT + S	28	36
		S alone	30	15
Rosell *et al.* (1999) [6]	III	Ind. CT + S	30	17
		S alone	30	0
Andre *et al.* (2000) [10]	-	Retrospective, S alone	332	18
Ichinose *et al.* (2001) [1]	-	Prospective	104	27
Nagai *et al.* (2003) [8]	III	Ind. CT + S	31	10
		S alone	31	22
Meerbeek *et al.* (2007) [4]	III	Ind. CT + S	167	15.7
		Ind. CT + RT	165	14
Albain *et al.* (2009) [3]	III	Ind. CRT + S	202	27
		Ind. CRT + definitive RT	194	20
Yoshino *et al.* (2012) [2]	-	Retrospective	436	30
		S alone	137	33.7

CT: chemotherapy; CRT: chemoradiotherapy; S: surgery; Ind.: induction; RT: radiotherapy.

evaluating clinical trials. Another important finding was that clinical single-station N2 is not always pathological single-station N2 disease.

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Prognostic Role of Positron Emission Tomography and High-Resolution Computed Tomography in Clinical Stage IA Lung Adenocarcinoma

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Background. This multicenter study aimed to validate the ability of ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT) plus high-resolution computed tomography (HR-CT) to predict the malignant behavior and prognosis of early adenocarcinomas of the lung.

Methods. We calculated maximum standardized uptake values (maxSUV) from PET/CT images and ground-glass opacity (GGO) ratios on HR-CT images before complete surgical intervention in 610 patients with clinical stage IA lung adenocarcinoma. Pathologic invasiveness and survival were compared with clinical factors and radiographic findings including the maxSUV, which was revised to correct for interinstitutional discrepancies that confer limitations upon multicenter PET studies.

Results. Analyses of receiver-operating characteristic curves revealed optimal maxSUV and GGO ratio cutoffs to predict recurrence of 2.9 and 25%, respectively. Both the maxSUV and GGO ratio reflected tumor invasiveness, nodal metastasis, recurrence, and patient survivals, and were significant prognostic factors for recurrence-free and cancer-specific survivals on multivariate Cox analysis (all, $p < 0.001$). The combination of maxSUV and GGO ratio is a better predictor of malignant tumor grade than either alone.

Conclusions. The combination of maxSUV and GGO ratio as well as each alone are important predictors of prognosis in patients with clinical stage IA adenocarcinoma of the lung and should be considered before selecting therapeutic strategies.

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Recent progress in diagnostic imaging such as high-resolution computed tomography (HR-CT) and integrated ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) as well as the widespread application of screening using CT have enhanced the discovery of small lung cancers, which are predominantly biologically heterogeneous adenocarcinomas [1, 2] with unpredictable malignant aggressiveness at the time of diagnosis [3, 4].

Adenocarcinoma in situ is histologically classified by the World Health Organization as a noninvasive adenocarcinoma having pure lepidic growth without vascular, stromal, or pleural invasion. The components of lepidic growth appear as areas of ground-glass opacity (GGO) on HR-CT. Thus, the GGO ratio might be associated with the grade of malignancy in adenocarcinomas. Conversely, PET/CT that reflects the metabolic activity and proliferative potential of tumors was first introduced into clinical practice in the early 2000s and, with CT, it is currently one of the best noninvasive modalities for diagnosing cancer [5, 6]. The uptake of FDG is quantified on PET/CT images based on maximum standardized uptake values (maxSUV). Although maxSUV is widely and increasingly used to diagnose, stage, and therapeutically assess lung cancer, the malignancy grade of tumors assessed by maxSUV has not been investigated in detail and only a few small-scale studies have demonstrated a role for PET/CT in assessing the biological malignancy of lung cancers [7]. A prospective multicenter study was implemented but the findings were limited by a short follow-up period [8, 9].

Here, we examined 5-year survival rates and compared the ability of PET/CT and HR-CT to predict the malignant behavior, prognosis, and recurrence of clinical early-stage adenocarcinomas of the lung.

Patients and Methods

We enrolled 610 patients with clinical T1N0M0 stage IA lung adenocarcinoma, for whom HR-CT and PET/CT were followed by complete R0 resection between August 2005 and June 2010 at four institutes. Tumors were staged according to the seventh edition of the TNM classifi

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Abbreviations and Acronyms

AUC = area under the curve
CT = computed tomography
FDG = ^{18}F-fluorodeoxyglucose
GGO = ground-glass opacity
HR = high resolution
IRB = Institutional Review Board
maxSUV = maximum standardized uptake value
PET = positron emission tomography
RFS = recurrence-free survival
SUV = standardized uptake value

cation of malignant tumors [10]. The Ethics Committees and Institutional Review Board (IRB) at each participating institution approved this multicenter study and the analysis of a prospective database (Hiroshima University Hospital IRB, no. EKI-644; Kanagawa Cancer Center IRB, no. KEN-31; Cancer Institute Hospital IRB, no. 2008-1018; Hyogo Cancer Center IRB, no. H20-RK-15).

All patients were followed up from the day of surgery, and assessed by a physical examination and chest radiography every 3 months and by chest and abdominal CT images every 6 months for the first 2 years. Thereafter, they were assessed physically and with chest radiography every 6 months and annual chest CT imaging.

Chest images were obtained using a 16-row multidetector CT, independently of the subsequent PET/CT examinations. High-resolution images of the tumor were acquired under the following conditions: 120 kilovoltage peak, 200 mA, 2-mm section thickness, pitch 1, 1-mm to 2-mm section thickness, 512 × 512 pixel resolution, scanning duration 0.5 to 1 s, and 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. We defined GGO as a misty increase in lung attenuation that did not obscure underlying vascular markings, and the GGO ratio (%) as (1 − [maximum dimension of consolidation of lung windows / maximum dimension of tumor of lung windows]) × 100.

The patients fasted for at least 4 hours before receiving an intravenous injection of 74 to 370 MBq FDG and were then allowed to relax for at least 1 hour before FDG-PET/CT scanning. Patients were excluded from PET/CT imaging if blood glucose values before tracer injection were 150 mg/dL or greater. Images were acquired as fusion PET/CT images using Discovery ST (GE Healthcare, Little Chalfont, UK), Aquiduo (Toshiba Medical Systems, Tochigi, Japan), or Biograph Sensation16 (Siemens Healthcare, Erlangen, Germany) integrated PET/CT scanners. Low-dose, unenhanced CT images of 2-mm to 4-mm thick sections for attenuation correction and localization of lesions identified by PET were acquired from the head to the pelvic floor of each patient using a standard protocol. Immediately after CT, PET covered the identical axial field of view for 2 to 4 minutes per table position, depending on the condition of the patient and scanner performance. All

Table 1. Summary of Clinical Characteristics of Patients With cT1N0M0 Adenocarcinoma

Clinical Characteristics	Patients (n = 610)	MaxSUV ≤2.9/>2.9 (n = 456/154)	*p* Value	GGO Ratio ≥25%/<25% (n = 334/276)	*p* Value
Age, years, mean ± SD	65.8 ± 9.6	65.8 ± 9.7/65.8 ± 9.6	0.9933	65.4 ± 9.5/66.2 ± 9.8	0.3044
Sex					
Male	268	182/86	0.0006	130/138	0.0061
Female	342	274/68		204/138	
CEA, ng/mL					
≤5	549	425/124	<0.0001	319/230	<0.0001
>5	61	31/30		15/46	
Tumor size, mm					
≤20	354	286/68	<0.0001	206/148	0.0448
>20	256	170/86		128/128	
Lymphatic invasion					
Positive	89	32/57	<0.0001	9/80	<0.0001
Negative	521	424/97		325/196	
Blood vessel invasion					
Positive	104	30/74	<0.0001	7/97	<0.0001
Negative	506	426/80		327/179	
Pleural invasion					
Positive	66	20/46	<0.0001	7/59	<0.0001
Negative	544	436/108		327/217	
Lymph node metastasis					
Positive	41	13/28	<0.0001	5/36	<0.0001
Negative	569	443/126		329/240	

CEA = carcinoembryonic antigen; GGO = ground-glass opacity; maxSUV = maximum standardized uptake value.

PET images with a 50-cm field of view were reconstructed using an iterative algorithm with CT-derived attenuation correction. Variations in SUV among institutions were minimized using an anthropomorphic body phantom [11]. A calibration factor was created by dividing the actual SUV by the gauged mean SUV in the phantom background to decrease interinstitutional SUV inconsistencies [12]. The adjustment of the interinstitutional variability in SUV narrowed the range (from 0.89 to 1.24, to 0.97 to 1.18) when the maxSUV ratio was expressed as the maxSUV of each institution relative to the maxSUV of the control institution.

Statistical Analysis

Data are presented as numbers, ratios (%), or means ± SD, unless otherwise stated. Receiver-operating characteristic curves of maxSUV and GGO ratios to predict recurrence were generated to determine the cutoff value that yielded optimal sensitivity and specificity using the Youden index [13]. Recurrence-free survival (RFS) was defined as the interval from the date of surgery until the first event (relapse or death from any cause) or the last follow-up visit. For cancer-specific survival, deaths that were attributed to cancer were treated as deaths, and survival durations were censored at the date of a patient becoming lost to follow-up, or the date of death from causes not considered as being due to the cancer. Survival duration was analyzed using the Kaplan-Meier method, and differences were assessed using the log rank test. Independent variables for predicting RFS were determined using multivariate Cox proportional analyses. All data were statistically analyzed using the Statistical Package for Social Sciences software, version 20 (SPSS, Chicago, IL).

Results

Table 1 summarizes the clinical and pathologic characteristics of the 342 (56%) female and 268 (44%) male patients (mean age 65.8 years). The diameter of the primary tumor on HR-CT was 20 mm or less in 354 patients (58%) and greater than 20 mm in 256 (42%). Lymphatic, blood vessel, and pleural invasion and lymph node metastases were pathologically confirmed in 89 patients (15%), 104 (17%), 66 (11%), and 41 (7%), respectively. The mean follow-up period after surgery was 41.8 months, with a disease recurrence rate of 9.5% (n = 58).

The receiver-operating characteristic curves for predicting recurrence and calculating the optimal cutoff values of maxSUV and GGO ratio were 2.9 (area under the curve [AUC] 0.816) and 25% (AUC 0.803), respectively (Fig 1). Both the cutoff values of maxSUV and GGO ratio significantly correlated with sex, carcinoembryonic antigen value, tumor size, lymphatic invasion, blood vessel invasion, pleural invasion, and lymph node metastasis (Table 1). We then compared possible predictors of RFS with preoperative clinical and radiographic factors (Table 2). Univariate analyses identified the maxSUV and GGO ratio as significant determinants and carcinoembryonic antigen and tumor size as marginally significant. Moreover, multivariate analysis

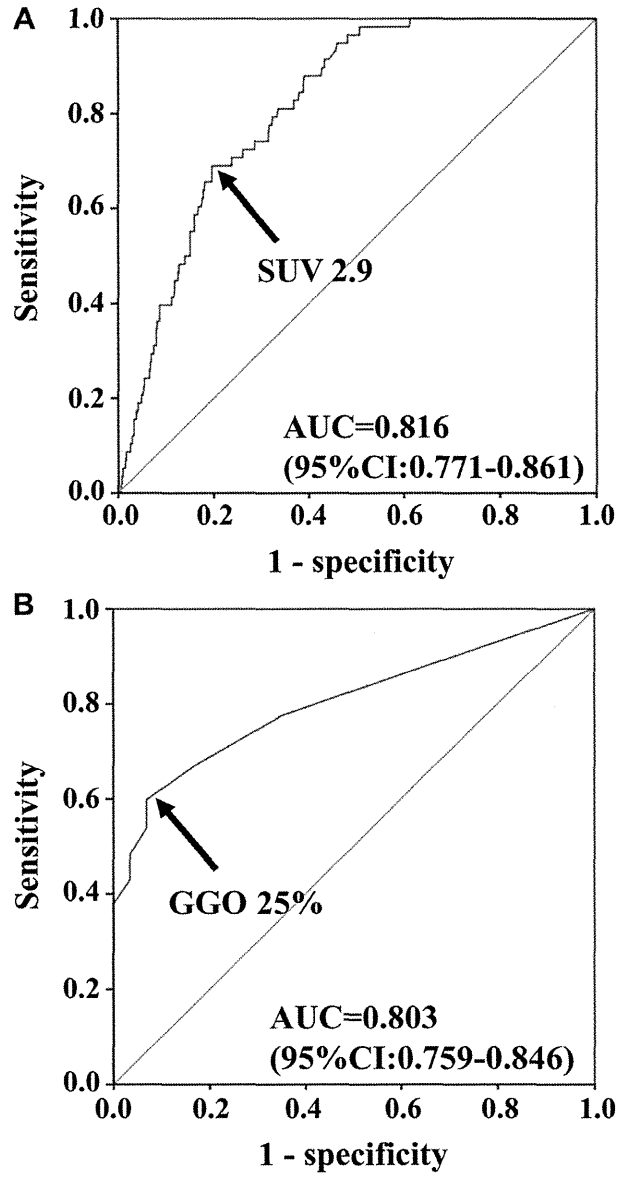


Fig 1. Area under the receiver-operating characteristics (ROC) curve (AUC) for recurrence using (A) maximum standardized uptake value (maxSUV) on ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT); and (B) ground-glass opacity (GGO) ratio on high-resolution computed tomography. Optimal cutoff of maxSUV and GGO ratio were 2.9 (AUC 0.816, 95% confidence interval [CI]: 0.771 to 0.861, $p < 0.001$) and 25% (AUC 0.803, 95% CI: 0.759 to 0.846, $p < 0.001$), respectively, for predicting recurrence according to ROC curves.

demonstrated that maxSUV and GGO ratio were significant independent determinants for RFS.

Significant differences in RFS ($p < 0.001$) were identified between tumors having a maxSUV of 2.9 or less (5-year RFS ratio 95%) and greater than 2.9 (72%), and between tumors with GGO ratios 25% or greater (98%) and less than 25% (79%; Figs 2A, 2B). Likewise, maxSUV

Table 2. Univariable and Multivariable Analysis Using Cox Model for Recurrence-Free Survival

			Univariable Analysis		Multivariable Analysis	
Factors	Favorable	Unfavorable	Hazard Ratio (95% CI)	*p* Value	Hazard Ratio (95% CI)	*p* Value
Age, years	≤65.8	>65.8	1.05 (0.63–1.76)	0.856	0.95 (0.56–1.60)	0.849
Sex	Female	Male	1.05 (0.62–1.76)	0.864	0.74 (0.43–1.25)	0.259
CEA, ng/mL	≤5	>5	1.99 (1.01–3.94)	0.048	1.04 (0.51–2.08)	0.924
Size, mm	≤20	>20	1.61 (0.96–2.70)	0.069	1.07 (0.63–1.82)	0.810
MaxSUV	≤2.9	>2.9	7.52 (4.31–13.12)	<0.001	3.23 (1.76–5.93)	<0.001
GGO ratio, %	≥25	<25	17.24 (6.24–47.60)	<0.001	9.53 (3.23–28.07)	<0.001

CEA = carcinoembryonic antigen; CI = confidence interval; GGO = ground-glass opacity; maxSUV = maximum standardized uptake value.

and the GGO ratio were significant prognostic factors for cancer-specific survival ($p < 0.001$; Figs 2C, 2D).

We examined the relationship between maxSUV and GGO ratio as predictors of pathologic tumor invasiveness and recurrence status (Table 3). We classified the patients based on GGO ratios and maxSUV, respectively, of 25% or greater and 2.9 or less (n = 319; group 1); 25% or greater and more than 2.9 or less than 25% and 2.9 or less (n = 152; group 2); and less than 25% and greater than 2.9 (n = 139; group 3). The frequencies of lymphatic, blood vessel, pleural, and lymph nodal involvement as well as recurrence were stratified by this classification. The RFS ($p < 0.001$) also significantly differed among the groups (5-year RFS rates in groups 1, 2, and 3: 99%, 88%, and 70%, respectively; Fig 3). These data show that both maxSUV and the GGO ratio, especially in combination, are important for predicting the malignant grade of tumors and patient prognosis. Figure 4 shows examples of HR-CT findings and FDG-PET/CT findings of tumors in each groups.

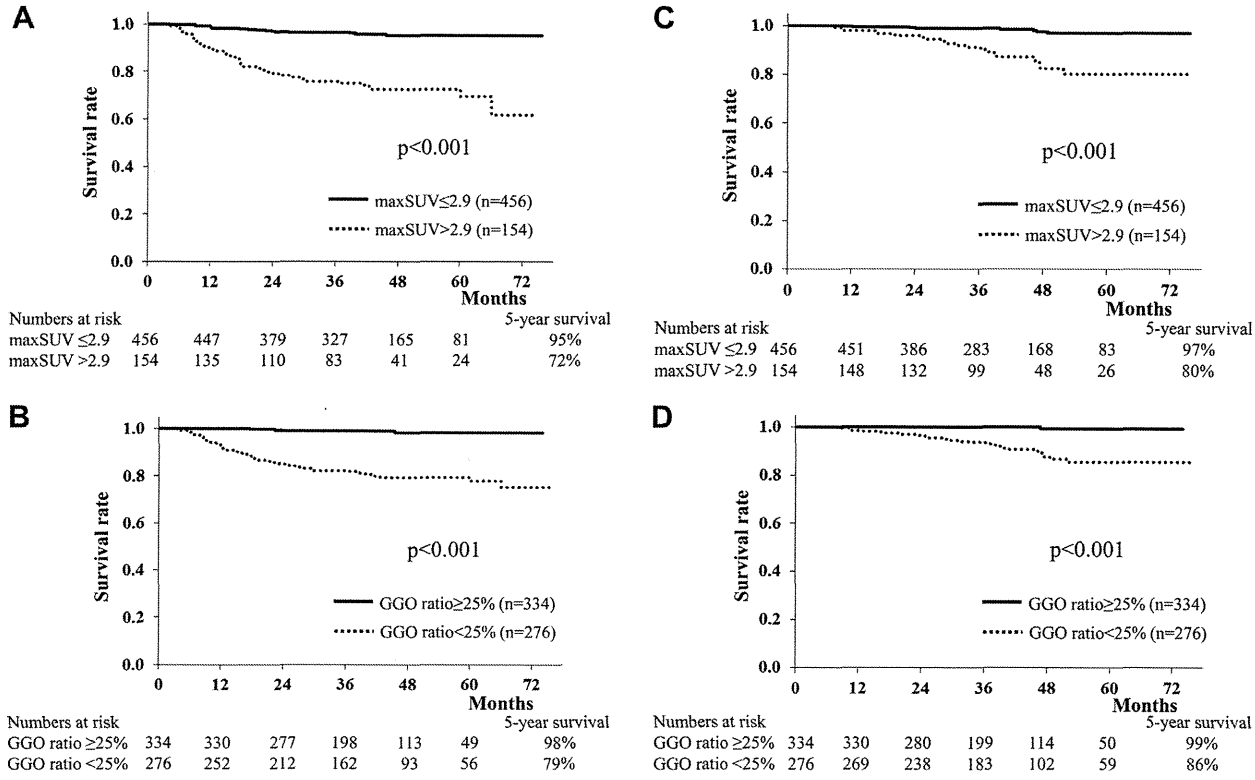


Fig 2. Recurrence-free survival (RFS) curves according to (A) maximum standardized uptake value (maxSUV) and (B) ground-glass opacity (GGO) ratio. Significant differences in RFS ($p < 0.001$) were identified between patients with maxSUV of 2.9 or less (n = 456; 5-year RFS ratio 95% [solid line]) and greater than 2.9 (n = 154; 5-year RFS ratio 72% [dotted line]), and between patients with GGO ratios of 25% or more (n = 334; 5-year RFS ratio 98% [solid line]) and less than 25% (n = 276; 5-year RFS ratio 79% [dotted line]). Cancer-specific survival curves according to (C) maxSUV and (D) GGO ratio. Cancer-specific survival ($p < 0.001$) significantly differed between patients with maxSUV of 2.9 or less (n = 456; 5-year survival 97% [solid line]) and greater than 2.9 (n = 154; 5-year survival 80% [dotted line]), and between patients with GGO ratios of 25% or greater (n = 334; 5-year survival 99% [solid line]) and less than 25% (n = 276, 5-year survival 86% [dotted line]).

Table 3. Relationship Between Ground-Glass Opacity Ratio and Revised Maximum Standardized Uptake Value as Predictors for Lymphatic, Blood Vessel, and Pleural Invasion, and Lymph Node Metastasis Factors and Recurrence Status

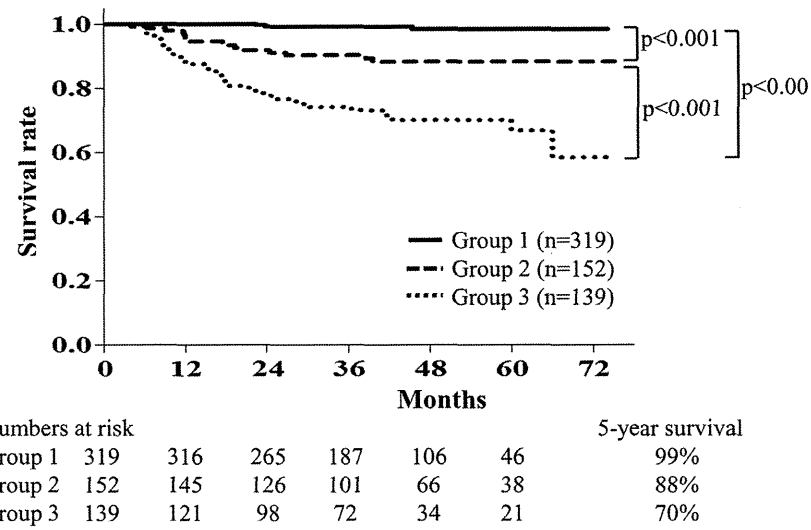
Relationships	Lymphatic Invasion Positive/Negative	Blood Vessel Invasion Positive/Negative	Pleural Invasion Positive/Negative	LN Metastasis Positive/Negative	Recurrence Positive/Negative
Group 1 (n = 319): GGO ≥25% and maxSUV ≤2.9	6/313 (2%)	6/313 (2%)	6/313 (2%)	3/316 (1%)	3/316 (1%)
Group 2 (n = 152): GGO ≥25% and maxSUV >2.9; GGO <25% and maxSUV ≤2.9	29/123 (19%)	25/127 (16%)	15/137 (10%)	12/140 (8%)	16/136 (11%)
Group 3 (n = 139): GGO <25% and maxSUV >2.9	54/85 (39%)	73/66 (53%)	45/94 (32%)	26/113 (19%)	39/100 (28%)
Group 1 versus Group 2, *p* value	<0.001	<0.001	<0.001	<0.001	<0.001
Group 2 versus Group 3, *p* value	<0.001	<0.001	<0.001	0.006	<0.001

GGO = ground-glass opacity; LN = lymph node; maxSUV = maximum standardized uptake value.

We assessed the impact of tumor size on maxSUV and its association with patient prognosis. The receiver-operating characteristic curves for recurrence identified optimal maxSUV cutoffs of 1.5 (AUC 0.722), 2.4 (AUC 0.835), 2.9 (AUC 0.862), and 4.6 (AUC 0.746), respectively, for tumors with diameters of 15 mm or less (n = 180), 15 to 20 mm (n = 174), 20 to 25 mm (n = 150), and greater than 25 mm (n = 106). These maxSUV cutoffs for groups classified by tumor size sharply distinguished patients at high risk and patients at low risk for recurrence (Fig 5).

Comment

A phantom study has revealed a powerful dependence of SUV on image resolution, noise, and region of interest methodology [14], and SUV variability might hinder direct comparisons and the interchange of results generated at different institutions. Thus, multicenter trials should have standardized protocols for acquisition, reconstruction, and data analysis. The phantom study of Westerterp and colleagues [11] discovered differences in SUV quantitation of as much as 30% among three institutions and that recovery coefficients obtained from each were equal to within 15% after application-specific calibration. Characteristics of the PET scanner and its imaging methods differ according to the model; therefore, it results in inevitable variations in SUV quantitation. In this regard, we believed that we could resolve those questions by using common phantom (NEMA body phantom) conducting imaging with clinical imaging methods at each center, finding out the variation of SUV, calculating correction coefficient of each scanner, and applying them to clinical data. We attempted to overcome these limitations by using the same or similar image reconstruction and data analysis software and SUV revision. Therefore, the variation in this study is probably smaller than that generated by a multiinstitution trial with larger differences. However, some limitations persist even under relatively more ideal circumstances and adjustments.



Numbers at risk							5-year survival
Group 1	319	316	265	187	106	46	99%
Group 2	152	145	126	101	66	38	88%
Group 3	139	121	98	72	34	21	70%

Fig 3. Recurrence-free survival (RFS) curves according to groups classified by maximum standardized uptake value (maxSUV) and ground-glass opacity (GGO) ratio: group 1 (solid line), GGO 25% or greater and maxSUV 2.9 or less (n = 319); group 2 (broken line), GGO 25% or greater and maxSUV greater than 2.9, or GGO less than 25% and maxSUV 2.9 or less (n = 152); and group 3 (dotted line), GGO less than 25% and maxSUV greater than 2.9 (n = 139). Significant differences in RFS ratios were identified (p < 0.001) among groups 1, 2, and 3 (5-year RFS 99%, 88%, and 70%, respectively).

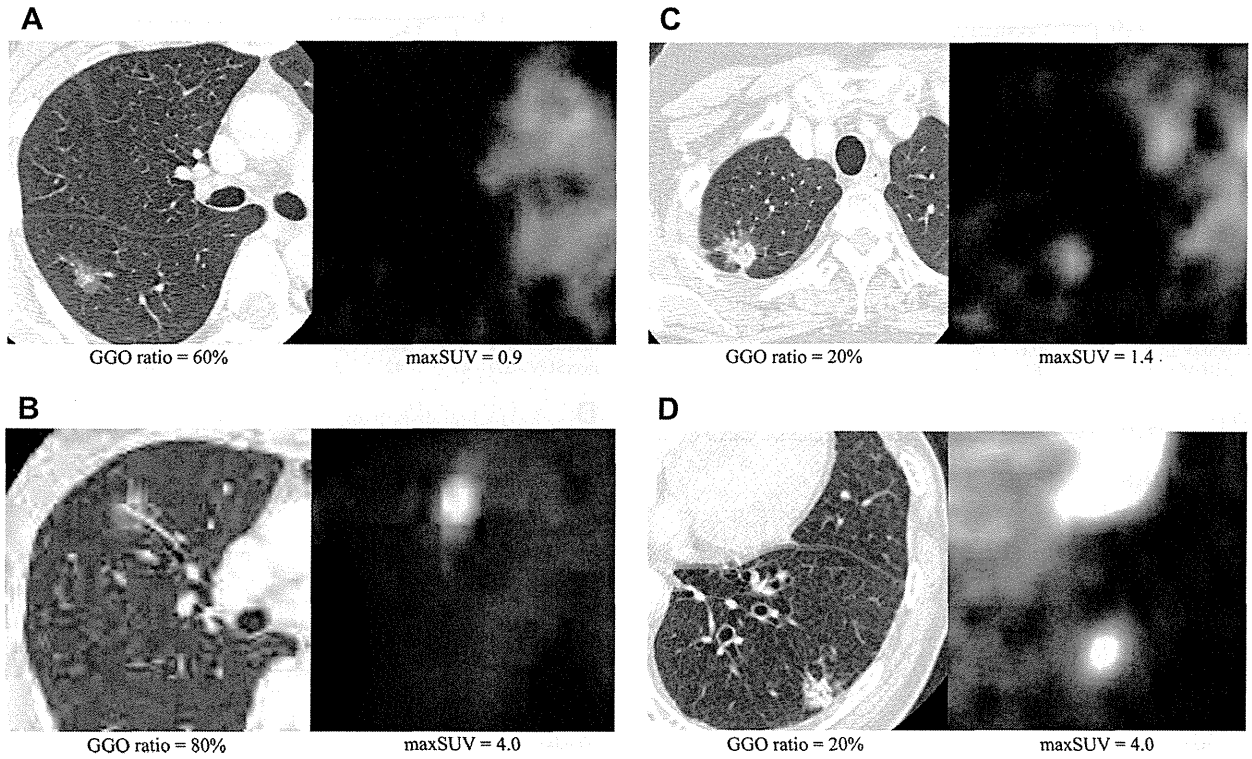


Fig 4. Examples of tumors on high-resolution computed tomography and ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) in each group based on (left panels) ground-glass opacity (GGO) ratio and (right panels) maximum standardized uptake value (maxSUV): (A) 2.0 cm tumor, GGO ratio 60%, maxSUV 0.9 (group 1); (B) 2.0 cm tumor, GGO ratio 80%, maxSUV 4.0 (group 2); (C) 2.0 cm tumor, GGO ratio 20%, maxSUV 1.4 (group 2); and (D) 2.0 cm tumor, GGO ratio 20%, maxSUV 4.0 (group 3).

Because the frequency of detection has increased and the size of resected lung tumors has relatively decreased, prediction of the biological features of small adenocarcinomas, especially lepidic growth component, has become important for the selection of appropriate surgical options. Among the two major histologic subtypes of non-small cell lung cancer, maxSUV of the primary tumor is a powerful prognostic determinant for patients with adenocarcinoma, but not squamous cell carcinoma [15], probably because adenocarcinomas are highly heterogeneous. The positive ratio of FDG uptake in adenocarcinomas including a lepidic growth component is lower, and adenocarcinoma in situ is more likely to escape detection by PET/CT. Lower metabolic activity in adenocarcinomas containing a lepidic growth component should be secondary to the slower pace of adenocarcinoma in situ proliferation compared with other invasive adenocarcinomas, suggesting that higher metabolic activity is linked to more malignant aggressiveness.

Preoperative understanding of the tumor behavior is essential to select optimal surgical strategies, particularly radical sublobar resection of small adenocarcinomas for patients who can tolerate lobectomy. A large-scale and long-term multiinstitutional investigation of the malignant grades of small lung cancers using PET/CT has not been conducted, and published series [8, 9] have the serious limitation of a short postoperative observation period. The present findings including survival data imply that the maxSUV and GGO ratio and their combination are potentially promising determinants for surgical indications. The frequency of lymphatic, vessel, or pleural invasion was 2% among tumors with GGO of 25% or greater and maxSUV of 2.9 or less, which accounted for almost half (319 of 601) of all clinical T1N0M0 adenocarcinomas, and the 1% incidence of nodal metastasis or recurrence suggested that sublobar resection could be considered.

We also examined the relationship between maxSUV and tumor size in cT1N0M0 adenocarcinomas, although the former is a more powerful determinant for grade of malignancy. The findings that a larger tumor is associated with a higher maxSUV indicates that the malignant aggressiveness of a tiny adenocarcinoma with a lower FDG uptake should be carefully considered. For example, a tumor approximately 10 mm in diameter with a relatively low maxSUV of approximately 2.0 might have high malignant potential. The notion that PET/CT assessment is useless for small adenocarcinomas of the lung must be obliterated.

To understand the underlying significance of maxSUV for determining the malignant grade of adenocarcinoma, the remarkable difference in the relationships between the maxSUV and the GGO ratio to the pathologic lepidic growth component ratio should be taken into account.

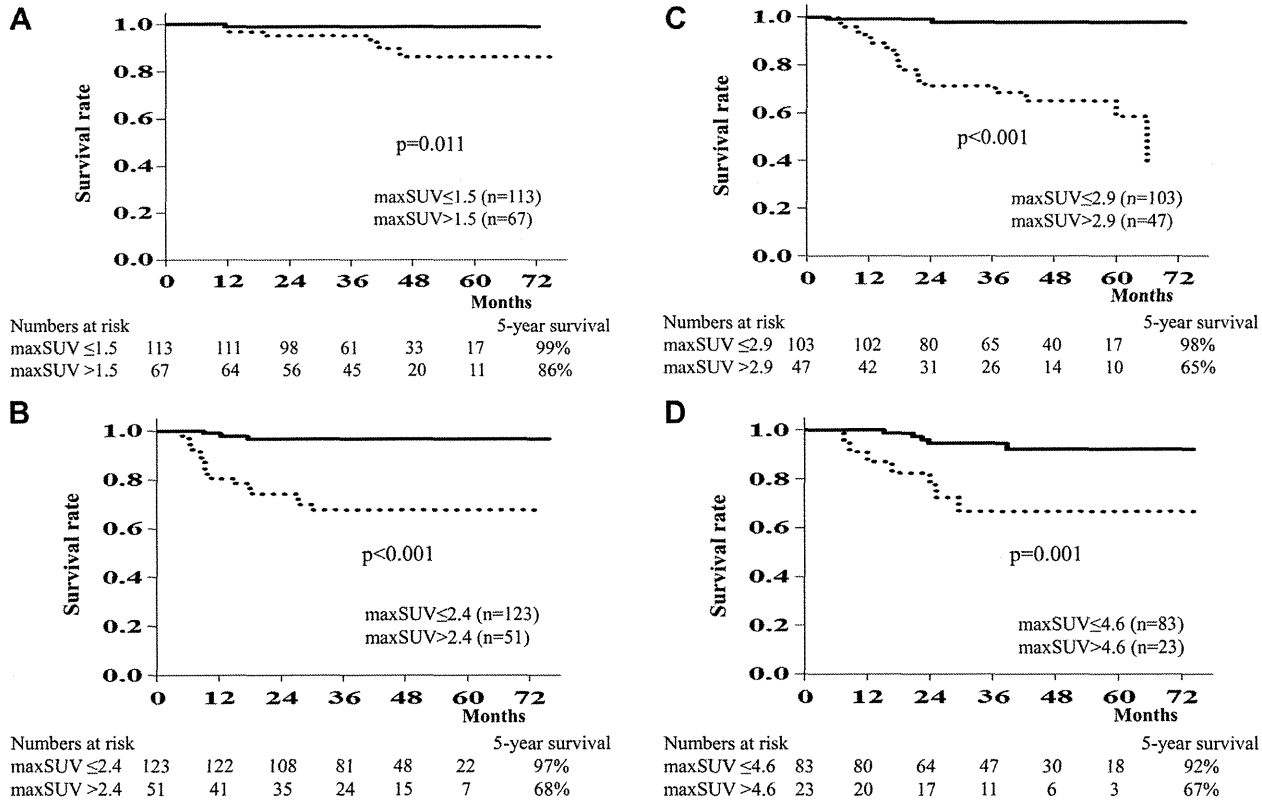


Fig 5. Recurrence-free survival (RFS) curves according to maximum standardized uptake value (maxSUV). Significant differences in RFS rates were identified between patients with maxSUV of 1.5 or less (solid line, 5-year RFS 99%) and greater than 1.5 (dotted line, 5-year RFS 86%), between patients with maxSUV of 2.4 or less (solid line, 5-year RFS 97%) and greater than 2.4 (dotted line, 5-year RFS 68%), between patients with maxSUV of 2.9 or less (solid line, 5-year RFS 98%) and greater than 2.9 (dotted line, 5-year RFS 65%), and between patients with maxSUV of 4.6 or less (olid line, 5-year RFS 92%) and greater than 4.6 (dotted line, 5-year RFS 67%), in adenocarcinomas of (A) 15 mm or less, (B) 15 to 20 mm or less, (C) 20 to 25 mm or less, and (D) greater than 25 mm, respectively.

We emphasize that the extent of GGO areas on radiographic findings closely correlated with pathologic findings of lepidic growth, although maxSUV was less associated with the lepidic growth proportion, that is, more independent of the lepidic growth component. This discrepancy can explain why the combination of the maxSUV and GGO ratio is a vital predictor of the grade of tumor malignancy.

In conclusion, the combination of maxSUV and GGO ratio, as well as each alone, are important predictors of prognosis for patients with clinical stage IA adenocarcinoma of the lung and should be considered before selecting therapeutic strategies.

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