Table 5. Multivariate Analysis of Disease-Free Survival

Variable	Wald Statistic	Hazard Ratio	95% CI	*p* Value
Proportion of GGO (%)	13.69	0.977	0.965–0.989	<0.001
Solid diameter (mm)	10.00	1.081	1.030–1.134	0.002
Nodule diameter (mm)	0.750	1.020	0.975–1.068	0.386

Adjusted for age, sex, histologic type, pathologic T status, pathologic N status, type of operation, and extent of nodal dissection.

CI = confidence interval; proportion of GGO = proportion of ground-glass opacity.

study, the solid area diameter was significantly superior to the whole nodule diameter for the prediction of less invasive lung cancer, and there was a trend toward superiority in predicting recurrence. Furthermore, on multivariate analyses of DFS, the solid area diameter and not the whole nodule diameter was found to be an independent prognostic factor. On the basis of findings from the study of Tsutani and colleagues [14] and our current study, we believe that using the solid area diameter as the T descriptor is more effective than using the whole nodule diameter as in the current TNM classification.

The primary aim of this study was to compare the proportion of GGO and the solid area diameter in predicting less invasive lung cancer to select candidates for limited resection. ROC analysis revealed that the area under the ROC curve value was larger for the proportion of GGO than that of the solid area diameter, although the difference between the 2 values did not reach significance. Moreover, we compared the number of patients in the categories that consist only of patients with less invasive lung cancer. According to the proportion of GGO, all patients with nodules that showed a GGO area greater than 80% had less invasive lung cancer (76 patients). In contrast, according to the solid area diameter, all patients with nodules showing a solid area diameter smaller than 5 mm had less invasive lung cancer (56 patients). Therefore, more patients with less invasive lung cancer could be identified using the proportion of GGO rather than the solid area diameter. Furthermore, we conducted multiple logistic regression analyses and found that proportion of GGO was the only independent factor of the 3 measurements. These findings demonstrated that the proportion of GGO will be more effective in predicting less invasive lung cancer when selecting a candidate for limited surgical resection. In other words, a tumor with the same solid area diameter but a greater proportion of GGO is much less invasive than that with a smaller proportion of GGO. However, all patients who had tumors with GGO less than 80% but a solid area smaller than 5 mm had less invasive lung cancer. Furthermore, patients who had tumors with GGO less than 50% but a solid area smaller than 10 mm all showed a recurrence-free status. These findings indicated that in addition to the proportion of GGO, the solid area diameter may provide additional information for predicting less invasive lung cancer or recurrence. Ideally, combining the proportion of GGO and solid area diameter is the best method to predict less invasive lung cancer and recurrence. However, such a method is far more complicated in regard to the staging system. Therefore, we propose using the solid area diameter as the T descriptor in the future revision of the TNM classification. In contrast, we recommend that for the selection of less invasive lung cancer, both the proportion of GGO and solid nodule diameter be combined. For example, GGO greater than 80% in any solid area diameter, GGO greater than 10% and a diameter of solid area smaller than 10 mm, and a diameter of solid area smaller than 5 mm in any proportion of GGO may be the best criteria for predicting less invasive lung cancer. The number of patients who were diagnosed with less invasive lung cancer on HRCT increased to 99 using this combined method from 76 using only the proportion of GGO and from 56 using only the solid area diameter.

Tables 3 and 4 show that among the same proportion of GGO categories, a smaller solid area diameter was associated with a higher percentage of less invasive lung cancer and a lower recurrence rate. However, there were several exceptions. For example, the recurrence rate in patients with lung cancer showing a solid area diameter of 10 to 15 mm and a proportion of GGO less than 10% was higher than in patients with lung cancer showing a solid area measuring 15 to 20 mm and the same proportion of GGO (Table 4). We speculate that some of these results occurred by chance, because each category included few cases and some resulted from other compounding factors such as the type of operation, because multivariate analysis disclosed that nonanatomical resection for compromised patients was significantly associated with a poorer DFS.

The previous studies investigated only patients with adenocarcinoma [14]. The reason for focusing on adenocarcinoma was that GGO is usually observed only in this histologic type. However, we analyzed all histologic types instead of focusing on adenocarcinoma. This is because our study involved a preoperative setting, and the histologic diagnosis may not be determined preoperatively, especially when the nodule size is small. In addition, we believe that all histologic types should be included for the TNM classification. When we analyzed only adenocarcinoma cases, the core results remained unchanged.

In conclusion, the solid area diameter is a simple and more effective measurement than the whole nodule diameter for predicting less invasive lung cancer or postoperative recurrence. Therefore, this measurement should be tested as a candidate T descriptor in the next revision of the TNM classification. Conversely, the proportion of GGO remains important for the selection of patients with less invasive lung cancer who may benefit from limited surgical resection.

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INVITED COMMENTARY

The early detection of lung cancer can provide an important opportunity to decrease mortality. Recent data from the National Lung Screening Trial, which assessed the risks and benefits of helical low-dose computed tomography of the chest (LDCT) compared with chest radiographs for detecting lung cancer, supported using LDCT to screen selected patients who are at high risk for lung cancer (http://www.cancer.gov/nlst).

Japan is the most well-equipped country in terms of CT instrumentation, and all individuals have an equal chance to undergo LDCT or ordinary CT, regardless of their theoretical risk of the development of lung cancer, because of the establishment of the Japanese national insurance system. Over the past 20 years, more than half of the individuals who underwent operation for lung cancer in Japan have had clinical stage I disease.

Matsuguma and colleagues [1] retrospectively assessed the relationships of the proportion of ground-glass opacity, the whole tumor diameter, and the solid tumor diameter in patients with resected clinical stage I non–small-cell lung cancer with the clinicopathologic factors, including the invasiveness and recurrence of the cancer after operation. The results showed that the solid area diameter might be a more useful predictor of less invasive lung cancer than the whole tumor diameter. Moreover, the proportion of ground-glass opacity was found to be useful for selecting patients with less invasive lung cancer who might benefit from limited surgical resection. However, in this study, Table 1 indicated that 25% and 16.9% of the patients had undergone limited resection, such as segmentectomy or wedge resection, or no nodal dissection at all, respectively. These percentages might indicate that the authors had a bias toward patients who would have a noninvasive cancer (nonsolid tumor), for which it would be unnecessary to perform the standard lobectomy or mediastinal node dissection. An additional bias might include the fact that those patients who received only limited resection for their nodular shadow, regardless of whether they had a nonsolid or solid tumor, might have poor pulmonary function. To rule out such bias, this kind of retrospective cohort study should exclude those patients from the study.

The important findings of the present paper are the following: (1) It may be possible to identify minimally invasive adenocarcinoma, which is defined as a lepidic predominant tumor with 5 mm or less invasion noted by pathologic examination at clinical staging and (2) a prospective study of prognostic factors in partially solid tumors (measurement of the solid part versus the whole tumor) should be conducted.

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Prognostic Impact of Tumor Size Eliminating the Ground Glass Opacity Component

Modified Clinical T Descriptors of the Tumor, Node, Metastasis Classification of Lung Cancer

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Introduction: The presence of ground glass opacity (GGO) on high-resolution computed tomography (HRCT) is well known to be pathologically closely associated with adenocarcinoma in situ. Recently, measuring the tumor diameter including areas of GGO on HRCT has been reported to possibly overestimate the T status. The purpose of this study was to evaluate the significance of the tumor size measured eliminating the area of GGO on HRCT as a prognostic factor and to propose a refined TNM classification based on modified T descriptors.

Methods: Four hundred seventy-five patients with clinical T1a-T2bN0M0 non-small-cell lung cancer underwent surgical resection. All tumors were reclassified based on the diameter measured eliminating the GGO area on HRCT according to the seventh TNM classification of lung cancer. We defined this new classification as modified T descriptors categorizing into five groups: mTis, mT1a, mT1b, mT2a, and mT2b. The overall survival rates of the patients in the current and modified staging groups were evaluated.

Results: The 5-year survival rates were 88% and 82% in the patients with T1a and T1b tumors and 90% and 75% in the patients with mT1a and mT1b tumors, respectively. The differences in the survival rate of the patients classified by using mT1a and the other modified T descriptors were more clearly separated statistically than those of the patients classified by using the current T1a and other T descriptors.

Conclusion: The modified T descriptors of the tumor size measured eliminating the GGO component on HRCT more clearly classified the prognoses of patients with early lung cancer than did the current T classification.

Key Words: Tumor, node, metastasis classification, Lung cancer, Staging, Tumor size, Ground glass opacity.

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Since the introduction of low-dose helical computed tomography (CT) in lung cancer screening, small primary lung cancers that could not previously be detected with conventional radiography have become identifiable at earlier and potentially more curable stages.[1,2] Among the small nodules detected during CT screening, many cases of adenocarcinoma have been found.[1,3] The prevalence of adenocarcinoma, especially that of adenocarcinoma with a lepidic growth pattern, has markedly increased in recent years as the most frequent histologic subtype of lung cancer.[4–6]

Some cases of adenocarcinoma exhibit areas of ground glass opacity (GGO) on high-resolution CT (HRCT) which reflect a lepidic growth pattern of tumor cells microscopically.[7] Therefore, lung tumors that display areas of focal GGO on HRCT contain components of pathologic lepidic tumor growth.[8] The majority of areas of pure GGO on HRCT have been shown to be adenocarcinoma in situ lesions pathologically.[9,10] Lung adenocarcinomas exhibiting part-solid nodules with a large proportion of GGO have also been demonstrated to tend to be less invasive than solid or mostly solid tumors of the same size.[7,8,11,12] These findings are reflected in the recently revised international multidisciplinary classification of lung adenocarcinoma sponsored by the International Association for the Study of Lung Cancer, American Thoracic Society and European Respiratory Society.[13] In these new criteria, the radiologic features are described as part of a multidisciplinary approach to the comprehensive classification of adenocarcinoma. With respect to early adenocarcinoma in particular, a crucial question has been raised: *How should the tumor size be measured?*

Since mid-1970s, the tumor size has been a primary descriptive and significant prognostic factor for lung cancer in the tumor, node, metastasis (TNM) classification of the Union for International Cancer Control (UICC) staging system.[14] According to the present classification[15] revised in 2009, the T classification of T1a to T3 was changed as follows: tumors with diameter of 2 cm or less are classified as T1a, tumors with diameter of greater than 2 cm but not more than 3 cm are classified as T1b, tumors with diameter of greater than 3 cm but more than 5 cm are classified as T2a, tumors with diameter of greater than 5 cm but not more than 7 cm are classified as T2b, and tumors with diameter of greater than 7 cm are classified as T3. Recently, suggestions for the next revisions of the UICC and American Joint Committee on Cancer staging systems have been proposed. Tsutani et al.,[16] Matsuguma et al.,[17] and Maeyashiki et al.[18] demonstrated that the solid-area diameter without GGO on HRCT is a more effective measurement of tumor nodules for predicting the prognoses of patients with non–small-cell lung cancer and proposed the measurement of the solid-area diameter as the T descriptor in the future revision of the TNM classification.

The purpose of this study was to evaluate the significance of the tumor size measured eliminating the area of GGO as a prognostic factor based on modified T descriptors.

PATIENTS AND METHODS

This study was approved by the institutional review board of Nagoya University Hospital, Nagoya, Japan. Between January 2005 and December 2010, 700 patients with primary lung cancer underwent surgical resection with curative intent at our institution. Of these patients, 490 were given a clinical diagnosis of T1aN0M0 to T2bN0M0 non–small-cell carcinoma. Among them, 475 underwent HRCT and provided follow-up data; these patients constituted the study population. All patients underwent physical examination, chest radiography, and magnetic resonance imaging of the brain and CT of the chest and abdomen for tumor staging and an evaluation of resectability before surgery. The patients were scheduled for checkups every 1 to 3 months for 2 years after surgery and every 6 months thereafter. In patients with a high risk of recurrence, chest CT was performed every 6 to 12 months by physician's recommendation. Furthermore, when the occurrence of recurrence was suspected, additional imaging surveys were performed.

HRCT images were obtained with use of 4- or 16-row multislice CT scanners (Aquilion; Toshiba Medical Systems, Tokyo, Japan) without contrast medium. An image sliced transversely at the center of the nodule was selected to measure the tumor diameter. For image reconstruction, we used a 0.5- to 2.0-mm slice thickness and a lung algorithm (FC50, FC82, FC83). The image size was 512 × 512 pixels. Image data stored in the Digital Imaging and Communications in Medicine format were transferred from the CT scanner to a personal computer for the image analysis. The images were displayed at lung window settings of a level of −600 HU and a width of 1,500 HU. Two authors (SN and TF) manually measured the maximum diameter of the pulmonary nodules on a computer screen and distinguished areas of GGO from solid regions, removing air space, air bronchograms, and large vessels.

GGO was defined as the presence of a hazy increased opacity of the lung with preservation of the bronchial and vascular margins. The solid area of the tumor was defined as the area observed after eliminating all regions of GGO in the entire nodule. We defined the size of the solid component as the maximum dimension of the solid component after excluding the areas of GGO at the lung windows (Fig. 1). The tumor size calculated eliminating the GGO component was primarily measured on axial slices, and when the maximum size was obtained on a coronal or sagittal slice of HRCT, the largest size on the slice was selected. Discrepancies in evaluating the diameter of the solid component were resolved by averaging. All tumors were reclassified on the basis of the diameter

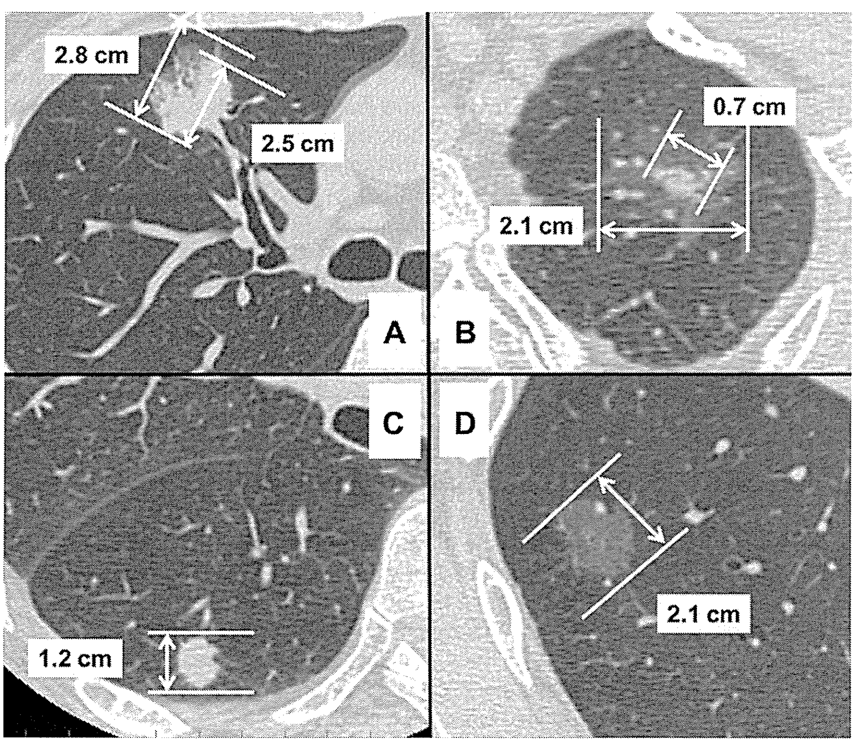

FIGURE 1. Examples of whole tumor sizes and tumor sizes calculated eliminating the areas of GGO (solid tumor size) on high-resolution computed tomography. *A*, Whole tumor size: 2.8 cm (T1b) and solid tumor size: 2.5 cm (mT1b). *B*, Whole and solid tumor sizes: 2.1 cm (T1b) and 0.7 cm (mT1a). *C*, Whole and solid tumor sizes: 1.2 cm (T1a) and 1.2 cm (mT1a). *D*, Whole and solid tumor sizes: 2.1 cm (T1b) and 0.0 cm (mTis). GGO, ground glass opacity.

measured eliminating the area of GGO according to the seventh TNM classification of lung cancer, and this new classification was defined as *modified T descriptors* categorizing into five groups: mTis, mT1a, mT1b, mT2a, and mT2b. The rates of overall survival (OS) and disease-free survival (DFS) were evaluated according to the current and modified staging groups.

The concordance of the categorizations of the current and modified T descriptors was examined using the weighted κ coefficient. OS was defined as the time from surgery to death from any cause or to the date of the last visit of patients without events. DFS was defined as the time from surgery to the detection of relapse and metastasis, to death from any cause, or to the date of the last visit of patients without events. OS and DFS curves were estimated by using the Kaplan–Meier method and compared by using the log-rank test. Univariate and multivariate Cox regression analyses were used to estimate the hazard ratios, 95% confidence intervals, and effects of the clinical variables on the survival rates. The separation index proposed by Sauerbrei et al.[19] was used to evaluate the degree of separation of the survival curves among the four groups determined on the basis of the two T classifications. A larger separation index indicates a better degree of separation. A two-sided p value of less than 0.05 was considered to be statistically significant. All statistical analyses were performed by using the SAS software package (version 9.3; SAS Institute Inc., Cary, NC).

TABLE 1. Patient Demographics

Total patients	475
Observation period (month)	
Median	40
Range	2–101
Age (yr)	
Median	69
Range	26–87
Sex	
Men	304 (64.0%)
Women	171 (36.0%)
Maximum tumor diameter including GGO area (mm)	
Median	26
Range	7–70
Maximum tumor diameter eliminated GGO area (mm)	
Median	25
Range	0–70
Clinical stage according to the current TNM classification	
T1a N0 M0	191 (40.2%)
T1b N0 M0	147 (30.9%)
T2a N0 M0	124 (26.2%)
T2b N0 M0	13 (2.7%)
Histology	
Adenocarcinoma	353
Squamous cell carcinoma	77
Others	45

GGO, ground glass opacity; TNM, tumor, node, metastasis.

RESULTS

The characteristics of the 475 patients are summarized in Table 1. According to the current TNM staging system, the tumors were distributed as follows: T1a, n = 191 (40.2%); T1b, n = 147 (30.9%); T2a, n = 124 (26.2%); and T2b, n = 13 (2.7%). When applying the modified T classification, the tumors were distributed as follows: mTis, n = 16 (3.4%); mT1a, n = 253 (53.3%); mT1b, n = 112 (23.6%); mT2a, n = 81 (17.1%); and mT2b, n = 13 (2.7%). Comparing the two distributions classified according to each T descriptor, the proportion of tumors in the mT1a class was remarkably increased after the reclassification of T1b and T2a diseases. Sixteen tumors were shifted to the mTis status from the T1a, T1b, and T2a status, and 62 tumors were shifted to the mT1a status from the T1b and T2a status, with most tumors changing from T1b to mT1a (n = 50) (Fig. 2). The weighted κ coefficient of the concordance of categorization between the current and modified T classifications was 0.73.

The OS curves and 5-year survival rates according to the current and modified T staging systems are shown in Figure 3. Table 2 shows the results of the univariate and multivariate Cox regression analyses of OS based on the current and modified T classifications. Other prognostic factors in the analyses included age, sex, and histological type. The difference in the survival functions between mT1a and mT1b was statistically significant (p = 0.0042 and p = 0.0446 for the univariate and multivariate analyses, respectively), whereas no significant differences were observed between T1a and T1b (p = 0.1524 and p = 0.2158 for the univariate and multivariate analyses, respectively). The differences in the survival functions between mT1a and all other modified T descriptors except mTis were significant, as were the differences between T1a and the other T descriptors except for T1b. The separation indices of the OS curves for the current and modified T classifications were 4.75 and 5.31, respectively.

The DFS curves and 5-year DFS rates according to the current and modified T classification systems are shown in Figure 4. Table 3 shows the results of the univariate and

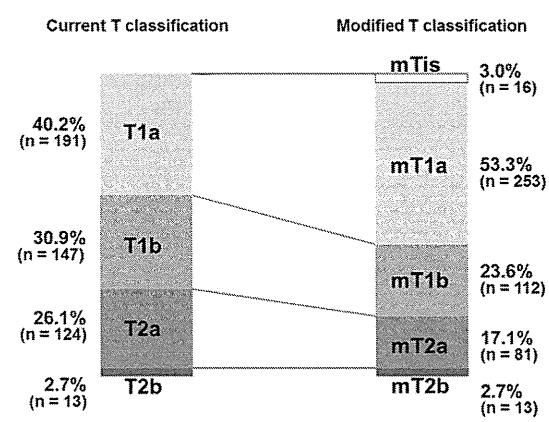

FIGURE 2. Distribution of the patients according to the current and modified T status groups. The proportion of patients with mT1a disease increased remarkably because these tumors were reclassified from T1b and T2a.

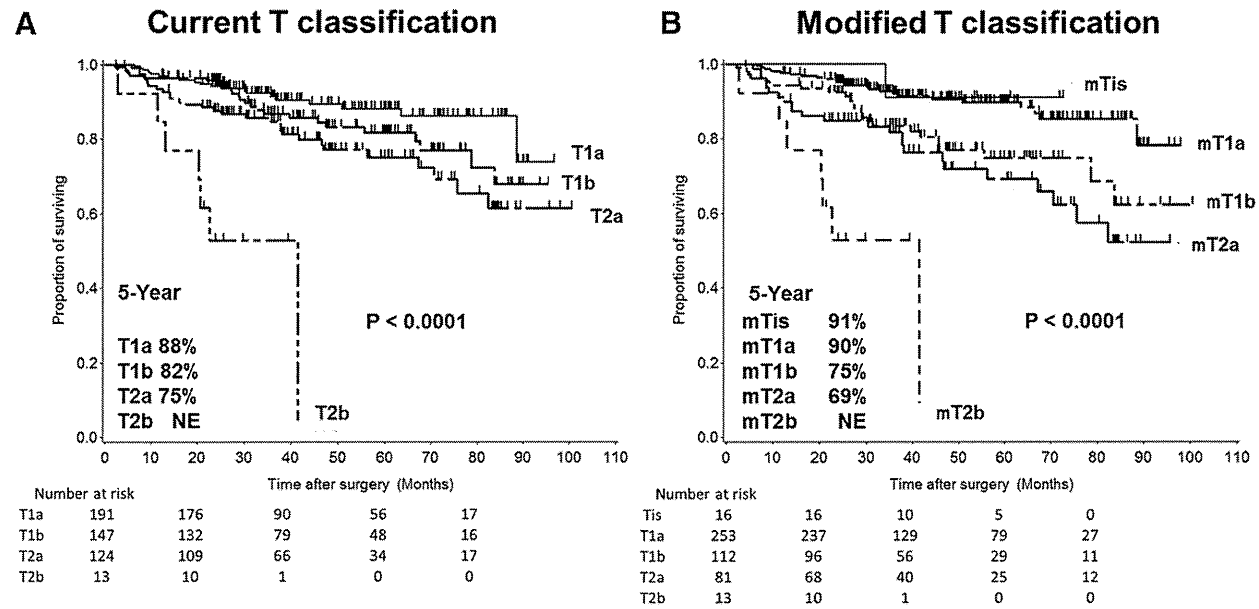

FIGURE 3. Overall survival based on the current T classification (*A*) and modified T classification (*B*). NE, not evaluable.

multivariate Cox regression analyses of DFS based on the current and modified T classifications. The difference in the survival functions between mT1a and mT1b was statistically significant ($p = 0.0007$ and $p = 0.0033$ for the univariate and multivariate analyses, respectively), whereas no significant differences were observed between T1a and T1b ($p = 0.1840$ and $p = 0.2344$ for the univariate and multivariate analyses, respectively). Similar to the results for OS, according to the univariate and multivariate Cox regression analyses, the differences in the survival functions between mT1a and all other modified T descriptors except mTis were significant, as were the differences between T1a and the other T descriptors except for T1b. The separation indices of the DFS curves for the current and modified T classifications were 4.77 and 6.69, respectively.

The correlations between the current and modified T statuses and pathological findings are shown in Table 4. Among the tumors downstaged by modifying the T status, all except one case of squamous cell carcinoma were adenocarcinomas. The squamous cell carcinoma lesion presented as a peripheral part-solid nodule of the right lower lobe of the lung on HRCT. The GGO area was pathologically revealed to be obstructive pneumonia in contact with the solid part of the tumor. All tumors classified as having an mTis status presenting as pure GGO nodules on HRCT were revealed to be early adenocarcinomas pathologically, and all patients with mTis

TABLE 2. Results of the Univariate and Multivariate Cox Regression Analyses of Overall Survival According to the Current and Modified T Classifications

		Univariate			Multivariate		
Clinical Staging	**Number**	**HR**	**95% CI**	***p***	**HR[a]**	**95% CI**	***p***
Current							
T1a	191	1			1		
T1b	147	1.52	(0.85–2.79)	0.1524	1.46	(0.80–2.66)	0.2158
T2a	124	2.22	(1.26–3.93)	0.0061	1.90	(1.07–3.38)	0.0295
T2b	13	10.68	(4.44–25.71)	<0.0001	7.62	(3.11–18.67)	<0.0001
Modified							
mTis	16	0.63	(0.09–4.64)	0.6491	0.76	(0.10–5.66)	0.7912
mT1a	253	1			1		
mT1b	112	2.29	(1.30–4.03)	0.0042	1.81	(1.01–3.23)	0.0446
mT2a	81	3.14	(1.79–5.50)	<0.0001	2.65	(1.47–4.79)	0.0012
mT2b	13	11.76	(4.99–27.73)	<0.0001	8.50	(3.53–20.46)	<0.0001

Multivariate analysis: HR adjusted by age, sex, and histological types.
HR, hazard ratio; CI, confidence interval.

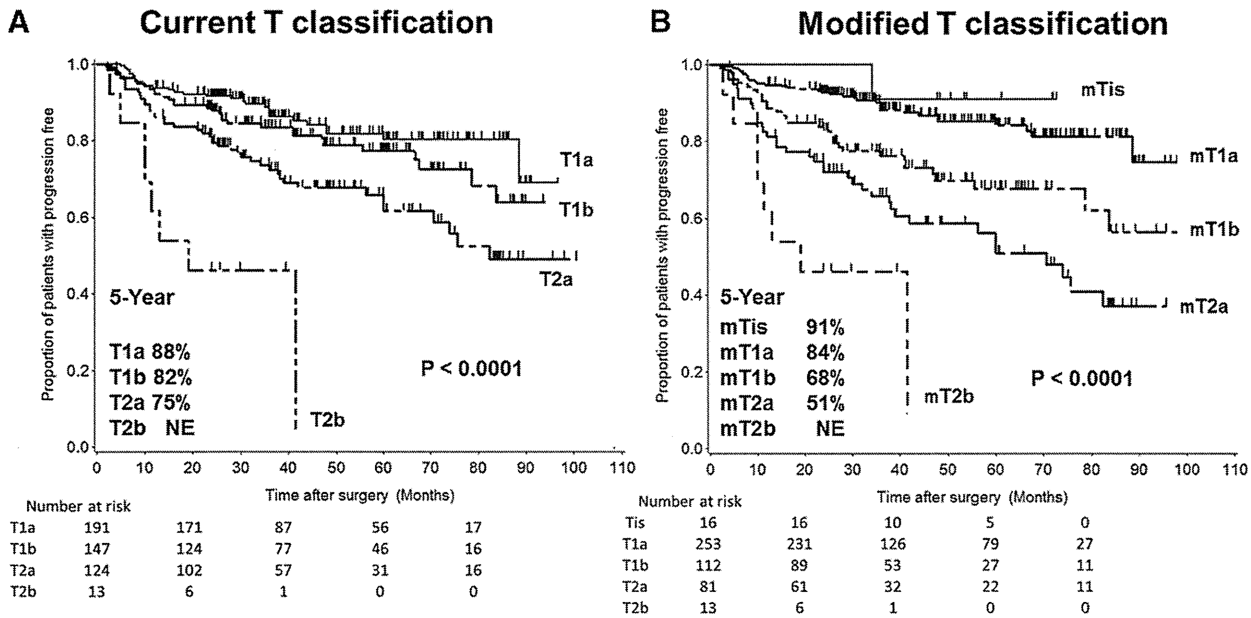

FIGURE 4. Disease-free survival based on the current T classification (*A*) and modified T classification (*B*). NE, not evaluable

tumors survived without recurrence, except for one who died of other disease.

DISCUSSION

The TNM classification of cancers proposed by the UICC is a widely accepted guide for estimating prognosis, selecting therapy, and facilitating the development of new treatment strategies. In 1974, the American Joint Committee on Cancer and UICC applied the TNM cancer staging system to lung cancer.[20] In the current edition issued in 2009, the International Association for the Study of Lung Cancer Staging Committee changed the size classification of T1a to T3.[15] According to the TNM classification, the T descriptor defines the primary tumor based on the size, airway location, and degree of local invasion. The tumor size is one of the most important prognostic determinants in this classification and can be determined before surgery by using radiological imaging.

Recent improvements in imaging technology and the widespread use of CT scans for screening have increased the probability of detecting small-sized lung cancers. Small-sized lung cancers often contain nonsolid components exhibiting areas of GGO with various proportions of solid components on HRCT. Many investigators have reported that the presence of GGO on HRCT is closely associated with a lepidic growth pattern in patients with adenocarcinoma of the lungs.[21–23]

TABLE 3. Results of the Univariate and Multivariate Cox Regression Analyses of Disease-Free Survival According to the Current and Modified T Classifications

		Univariate			Multivariate		
Clinical Staging	**Number**	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***
Current							
T1a	191	1			1		
T1b	147	1.41	(0.85–2.34)	0.1840	1.36	(0.82–2.27)	0.2158
T2a	124	2.41	(1.50–3.85)	0.0003	2.16	(1.34–3.48)	0.0016
T2b	13	7.97	(3.61–17.59)	<0.0001	6.46	(2.89–14.46)	<0.0001
Modified							
mTis	16	0.45	(0.06–3.31)	0.4341	0.48	(0.07–3.51)	0.4682
mT1a	253	1			1		
mT1b	112	2.32	(1.43–3.78)	0.0007	2.10	(1.28–3.46)	0.0033
mT2a	81	3.89	(2.44–6.20)	<0.0001	3.72	(2.28–6.06)	<0.0001
mT2b	13	9.33	(4.27–20.38)	<0.0001	8.11	(3.66–17.98)	<0.0001

Multivariate analysis: HR adjusted by age, sex, and histological types
HR, hazard ratio; CI, confidence interval.

TABLE 4. Comparison between the Current and Modified T Statuses and Pathological Findings

	Adenocarcinoma				
Clinical Staging	**AIS***	**MIA***	**IA***	**SQ**	**Others**
Current					
T1a	16	23	107	26	19
T1b	6	16	90	25	10
T2a	0	12	75	22	15
T2b	0	0	8	4	1
Modified					
mTis	12	4	0	0	0
mT1a	10	43	154	27	19
mT1b	0	4	74	24	10
mT2a	0	0	44	22	15
mT2b	0	0	8	4	1

AIS, adenocarcinoma in situ; MIA, minimally invasive adenocarcinoma; IA, invasive adenocarcinoma; SQ, squamous cell carcinoma.

Furthermore, a large prospective study on clinical stage IA cancer of the lungs led to a definition of radiological noninvasive adenocarcinoma of the lungs based on the findings of CT scans.[24,25] Those data demonstrated that patients with radiological noninvasive adenocarcinoma of the lungs have very good prognoses, with tumors that are found to exhibit a minimally invasive nature on pathological examinations. On the basis of the results of these studies, measuring the tumor diameter, including the area of GGO, on HRCT has been reported to possibly overestimate the T status.[8,9,26] The findings of these reports are reflected in the recently revised international multidisciplinary classification of lung adenocarcinoma.[13] With respect to the radiologic features of early adenocarcinoma, a crucial question has been raised: *How should the tumor size be measured?*

Many investigators have reported methods for assessing part-solid tumors. Nevertheless, a few reports have investigated the relevance of the tumor appearance for the prognosis or possibility of recurrence. Tsutani et al.[16] evaluated the role of the solid tumor size in cases of clinical stage IA lung adenocarcinoma and retrospectively compared the prognostic significance of the solid tumor size with that of the size of the entire tumor. They found that the solid tumor size more clearly reflects the pathologic findings related to tumor aggressiveness and/or prognosis. Subsequently, Matsuguma et al.[17] compared the solid area and whole nodule diameters with the proportion of GGO in tumors with respect to estimating tumor invasiveness and recurrence and demonstrated that evaluating the combination of the solid-area diameter and the proportion of GGO was the best method. Nevertheless, they also reported that adding the proportion of GGO for assessing tumors is complicated with regard to the staging system and difficult to perform in daily practice. Consequently, they concluded that the solid-area diameter is more suitable for predicting less invasive lung cancer and/or postoperative recurrence than the whole tumor diameter. These results supported and encouraged our present study, which assessed the value of this measurement method as a prognostic factor.

Concerning the image settings of HRCT for assessing lung nodules, many other studies, including above mentioned two studies and our study, used almost the same lung window settings and arrived at similar results.[10,18,24,27–29] We believe that lung window settings used in daily practice are the most useful and reasonable settings.

The general rules of the TNM system state in the TNM supplement[30] that *when size is a criterion for the T category, it is a measurement of the invasive component*, which means that measurements of the tumor diameter should eliminate the area of GGO on HRCT. This description also prompted us to examine the significance of measuring the tumor size eliminating the area of GGO, in other words, measuring the tumor size including only the *invasive* area on HRCT.

In our series, the OS curves of the patients classified with our *modified T descriptors* were more clearly separated than those of the patients classified with the current T descriptors included in the seventh edition of the TNM classification. Similarly, the DFS curves of the patients classified with the *modified T descriptors* were more clearly separated in each curve than those of the patients classified by using the current system. The *modified T classification* divided the survival curves more clearly than the current T classification because the component of a lepidic growth pattern (the noninvasive component) was eliminated from the whole tumor diameter radiologically by eliminating the area of GGO on HRCT. In other words, the eliminated area of GGO may not influence the patient's survival.

Nevertheless, the T status of all but one nonadenocarcinoma case was not affected by the use of our modified T descriptors. This is because almost all nonadenocarcinoma nodules presented as pure-solid lesions on HRCT. Moreover, the survival of these patients was compatible with that of the adenocarcinoma patients according to the modified T descriptors. On the basis of these results, we considered that the method which measures the tumor size by eliminating the GGO component can be adapted for both adenocarcinoma and other non–small-cell lung cancers. Matsuguma et al.[17] reported the effectiveness of measuring only the solid diameter of the tumor for predicting less invasive lung cancer and the occurrence of postoperative recurrence in patients with non–small-cell lung cancer.

To examine the ability to predict the prognosis based on the modified T classification, we compared the separation index, a measure of the degree of separation of the survival curves among the four groups, between the modified and current T classifications. The index was calculated by using the hazard ratios determined after adjusting for age, sex, and histological type, as shown in Tables 3 and 4. A larger value indicates a better degree of separation. The adjusted hazard ratios for OS and DFS and their separation indices demonstrated that our modified classification more effectively predicted the prognosis than the current classification.

Our study had several limitations. First, our study was of retrospective design. Nevertheless, in this study, we analyzed patient survival by using two methods of measuring the tumor diameter based only on preoperative characteristics, regardless of the postsurgical results. Second, we did not investigate the relationship between the T descriptors and positron emission tomography/CT findings in our cohort. Although the maximum standardized uptake value on positron emission tomography/CT is still not integrated into the TNM classification, it may provide additional information preoperatively.[31]

In conclusion, we reclassified tumors according to the size eliminating the area of GGO on HRCT and confirmed the OS and DFS rates in patients with clinical T1aN0M0 to T2bN0M0 non–small-cell lung cancer. Our present results showed that the modified T descriptors eliminating the area of GGO on HRCT more clearly classify the prognoses of patients with clinically early lung cancer than the current T classification did. We believe that our modified T descriptors are powerful prognostic factors and indicators for identifying the prognosis more clearly. Further investigations are needed to assess and compare this method with other measuring methods and window settings on HRCT of lung nodules with respect to accurately reflecting patient survival.

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ORIGINAL ARTICLE

Differences in the prognosis of resected lung adenocarcinoma according to the histological subtype: a retrospective analysis of Japanese lung cancer registry data

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Abstract

OBJECTIVES: This study intended to assess the clinicopathological features of the histological subtypes of adenocarcinoma of the lung in a large registry population.

METHODS: The Japanese Joint Committee of Lung Cancer Registry performed a nationwide retrospective registry study on the prognosis and clinicopathological profiles of 11 663 patients who underwent resection for primary lung neoplasm in 2004. The registry data of 7921 (62.5%) patients with adenocarcinoma were analysed regarding the prognosis and clinicopathological features according to the histological subtype of adenocarcinoma. The histological subtypes were defined according to the 1999 World Health Organization classification (third edition), where bronchioloalveolar carcinoma (BAC) is defined as adenocarcinoma with a pure bronchioloalveolar growth pattern without invasion.

RESULTS: The distribution of the histological subtype was acinar in 471 patients (7.5%), papillary in 2004 (32.2%), BAC in 1385 (22.3%), solid adenocarcinoma with mucin in 103 (1.7%) and adenocarcinoma with mixed subtypes (AMS) in 2257 (36.3%). The 5-year overall survival rates according to histological subtype were 63.4% for acinar, 72.9% for papillary, 90.3% for BAC, 54.4% for solid adenocarcinoma with mucin and 73.7% for AMS. While the survival rate in patients with BAC was significantly better than those for the other histological subtypes, acinar and solid adenocarcinoma with mucin had significantly worse prognoses than the other histological subtypes. The histological subtype was an independent predictor of survival in a multivariate analysis ($P < 0.001$). Regarding BAC, the pathological stage included not only Stage IA/IB ($n = 1275$; 92.1%), but also Stage II–IV ($n = 110$; 7.9%). One hundred twenty-five patients (9.0%) with BAC had recurrence, including both local and distant recurrence.

CONCLUSIONS: The histological subtype in adenocarcinoma significantly correlated with the prognosis. In BACs with recurrence or pathological stage II–IV, these tumours might have been classified as invasive adenocarcinoma rather than as BAC. The need for the rigorous pathological evaluation of adenocarcinomas that are considered to be a preinvasive or minimally invasive tumour should be addressed in the new lung adenocarcinoma classification to be proposed by the International Association for the Study of Lung Cancer, the American Thoracic Society and the European Respiratory Society.

Keywords: Database • Histology • Lung cancer surgery • Lung pathology • Outcomes

INTRODUCTION

Adenocarcinoma of the lung is the most common histology of lung cancer in Japan, and the proportion of adenocarcinoma has been increasing in many countries [1, 2]. Adenocarcinomas frequently exhibit a heterogeneous histology, while combining bronchioloalveolar (lepidic), papillary, acinar and solid growth patterns [1]. The histological subtyping of lung adenocarcinoma has developed over the past several decades as reflected in the World Health Organization (WHO) classification. The most significant change was introduced in the third edition of the latter in 1999 [3]. In the third edition, the histological subtype of adenocarcinoma consisted of five subtypes based on the histological growth pattern, i.e. four pure forms [acinar, papillary, bronchioloalveolar carcinoma (BAC) and solid adenocarcinoma with mucin] and one heterogeneous form [adenocarcinoma with mixed subtypes (AMS), which shows a variable admixture of more than one histological subtype pattern]. In particular, BAC was strictly defined as a noninvasive tumour with a pure lepidic growth pattern [3].

Several important prognostic factors have been identified, such as tumour-node-metastasis (TNM) stage, performance status, gender, age, histology and so forth [4, 5]. Although it has been speculated that the particular biological behaviour likely influences the presence of specific histological growth patterns of adenocarcinoma [6], the relationship between the histological subtype of adenocarcinoma and prognosis has not been clearly demonstrated in a large cohort. For BACs, an excellent prognosis should be expected based on the definition of BAC as a noninvasive tumour. Nevertheless, in previous reports based on the 1999 WHO classification, resected BACs were not necessarily associated with satisfactory prognosis even if they were in stage I [6–8].

In Japan, the task force committee of the Japanese Joint Committee of Lung Cancer Registry has periodically performed nationwide registry studies on the prognosis and clinicopathological profiles of lung neoplasms [2, 4]. Recently, the committee reported a retrospective registry study that focused on 11 663 cases of lung cancer resected in 2004 after a 5-year follow-up period [2]. The present study deals with this retrospective registry for patients with lung cancer resected in 2004. This registry data has been used in other publications previously without direct overlap with the present study [9].

The aim of this study was to evaluate the clinicopathological characteristics and prognostic implications according to the histological subtypes of lung adenocarcinoma based on the 1999 third edition of the WHO classification [3], and furthermore to investigate the pattern of recurrence in BAC, which has been defined as a noninvasive adenocarcinoma.

PATIENTS AND METHODS

Registry

In 2010, the Japanese Joint Committee of Lung Cancer Registry performed a nationwide retrospective registry study on the prognosis and clinicopathological profiles of resected lung neoplasms in Japan. The committee received the registries of 11 663 patients from 253 teaching hospitals. The registered data included the clinicopathological and prognostic items, which had been described previously [2]. Recurrent or multiple lung cancers were not included in this registry. Cancer recurrence was divided into three categories according to the site of the initial relapse: loco-regional, distant and at both sites simultaneously. Loco-regional recurrence was defined as any recurrent disease within the ipsilateral hemithorax, mediastinum or supraclavicular lymph nodes. All other sites of recurrence were considered distant recurrence. The cause of death was recorded as either lung-cancer-related, other disease or unknown. The data relating to survival time, recurrence, and cause of death were collected from a medical chart or a national death registry in the respective teaching hospitals. Although the method of data collection for the postoperative follow-up was not standardized because of a retrospective study, the postoperative follow-up was regularly scheduled in the respective teaching hospitals. All patients were staged on the basis of the seventh edition of the Union for International Cancer Control TNM Classification of the malignant tumour staging system published in 2009 [10]. Tumour histology was described according to the third edition of the WHO classification published in 1999 [3], where lung adenocarcinomas were subclassified into the following five histological subtypes: acinar, papillary, BAC, solid adenocarcinoma with mucin and AMS, and variants such as well-differentiated foetal adenocarcinoma, colloid adenocarcinoma, mucinous cystadenocarcinoma, signet-ring adenocarcinoma or clear cell adenocarcinoma. In addition, BAC was cytologically subdivided into three groups: non-mucinous, mucinous and mixed mucinous and non-mucinous or indeterminate.

Patients

The study focused on patients with an adenocarcinoma histology. Of the 11 663 registered patients, 7921 (62.5%) had adenocarcinoma. Patients with variants such as well-differentiated foetal adenocarcinoma ($n = 3$), colloid adenocarcinoma ($n = 4$), mucinous cystadenocarcinoma ($n = 3$), signet-ring adenocarcinoma ($n = 9$) or clear cell adenocarcinoma ($n = 11$) and those ($n = 1671$) with incomplete data regarding the histological subtype of adenocarcinoma were excluded. The remaining 6220 patients were analysed in terms of prognosis and clinicopathological characteristics according to the histological subtype of adenocarcinoma.

Statistical analysis

The χ^2 test and one-way analysis of variance were used to evaluate the differences in categorical variables and continuous variables, respectively. The survival time was defined as the time between the date of surgery and the last follow-up date. The survival curves were estimated by the Kaplan–Meier method, and differences in survival were assessed by the log-rank test. Overall survival was defined as the time between the operation and death from any cause. Disease-free survival was defined as the time between the operation and disease recurrence, lung cancer-related death or the last follow-up. A multivariate analysis by a Cox proportional hazards model was used to test the significance of prognostic factors, including gender, age, smoking status, operative mode, surgical curability, histological subtype of adenocarcinoma, tumour size, p-T status and p-N status. Significance was defined as a P-value of <0.05. All statistical analyses were performed with the SAS version 9.1.3 (SAS Institute, Inc., Cary, NC, USA) or with IBM SPSS version 19 (IBM Corporation, NY, USA).

RESULTS

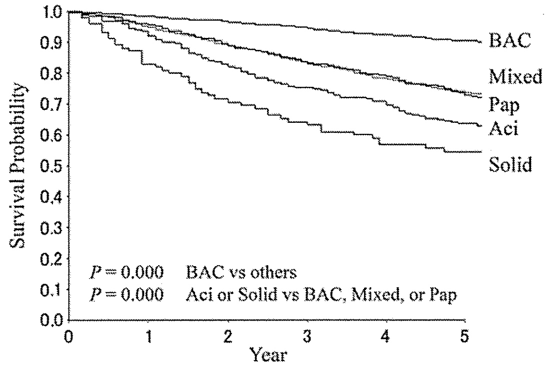
Clinicopathological features

The distribution of histological subtypes in adenocarcinoma is as follows. The most common subtype was AMS ($n = 2257$; 36.3%), followed by papillary ($n = 2004$; 32.2%), BAC ($n = 1385$; 22.3%), acinar ($n = 471$; 7.5%) and solid adenocarcinoma ($n = 103$; 1.7%). Of the 1385 patients with BAC, 1110 (80.1%) had non-mucinous type, 102 (7.4%) had mucinous type and 173 (12.5%) had mixed mucinous and non-mucinous or indeterminate type. The clinicopathological features according to the histological subtype are summarized in Table 1. The mean age at surgical resection for patients with solid adenocarcinoma was significantly younger than that for patients with other subtypes. With regard to gender, the proportion of females in BAC was significantly greater than that in other subtypes, whereas the proportion of males in solid adenocarcinoma was significantly greater than that in other subtypes. The proportion of smokers was significantly higher in those with acinar and solid adenocarcinoma than in those with other subtypes, whereas it was significantly lower in patients with BAC than in those with other subtypes. One hundred fifty-seven patients (2.5%) of all the 6220 patients received neoadjuvant therapy. The neoadjuvant therapy included chemotherapy (*n* = 111; 1.8%), radiotherapy (*n* = 4; 0.1%), chemoradiotherapy (*n* = 34; 0.5%) and others (*n* = 8; 0.1%). The proportion of patients who received neoadjuvant therapy was significantly higher in patients with solid adenocarcinoma than in those with other subtypes, whereas it was significantly lower in patients with BAC than in those with other subtypes. With regard to the operative mode, the proportion of pneumonectomy was higher in patients with solid adenocarcinoma than in those with other subtypes, whereas the proportion of segmentectomy/wedge resection was higher in patients with BAC than in those with other subtypes. Regarding tumour size, BAC was significantly smaller and solid

Table 1: Clinicopathological features of patients with resected adenocarcinoma of the lung according to the histological subtype

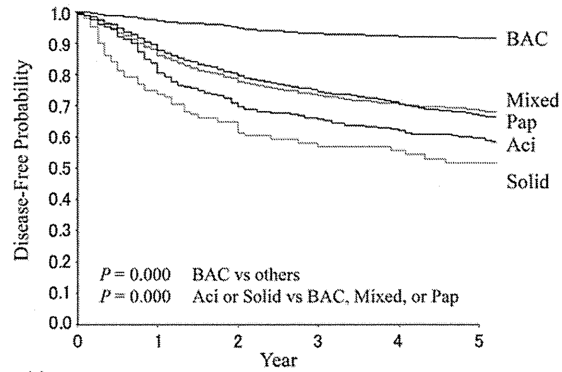
Characteristic	BAC (*n* = 1385)	Acinar (*n* = 471)	Papillary (*n* = 2004)	Solid (*n* = 103)	AMS (*n* = 2257)	*P*
Age (year)						
Mean	65.1 ± 10.3	66.0 ± 10.0	66.6 ± 9.7	63.9 ± 9.7	65.9 ± 9.7	<0.001
Sex						
Male	551 (39.8%)	309 (65.6%)	1024 (51.1%)	76 (73.8%)	1186 (52.5%)	<0.001
Female	834 (60.2%)	162 (34.4%)	980 (48.9%)	27 (26.2%)	1071 (47.5%)	
Smoking status						
Non-smoker	834 (65.3%)	158 (36.8%)	964 (51.7%)	23 (22.8%)	1093 (50.8%)	<0.001
Ex-smoker	223 (17.4%)	93 (21.7%)	341 (18.3%)	21 (20.8%)	456 (21.2%)	
Current smoker	221 (17.3%)	178 (41.5%)	560 (30.0%)	57 (56.4%)	602 (28.0%)	
Serum CEA level						
Normal	1217 (87.9%)	308 (65.4%)	1488 (74.3%)	59 (57.3%)	1616 (71.6%)	<0.001
High	168 (12.1%)	163 (34.6%)	516 (25.7%)	44 (42.7%)	641 (28.4%)	
Clinical stage						
IA	1189 (85.8%)	248 (52.7%)	1226 (61.2%)	40 (38.8%)	1374 (60.9%)	<0.001
IB	150 (10.8%)	113 (24.0%)	494 (24.7%)	28 (27.2%)	545 (24.1%)	
IIA	4 (0.3%)	5 (1.1%)	30 (1.5%)	6 (5.8%)	48 (2.1%)	
IIB	12 (0.9%)	39 (8.3%)	81 (4.0%)	10 (9.7%)	108 (4.8%)	
IIIA	13 (0.9%)	41 (8.7%)	96 (4.8%)	12 (11.7%)	113 (5.0%)	
IIIB/IV	17 (1.2%)	25 (5.2%)	77 (3.8%)	7 (6.8%)	69 (3.1%)	
Neoadjuvant therapy						
No	1374 (99.2%)	450 (95.5%)	1952 (97.4%)	93 (90.3%)	2194 (97.2%)	<0.001
Yes	11 (0.8%)	21 (4.5%)	52 (2.6%)	10 (9.7%)	63 (2.8%)	
Operative mode						
Pneumonectomy	2 (0.1%)	8 (1.7%)	27 (1.4%)	8 (7.9%)	31 (1.4%)	<0.001
Lobectomy	844 (61.2%)	382 (82.4%)	1680 (84.6%)	74 (73.3%)	1900 (85.4%)	
Segmentectomy/wedge resection	533 (38.6%)	74 (16.0%)	279 (14.1%)	19 (18.8%)	295 (13.2%)	
Curability						
R0	1364 (99.3%)	482 (92.0%)	1887 (94.8%)	98 (95.1%)	2134 (95.5%)	<0.001
R1	4 (0.3%)	15 (3.2%)	56 (2.8%)	3 (2.9%)	45 (2.0%)	
R2	6 (0.4%)	22 (4.7%)	48 (2.4%)	2 (1.9%)	56 (2.5%)	
Tumour size						
Mean	1.9 ± 1.6	3.0 ± 1.6	2.7 ± 1.5	3.5 ± 2.0	2.8 ± 1.7	<0.001
Pleural invasion						
pl0	1297 (93.8%)	286 (61.4%)	1328 (66.6%)	62 (60.2%)	1588 (71.0%)	<0.001
pl1/pl2	82 (5.9%)	139 (29.8%)	559 (28.0%)	29 (28.2%)	512 (22.9%)	
pl3	4 (0.2%)	41 (8.8%)	107 (5.4%)	12 (11.6%)	138 (6.2%)	
Pathological stage						
IA	1143 (82.5%)	165 (35.0%)	883(44.1%)	31 (30.1%)	1046 (46.4%)	<0.001
IB	132 (9.5%)	118 (25.1%)	502 (25.1%)	18 (17.5%)	489 (21.7%)	
IIA	25 (1.8%)	42 (8.9%)	135 (6.7%)	11 (10.6%)	142 (6.3%)	
IIB	32 (2.3%)	36 (7.7%)	83 (4.1%)	14 (13.6%)	106 (4.7%)	
IIIA	40 (2.9%)	84 (17.8%)	297 (14.8%)	25 (24.3%)	367 (16.2%)	
IIIB/IV	13 (1.0%)	26 (5.5%)	104 (5.2%)	4 (3.9%)	107 (4.7%)	
Adjuvant chemotherapy						
No	1235 (91.4%)	295 (65.0%)	1403 (72.3%)	61 (61.0%)	1604 (74.0%)	<0.001
Yes	116 (8.6%)	159 (35.0%)	538 (27.7%)	39 (39.0%)	565 (26.0%)	

BAC: bronchioloalveolar carcinoma; Solid: solid adenocarcinoma with mucin; AMS: adenocarcinoma with mixed subtypes.



No. at risk						
BAC	1385	1321	1269	1220	1131	922
Mixed	2257	2099	1921	1729	1543	1278
Pap	2004	1856	1686	1505	1347	1121
Aci	471	424	363	318	282	223
Solid	103	81	69	60	53	45

Figure 1: Overall survival curves based on the histological subtype of adenocarcinoma. There is a significant difference in survival between BAC and the other subtypes ($P < 0.001$) and between acinar or solid and BAC, mixed subtypes or papillary ($P < 0.001$). BAC: bronchioloalveolar carcinoma; Mixed: adenocarcinoma with mixed subtypes; Aci: acinar; Pap: papillary; Solid: solid adenocarcinoma with mucin.



No. at risk						
BAC	1385	1283	1217	1160	1073	886
Mixed	2257	1847	1601	1436	1295	1099
Pap	2004	1646	1419	1266	1127	930
Aci	471	354	286	251	221	187
Solid	103	68	57	48	45	37

Figure 2: Disease-free survival curves based on the histological subtype of adenocarcinoma. There is a significant difference in survival between BAC and the other subtypes ($P < 0.001$) and between acinar or solid and BAC, mixed subtypes or papillary ($P < 0.001$). BAC: bronchioloalveolar carcinoma; Mixed: adenocarcinoma with mixed subtypes; Aci: acinar; Pap: papillary; Solid: solid adenocarcinoma with mucin.

adenocarcinoma was significantly larger, compared with the other subtypes. Pleural invasion was significantly infrequent in BAC compared with the other subtypes. With regard to the pathological stage, BAC had significantly more cases in Stage IA and solid adenocarcinoma had more cases in Stage IIIA, compared with the other subtypes.

Survival according to the histological subtype of adenocarcinoma

The postoperative follow-up was complete in 87% of all the patients. The overall 5-year survival rates according to the histological subtype of adenocarcinoma were 90.3% in BAC, 73.7% in AMS, 72.9% in papillary, 63.4% in acinar and 54.4% in solid adenocarcinoma. The survival curves are shown in Fig. 1. Patients with BAC had significantly better overall survival than those with other subtypes ($P < 0.001$). Patients with acinar or solid adenocarcinoma had significantly worse overall survival than those with BAC, AMS or papillary subtype ($P < 0.001$). Disease-free 5-year survival rates according to the histological subtype in adenocarcinoma were 91.4% in BAC, 68.3% in mixed subtypes, 66.6% in papillary, 59.4% in acinar and 51.5% in solid adenocarcinoma with mucin (Fig. 2). Patients with BAC had significantly better disease-free survival than those with other subtypes ($P < 0.001$). Patients with acinar or solid adenocarcinoma with mucin had significantly worse disease-free survival than those with BAC, mixed subtypes or papillary subtype ($P < 0.001$).

In a Cox proportional hazards model to predict overall survival, the following factors persisted as important prognostic factors: gender, age, operative mode, histological subtype of adenocarcinoma, surgical curability, tumour size, p-T status and p-N status (Table 2). With regard to histological subtype of adenocarcinoma, BAC had a significantly better prognosis, whereas solid adenocarcinoma and acinar subtype had significantly worse prognoses.

The prognosis among histological subtypes was further examined with regard to each pathological stage. In patients with pathological stage IA, BAC had significantly better overall survival than other subtypes ($P < 0.001$) (Fig. 3A). In patients with pathological stage IB, BAC had significantly better survival than acinar or solid adenocarcinoma (Fig. 3B). In patients with pathological stage II, solid adenocarcinoma had significantly worse survival than BAC, AMS or papillary subtype (Fig. 3C). In patients with pathological stage IIIA, there were no significant differences among histological subtypes (Fig. 3D).

Death was observed in 139 (10.0%) of the 1385 patients with BAC, 168 (35.7%) of the 471 patients with acinar, 538 (26.8%) of the 2004 patients with papillary, 44 (42.7%) of the 103 patients with solid adenocarcinoma and 597 (26.5%) of the 2257 patients with AMS in their clinical course. The distribution of cause of death in patients with adenocarcinoma according to the histological subtype is given in Table 3. With regard to cause of death, patients with BAC significantly had more death from diseases other than lung cancer ($P < 0.001$) more frequently.

The recurrence was observed in 125 (9.0%) of the 1385 patients with BAC, 198 (42.0%) of the 471 patients with acinar, 658 (32.8%) of the 2004 patients with papillary, 46 (44.7%) of the 103 patients with solid adenocarcinoma and 738 (32.7%) of the 2257 patients with AMS in their clinical course. The distribution of mode of recurrence in patients with adenocarcinoma according to the histological subtype is given in Table 4. There were no significant differences in mode of recurrence among the histological subtypes ($P = 0.089$).

Prognosis of bronchioloalveolar carcinoma

Regarding the mode of recurrence, 71 (56.8%) were distant, 38 (30.4%) were loco-regional and 7 (5.6%) were both simultaneously as given in Table 4. The distribution of pathological stage in BAC patients with recurrence was 40 patients in Stage IA, 19 in Stage IB, 25 in Stage II and 41 in Stage III/IV. The recurrence in BACs in

Table 2: Multivariate analysis of overall survival for resected cases of adenocarcinoma of the lung: Cox proportional hazard model (n = 6220)

Variable	HR	95% CI	*P*
Gender			
Men	1.000		
Women	0.665	0.568–0.778	<0.001
Age (year)			<0.001
<50	1.000		
50–70	1.177	0.902–1.537	0.230
>70	2.000	1.562–2.620	<0.001
Smoking status			0.052
Non-smoker	1.000		
Ex-smoker	1.151	0.962–1.376	0.124
Current smoker	1.227	1.040–1.446	0.015
Operative mode			<0.001
Pneumonectomy	1.000		
Lobectomy	0.633	0.461–0.868	0.005
Segmentectomy	0.951	0.653–1.386	0.795
Wedge resection	1.160	0.804–1.674	0.427
Surgical curability			
Complete	1.000		
Incomplete	1.772	1.449–2.166	<0.001
Histological subtype			<0.001
Acinar	1.000		
Papillary	0.844	0.697–1.023	0.084
BAC	0.508	0.393–0.656	<0.001
Solid with mucin	1.146	0.808–1.625	0.445
Mixed subtypes	0.817	0.676–0.988	0.037
Tumour size	1.099	1.064–1.134	<0.001
p-T status			<0.001
T1a	1.000		
T1b	1.445	1.204–1.734	<0.001
T2a	1.895	1.605–2.237	<0.001
T2b	1.701	1.228–2.355	0.001
T3	2.757	2.210–3.439	<0.001
T4	2.431	1.716–3.444	<0.001
p-N status			<0.001
N0	1.000		
N1	2.251	1.883–2.691	<0.001
N2	3.462	3.058–3.919	<0.001
N3	6.166	3.805–9.990	<0.001

HR: hazard ratio; CI: confidence interval; BAC: bronchioloalveolar carcinoma.

Stage I accounted for 3.5% of all BACs in Stage IA and 14.4% of those in Stage IB.

DISCUSSION

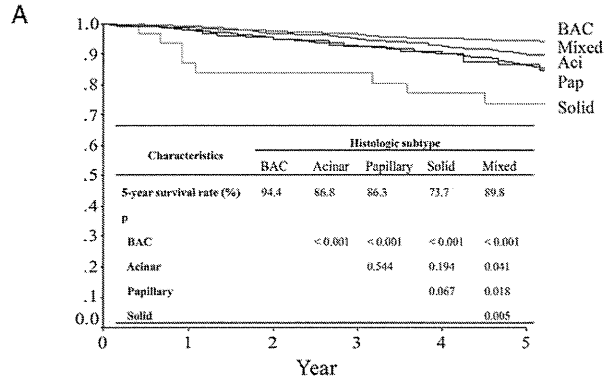
In this Japanese Lung Cancer Registry Study of 6,220 patients with resected lung adenocarcinoma, we showed that the histological subtype was a significant predictor of prognosis, independent of T- or N-factor in staging for lung cancer. In the WHO classification, the histological subtype of lung adenocarcinoma is classified according to the histological growth pattern. In our study, BAC had a significantly better prognosis, whereas solid adenocarcinoma and acinar subtype had significantly worse prognoses. In addition, the proportion of patients with advanced stage (Stage II–III) was higher in solid subtype than in other subtypes. We supposed that this could be the reason why the proportion of patients with pneumonectomy or patients who received neoadjuvant therapy was higher in patients with solid subtype than those with other subtypes.

In the present study, we investigated the clinicopathological features of histological subtypes of lung adenocarcinoma based on the 1999 WHO histological classification [3]. AMS is likely to be the most common histological subtype of lung adenocarcinoma because most lung adenocarcinomas are histologically heterogeneous and consist of more than one subtype even if they are small [1, 11, 12]. According to recent reports [12, 13], >80–90% of adenocarcinomas were classified as AMS when qualified expert pathologists re-reviewed the tumour histology in surgically resected adenocarcinoma using the 1999 WHO classification. However, AMS accounted for only 36.3% of adenocarcinomas in the present study. This may expose potential problems in the reproducibility of diagnosis with regard to the histological subtyping of lung adenocarcinoma among pathologists. Poor interobserver concordance regarding interpretation of the histological pattern in lung adenocarcinoma has been pointed out for some time [14].

BAC was once considered a well-differentiated adenocarcinoma that grew along the alveolar wall or underwent aerogenous spread [1]. The clinical manifestations varied, such as a single pulmonary nodule, multiple pulmonary nodules, localized infiltrates and diffuse pulmonary involvement (pneumonic-type) [1, 6]. In the 1999 WHO classification, the term BAC was newly defined as adenocarcinoma that showed the lepidic growth without evidence of stromal, vascular or pleural invasion. Thus, there should be no evidence of invasion for a diagnosis of BAC. If an invasive component is identified, the tumour is classified as AMS rather than BAC. Naturally, patients with BAC might be expected to have early stage without lymph node metastasis, and thus would have an excellent prognosis without recurrence. However, of the 1385 patients with BAC in the present study, 7.9% were in pathological stage II–IV and 9.0% had recurrence, including both local and distant recurrence. This recurrence was seen even in Stage I BACs. Consequently, the disease-free 5-year survival rate in BAC reached no further than 91.4%. Perhaps these BACs with recurrence or a positive-node should have been classified as invasive adenocarcinoma, i.e. AMS, rather than as BAC, although it is not possible to perform a detailed histological review to confirm the diagnosis in each case with such a large number of BAC patients from a variety of hospitals. In past reports on BAC as determined based on the 1999 WHO classification, resected BACs were not necessarily associated with excellent survival, as given in Table 5 [6–8, 11, 15–22]. In addition, these reports on BAC also included patients with distant as well as loco-regional recurrence. Surprisingly, reports that refer to BAC with N1 and N2 disease are still being published [23]. The issue of a strict pathological evaluation of 'invasion' must be clarified. The increasing importance of the precise definition and education on interpretation of pathological 'invasion' is also advocated in the recent report [24].

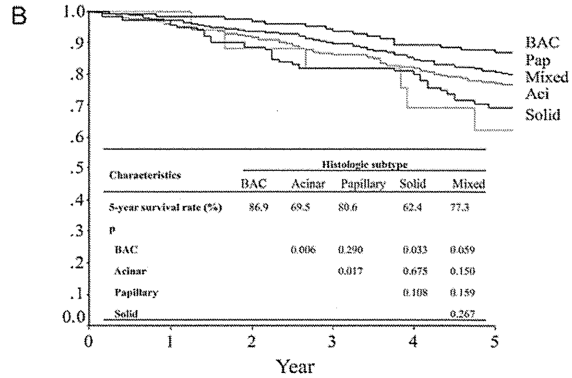
On the other hand, despite recent remarkable advances in our understanding of lung adenocarcinoma in the fields of medical oncology, molecular biology and radiology, there remains a need for a universally accepted classification of adenocarcinoma subtypes. Many reports have demonstrated a correlation between the predominant histological growth pattern of adenocarcinoma and survival [6, 13]. Tumours with a predominant lepidic growth pattern are associated with a better prognosis [6, 13], while those with a predominantly solid pattern or papillary pattern are more aggressive [5, 13]. Molecular markers such as epidermal growth factor receptor (EGFR) mutation, K-ras mutation or fusion of anaplastic lymphoma kinase (ALK) rearrangement are likely to be

A



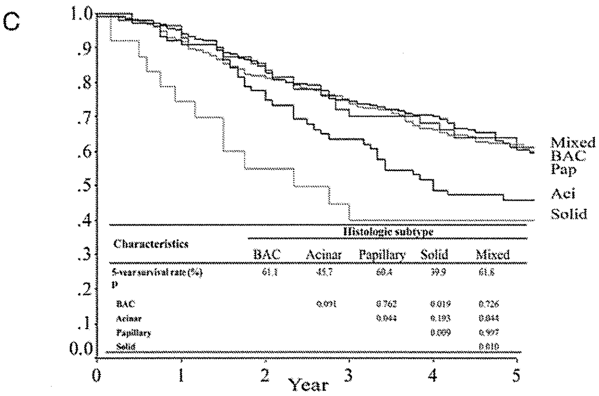
No. at risk						
BAC	1143	1090	1057	1028	961	794
Mixed	1046	1016	969	921	857	726
Pap	883	836	797	748	690	597
Aci	165	158	150	141	131	109
Solid	31	27	26	25	23	20

B



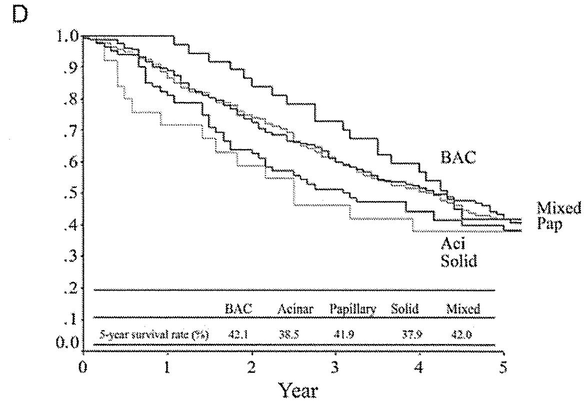
No. at risk						
BAC	132	128	124	117	106	91
Mixed	489	458	427	333	352	288
Pap	502	473	440	401	357	293
Aci	118	112	98	86	79	59
Solid	18	17	15	13	11	9

C



No. at risk						
BAC	57	54	45	38	32	23
Mixed	248	226	196	173	143	123
Pap	218	202	170	141	129	103
Aci	78	70	57	45	35	27
Solid	25	16	11	9	8	7

D



No. at risk						
BAC	40	38	32	27	22	10
Mixed	367	315	256	197	159	116
Pap	297	258	207	163	132	98
Aci	84	65	46	37	31	25
Solid	25	17	14	11	9	8

Figure 3: (**A**) Overall survival curves based on the histological subtype of pathological stage IA in adenocarcinoma. The 5-year survival rates according to the histological subtype and *P* values in survival differences among histological subtypes are shown in the cross-table. BAC: bronchioloalveolar carcinoma; Mixed: adenocarcinoma with mixed subtypes; Aci: acinar; Pap: papillary; Solid: solid adenocarcinoma with mucin. (**B**) Overall survival curves based on the histological subtype of pathological stage IB in adenocarcinoma. The 5-year survival rates according to the histological subtype and *P* values in survival differences among histological subtypes are shown in the cross-table. (**C**) Overall survival curves based on the histological subtype of pathological stage II in adenocarcinoma. The 5-year survival rates according to the histological subtype and *P* values in survival differences among histological subtypes are shown in the cross-table. (**D**) Overall survival curves based on the histological subtype of pathological stage IIIA in adenocarcinoma. The 5-year survival rates according to the histological subtype and *P* values in survival differences among histological subtypes are shown in the cross-table.

Table 3: Cause of death in patients with resected adenocarcinoma according to the histological subtype

Cause of death	BAC	Acinar	Papillary	Solid	AMS
Lung-cancer-related	69 (49.6%)	132 (78.6%)	418 (77.7%)	34 (77.3%)	467 (78.2%)
Other disease	67 (48.2%)	34 (20.2%)	115 (21.4%)	10 (22.7%)	117 (19.6%)
Unknown	3 (2.2%)	2 (1.2%)	5 (0.9%)	0 (0%)	13 (2.2%)
Total number of death	139	168	538	44	597

BAC: bronchioloalveolar carcinoma; Solid: solid adenocarcinoma with mucin; AMS: adenocarcinoma with mixed subtypes.

THORACIC

Table 4: Mode of recurrence in patients with resected adenocarcinoma according to the histological subtype

Mode of recurrence	BAC	Acinar	Papillary	Solid	AMS
Loco-regional	38 (30.4%)	53 (26.8%)	202 (30.7%)	14 (30.4%)	210 (28.5%)
Distant	71 (56.8%)	112 (56.6%)	328 (49.8%)	29 (63.0%)	384 (52.0%)
Both simultaneously	7 (5.6%)	21 (10.6%)	98 (14.9%)	2 (4.3%)	105 (14.2%)
Unknown	9 (7.2%)	12 (6.1%)	30 (4.6%)	1 (2.2%)	39 (5.3%)
Total number of recurrence	125	198	658	46	738

BAC: bronchioloalveolar carcinoma; Solid: solid adenocarcinoma with mucin; AMS: adenocarcinoma with mixed subtypes.
No statistical significant difference in mode of recurrence among the histological subtypes ($P = 0.089$).

Table 5: Postoperative 5-year survival rates for patients with BAC diagnosed according to the 1999 WHO classification

Author (year)	Number of patients	Pathological stage	5-year survival rate
Breathnach and colleagues (2001)	33	I	74%/83%, DFS/OS
Volpino and colleagues (2001)	34	IA	74.9%, OS
Ebright and colleagues (2002)	47	I	83.3%, OS
Rena and colleagues (2003)	28	I	81%, DFS
Furak and colleagues (2003)	67	All (IA/IB)	61.9%, OS (71%/77%, OS)
Sakurai and colleagues (2004)	85	IA (≤2 cm)	100%, DFS
Campione and colleagues (2004)	54	IA	88%, OS
Zell and colleagues (2007)	627	I	65%, OS
Koike and colleagues (2009)	46	I	93%, DFS
Casali and colleagues (2010)	40	All (I)	51%/64%, DFS/OS (69%/79%, DFS/OS)
Ebbert and colleagues (2010)	78	All	83.5%, OS
Whitson and colleagues (2012)	5532	All (lobectomy cases)	59.5%, OS
Present study	1385	All	91.4%/90.3%, DFS/OS

BAC: bronchioloalveolar carcinoma; WHO: World Health Organization; DFS: disease-free survival; OS: overall survival.

associated with a particular histological growth pattern of adenocarcinoma [1]. Moreover, these molecular markers can be used to predict the response to targeted therapy, particularly after the discovery of EGFR mutations and their association with sensitivity to EGFR tyrosine kinase inhibitors (EGFR TKIs) such as gefitinib [1]. It has been reported that EGFR mutations are more prevalent in the lepidic growth predominant subtype and ALK rearrangement in the acinar predominant subtype [1]. According to radiological-pathological studies, tumours that show ground-glass opacity on high-resolution computed tomography seem to be BACs or adenocarcinomas like BAC with a lepidic growth pattern accompanied by minimal invasion [1]. However, most of these adenocarcinomas will be classified as 'AMS' based on the 1999 WHO classification despite having such widely varied clinical behaviours. Therefore, the 1999 WHO classification has limited clinical utility. Ultimately, AMS includes tumours that are minimally invasive to overtly invasive. Additionally, with regard to BAC tumours, a discrepancy still exists between the rigorous pathological definition of BAC according to the 1999 WHO classification and the clinical use of the term. To address these issues, a new adenocarcinoma classification has recently been proposed by international multidisciplinary lung cancer experts including medical oncologists, respiratory physicians, pathologists, surgeons, molecular biologists and radiologists, who are sponsored by the International Association for the Study of Lung Cancer (IASLC), the American Thoracic Society (ATS), and the European Respiratory Society (ERS) [1]. This was published as the new IASLC/ATS/ERS International Multidisciplinary Lung Adenocarcinoma Classification in 2011. Although we had too much incomplete data on histological subtype in adenocarcinoma in the present study, detailed pathological evaluation of histological subtype is becoming more important for clinical practice in the future. Pathologists need to put the focus on identifying the histological subtype of adenocarcinoma.

Regarding EGFR mutations in lung adenocarcinoma for a matter peculiar to a Japanese, EGFR TKIs have been developed as a targeted therapy in this disorder. East-Asians and patients with bronchioloalveolar pathological subtype have been shown to be significantly associated with a favourable response to EGFR TKIs [1]. Although the proportion of BAC in adenocarcinoma was ~20% in this Japanese registry data, it was reportedly lower in Western countries. Actually, the proportion of BAC in adenocarcinoma, even if it includes bronchioloalveolar-growth predominant subtype, has been reported to be only ~8% in Western countries [12, 13]. The distribution of the histological subtype in adenocarcinoma could be quite different among countries. The difference might affect the future drug development of targeted therapy among countries.

In the new proposed classification [1], the terms BAC and AMS were made obsolete. A BAC is called 'adenocarcinoma *in situ*' as a preinvasive lesion and the category of 'minimally invasive adenocarcinoma' was added, whereas invasive tumours other than minimally invasive adenocarcinoma are classified according to their predominant growth pattern, i.e. lepidic predominant, acinar predominant, papillary predominant, micropapillary predominant and solid predominant with mucin production. Hereafter, the issue of interobserver concordance in the pathological diagnosis of adenocarcinoma subtypes will become increasingly important [25], although the new classification is currently being verified by several researchers [13, 24]. Unless the histological subtyping of adenocarcinoma can be accurately determined, the true clinicopathological characteristics will still be equivocal regardless of the revision of the histological classification.

In conclusion, we found a significant correlation between the prognosis and histological subtype of adenocarcinoma based on the 1999 WHO classification. In particular, BACs were significantly associated with a better prognosis compared with the other subtypes. On the other hand, even though BAC is defined as non-invasive adenocarcinoma in the 1999 WHO classification, some of the patients in our registry with BAC had lymph node metastasis, pleural invasion or recurrence. The reproducible pathological evaluation of preinvasive or minimally invasive findings or the growth pattern of adenocarcinoma should be discussed in the forthcoming WHO classification of lung adenocarcinoma to be proposed by IASLC/ATS/ERS.

Conflict of interest: none declared.

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Clinicopathological characteristics and surgical results of lung cancer patients aged up to 50 years: The Japanese Lung Cancer Registry Study 2004

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ABSTRACT

Objective: The clinicopathological characteristics and surgical results of young lung cancer patients were investigated.
Materials and methods: Seven hundred and four (6.0%) patients with lung cancer, aged up to 50 years, were enrolled from among the 11,663 patients registered in the Japanese Lung Cancer Registry Study 2004, and their clinical data were compared with those of 10,959 patients older than 50 years. This epidemiological study is based on the single year registration of surgically treated patients in the major institutes in Japan.
Results: The 5-year overall survival rate (5Y-OS) and the 5-year lung cancer-related survival rate was 79.2%/69.0% ($p < 0.001$) and 81.3%/76.6% ($p = 0.005$) in the young/old groups, respectively. In the young/old groups, lobectomy and pneumonectomy was performed in 76.9%/78.0% and 5.7%/3.2%, respectively; adjuvant therapies were given preoperatively in 10.4%/4.7% ($p < 0.001$) and postoperatively in 31.4%/24.5% ($p < 0.001$). The proportions of patients with p-stage IIIA (18.2%) and adenocarcinoma histology (78.7%) were higher in the young group. The 5Y-OS was 94.8%/86.2% for p-stage IA ($p < 0.001$), 87.0%/73.2% for p-stage IB ($p = 0.001$), 61.0%/61.6% for p-stage IIA ($p = 0.595$), 71.0%/48.4% for p-stage IIB ($p = 0.003$), 49.6%/39.4% for p-stage IIIA ($p = 0.020$), and 80.0%/24.8% for p-stage IIIB ($p = 0.012$); it was 83.5%/80.7% for females ($p = 0.106$) and 75.1%/62.3% for males ($p < 0.001$) in the young/old groups. The postoperative survival was significantly better with all operative procedures in the young group. The 5Y-OS after recurrence was 17.9%/13.4% in the young/old groups ($p = 0.016$). In the young group, the 5Y-OS was better in females (83.5%) than in males (75.1%, $p = 0.002$), and for patients with adenocarcinoma (80.3%) than for those with squamous cell carcinoma (68.5%, $p = 0.013$). Age up to 50 years was identified as an independent better prognostic factor on multivariate analysis.
Conclusions: The postoperative survival in lung cancer patients aged up to 50 years was better than that in patients older than 50 years.

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1. Introduction

Lung cancer is a leading cause of malignancy-related death. The American Cancer Society estimates that 226,160 people will be diagnosed and 160,340 patients will die of lung cancer in the United States in 2012 [1]. Lung cancer occurs mainly in older people, and fewer than 2% of all cases are found in people younger than 45 years in the USA [1]. The Ministry of Health, Labor, and Welfare, Japan, reported that 69,813 people died of lung cancer in 2010 in Japan, and the number is still increasing. According to the Japanese Lung Cancer Registry Study, the number of patients younger than 50 years ranged from 5.0% to 8.2% of all resected cases since 1994 [2]. Because of the small size of the young population, the clinical features of young lung cancer patients remain unclear.

Better survival of lung cancer patients in the middle-aged group (45–60 years) as compared to the young (<45 years) or old group (>60 years) was reported by a multicenter study [3]. Several previous studies also revealed better postoperative survival rate in the young lung cancer patients [4–6], while other reports showed equivalent survival outcome to the old patients [7,8]. So, the survival superiority of the young patients is still controversial in lung cancer. Active treatment with multiple modalities was recommended in young patients in association with these results, while the study cohort included all lung cancer patients treated with surgery, chemotherapy, and irradiation [3]. However, the clinicopathological characteristics and surgical results of young patients with lung cancer have not yet been identified. Recent developments in chemotherapy and molecular targeted therapy might contribute to prolonged survival and improvement of results with multimodality management, especially in young patients, who are expected to be able to tolerate active treatments.

Patients aged up to 50 years extracted from the Japanese Lung Cancer Registry Study 2004 who underwent surgical resection were evaluated in order to clarify their clinicopathological characteristics and the results of surgical intervention in the present study [2].

2. Materials and methods

2.1. Patients

A total of 704 lung cancer patients aged up to 50 years were extracted from among the 11,663 patients listed in the Japanese Lung Cancer Registry Study 2004, which was conducted as a multicenter surveillance study of patients who underwent surgery by the Japanese Joint Committee of the Lung Cancer Registry (JJCLCR) [2]. JJCLCR is officially authorized by The Japan Lung Cancer Society, The Japanese Association for Chest Surgery, The Japanese Respiration Society, and The Japan Society for Respiratory Endoscopy. Of the 605 teaching hospitals certified by the Japanese Board of General Thoracic Surgery, 253 participated in this registry. All patients analyzed in the present study underwent surgery in 2004 and the single year registration included the following data: (1) demographic background (age and sex), (2) preoperative status (Eastern Cooperative Oncology Group performance status (ECOG PS), preoperative comorbidity, smoking status, tumor markers), (3) clinical TNM, (4) induction therapy, (5) operative procedure, (6) postoperative morbidity, (7) tumor histology, (8) adjuvant therapy, (9) pathological TNM. The clinicopathological characteristics and the results of surgical intervention in patients aged up to 50 years were analyzed in detail and compared to those of 10,959 patients older than 50 years. The data collected using the UICC-TNM staging system (version 6) were converted to the UICC-TNM staging system (version 7) to assess the extent of lung cancer [9].

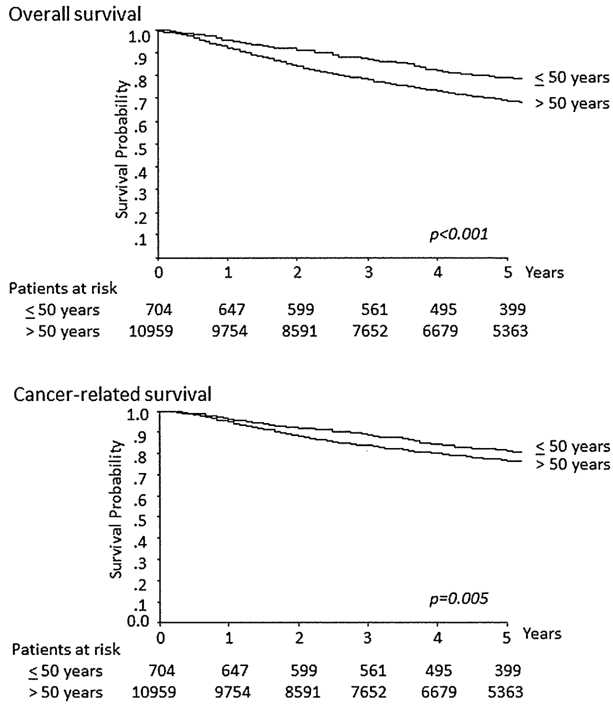

Fig. 1. The overall and lung-cancer related survival rates for patients aged up to and older than 50 years with surgical intervention. The postoperative survival rate was significantly better in the young group.

2.2. Statistical analyses

All data were extracted and analyzed by a JJCLCR member biostatistician (EM). Survival after pulmonary resection was estimated according to the Kaplan–Meier method, and survival differences were tested using the log-rank test. The prognostic effect of variables on survival was analyzed using the multivariate Cox regression model with variables of sex, ECOG-PS, smoking history, comorbidity, operative procedure, p-stage, histology, adjuvant chemotherapy. The χ^2-test was used to compare the rates between groups. A p value less than 0.05 was considered significant.

3. Results

Patients' characteristics, with a comparison of patients aged up to 50 years and older than 50 years, are shown in Table 1. The proportion of females was significantly higher in the young group than in the old group ($p < 0.001$). Performance status (ECOG) was significantly better in the young group ($p < 0.001$). Smoking history and preoperative comorbidity were significantly more frequent in the old group ($p < 0.001$). The operative procedure was significantly different ($p = 0.013$) and the rate of pneumonectomy was higher in the young group. The distribution of p-stage showed the significant difference, and the proportion of p-stage IB and IIA was lower and that of locally advanced disease with p-stage IIIA was higher in the young group as compared to the old group. The proportion of histopathology was significantly different ($p < 0.001$) and the rate of adenocarcinoma was higher in the young group. Young patients received both preoperative and postoperative adjuvant therapy more frequently than old patients.

The 5-year overall survival rate (5Y-OS) was 79.2% and 69.0% in the young and old groups, respectively ($p < 0.001$), as shown in Fig. 1. The 30-days mortality was 1/704 (0.1%) and 47/10959 (0.4%), and the hospital mortality was 2/704 (0.3%) and 134/10959 (1.2%) in the young and old groups, respectively. The morbidity was

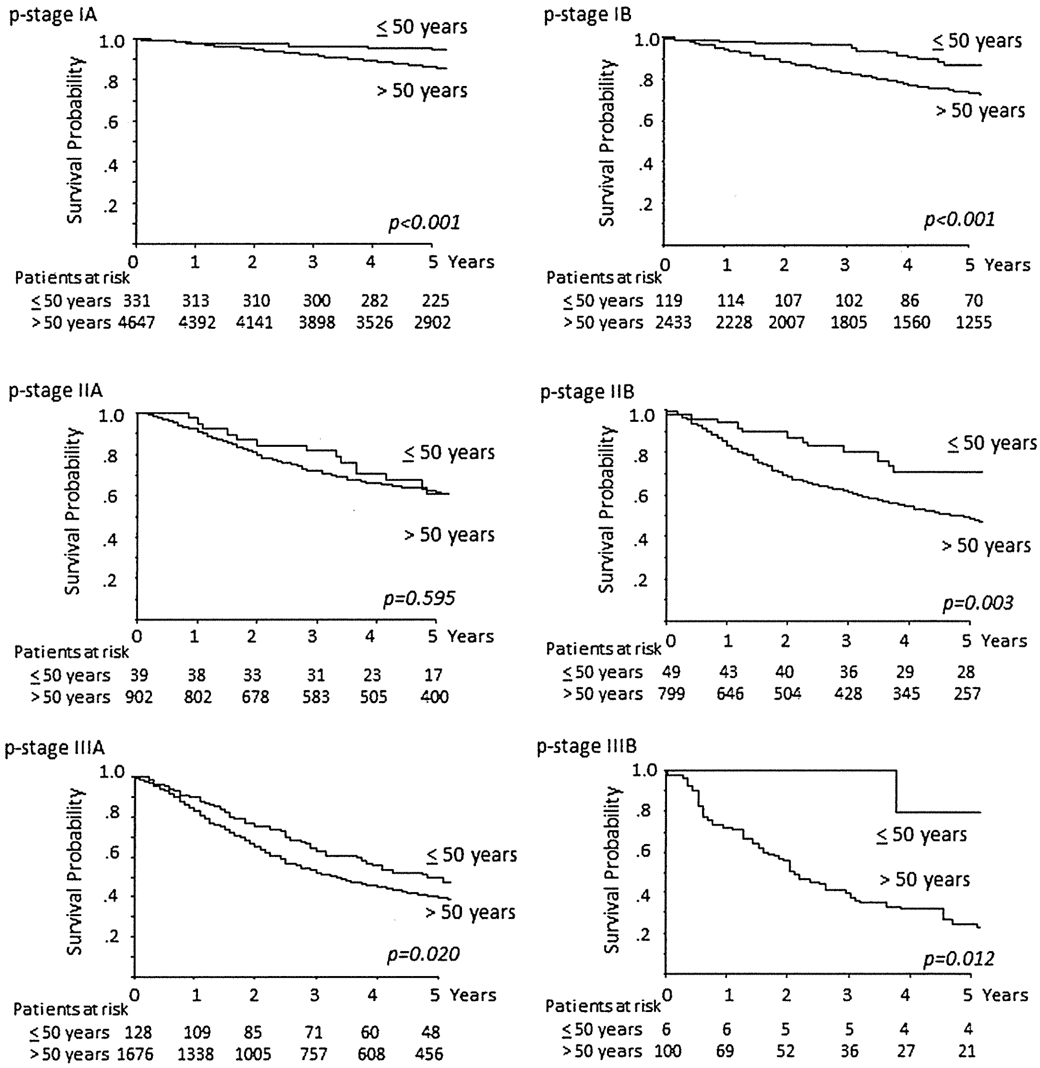

Fig. 2. The survival curves of patients aged up to and older than 50 years with surgery according to p-stage using UICC version 7. The postoperative survival was significantly better in the young group for each p-stage IA – IIIB except stage IIA.

58/704 (8.2%) and 1921/10959 (17.5%) in the young and old groups, respectively ($p < 0.001$). When analyzing disease-specific outcome, the 5-year lung cancer-related survival rate was 81.3% and 76.6% in the young and old groups, respectively ($p = 0.005$), as shown in Fig. 1. According to p-stage, the 5Y-OS was 94.8% and 86.2% for IA ($p < 0.001$), 87.0% and 73.2% for IB ($p < 0.001$), 61.0% and 61.6% for IIA ($p = 0.595$), 71.0% and 48.4% for IIB ($p = 0.003$), 49.6% and 39.4% for IIIA ($p = 0.020$), and 80.0% and 24.8% for IIIB ($p = 0.012$), in the young and old groups, respectively, as shown in Fig. 2.

Among male patients, the 5Y-OS was 75.1% and 62.3% in the young and old groups, respectively ($p < 0.001$), although there was no significant difference among female patients and the 5Y-OS was 83.5% and 80.7%, respectively (Fig. 3). The cause of death, preoperative comorbidities, smoking history, and adjuvant therapy were examined by age and sex. Lung cancer-unrelated death was higher (25.3%) in the old group than that in the young group (6.8%) in males ($p < 0.001$), while no significant difference was observed in females. Preoperative comorbidities were frequent in the old group in both male and female patients. Smoking history was significantly more frequent in the old group in males, while it was less frequent in females. Male patients in the young group more frequently had both preoperative and postoperative adjuvant therapies as compared to the old group, while no significant difference was found in female patients.

According to operative procedure, the 5Y-OS was better in the young group than in the old group for all procedures: 59.1% and 42.0% for pneumonectomy ($p = 0.050$), 79.9% and 71.7% for lobectomy ($p < 0.001$), 87.3% and 73.1% for segmentectomy ($p = 0.034$), and 93.5% and 65.9% for wedge resection ($p < 0.001$), in the young and old groups, respectively (Fig. 4). According to histological type, the 5Y-OS for adenocarcinoma was 80.3% in the young group which was significantly better than 74.5% in the old group, though no significant survival difference was observed for squamous cell carcinoma. The 5Y-OS after recurrence was 17.9% and 13.4% in the young and old groups, respectively ($p = 0.016$). In the young group, the 5Y-OS was significantly better for female patients (83.5%) than for male patients (75.1%, $p = 0.002$). 5Y-OS was better for the histology of adenocarcinoma (80.3%) than for squamous cell carcinoma (68.5%, $p = 0.013$).

Since the comparison of survival difference between young and old patients might be affected by patients older than 70 years, who are expected to have poor long-term survival, another comparison of survival difference between patients aged up to 50 years ($n = 704$) and those 50–70 years ($n = 6152$), which was a young elderly cohort,