Original Article

Prognostic significance of histologic classification and tumor disappearance rate by computed tomography in lung cancer

Dohun Kim[1,2], Hong Kwan Kim[1], Seok-Hyung Kim[3], Ho Yun Lee[4], Jong Ho Cho[1], Yong Soo Choi[1], Kwhanmien Kim[1], Jhingook Kim[1], Jae Ill Zo[1], Young Mog Shim[1]

[1]Department of Thoracic and Cardiovascular Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [2]Department of Thoracic and Cardiovascular Surgery, Chungbuk National University and Chungbuk National University Hospital, Cheongju, Korea; [3]Department of Pathology, [4]Department of Radiology and Center for Imaging Science, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Contributions: (I) Conception and design: D Kim, HK Kim; (II) Administrative support: HY Lee, YS Choi, J Kim, JI Zo, YM Shim; (III) Provision of study materials or patients: K Kim, JH Cho, HK Kim, J Kim, JI Zo, YM Shim; (IV) Collection and assembly of data: HK Kim, DK; (V) Data analysis and interpretation: HK Kim, D Kim; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Hong Kwan Kim, MD, PhD. Associate Professor, Department of Thoracic and Cardiovascular Surgery, Samsung Medical Center, 50 Ilwon-dong, Gangnam-gu, Seoul 135-710, Korea. Email: hkts.kim@samsung.com.

Background: We investigated the prognostic value of the International Association for the Study of Lung Cancer (IASLC)/American Thoracic Society (ATS)/European Respiratory Society (ERS) classification and assessed the relationship between pathologic invasiveness and tumor disappearance rate (TDR) in lung adenocarcinoma with ground-glass opacity (GGO).

Methods: We reviewed data from 202 consecutive patients operated on between 2000 and 2009 for clinical T1-2N0 lung adenocarcinoma with GGO and reclassified their histologic subtypes according to the IASLC/ATS/ERS classification. Thirty-nine patients had adenocarcinoma in situ (AIS), 29 minimally invasive adenocarcinoma (MIA), 75 lepidic predominant invasive adenocarcinoma (LPA), and 59 non-lepidic predominant invasive adenocarcinoma (NLPA). Survival outcomes were compared according to histologic subtype and TDR.

Results: The mean age was 58 years and 101 patients (50%) were male. Lobectomy was performed in 161 patients (79.7%), wedge resection in 34 (16.8%), and segmentectomy in 7 (3.5%). Patients with AIS, MIA, and LPA had significantly smaller tumor sizes, earlier pathologic T stages, and lower incidences of lymphatic/pleural invasion than those with NLPA. The 5-year recurrence-free survival (RFS) rates were 95.1%, 94.5%, and 87.6% in the AIS + MIA, LPA, and NLPA groups, respectively (P=0.029). Tumors with a TDR>75% were associated with lepidic predominant histologic subtype and less pathologic invasiveness. The 5-year RFS rates were 97.4% in tumors with a TDR >75% and 87.8% in tumors with a TDR ≤75% (P=0.0009).

Conclusions: Histologic subtype according to the IASLC/ATS/ERS classification and TDR both correlated with pathologic invasiveness and predicted survival in patients with lung adenocarcinoma with GGO.

Keywords: Adenocarcinoma of lung; computed tomography (CT); survival rate; pathology

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Introduction

Recent advances in imaging technology and the widespread use of computed tomography (CT) screening have greatly increased the probability of detecting early small-sized lung adenocarcinomas with a ground-glass appearance (1). Adenocarcinoma with ground-glass opacity (GGO) generally has a good prognosis due to its minimally invasive nature (2,3). GGO feature corresponds closely to histopathologically lepidic growth patterns replacing the alveolar wall (2,3). In a new classification system recently proposed by the International Association for the Study of Lung Cancer (IASLC), American Thoracic Society (ATS), and European Respiratory Society (ERS), adenocarcinomas with a lepidic growth pattern include adenocarcinoma *in situ* (AIS), minimally invasive adenocarcinoma (MIA), and lepidic predominant invasive adenocarcinoma (LPA) (4). Many studies have shown that these pathologically less invasive subtypes are associated with better prognoses compared with other subtypes (5-9).

However, the percentage of lepidic growth pattern varies among tumors within the radiologically similar category of adenocarcinoma with GGO feature. A larger proportion of lepidic growth pattern correlates with better prognosis, but the presence of lepidic growth pattern per se does not guarantee that adenocarcinomas with GGO feature are always non- or minimally invasive. Nonetheless, few studies have thoroughly examined the histologic subtypes and the percentage of each subtype according to the new IASLC/ATS/ERS classification, especially focusing on adenocarcinoma with GGO feature.

Currently, the standard extent of resection for lung adenocarcinoma is lobectomy (10,11). However, multiple reports have suggested that small-sized peripheral lung adenocarcinoma can be treated by sublobar resection, yielding survival rates similar to those of lobectomy (12-15). However, when the extent of surgical resection is being decided either preoperatively or intraoperatively, it is difficult to accurately identify the predominant histologic subtypes because small biopsy samples do not provide sufficient material for comprehensive histological subtyping, considering the histologic heterogeneity of lung adenocarcinoma (5,16). To help surgeons decide the extent of pulmonary resection preoperatively, some researchers have attempted to predict pathologic invasiveness based on various radiologic parameters including the GGO ratio and the tumor disappearance rate (TDR) (17-20). Although several studies have investigated the relationship between radiologic parameters and pathologic features of lung adenocarcinoma based on the new IASLC/ATS/ERS classification system (21-25) few reports have focused on adenocarcinoma with GGO feature.

Therefore, we conducted a retrospective review of patients who underwent curative-intent surgery for lung adenocarcinoma with GGO morphology. The objectives of our study were (1) to investigate the prognostic value of the new IASLC/ATS/ERS classification system and (2) to assess the relationship between pathologic invasiveness and TDR.

Methods

Patients

Patients were included in the study if they had clinical T1-2N0 lung adenocarcinoma with GGO feature. GGO was defined as an area of a hazy increase in attenuation that did not obscure any underlying lung structures on CT scans. The consolidation component was defined as an area of increased opacification that completely obscured the underlying vascular markings. Pure GGO (no consolidation component) and mixed GGO (both a pure GGO and a consolidated region) were all included in the study. Patients were excluded if they had clinical T3, T4, N1, N2, N3, or M1 metastases; underwent resection for multiple tumors; received neoadjuvant treatment; or had prior pulmonary resection. After application of these criteria, between January 2000 and December 2009, a total of 202 patients were eligible for the study. The Institutional Review Board of Samsung Medical Center (2011-08-039-001) approved this study.

Staging workup and operation

Patients were staged according to the seventh edition of the American Joint Committee on Cancer staging manual (26) and the TNM classification manual from the International Union Against Cancer (27). Operative procedures included resection of the affected lung plus lymph node dissection of the ipsilateral hilum and the mediastinum. Lobectomy was chosen as the standard treatment, while segmentectomy or wedge resection was selectively performed when the tumor was considered to be resected with adequate resection margin. Patients were regularly evaluated by chest CT and/or PET/CT every 3 months for the first 2 years following surgery, and every 6 months thereafter.

TDR and histologic subtyping

The TDR (%) was defined as follows: [1-(maximum area of consolidation on the mediastinal window setting/ maximum area of tumor on the lung window setting) x100]. Preoperative CT images were reviewed by a single radiologist blinded to pathologic results. All specimens were evaluated microscopically by a single pathologist blinded to clinical and radiologic data. Comprehensive histologic subtyping was performed according to the new IASLC/ ATS/ERS classification system (4). As mentioned above, the study group was divided into 4 categories by histology; AIS, MIA, LPA, and non-lepidic predominant invasive adenocarcinoma (NLPA). AIS is defined as a solitary tumor ≤3 cm and pure lepidic pattern. MIA is also a solitary tumor ≤3 cm but predominantly lepidic. Moreover, an invasive component existed but should be ≤5 mm. If the tumor shows predominantly lepidic pattern, but could not be included in the AIS or MIA criteria, then it was defined as LPA. Other tumors which could not be included above criteria were defined as non-LPA. The percentage of each histologic component was recorded in 5% increments. The predominant pattern was defined as the pattern with the greatest percentage.

Statistical analysis

Student's *t* tests or the Wilcoxon rank sum tests were used for continuous variables, whereas categorical variables were compared by the χ^2 test or Fisher's exact tests. One-way analysis of variance or the Kruskal-Wallis test was used to compare the continuous variables among the three groups. Overall survival (OS) was defined as the time from the date of surgical resection to death from any cause. Recurrence-free survival (RFS) was defined as the time from the date of surgical resection to recurrence or death. Survival curves were prepared using the Kaplan-Meier method and compared using the log-rank test. To determine prognostic factors, multivariate analysis was performed using the Cox proportional hazards model. All statistical tests were two-sided with a significance level set at 0.05 and were performed using Stata software version 10.0 (Stata, College Station, TX, USA).

Results

Patient data

Lobectomy was performed in 161 (80%) and sublobar resection in 41 (20%) patients. Patients who underwent sublobar resection had significantly larger areas of a lepidic growth pattern, less frequent NLPA, smaller tumor sizes, earlier pathologic T stages, less frequent pleural invasions and greater TDRs than those who underwent lobectomy (*Table 1*). The mean follow-up duration was 82.3 months (range, 2.2–180.8 months). During follow-up, 13 patients (6.4%) died and 12 (5.9%) developed recurrence. The 5- and 10-year OS rates were 96.9% and 89.6%, respectively. The 5- and 10-year RFS rates were 93.3% and 86.3%, respectively.

Comparative analysis according to histologic subtypes

Thirty-nine patients (19%) had AIS, 29 (14%) had MIA, 75 (37%) had LPA, and 59 (29%) had NLPA (*Table 2*). Patients with NLPA had significantly smaller areas of a lepidic growth pattern, greater tumor sizes, more lymphatic and pleural invasion, and more advanced clinical and pathologic T stages (*Table 2*). There was no lymph node metastasis or lymphatic invasion in MIA but five patients had unexpected lymph node metastasis (4 pN1, 1 pN2), all of whom had invasive adenocarcinoma (2 LPA, 3 NLPA). Most recurrences occurred in patients with invasive adenocarcinoma (3 LPA, 7 NLPA), except for one with AIS and one with MIA. The 5-year OS and RFS rates were 99% and 95% in the AIS + MIA group, 96% and 95% in the LPA group, and 97% and 88% in the NLPA group, respectively (OS, P=0.069, *Figure 1A*; RFS, P=0.029, *Figure 1B*).

Comparative analysis according to TDR

The mean TDR was 90% in the AIS + MIA group, 74% in the LPA group, and 66% in the NLPA group (P<0.001, AIS + MIA *vs.* LPA, P=0.006, LPA *vs.* NLPA). ROC curve identified the optimal TDR cut-off value for predicting the pathologic invasiveness as 75% (AUC, 0.693; 95% CI, 0.63–0.76). The relationship between TDR and pathologic invasiveness was investigated using this cut-off value (*Table 3*). No patient with a tumor with a TDR >75% experienced recurrence. The 5-year OS and RFS rates were 97% and 97% in patients with tumors with a TDR >75% and 96% and 88% in a TDR ≤75%, respectively (OS, P=0.159, *Figure 2A*; RFS, P=0.0009, *Figure 2B*).

Prognostic factor analysis

Univariable analysis indicated that age, tumor size,

Table 1 Clinical and pathologic characteristics according to the type of surgery

Characteristics	Lobectomy (n=161)	Sublobar resection (n=41)	All (n=202)	P value
Age (year, mean)	58.5 [39–79]	56.6 [37–78]	58.1 [37–79]	0.228
Men [%]	82 [51]	19 [46]	101 [50]	0.6
Smoking [%]	42 [26]	13 [32]	55 [27]	0.47
Histologic subtype* [%]				0.001
AIS	22 [14]	17 [42]	39 [19]	–
MIA	19 [12]	10 [24]	29 [14]	–
Lepidic	65 [40]	10 [24]	75 [37]	–
Acinar	26 [16]	4 [10]	30 [15]	–
Papillary	24 [15]	–	24 [12]	–
Solid	2 [1]	–	2 [1]	–
Micropapillary	3 [2]	–	3 [2]	–
Histologic group [%]				<0.001
AIS/MIA	41 [26]	27 [66]	68 [34]	
LPA	65 [40]	10 [24]	75 [37]	
NLPA	55 [34]	4 [10]	59 [29]	
Tumor size (mean, cm)	1.97 (0.7–5)	1.14 (0.6–2.5)	1.8 (0.6–5)	0.143
Peripheral location [%]	157 [98]	40 [98]	197 [98]	0.987
Pathologic T stage [%]				<0.001
T1a	92 [57]	37 [90]	129 [64]	
T1b	37 [23]	3 [7]	40 [20]	
T2a	32 [20]	1 [3]	33 [16]	
Pathologic N stage [%]				0.668
N0	156 [96]	41 [100]	197 [97]	
N1	4 [3]	–	4 [2]	
N2	1 [1]	–	1 [1]	
Lymphatic invasion [%]	13 [8]	1 [2]	14 [7]	0.309
Pleural invasion [%]	25 [16]	1 [2]	26 [13]	0.025
TDR [%]	73 [1–100]	94 [35–100]	77 [1–100]	<0.001

*, lepidic, acinar, papillary, solid, and micropapillary means the predominant patterns of invasive adenocarcinoma. TDR, tumor disappearance rate; AIS, adenocarcinoma in situ; MIA, minimally invasive adenocarcinoma; LPA, lepidic predominant invasive adenocarcinoma; NLPA, non-lepidic predominant invasive adenocarcinoma.

and percentage lepidic growth pattern were significant prognostic factors for OS (*Table 4*). Moreover, age, tumor size, pathologic T and N stage, lymphatic invasion, percentage lepidic growth pattern, and TDR were significant prognostic factors for RFS (*Table 4*). The results of the multivariate analyses are summarized in *Table 5*. Tumor size and lepidic predominant growth pattern were identified as independent predictive factors associated with OS. Tumor size and lymphatic invasion were found to be independent predictive factors associated with RFS.

Table 2 Clinical and pathologic characteristics according to the histologic subtype

Characteristics	AIS + MIA (n=68)	LPA (n=75)	NLPA (n=59)	P value
Age (year, mean)	57.6 [37–78]	57.8 [43–79]	59.1 [39–78]	0.287
Men [%]	41 [60]	28 [37]	32 [54]	0.017
Smoking [%]	22 [32]	16 [21]	17 [29]	0.318
Extent of surgery				<0.001
Lobectomy	41 [60]	65 [87]	55 [93]	–
Sublobar resection	27 [40]	10 [13]	4 [7]	–
Histologic pattern (mean, %)				
Lepidic	100	81.6 [50–100]	17.3 (0–40)	0.0001
Acinar	–	14.5 (0–50)	41.7 (0–100)	0.0001
Papillary	–	3.9 (0–50)	33.4 (0–90)	0.0001
Solid	–	–	3.1 (0–100)	0.0875
Micropapillary	–	–	4.5 (0–90)	0.0001
Tumor size (mean, cm)	1.4 (0.6–3)	1.94 (0.6–5)	2.1 (0.8–5)	0.0001
Pathologic T stage [%]				<0.001
T1a	57 [84]	45 [60]	27 [46]	–
T1b	11 [16]	16 [21]	13 [22]	–
T2a	–	14 [19]	19 [32]	–
Pathologic N stage [%]				0.188
N0	68 [100]	73 [98]	56 [95]	–
N1	–	1 [1]	3 [5]	–
N2	–	1 [1]	–	–
Lymphatic invasion [%]	–	2 [3]	12 [20]	<0.001
Pleural invasion [%]	–	13 [17]	13 [22]	<0.001
Differentiation [%]				<0.001
Well	40 [59]	55 [73]	37 [63]	
Moderate	5 [7]	11 [15]	19 [32]	
Poor	–	–	1 [2]	
Undetermined	23 (34%)	9 [12]	2 [3]	
TDR (mean, %)	90 [17–100]	74 [3–100]	66 [1–100]	0.0001

AIS, adenocarcinoma in situ; MIA, minimally invasive adenocarcinoma; LPA, lepidic predominant invasive adenocarcinoma; NLPA, non-lepidic predominant invasive adenocarcinoma; TDR, tumor disappearance rate.

Discussion

In this study focusing on patients with GGO-type lung adenocarcinoma, more than 70% of the study cohort had lepidic predominant. This observation is in contrast to previous studies that included patients with lung adenocarcinoma irrespective of CT morphology. In previous reports, the frequencies of LPA ranged from 5.6% to 8.1% (5,7). Therefore, to the best of our knowledge, this study is the largest series of lepidic predominant adenocarcinomas

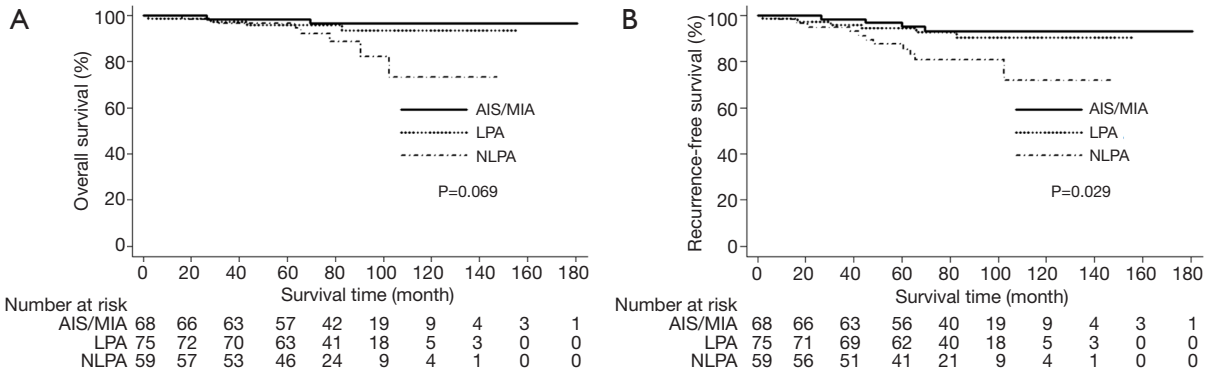

Figure 1 Overall survival (A) and recurrence-free survival (B) according to the histologic subtypes. AIS, adenocarcinoma in situ; MIA, minimally invasive adenocarcinoma; LPA, lepidic predominant invasive adenocarcinoma; NLPA, non-lepidic predominant invasive adenocarcinoma.

Table 3 Clinical and pathologic characteristics according to tumor disappearance rate

Characteristics	TDR ≤75% (n=86)	TDR >75% (n=116)	P value
Age (year, mean)	59.5 [43–79]	57.1 [37–78]	0.058
Men [%]	34 [40]	67 [58]	0.01
Smoking [%]	24 [28]	31 [27]	0.852
Extent of surgery [%]			<0.001
Lobectomy	81 [94]	80 [69]	–
Sublobar resection	5 [6]	36 [31]	–
Histologic pattern (mean, %)			
Lepidic	54.2 (0–100)	80 (0–100)	<0.001
Acinar	25.1 (0–90)	12 (0–100)	0.0002
Papillary	18.3 (0–90)	5.9 (0–90)	0.0025
Solid	–	1.6 (0–100)	0.222
Micropapillary	2.4 (0–90)	0.5 (0–60)	0.0093
Tumor size (mean, cm)	2.3 (0.8–5)	1.4 (0.6–5)	<0.001
Pathologic T stage [%]			<0.001
T1a	33 [39]	96 [83]	–
T1b	26 [30]	14 [12]	–
T2a	27 [31]	6 [5]	–
Pathologic N stage [%]			0.013
N0	81 [94]	116 [100]	–
N1	4 [5]	–	–
N2	1 [1]	–	–

Table 3 *(continued)*

Table 3 *(continued)*

Characteristics	TDR ≤75% (n=86)	TDR >75% (n=116)	P value
Lymphatic invasion [%]	12 [14]	2 [2]	0.001
Pleural invasion [%]	22 [26]	4 [4]	<0.001
Differentiation [%]			<0.001
Well	59 [69]	73 [63]	–
Moderate	25 [29]	10 [9]	–
Poor	–	1 [1]	–
Undetermined	2 [2]	32 [27]	–

TDR, tumor disappearance rate.

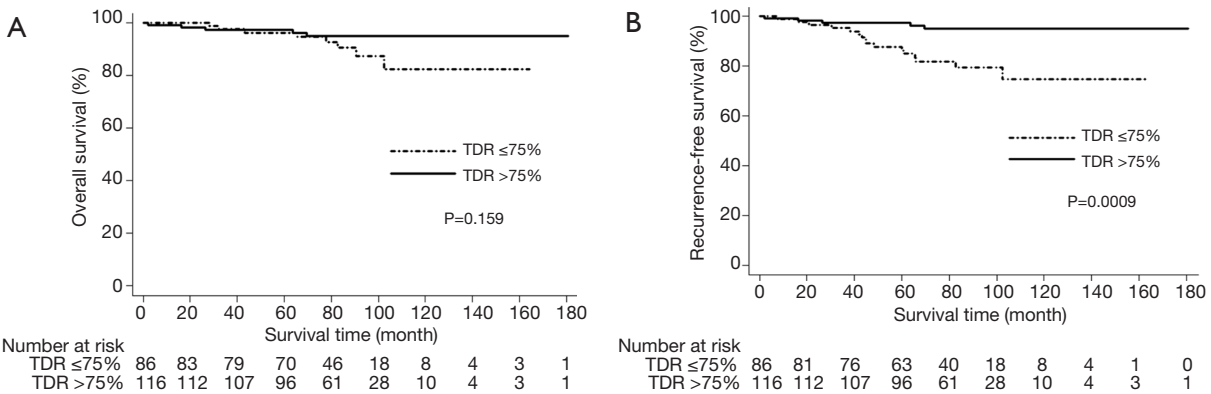

Figure 2 Overall survival (A) and recurrence-free survival (B) according to tumor disappearance rate. TDR, tumor disappearance rate.

Table 4 Univariate analyses for overall survival and recurrence-free survival

Variable	Overall survival			Recurrence-free survival		
	HR	95% CI	P value	HR	95% CI	P value
Age, years	1.12	1.05–1.19	0.001	1.07	1.01–1.12	0.012
Male	1.12	0.38–3.34	0.838	0.88	0.37–2.07	0.766
Tumor size, cm	2.26	1.47–3.47	0.0001	2.42	1.69–3.45	0.0001
pT stage	1.85	0.99–3.45	0.053	2.09	1.29–3.42	0.003
pN stage	1.97	0.41–9.55	0.4	7.02	2.93–16.86	0.0001
Lepidic predominant ADC*	0.25	0.08–0.78	0.017	0.31	0.13–0.74	0.008
Lepidic histologic pattern, %	0.99	0.97–0.99	0.036	0.99	0.97–0.99	0.009
Lymphatic invasion	–	–	–	4.69	1.55–14.23	0.006
Pleural invasion	1.13	0.25–5.12	0.871	1.54	0.52–4.58	0.437
TDR, %	0.18	0.03–1.15	0.07	0.07	0.02–0.29	0.0001

*, lepid predominant adenocarcinoma included adenocarcinoma *in situ*, minimally invasive adenocarcinoma and lepidic predominant invasive adenocarcinoma. HR, hazard ratio; CI, confidence interval; pT stage, pathologic T stage; pN stage, pathologic N stage; ADC, adenocarcinoma; TDR, tumor disappearance rate.

Table 5 Multivariate analyses for overall survival and recurrence-free survival

Variable	Overall survival			Recurrence-free survival		
	HR	95% CI	P value	HR	95% CI	P value
Age, years	1.08	0.99–1.17	0.051	1.02	0.98–1.07	0.34
Tumor size, cm	5.25	1.79–15.4	0.003	2.95	1.29–6.78	0.011
pT stage	0.28	0.06–1.23	0.092	2.09	0.19–1.44	0.209
pN stage	0.14	0.01–3.27	0.219	1.39	0.33–5.84	0.65
Lepidic predominant ADC*	0.28	0.08–0.98	0.047	0.52	0.19–1.41	0.199
Lymphatic invasion	–	–	–	3.72	1.06–13.01	0.04
TDR, %	1.78	0.08–42.3	0.72	0.6	0.98–1.07	0.636

*, lepid predominant adenocarcinoma included adenocarcinoma *in situ*, minimally invasive adenocarcinoma and lepidic predominant invasive adenocarcinoma. HR, hazard ratio; CI, confidence interval; pT stage, pathologic T stage; pN stage, pathologic N stage; ADC, adenocarcinoma; TDR, tumor disappearance rate.

for which the radiologic findings and pathologic features according to the IASLC/ATS/ERS classification system were comprehensively assessed.

We observed obvious prognostic differences between the histologic subtypes. Patients with AIS, MIA, and LPA had more favorable OS and significantly better RFS than those with NLPA. The differences in prognoses are possibly due to the pathologic invasiveness between them. Patients with AIS, MIA, and LPA had significantly smaller tumor sizes, earlier T stages, and lower incidences of lymphatic and pleural invasion than those with NLPA. No lymph node metastases were detected in any of the patients with AIS or MIA. As predicted, we also observed significant differences in the percentages of lepidic pattern between the histologic subtypes (AIS/MIA 100%, LPA 86.7%, NLPA 17.3%). Specifically, higher percentages of lepidic pattern were associated with lower risks of recurrence and better survival. This finding is consistent with previous reports (28,29).

The standard management for early-stage lung adenocarcinoma remains lobectomy (10,11). However, some suggested that small-sized peripheral lung adenocarcinoma can be treated by sublobar resection, yielding survival rates similar to those of lobectomy (12-15). In this study, among the 41 patients who underwent sublobar resection, more than 90% had lepidic predominant adenocarcinoma. Consequently, they had smaller tumor sizes, earlier T stages, lower incidences of pleural invasion, and lower percentages of lepidic growth pattern. These findings might be related to the tendency that we have conservatively selected the candidates for sublobar resection and thus suggest that patients with less aggressive pathologic features can be effectively treated with sublobar resection.

However, since accurate subtype can be known after surgery, radiologic parameters have been attempted to replace pathologic results (17-25). Takahashi *et al.* demonstrated that GGO ratio, TDR, and consolidation diameter were strong indicators of tumor invasiveness according to the new classification system (22). These findings were consistent with our study. We found that tumors with a TDR >75% were pathologically less invasive in terms of the predominant histologic subtype, tumor size, tumor invasiveness, and lymph node metastasis. Consequently, patients with tumors with a TDR >75% had excellent survival rates and no recurrence compared with those with tumors with a TDR ≤75%.

Our study has several limitations. First, since this was a retrospective study, selection bias was inevitable. As discussed above, patients who underwent sublobar resection had more favorable clinicopathologic characteristics than those who underwent lobectomy. This might have led to better survival outcomes in patients with tumors with a TDR >75% despite the fact that they received limited sublobar resection more frequently than others. Therefore, our data suggest that selected patients with AIS, MIA, and even LPA (or tumors with a TDR >75%) can be effectively treated with sublobar resection. Second, interobserver variability must be considered. This issue is especially relevant to the TDR calculations, since estimation of tumor size is subject to considerable variability given that the border of the GGO shadow might be difficult to define. To minimize potential variations in measurement, the radiologist in our study followed predefined window

settings on the CT image for every calculation.

Conclusions

Here we comprehensively assessed radiologic parameters such as TDR and histologic subtype according to the new IASLC/ATS/ERS classification system in patients with GGO-type lung adenocarcinoma. We found that adenocarcinoma with a lepidic growth pattern was associated with less aggressive pathologic features and better survival outcomes. TDR was useful in predicting pathologic invasiveness and a lepidic growth pattern. Therefore, our data indicate that patients with tumors with 'a less aggressive' lepidic growth pattern and a high (>75%) TDR are good candidates for 'the limited, but less invasive' procedure of sublobar resection.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The Institutional Review Board of Samsung Medical Center (2011-08-039-001) approved this study.

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