Clinical Significance of Complex Glandular Patterns in Lung Adenocarcinoma

Clinicopathologic and Molecular Study in a Large Series of Cases

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ABSTRACT

Objectives: *To explore whether complex glandular patterns (CGPs) have a potential role in the clinical management of patients with lung adenocarcinoma.*

Methods: *We included 356 patients with lung adenocarcinoma with available clinicopathologic information, gene mutations, and clinical outcomes for analysis.*

Results: *We identified 54 (15.2%) CGP-predominant cases. The CGPs were associated with ALK rearrangement and HER2 mutation. Survival analysis showed that the clinical outcome of CGP-predominant patients was worse than that for acinar-predominant patients (overall survival [OS], 66.4 vs 90.3 months,* P < *.01; recurrence-free survival [RFS], 50.1 vs 73.1 months,* P = *.022) but was comparable with solid-predominant subtype tumors (OS, 66.4 vs 67.8 months,* P = *.558; RFS, 50.1 vs 41.3 months,* P = *.258). In particular, the coexistence of the cribriform and fused gland pattern was associated with the poorest survival, with a death risk increased by 2.25-fold (hazard ratio, 3.25; 95% confidence interval, 1.35-7.86,* P = *.009).*

Conclusions: *Our results provide new insight into the potential role of CGPs in clinical management and will be beneficial for treatment decision making in patients with lung adenocarcinoma.*

Lung cancer is one of the most common cancer types and also the leading cause of cancer-related deaths worldwide.[1,2] In 2011, the International Association for the Study of Lung Cancer (IASLC), American Thoracic Society (ATS), and European Respiratory Society (ERS) proposed a new classification scheme for lung adenocarcinoma.[2] Four years later, the World Health Organization (WHO) proposed the classification of tumors of the lung, with only minor changes compared with the lung adenocarcinoma classification (2011) published by the IASLC/ATS/ERS, which classified lung cancer into five main pathologic subtypes, including acinar, solid, micropapillary, papillary, and lepidic.[3] Both the 2011 IASLC/ATS/ERS and 2015 WHO classifications were widely adopted in clinical and pathologic practice, and their predictive roles for patient clinical outcomes had been confirmed by several studies.[4-7] Interestingly, during the clinical practice of the 2015 WHO classification, we noted that some complex glandular patterns (CGPs) (eg, cribriform and fused gland) presented distinct pathologic features apart from the five main subtypes of adenocarcinoma (acinar, solid, micropapillary, papillary, and lepidic). In a white population-based study, CGPs were mainly found in high-grade lung adenocarcinoma.[8] Before the 2015 WHO classification was published, whether CGPs, especially the cribriform pattern,

should be classified as a new type of lung adenocarcinoma remained controversial.[8-10]

With aims to explore whether CGPs have a potential role in the clinical management of patients with lung adenocarcinoma, we included 356 patients with lung adenocarcinoma who had available clinical information and survival data. This cohort represented a relatively homogeneous and well-defined eastern Asian population. Furthermore, we investigated the associations of CGPs with some related gene mutations and rearrangement to reveal whether genetic alternation may be induced by CGPs. In particular, the coexistence of the cribriform and fused gland (CCFG) pattern was also taken into investigation as a distinct CGP subtype for its association with survival and clinical characteristics of these patients.

Materials and Methods

Source of Clinical Data

In the present study, we included 356 patients with lung adenocarcinoma (stages I-III) who had undergone surgical resection at the Fudan University Shanghai Cancer Center from 2006 to 2013. Patients were restaged according to the eighth edition of the TNM classification.[11] The last follow-up date was October 9, 2016. All procedures performed in the present study involving human participants were in accordance with the ethical standards of the Committee for Ethical Review of Research of Fudan University Shanghai Cancer Center and also conformed to the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Tumor tissues were obtained with signed consent for the purpose of scientific research from the included patients.

Histologic Analysis and Evaluation

All resected specimens were formalin fixed immediately after resection and stained with H&E. The slides were measured independently by two pathologists (X.S. and Y.L.) who were blinded to the clinical data. The evaluation criterion was according to the WHO and IASLC/ATS/ERS classification of adenocarcinoma.[2,3] The criterion of the cribriform pattern was in accordance with Moreira et al,[8] who defined the cribriform pattern as nests of tumor cells with a sieve-like perforation and the fused gland pattern as fused glands with irregular borders, back-to-back glands without intervening stroma, or ribbon-like formations. In the present study, CGPs were subdivided into the single cribriform pattern, single fused gland pattern, and CCFG pattern. The single cribriform pattern (SCP) is judged according to the following criteria: SCP ≥10% and single fused gland (SFG) ≤9%. The SFG is judged according to the following criteria: SFG ≥10% and SCP ≤9%. CCFG pattern was defined as coexistence of cribriform (≥10%) and fused glands (≥10%).

Statistical Analysis

The χ^2 test was applied to compare the association between CGPs (including three subtypes, respectively) and clinical features as well as several gene mutations (the Fisher exact test was used when the number of patients in one compared group was fewer than five). Overall survival (OS) was defined as the time from resection to death from any cause. Recurrence-free survival (RFS) was defined as the time from resection to the first time of recurrence. The Kaplan-Meier method was used to assess the association of clinicopathologic factors (eg, the CGPs and five main pathologic subtypes) with OS and RFS. Univariate and multivariable analyses for the related association with death or recurrence risk of the patients were performed using the Cox regression hazards model. A two-tailed *P* value less than .05 was considered statistically significant for interpretation of the results. All statistical analyses were performed using SPSS version 20.0 (SPSS, Chicago, IL).

Results

Distribution of CGPs in the Predominant Type of Adenocarcinoma

The stained results for nonstandard, cribriform, and fused gland biopsy specimens are shown in **Image 1**. Of all 356 cases, 172 (48.3%) were diagnosed as acinar predominant, 40 (11.2%) as solid predominant, 61 (17.1%) as micropapillary predominant, 47 (13.2%) as papillary predominant, and 36 (10.1%) as lepidic predominant according to the 2015 WHO classification criteria (Supplementary Table 1; all supplemental materials can be found at *American Journal of Clinical Pathology* online). A total of 156 (43.82%) patients with CGPs were also identified, and 54 (15.2%) were CGP predominant. The single cribriform pattern, single fused gland pattern, and CCFG pattern were observed in 50 (14.0%), 89 (25.0%), and 17 (4.8%) tumors, respectively. CGPs had a significant tendency to coexist with acinar subtypes ($P < .01$, Supplementary Figure 1A). The single fused gland pattern was more likely to coexist with the acinar subtype ($P < .01$, Supplementary Figure 1B), while the single

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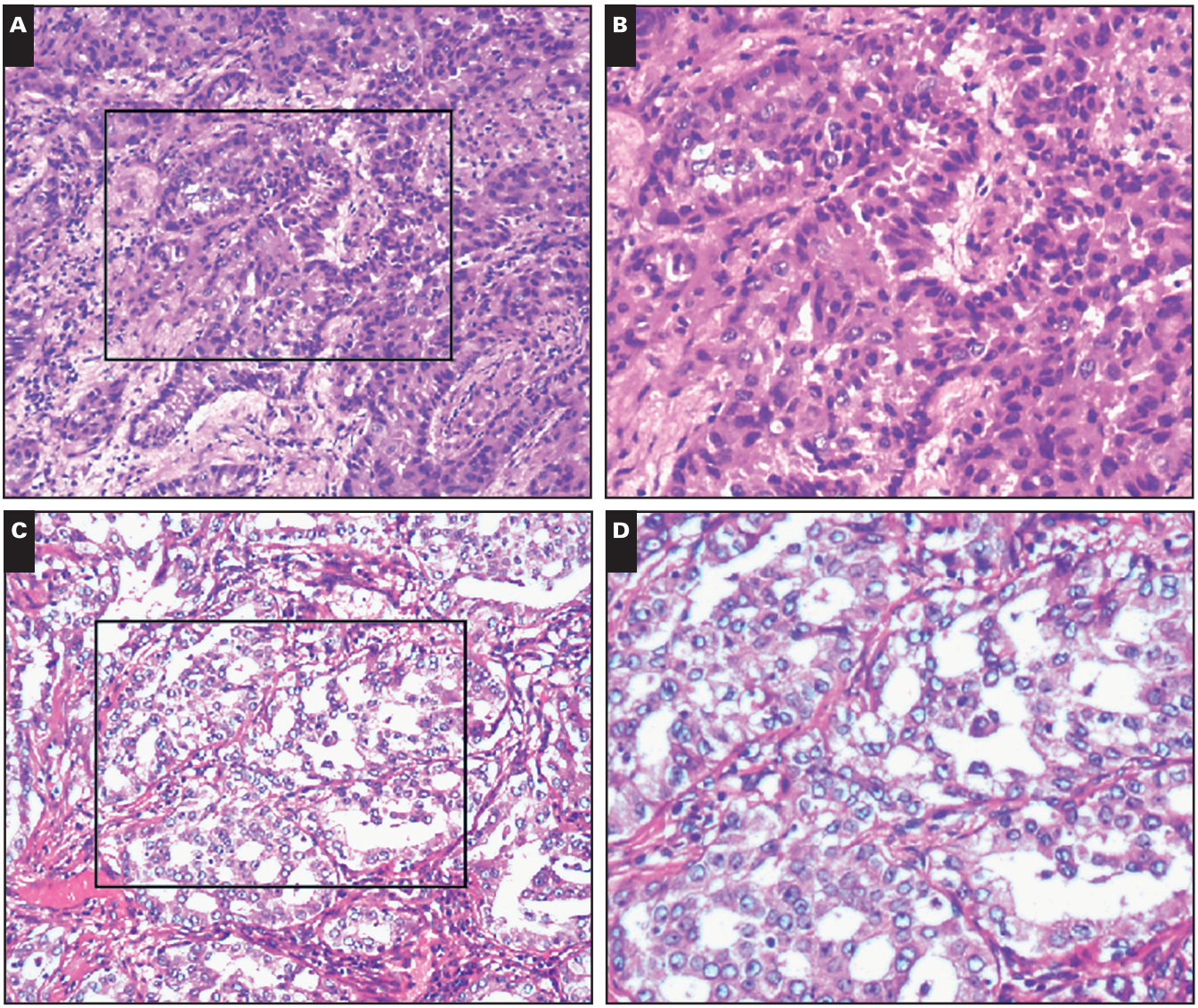

Image 1 Corresponding paraffin-embedded complex glandular pattern tissues were subjected to H&E staining. **A**, **B**, Fused gland (×20). **C**, **D**, Cribriform (×20).

cribriform pattern was most likely to coexist with the solid subtype ($P < .01$, Supplementary Figure 1C).

Association Between Clinicopathologic Characteristics and CGPs

CGPs had strong associations with lymph/vascular invasion ($P = .001$) and higher TNM stage ($P = .035$) Table 1. Further analysis revealed that the single fused gland pattern was correlated with a higher TNM stage ($P = .041$) and a tumor size of 20 mm or less ($P = .020$), and the single cribriform pattern was associated with lymph/vascular invasion ($P < .001$), a tumor size greater than 20 mm ($P = .021$), and a higher TNM stage ($P < .001$), while no clinicopathologic features were significantly associated with the CCFG pattern.

Gene Mutations Analysis in CGPs

With a further interest to find out CGP-related gene mutations, we evaluated the *EGFR*, *KRAS*, *AKT1*, *HER2*, *BRAF*, *ALK*, *ROS1*, and *P110* mutational profile in these 356 adenocarcinomas. The CGPs were associated with *ALK* rearrangement ($P = .006$) and *HER2* mutation ($P = .047$) Table 2. The single cribriform pattern was associated with *ALK* rearrangement ($P < .001$), *EGFR* mutation ($P = .003$), and *AKT1* mutation ($P = .013$). However, we did not find a significant association of the single fused gland group and CCFG group with all molecular alterations and gene mutations. To compare with previous studies, we also analyzed whether these potential genetic associations were exhibited in the cribriform pattern and fused gland pattern. As indicated by our

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Table 1
Associations of CGPs With Clinical Characteristics in Patients With Lung Cancer

Characteristic	No. of Cases	Predominant Pattern, No. (%)		χ^2	*P* Value
		Patterns With CGPs	Patterns Without CGPs		
Age, y					
≤59	186	80 (43.0)	106 (57.0)	0.104	.747
>59	170	76 (44.7)	94 (55.3)		
Sex					
Male	140	60 (42.9)	80 (57.1)	0.087	.768
Female	216	96 (44.4)	120 (55.6)		
pT					
1	205	90 (43.9)	115 (56.1)	0.296	.961
2	138	60 (43.5)	78 (56.5)		
3	10	5 (50.0)	5 (50.0)		
4	3	1 (33.3)	2 (66.7)		
pN					
0	259	103 (39.8)	156 (60.2)	6.342	.042
1	24	13 (54.2)	11 (45.8)		
2	73	40 (54.8)	33 (45.2)		
3	—	—	—	—	—
Stage					
1	251	99 (39.4)	152 (60.6)	6.713	.035
2	27	14 (51.9)	13 (48.1)		
3	78	43 (55.1)	35 (44.9)		
Tumor size					
Small (≤20 mm)	182	80 (3.8)	102 (56.0)	0.003	.958
Large (>20 mm)	174	76 (5.7)	98 (56.3)		
Lymph/vascular invasion					
No	266	103 (38.7)	163 (61.3)	11.110	.001
Yes	90	53 (58.9)	37 (41.1)		
Smoking					
Nonsmoker	258	111 (43.0)	147 (57.0)	0.242	.623
Current/ex-smoker	98	45 (45.9)	53 (54.1)		

CGP, complex glandular pattern.

results, the cribriform pattern was associated with *EGFR* mutation ($P = .016$), *AKT1* mutation ($P = .038$), and *ALK* rearrangement ($P < .001$), while the fused gland pattern was associated with *EGFR* mutation ($P = .049$).

Clinical Outcome in Cases With CGPs

Survival analysis was performed for the clinicopathologic factors listed in Table 3. In this cohort, we set up several sets of histologic classification systems: one was consistent with the current WHO classification system Figure 1A and Figure 1B, and the second made some changes by defining CGPs as a new independent type of invasive lung adenocarcinoma Figure 1C and Figure 1D. CGP-predominant patients had a worse clinical outcome (mean OS, 66.4 months; mean RFS, 50.1 months) compared with acinar-predominant patients, whose survival was closer to that of patients with solid and micropapillary predominant tumors. Last, we compared the clinical outcomes among patients with the single cribriform pattern, single fused gland pattern, CCFG pattern, and those without CGPs Figure 1E and Figure 1F. Patients with CCFG pattern tumors had the worst clinical outcome, with a mean OS of 60.8 months and mean RFS of 42.0 months. Multivariable analysis for the association with death risk was carried out using the Cox regression model Table 4. Our results showed that pT ($P = .005$), pN ($P < .001$), and CCFG pattern ($P = .009$) were independent prognostic factors. To restrict the survival analysis to a more homogeneous group of patients, we carried out a multivariate Cox regression analysis in stage I patients treated with lobectomy/segmentectomy (Supplementary Table 2). This subgroup contained 228 patients; lymph/vascular invasion (hazard ratio [HR], 2.18; 95% confidence interval [CI], 1.03-4.61; $P = .042$) was able to independently and adversely affect the RFS, and the CCFG pattern (HR, 6.87; 95% CI, 1.34-35.34; $P = .021$) was an independent and negative predictor for OS after adjustment for age, sex, smoking status, pathologic pattern, and lymph/vascular invasive status, which was consistent with the results calculated from the overall population. Although the impact on RFS by CCFG reached only a borderline significance ($P = .086$), we observed a similar trend toward unfavorable RFS in

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Table 2
Correlations Between CGPs and Related Gene Mutations

Gene Mutation	No. of Cases	Predominant Pattern, No. (%)		χ^2	*P* Value
		Patterns With CGPs	Patterns Without CGPs		
EGFR					
No	120	54 (45.0)	66 (55.0)	0.102	.749
Yes	236	102 (43.2)	134 (56.8)		
ALK					
No	332	139 (41.9)	193 (58.1)	7.628	.006
Yes	24	17 (70.8)	7 (29.2)		
KRAS					
No	335	146 (43.6)	189 (56.4)	0.131	.718
Yes	21	10 (47.6)	11 (52.4)		
AKT1					
No	355	155 (43.7)	200 (56.3)	1.286	.257
Yes	1	1 (100)	0 (0)		
HER2					
No	351	156 (44.4)	195 (55.6)	3.956	.047
Yes	5	0 (0)	5 (100)		
BRAF					
No	355	155 (43.7)	200 (56.3)	1.286	.257
Yes	1	1 (100)	0 (0)		
ROS1					
No	355	156 (43.9)	199 (56.1)	0.782	.376
Yes	1	0 (0)	1 (100)		
P110					
No	346	150 (43.4)	196 (56.6)	0.531	.466
Yes	9	5 (55.6)	4 (44.4)		

CGP, complex glandular pattern.

the presence of CCFG (HR, 2.52), further indicating the clear role of CCFG in the poor prognosis of patients with lung cancer.

Discussion

CGPs, especially the cribriform pattern, have been regarded as a subtype of adenocarcinoma or a distinct prognostic factor in many types of tumors.[12-14] Moreira et al[8] suggested that cribriform and fused glands should be considered patterns of high-grade pulmonary adenocarcinoma in a population-based homogeneous white cohort. In 2015, the WHO proposed a new classification of lung adenocarcinoma[3] based on the 2011 IASLC/ATS/ERS classification.[2] However, CGPs were not classified as one of the main subtypes of lung adenocarcinoma according to that classification strategy. In this study, we described the distribution of CGPs in lung adenocarcinoma and further investigated the clinical relevance of CGPs on common clinicopathologic characteristics, gene mutations, and patients' prognosis. Once they are validated by larger studies, our results will provide some new evidence to support taking the CGPs into clinical practice to make more reasonable treatment decisions for patients with lung cancer.

In the present study, we found that CGPs were associated with lymph/vascular invasion and a higher TNM stage, which is in accordance with previous studies.[15,16] However, results in the present cohort do not support a significant correlation between CGPs and smoking history, which is inconsistent with a previous study.[9] Furthermore, the cribriform and fused gland patterns had different clinicopathologic correlations, as indicated by our results: the single cribriform pattern was associated with lymph/vascular invasion, a tumor size greater than 20 mm, and a higher TNM stage, while the single fused gland pattern was associated with a higher TNM stage and a tumor size of 20 mm or less. Interestingly, as a coexistence pattern of SCP and SFG, CCFG showed a worse prognosis, but there was no significant relationship between CCFG and clinicopathologic factors in this cohort.

The *EGFR* mutation is more prevalent in Asian people.[17] In our study, the most frequent gene mutation in CGP adenocarcinoma was *EGFR* (more than 50% of CGP cases). In the present study, *HER2* and *ALK* mutations had significant correlations with CGPs, but results became insignificant for the association between *KRAS* rearrangement and CGPs, which is inconsistent with a previous study, likely due to racial discrepancy.[10] By further analysis, we found that *EGFR* and *AKT1* mutations and *ALK* rearrangement were associated with the single

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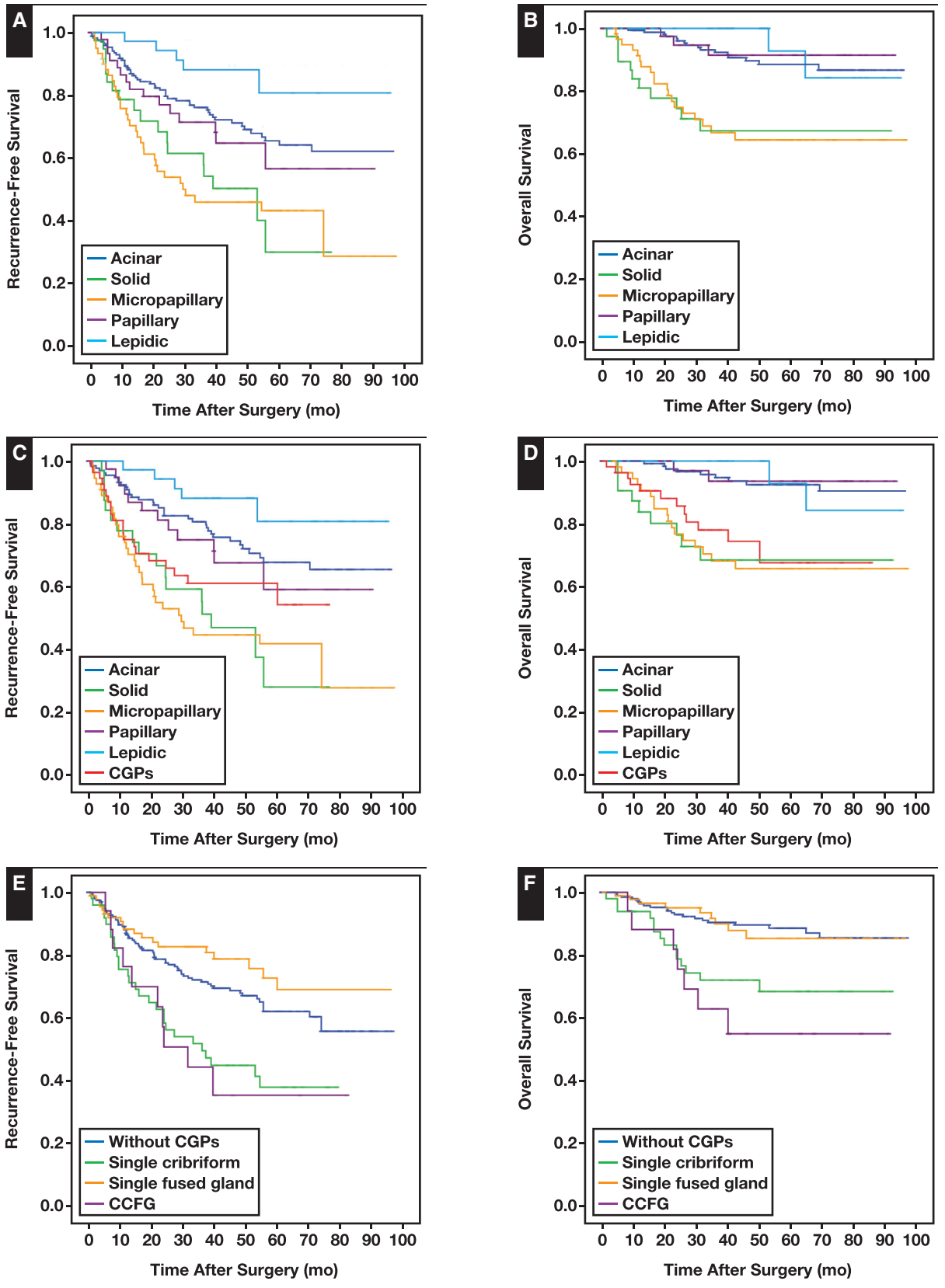

Figure 1 Survival analysis stratified by pathologic type of patients with lung cancer. **A**, **B**, Recurrence-free survival (RFS) and overall survival (OS) curve for current World Health Organization–based five main subtypes of lung adenocarcinoma. **C**, **D**, RFS and OS curve for all predominant growth pathologic patterns, and CGPs were also included for analysis as an additional subtype. **E**, **F**, RFS and OS curve for patients with three subtypes of CGPs and those without CGPs, respectively. $P < .001$.

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Table 3
Survival Analysis for Clinical Characteristics of the Patients

Parameter	No. of Patients	OS, mo		RFS, mo	
		Mean (SD)	*P* Value	Mean (SD)	*P* Value
Age, y					
≤59	186	83.5 (2.3)	.771	69.0 (3.0)	.151
>59	170	82.8 (2.3)		60.6 (3.2)	
Sex					
Male	140	77.9 (2.9)	.021	57.6 (3.5)	.009
Female	216	86.9 (1.8)		70.2 (2.7)	
pT					
1	205	90.1 (1.6)	<.001	74.6 (2.6)	<.001
2	138	76.9 (3.0)		55.3 (3.6)	
3	10	31.3 (6.0)		17.2 (5.1)	
4	3	38.5 (9.0)		14.5 (5.0)	
pN					
0	259	90.9 (1.3)	<.001	77.3 (2.2)	<.001
1	24	62.4 (5.3)		36.6 (6.3)	
2	73	60.0 (4.6)		28.8 (3.3)	
3	—	—		—	
Stages					
1	251	91.7 (1.3)	<.001	79.2 (2.2)	<.001
2	27	64.1 (5.2)		34.3 (6.0)	
3	78	59.0 (4.5)		28.0 (3.0)	
Location					
Left lobes	145	86.7 (2.3)	.147	69.0 (3.4)	.274
Right lobes	211	81.2 (2.2)		62.8 (2.9)	
Tumor size					
Small (≤20 mm)	182	90.8 (1.6)	<.001	77.1 (2.6)	<.001
Large (>20 mm)	174	74.0 (2.7)		51.8 (3.2)	
Smoking					
Nonsmoker	258	86.1 (1.8)	.028	69.3 (2.5)	.009
Current/ex-smoker	98	74.3 (3.4)		53.8 (4.0)	
Operation					
Partial resection	24	73.3 (2.9)	.469	73.1 (3.0)	.028
Segmentectomy	7	54.0 (6.4)		38.2 (9.6)	
Lobectomy or more	325	83.4 (1.7)		64.3 (2.3)	
Lymph/vascular invasion					
No	266	89.3 (1.5)	<.001	75.2 (2.3)	<.001
Yes	90	64.5 (4.0)		35.5 (3.8)	

OS, overall survival; RFS, recurrence-free survival.

cribriform pattern, which is, however, in accordance with previous studies based on Japanese cohorts.[18,19] In addition to *ALK* rearrangements, alterations in *KRAS* and *ROS1* were detected in tumors with the cribriform pattern in a previous study,[20] while we did not find any significant correlation of *KRAS* and *ROS1* with the cribriform pattern in the present study. No related gene mutation presented significant associations with the single fused gland pattern and CCFG pattern in the present study. However, when CGPs were divided into two groups (cribriform and fused gland), the fused gland pattern was associated with *EGFR* mutations. These results might provide some implications to estimate which patients should benefit a great deal from a genetic target, such as anti-*EGFR* therapy.

Table 4
Multivariable Analysis for Assessing Death Risk Using Cox Regression Hazards Model

Characteristic	HR (95% CI)	*P* Value
Age	0.80 (0.45-1.41)	.443
Sex	0.57 (0.28-1.18)	.129
pT	1.84 (1.20-2.82)	.005
pN	2.05 (1.42-2.95)	<.001
Smoking	0.92 (0.44-1.94)	.821
With single cribriform pattern	1.11 (0.54-2.30)	.772
With single fused gland pattern	1.40 (0.63-3.13)	.409
With CCFG pattern	3.25 (1.35-7.86)	.009
Lymph/vascular invasion	1.79 (0.93-3.43)	.081

CCFG, cribriform coexisting with fused gland; CI, confidence interval; HR, hazard ratio.

Individualized therapy has reached great success in the past decades in light of novel molecular factors identified to be responsible for the variability in clinical outcome for patients with lung cancer. Our results were mostly in line with previous studies that suggested that the lepidic subtype was associated with prolonged survival,[21-24] while solid and micropapillary subtypes were associated with worse clinical outcomes.[25,26] Maeshima et al[27] reported

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first that the CGPs were associated with poor prognosis. Our study confirmed that the recurrence risk for patients with CGP lung adenocarcinoma was significantly higher than that for patients with acinar- or papillary-predominant adenocarcinoma but was close to that for patients with micropapillary- or solid-predominant adenocarcinoma. By further research on CGPs, we found that the CCFG pattern was associated with worst OS and RFS compared with the single cribriform pattern and single fused gland pattern, so we conducted a multivariate Cox analysis in which a much higher death risk was observed in the presence of the CCFG pattern, indicating a need for close survival surveillance of patients with this pathologic subtype of lung cancer.

The present study has some potential limitations that should be considered when interpreting the results. Like other single institution–based, retrospective, observational cohort studies, there was potential for referral and selection bias. In addition, given the relatively small number of patients included in the present study, further larger studies with sufficient statistical power are warranted to validate the association of CGPs with clinicopathologic characteristics, gene mutations, and clinical outcome of patients with lung cancer.

Conclusions

Although CGPs were not included in the new WHO pathologic classification criteria, it is notable that patients with cribriform and fused gland patterns tumors have been taken into account for predicting metastasis and survival of patients with multiple types of cancer.[28-30] Regarding CGPs as a new category of lung adenocarcinoma was also suggested based on recent studies.[5,10,31] In conclusion, based on the retrospective analysis in the present study, it is reasonable to classify CGPs as a new type of lung adenocarcinoma for advancing the clinical management of patients in terms of either survival surveillance or treatment decision.

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