ORIGINAL ARTICLE

Prognosis in Resected Invasive Mucinous Adenocarcinomas of the Lung: Related Factors and Comparison with Resected Nonmucinous Adenocarcinomas

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ABSTRACT

Introduction: In the 2015 World Health Organization classification, invasive mucinous adenocarcinoma (IMA) is categorized as one of various subtypes of lung invasive adenocarcinoma (ADC). However, no comprehensive analysis regarding the clinicoradiologic and prognostic features of IMA has been reported. We aimed to report prognostic factors in IMA and to compare the prognosis of IMAs with that of nonmucinous ADCs.

Methods: We included 81 patients with a solitary IMA of the lung and analyzed them from the standpoint of clinicoradiologic presentation. Survival rates were assessed and compared with those of 646 resected solitary invasive nonmucinous ADCs.

Results: Patients with IMA showed longer disease-free survival (DFS) than did those with nonmucinous ADCs, whereas overall survival (OS) did not differ significantly ($p = 0.023$ and $p = 0.824$, respectively). The DFS of patients with IMA was between that of patients with lepidic predominant (low-grade) and acinar/papillary predominant (intermediate-grade) ADC. In terms of OS, the survival curve of IMA was similar to that of acinar/papillary predominant ADC. Multivariate analysis revealed that tumor size (hazard ratio [HR] = 1.370, 95% confidence interval [CI]: 1.141–1.645, $p = 0.001$) and maximum standardized uptake value (HR = 1.338, 95% CI: 1.160–1.544, $p < 0.001$) were independent poor prognostic predictors for DFS. Regarding OS, tumor size (HR = 1.309, 95% CI: 1.092–1.570; $p = 0.004$) was the only predictor of poor prognosis.

Conclusion: Patients with IMA demonstrate a DFS between that of patients with low-grade nonmucinous ADC and that of patients with intermediate-grade nonmucinous ADC and an OS similar to that of patients with intermediate-grade nonmucinous ADC. In IMA, tumor size and maximum standardized uptake value are the factors related to mitigating DFS and tumor size is the only predictor for reduced OS.

Keywords: Lung; Adenocarcinoma; Mucinous; Classification; Prognosis

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Introduction

Mucinous adenocarcinoma (ADC) is characterized histopathologically by tumor cells having a goblet or columnar cell morphologic pattern with abundant intracytoplasmic mucin. In the 2011 classification system for lung ADC of the International Association for the Study of Lung Cancer (IASLC)/American Thoracic Society (ATS)/European Respiratory Society (ERS), invasive mucinous adenocarcinomas (IMAs) are classified as variants of invasive ADCs. IMAs are distinguished from nonmucinous ADCs because they have major differences from nonmucinous ADCs in terms of their clinical, radiologic, pathologic, and genetic aspects.[1–10] In the 2015 World Health Organization (WHO) classification, IMA is regarded as one of the various subtypes of invasive ADC.[11]

There have been several studies indicating that patients with mucinous bronchioloalveolar carcinoma (BAC) show poorer prognosis than do those with nonmucinous BAC.[3,12] Even after proposal of the 2011 IASLC/ATS/ERS classification scheme, Russell et al.[13] and Yoshizawa et al.[14] also suggested that IMAs are usually associated with poor survival outcome. However, the prognosis of IMAs remains controversial. In contrast, Warth et al.[15] reported that IMAs show better prognosis than do conventional nonmucinous ADCs. Because of the low incidence of lung mucinous ADCs, which account for only 2% to 5 % of all lung ADCs, the numbers of patients included in most previous studies have been relatively small.[13,14,16,17] Thus, the ultimate prognosis of patients in whom IMAs were diagnosed on the basis of the 2011 IASLC/ATS/ERS[1] and 2015 WHO criteria[11] still needs to be clarified with a large sample size.

In contrast to nonmucinous ADCs, IMAs have not been the subject of any reported comprehensive studies regarding their clinicopathologic and radiologic aspects, not to mention prognostic factors. Also, limited information has been reported on the prevalence of this tumor, its radiologic presentations, and its response to surgical treatment. Therefore, the purpose of this study was twofold: (1) to review the clinicopathologic and radiologic features of patients with surgically resected IMAs and (2) to compare the prognoses of patients with IMAs with that of patients with nonmucinous invasive ADCs in a large cohort.

Patients and Methods

The institutional review board approved this retrospective study, and informed consent was waived for the use of patients' medical data.

Study Population

We reviewed the surgical database of the Department of Thoracic Surgery at Samsung Medical Center, a tertiary referral center located in Seoul, Republic of Korea, to identify patients who had undergone curative surgery for lung ADCs. All of the glass slides of resected lung ADCs from September 2003 to November 2011 in the institute were reevaluated by experienced pathologists according to the new WHO classification.[11] A total of 942 solitary lung ADCs from 942 consecutive patients were identified. Of these patients, 113 were excluded for the following reasons: (1) insufficient pathologic slides for evaluation of the whole tumor (n = 42), (2) poor quality of the computed tomography (CT) image (n = 23), and (3) concomitant presence of other malignancy (n = 48). Patients with the following types of ADC were also excluded: mixed invasive mucinous and nonmucinous ADCs (n = 10); ADC in situ or minimally invasive ADC (n = 79); and colloid, fetal, and enteric ADCs (n = 13). Ultimately, 81 patients with completely resected solitary IMAs and 646 patients with invasive nonmucinous ADCs were included in this study.

Data on clinicoradiologic presentation, tumor stage, and survival outcome were obtained from electronic medical records. Surgical treatment methods were recorded. Tumor, node, and metastasis stage for each tumor was determined according to the seventh edition of the Cancer Staging Manual of the American Joint Committee on Cancer.[18] Survival and the presence of disease progression were also assessed according to the medical records and the data from the Korea National Statistical Office.

Preoperative Chest CT and Positron Emission Tomography/CT

On the basis of preoperative CT images, 81 IMAs were classified as having a nodular pattern or consolidative pattern according to the dominant presentation (Supplementary Fig. 1). The CT pattern was determined on the basis of tumor morphology. Nodular pattern was defined as a rounded opacity, whereas consolidative pattern referred to an increased parenchymal attenuation without definable shape or distribution. Other CT features such as site and number of involved lobes and tumor size were also assessed retrospectively.

For positron emission tomography (PET)/CT evaluation, regions of interest were identified in the most intense area of fludeoxyglucose F 18 (FDG) uptake in the primary tumor. FDG uptake within the regions of interest was analyzed to determine the maximum standardized uptake value (SUV_{max}).

Pathologic Evaluation

Two experienced lung pathologists (with 16 and 10 years of experience in lung pathology, respectively) interpreted all tissue sections and discussed them until

consensus was achieved. Histopathologic criteria for IMA included tumor cells having a goblet or columnar cell morphologic pattern with abundant intracytoplasmic mucin (Supplementary Fig. 2).[1,17] In terms of the predominant growth pattern of IMAs, it was stated in the 2011 IASLC/ATS/ERS classification[1] that IMAs might show a heterogenous mixture of lepidic, acinar, papillary, micropapillary, and solid growth as in nonmucinous tumors. However, in the novel 2015 WHO classification,[11] IMA was defined as what was called mucinous BAC in the 2004 WHO classification and was said to often show lepidic predominant growth. In this study, we adopted the recent proposal by WHO and included as IMAs only tumors showing lepidic predominant pattern.

With regard to the 646 invasive nonmucinous ADCs, pathologic evaluation was also carried out according to the criteria of the 2011 IASLC/ATS/ERS and 2015 WHO classifications, with the percentage of each histologic component recorded in 5% increments (lepidic, acinar, papillary, micropapillary, and solid).[1,11] The predominant pattern constituting the greatest percentage of tumor histopathologic findings was determined as the histopathologic subtype.

Next, we classified tumors into four subgroups. The subgrouping was based on previous various study results regarding the survival data for each ADC subtype[13,15,16,19,20]: lepidic predominant nonmucinous ADCs (low-grade nonmucinous ADCs), acinar/papillary predominant nonmucinous ADCs (intermediate-grade nonmucinous ADCs), micropapillary/solid predominant nonmucinous ADCs (high-grade nonmucinous ADCs), and IMAs.

Statistical Analysis

Student's t test, the Mann-Whitney U test, and Fisher's exact test were used for comparison between nodular and consolidative pattern IMAs. Disease-free survival (DFS) and overall survival (OS) were estimated using the Kaplan-Meier method, and the log-rank test was used to evaluate differences among subgroups. Multivariate analysis was used to assess the effect of covariates on DFS and OS, and it was performed using backward Cox proportional hazards regression with a step-down method. Variables with a p value less than 0.10 on univariate analysis were used as the input variables for the multivariate multivariable Cox regression analysis. The optimal cutoff values of SUV_{max} were calculated using receiver operating characteristic curve analysis. The statistical analysis was performed using SPSS version 15 statistical software for Windows (IBM, Armonk, NY). All p values less than or equal to 0.05 were considered statistically significant.

Results

Demographic Data

The distribution of histologic subtypes according to the 2015 WHO classification is summarized in Table 1. Approximately 10% of the cases were classified as IMA (36 males and 45 females, median age 61 years). As for the 646 patients with invasive nonmucinous ADCs (338 males and 308 females, median age 60 years), 125 (15%) had lepidic predominant ADCs, 319 (38%) had acinar predominant ADCs, 63 (8%) had papillary predominant ADCs, 24 (3%) had micropapillary predominant ADCs, and 115 (14%) had solid predominant ADCs. Detailed patient characteristics of IMAs and nonmucinous ADCs are shown in Table 2. The median follow-up period was 33.7 months (range 0.6–114.7).

T and N classification differed significantly between patients with IMA and those with invasive nonmucinous ADC ($p = 0.004$ and $p = 0.001$, respectively). In addition, histologic differentiation was also significantly different between two groups ($p < 0.001$). All IMAs were well-differentiated tumors histologically.

Survival Analyses between IMAs and Invasive Nonmucinous ADCs

On survival analyses of 81 patients with solitary IMAs, the 5-year DFS rate was 79% and the 5-year OS rate was 86%. In the analyses of 646 patients with invasive nonmucinous ADCs, the 5-year DFS rate was 65% and the 5-year OS rate was 87%. Figure 1*A* shows the survival curves of invasive mucinous and nonmucinous ADCs. DFS differed significantly between patients with IMAs and those with invasive nonmucinous ADCs ($p = 0.023$). Patients with IMAs showed longer

Table 1. Demographic Data on Total Lung Adenocarcinomas Seen during the Study Period

Histologic Type and Subtypes	No. Patients (%)
Lepidic adenocarcinoma	125 (15)
Acinar adenocarcinoma	319 (38)
Papillary adenocarcinoma	63 (8)
Micropapillary adenocarcinoma	24 (3)
Solid adenocarcinoma	115 (14)
Invasive mucinous adenocarcinoma	81 (10)
Mixed invasive mucinous and nonmucinous adenocarcinoma	10 (1)
Colloid, fetal, and enteric adenocarcinoma	13 (2)
Minimally invasive adenocarcinoma	
Nonmucinous	34 (4)
Mucinous	8 (1)
Adenocarcinoma in situ	
Nonmucinous	35 (4)
Mucinous	2 (0)

Note: Tumor types and subtypes according to the 2015 World Health Organization classification scheme.

Table 2. Patient Characteristics of IMA and Nonmucinous ADC

Characteristic	IMA	Invasive Nonmucinous ADC						*p* Value[a]
		Total	Lepidic	Acinar	Papillary	Micropapillary	Solid	
Mean age ± SD, y	58.4 ± 11.6	59.9 ± 9.9	59.9 ± 9.6	60.9 ± 9.7	60.6 ± 10.3	57.6 ± 10.9	61.5 ± 9.3	0.270
Smoking, n (%)	24 (30)	267 (41)	32 (26)	117 (37)	31 (49)	13 (54)	74 (64)	0.054
Sex, n (%)								0.196
Male	36 (44)	338 (52)	52 (42)	150 (47)	36 (57)	15 (63)	85 (74)	
Female	45 (56)	308 (48)	73 (58)	169 (53)	27 (43)	9 (37)	30 (26)	
Type of surgery, n (%)								0.196
Wedge resection	7 (8)	77 (12)	38 (30)	23 (7)	6 (10)	1 (4)	9 (8)	
Lobectomy	71 (88)	560 (87)	87 (70)	292 (92)	57 (90)	23 (96)	101 (88)	
Bilobectomy or pneumonectomy	3 (4)	9 (1)	0 (0)	4 (1)	0 (0)	0 (0)	5 (4)	
T classification, n (%)								**0.004**
1A	26 (32)	258 (40)	94 (76)	114 (36)	18 (29)	4 (17)	28 (21)	
1B	15 (19)	199 (31)	22 (17)	118 (37)	21 (33)	5 (21)	33 (29)	
2A	33 (41)	145 (22)	7 (6)	69 (22)	19 (30)	9 (37)	41 (35)	
2B	6 (7)	34 (5)	2 (1)	14 (4)	4 (6)	6 (25)	9 (8)	
3	1 (1)	10 (2)	0 (0)	4 (1)	1 (2)	0 (0)	5 (4)	
N classification, n (%)								**0.001**
N0	77 (95)	499 (77)	120 (96)	246 (77)	47 (75)	15 (62)	71 (62)	
N1	1 (1)	83 (13)	3 (2)	42 (13)	12 (19)	5 (21)	21 (18)	
N2	3 (4)	64 (10)	2 (2)	31 (10)	4 (6)	4 (17)	23 (20)	
Histologic differentiation, n (%)								**<0.001**
Well differentiated	81 (100)	170 (26)	101 (81)	58 (18)	10 (16)	0 (0)	1 (1)	
Moderately differentiated	0 (0)	342 (53)	24 (19)	223 (70)	46 (73)	22 (92)	27 (23)	
Poorly differentiated	0 (0)	133 (21)	0 (0)	38 (12)	7 (11)	2 (8)	87 (76)	
Adjuvant therapy, n (%)	40 (40)	273 (42)	9 (7)	142 (45)	35 (56)	13 (54)	74 (63)	0.694

Note: Boldface indicates *p* value less than 0.05.
[a]*p* Value is for the comparison between IMA and total nonmucinous ADC.
IMA, invasive mucinous adenocarcinomas; ADC, adenocarcinoma; y, year; SD, standard deviation.

DFS than did those with nonmucinous ADCs. In addition, the results of Cox proportional hazards analyses demonstrated that the DFS rates for IMA versus invasive nonmucinous ADC differed significantly even after adjustment of the pathologic stage ($p = 0.047$). However, there was no significant difference in OS between patients with IMA and those with invasive nonmucinous ADC ($p = 0.824$).

In subgrouping analysis, patients with lepidic predominant (low-grade) ADC showed significantly better OS and DFS than did those with other subtypes (all $p < 0.036$). Patients with micropapillary/solid predominant (high-grade) ADC showed significantly poorer OS and DFS than did those with lepidic predominant (low-grade) ADC and acinar/papillary predominant (intermediate-grade) ADC (all $p < 0.023$). Patients with IMA exhibited significantly poorer DFS than did those with lepidic predominant (low-grade) ADC ($p = 0.036$) but better DFS than did those with acinar/papillary predominant (intermediate-grade) and micropapillary/solid predominant (high-grade) ADC ($p = 0.007$ and $p < 0.001$, respectively). In terms of OS, patients with IMAs exhibited significantly poorer outcomes than did those with lepidic predominant (low-grade) ADC ($p = 0.018$). However, there was no significant difference in OS between patients with IMA and those with acinar/papillary predominant (intermediate-grade) or micropapillary/solid predominant (high-grade) ADC ($p = 0.655$ and $p = 0.111$, respectively). The OS curve of patients with IMA was similar to that of patients with acinar/papillary predominant (intermediate-grade) ADC (Fig. 1*B*).

Comparison between Nodular and Consolidative Pattern IMAs on CT Imaging

Of 81 patients with solitary IMAs, 62 (76%) presented with a nodular pattern and 19 (24%) presented with a consolidative pattern on CT imaging. The comparison of demographics, surgical methods, pathologic status, CT scan features, and SUV_{max} between nodular- and consolidative pattern IMAs is shown in Table 3 and Supplementary Figure 1. There was no significant difference in demographic data, including age, sex, and smoking history, between nodular and consolidative pattern IMAs. However, tumor, node, and metastasis stage, specifically T classification, differed significantly between the two patterns (all $p < 0.001$). The mean diameter of tumors with a nodular pattern was 28 mm

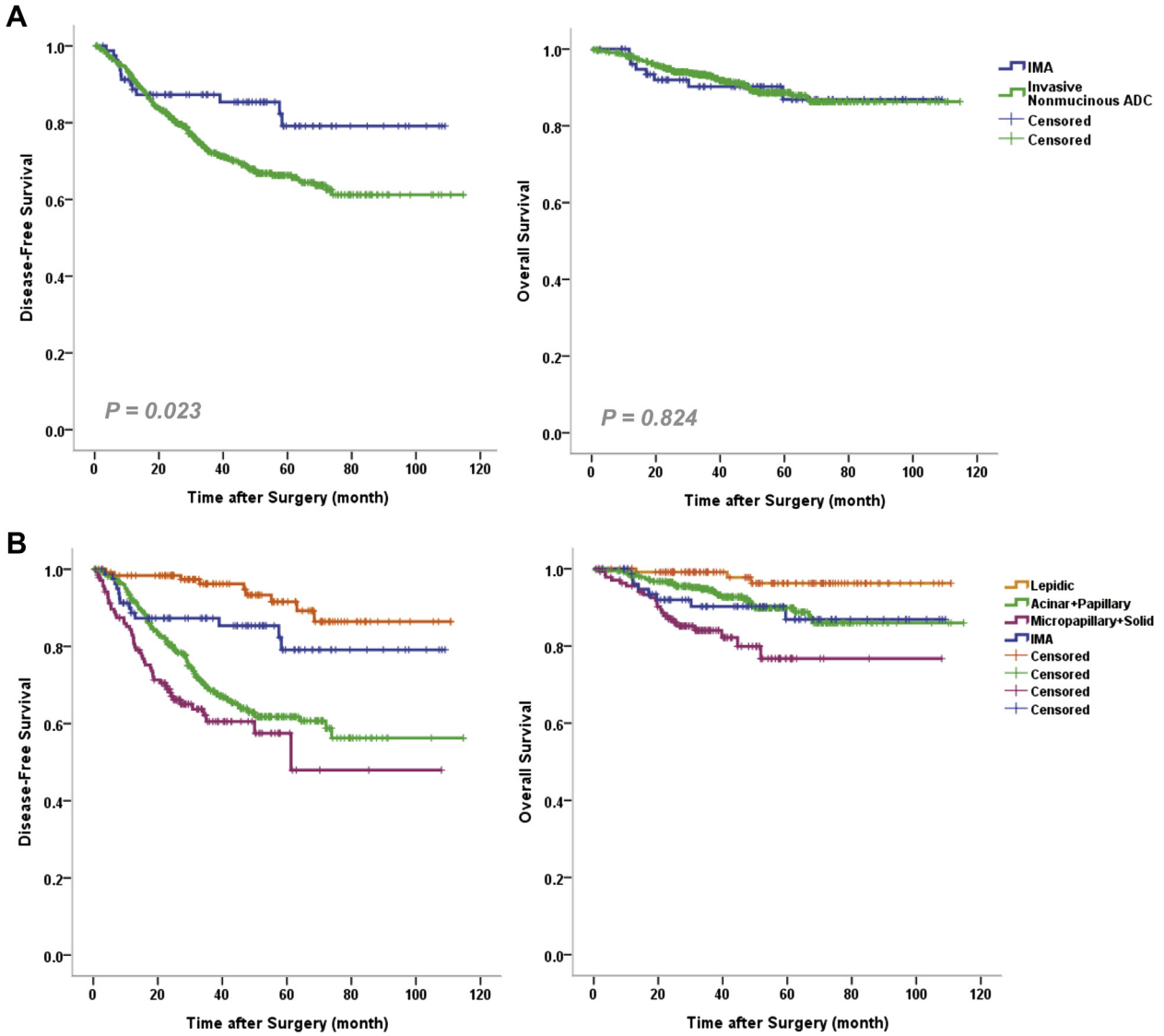

Figure 1. Kaplan-Meier survival curves for disease-free and overall survival. Survival curves of solitary invasive mucinous adenocarcinoma (IMA) and nonmucinous adenocarcinoma (ADC) (*A*) and outcome according to the subgroups based on the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society and 2015 World Health Organization histopathologic subtypes (*B*).

(range 6–91 mm) and that of tumors with a consolidative pattern was 62 mm (range 15–126 mm) ($p < 0.001$). The SUV_{max} of tumors with a consolidative pattern was significantly higher than that of tumors with a nodular pattern ($p = 0.033$).

Patient Survival and Relationship to Clinicopathologic and Imaging Findings

DFS and OS rates of patients with a nodular pattern tumor were relatively better than those of patients with a consolidative pattern tumor; however, the differences were not statistically significant ($p = 0.062$ and $p = 0.109$, respectively) (Fig. 2*A*). The 5-year DFS and OS rates of patients with nodular pattern tumors were 84% and 90%, whereas those of patients with consolidative pattern tumors were 65% and 77%, respectively. When survival rates were analyzed according to the SUV_{max}, tumors with an SUV_{max} less than 4.4 and those with an SUV_{max} of 4.4 or higher were associated with significantly different DFS rates ($p = 0.022$), but not OS rates ($p = 0.112$); tumors with a higher SUV_{max} tended to be associated with lower survival (Fig. 2*B*). After adjustment for smoking and T classification, the DFS and OS rates for patients with tumors having an SUV_{max} less than 4.4 were relatively higher than those for patients with tumors having an SUV_{max} of 4.4 or higher, although the differences were not statistically significant.

Table 3. Comparison between Nodular and Consolidative Pattern IMAs on CT Scan

Characteristic	Nodular Pattern (n = 62)	Consolidative Pattern (n = 19)	*p* Value
Demographic characteristics			
Mean age ± SD, y	56.7 ± 12.4	60.8 ±10.3	0.194
Sex, n (%)			0.198
Male	25 (40)	11 (58)	
Female	37 (60)	8 (42)	
Smoking history, n (%)			0.832
Never	44 (71)	13 (68)	
Ever	18 (29)	6 (32)	
Survival outcome, n (%)			
5-year DFS rate	84%	65%	0.062
5-year OS rate	90%	77%	0.109
Surgery-related factors			
Surgery type, n (%)			0.076
Wedge resection	7 (11)	0 (0)	
Lobectomy	54 (87)	17 (90)	
Bilobectomy	1 (2)	2 (10)	
T classification, n (%)			**<0.001**
1A	24 (39)	2 (11)	
1B	15 (24)	0 (0)	
2A	20 (32)	13 (68)	
2B	2 (3)	4 (21)	
3	1 (2)	0 (0)	
N classification, n (%)			0.998
N0	58 (94)	19 (100)	
N1	1 (1)	0 (0)	
N2	3 (5)	0 (0)	
TNM stage, n (%)			**<0.001**
IA	39 (63)	2 (11)	
IB	17 (27)	13 (68)	
IIA	2 (3)	4 (21)	
IIB	1 (2)	0 (0)	
IIIA	3 (5)	0 (0)	
CT scan result			
Mean size ± SD, cm	2.8 ± 1.5	6.2 ± 3.2	**<0.001**
PET scan result			
Mean SUV_{max} ± SD	2.8 ± 2.8	4.6 ± 3.9	**0.033**

Note: Boldface indicates *p* value less than 0.05.
IMA, invasive mucinous adenocarcinoma; CT, computed tomography; SD, standard deviation; y, year; DFS, disease-free survival; OS, overall survival; PET, positron emission tomography; SUV_{max}, maximum standardized uptake value.

Identification of Independent Prognostic Factors among Patients with IMA

On univariate analysis, patient's age, smoking history, consolidative pattern on a CT scan, SUV_{max}, pathologic stage (stage I versus others), and tumor size were considered input variables for DFS, whereas patient's age, consolidative pattern on a CT scan, SUV_{max}, and tumor size were regarded as input variables for OS on multivariate analysis. On the basis of the multivariate Cox proportional hazards analysis, tumor size (hazard ratio [HR] = 1.370, 95% confidence interval [CI]: 1.141–1.645, $p = 0.001$) and SUV_{max} (HR = 1.338, 95% CI: 1.160–1.544, $p < 0.001$) were significant independent poor prognostic predictors for DFS (Table 4). However, smoking, consolidative pattern on CT scan, patient's age, and pathologic stage were not related to DFS ($p = 0.234$, $p = 0.280$, $p = 0.957$, and $p = 0.864$, respectively). Regarding OS, tumor size (HR = 1.309, 95% CI: 1.092–1.570, $p = 0.004$) was the only predictor of poor prognosis.

Discussion

Many reports have shown that there are unique clinical and biological features in the subset of lung ADCs formerly classified as mucinous BAC.[2–10,12,21] Since the classification proposed by IASLC/ATS/ERS, there have also been studies showing different characteristics between IMAs and nonmucinous ADCs. However, the number of IMAs in previous studies has been too small to develop useful clinical standards.[13–15] To overcome the problem of low incidence of cases, we reevaluated all

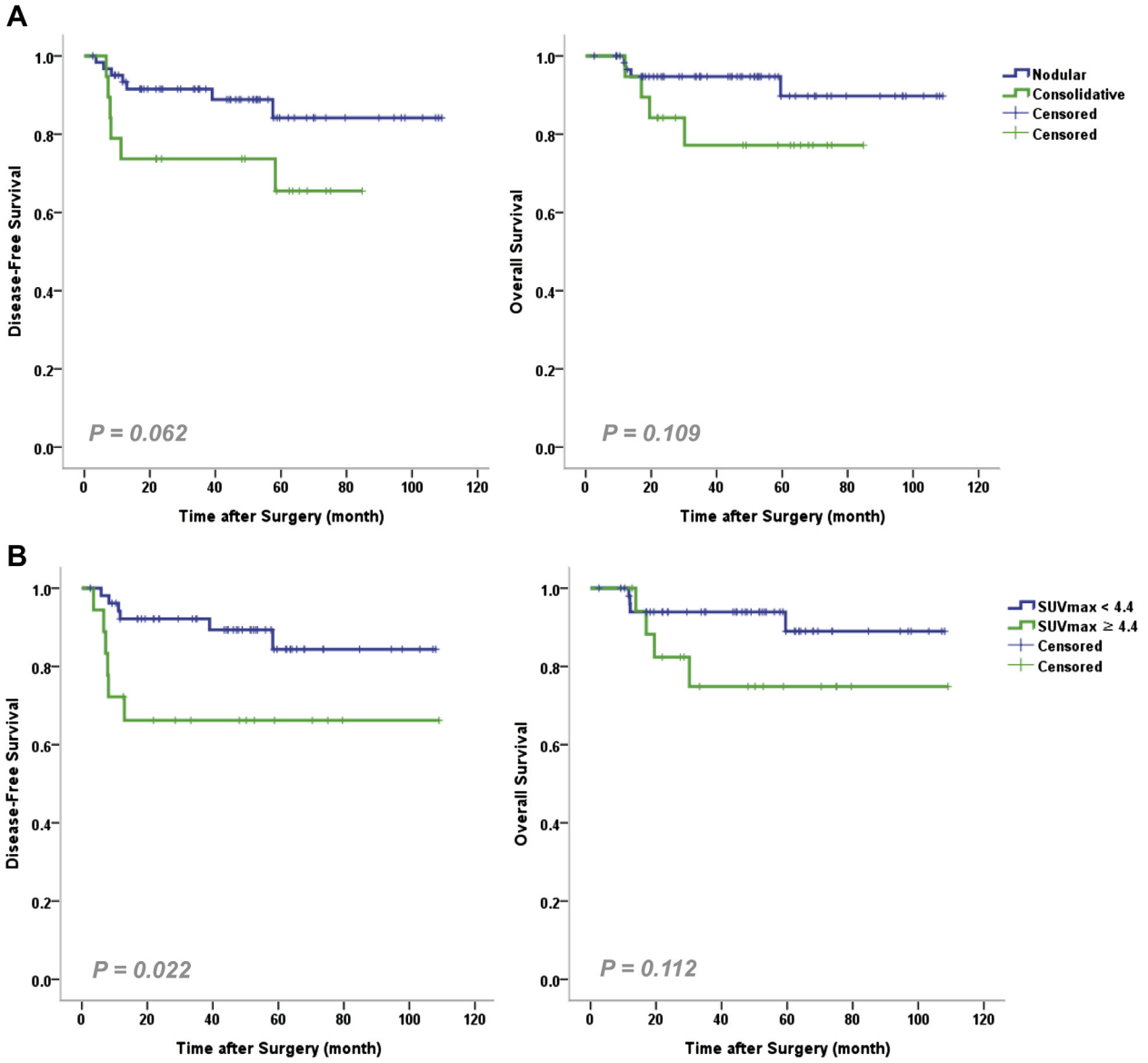

Figure 2. Kaplan-Meier survival curves of invasive mucinous adenocarcinomas for disease-free and overall survival according to computed tomography scan features (*A*) and maximum standardized uptake (SUV_{max}) with a cutoff value of 4.4 (*B*).

cases of resected lung ADCs at our institution during a period of more than 8 years and ultimately identified 81 patients with a solitary IMA. Then, we retrospectively analyzed the clinicopathologic and radiologic variables of the 81 patients to determine the ultimate impact on patient prognosis. To the best of our knowledge, this is the first large cohort study regarding IMA prognosis performed after proposal of the schemes for classification of lung ADCs by the IASLC/ATS/ERS and WHO.[1,11]

Survival analyses of IMAs demonstrated that the 5-year DFS rate is 79% with a median DFS time of 46.2 months, and the 5-year OS rate is 85% with a median survival time of 47.8 months. In our cohort, patients with IMA had a better DFS than did those with nonmucinous ADC. This result is in contrast with the results from the previous literature, suggesting an aggressive clinical course for mucinous BAC (IMAs in the new classification schemes).[2,3,9,12,22] When compared with invasive nonmucinous ADCs, IMA was characterized by a DFS curve running between those of lepidic predominant (low-grade) ADC and acinar/papillary predominant (intermediate-grade) ADC. The OS curve for IMA was running similarly to that of acinar/papillary predominant (intermediate-grade) ADC. This suggests that IMAs could be classified into low- to intermediate-grade groups of cancer when survival rates of all invasive ADCs are plotted by dividing them into four different groups, namely, IMAs, lepidic predominant, acinar/papillary predominant, and solid/micropapillary predominant nonmucinous ADCs. This fact is partly

Table 4. Cox Proportional Hazards Model of Disease-Free and Overall Survival in IMA

	Disease-Free Survival		
Multivariate Variables	Hazard Ratio	95% Confidence Interval	*P* values
Age	1.002	0.938-1.070	0.957
Smoking	2.123	0.614-7.334	0.234
CT feature, consolidative pattern	0.376	0.064-2.215	0.280
SUV_{max}	1.338	1.160-1.544	**< 0.001**
Tumor size	1.370	1.141-1.645	**0.001**
pStage I vs. other	0.853	0.139-5.244	0.864
	Overall Survival		
Multivariate Variables	Hazard Ratio	95% Confidence Interval	*P* values
Age	1.020	0.944-1.103	0.614
CT feature, consolidative pattern	0.447	0.054-3.706	0.456
SUV_{max}	1.133	0.956-1.342	0.149
Tumor size	1.309	1.092-1.370	**0.004**

Note: Boldface indicates *p* value less than 0.05.
IMA, invasive mucinous adenocarcinoma; y, year; SUV_{max}, maximum standardized uptake; pStage = pathologic stage.

supported by several recent studies that defined IMA as an intermediate-grade tumor group.[16,23]

One thing of particular note regarding IMAs in our study is that only 5% of the patients showed lymph node metastasis and 95% of the patients belonged to nodal stage N0 group. We thought that the number of patients with IMA without nodal metastasis was unusually high. However, this low figure for nodal metastasis is consistent with those of previous studies by Kakegawa et al.[24] and Russell et al.[12] In the study by Kakegawa et al.[24] lymph node metastasis was seen in only one of 12 patients with mucinous BAC.[12] In the study of Kakegawa et al.[24] lymph node metastasis was detected in none of 10 patients with IMA. Moreover, Kadota et al.[17] suggested that IMA is associated with a lower rate of nodal metastases and less lymphatic invasion. The difference between the N classification of IMA and that of nonmucinous ADC may imply that IMA and nonmucinous ADC are two obviously distinct entities. This implication is further corroborated by differences in their genetic mutations and immune profiles.[3,10,25,26] In addition, the poorer survival of patients with IMA than of those with lepidic predominant nonmucinous ADC in spite of similar rates of lymph node metastases in those two groups likely reflects the aggressiveness of the mucinous tumor and the high rate of tumor spread in IMA.

Consolidative pattern IMAs are more frequently manifested as larger and multilobar tumors than are nodular pattern IMAs. Thus, the T classification and pathologic stage were significantly higher in tumors of consolidative pattern IMAs than those in tumors of nodular pattern IMAs. Our study demonstrated that patients with IMAs with a consolidative pattern tended to have relatively poorer DFS and OS than did patients with IMAs having a nodular pattern. However, multivariate analyses revealed that the prognostic value of consolidative pattern IMAs was not significant.

Lee et al.[4] suggested that solitary nodular IMAs show a small amount of FDG uptake at PET. In our series, 76% of all IMAs presented as a solitary nodular lesion, and the mean SUV_{max} was 2.8 in these tumors. According to a study by Sauter et al.,[27] the mean SUV_{max} of lung ADCs (a total of 14 tumors) was 8.7 ± 4.4, which is relatively higher than that of the IMAs in our series. FDG uptake correlates directly with the number of living cancer cells, thus reflecting the grade of malignancy.[4] A recent study by Nakamura et al.[23] demonstrated that SUV_{max} is closely associated with ADC subtypes (classified with the IASLC/ATS/ERS scheme) and is a good predictor of postoperative patient survival. We think that low level of FDG uptake in IMAs, regardless of survival outcome, could be due to the presence of abundant mucin. According to a study by Shim and Han, nine of 11 mucin-producing non–small cell lung cancers demonstrated scanty FDG uptake at PET.[28] Nevertheless, our study demonstrated that SUV_{max} is one of the independent predictors for poor DFS in patients with IMAs. Although the level of FDG uptake in IMAs is relatively low, SUV_{max} itself can play an important role as a prognostic factor in clinical practice. This result concurs with the situation regarding invasive nonmucinous ADCs, corroborating the fact that FDG uptake is well correlated with the grade of tumor invasiveness and aggressiveness.[29]

Until now, many studies have reported that IMA is characterized by the absence of epidermal growth factor receptor gene (*EGFR*) mutation and the presence of Kirsten rat sarcoma viral oncogene homolog gene (*KRAS*) mutation; thus, IMAs are unlikely to respond to epidermal growth factor receptor tyrosine kinase inhibitors such as gefitinib and erlotinib.[25] Thus, a medical strategy for therapy of IMA has not been clearly established and the prediction of a patient's life expectancy has been uncertain. On multivariate analysis, tumor size and SUV_{max} were independent predictors for poor DFS and tumor size was the only predictor for poor OS. The prognostic factors derived from our study correspond to the previously well-known prognostic factors of lung cancers as a whole. However, we think that our results may have some clinical implications because the results are based on relatively large number of IMAs that have been strictly stratified according to the WHO classification scheme.

Our study has several potential limitations. First, it was a retrospective study performed at a single institution and follow-up periods were variable. However, we tried to include as many patients having IMA as possible by adopting a logical selection process to thus minimize selection bias. Additional studies need to be published to clarify the prognosis of IMA through external validation. Second, to secure a large enough sample size for this study, we included all available patients, which might have resulted in limited information regarding genetics. Further studies about the genetic information and treatment outcome of IMAs should be performed.

In conclusion, we demonstrated that as a whole, patients with IMAs have DFS rates between those of patients with low-grade nonmucinous ADC and those of patients with intermediate-grade nonmucinous ADC and OS rates similar to those of patients with intermediate-grade nonmucinous ADC. Multivariate analyses revealed that large tumor size and high SUV_{max} are the factors associated with reduced DFS and large tumor size is the only factor associated with reduced OS.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at http://dx.doi.org/10.1016/j.jtho.2016.03.011.

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