High WHO/ISUP Grade And Unfavorable Architecture, Rather Than Typing Of Papillary Renal Cell Carcinoma, May Be Associated With Worse Prognosis

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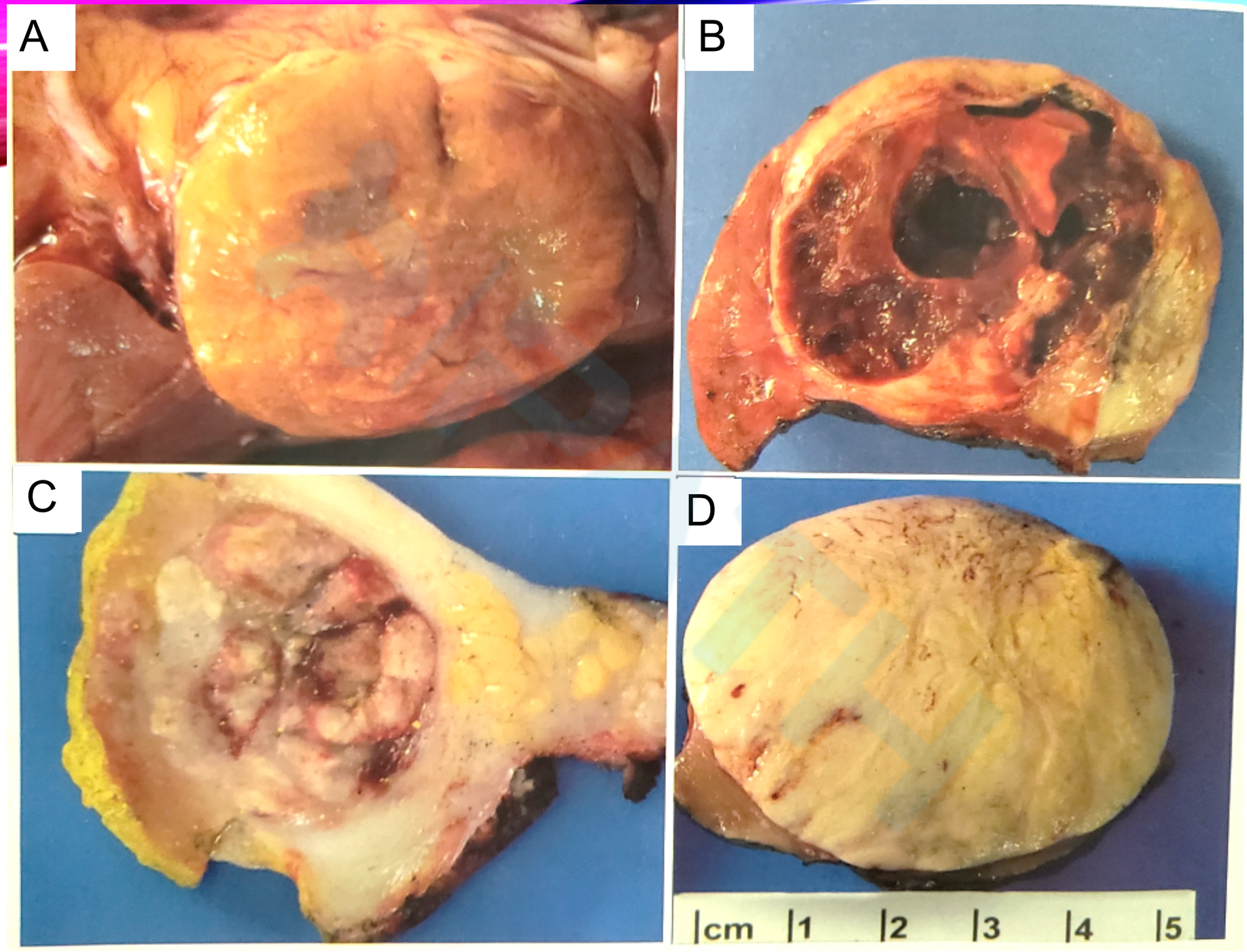
BACKGROUND

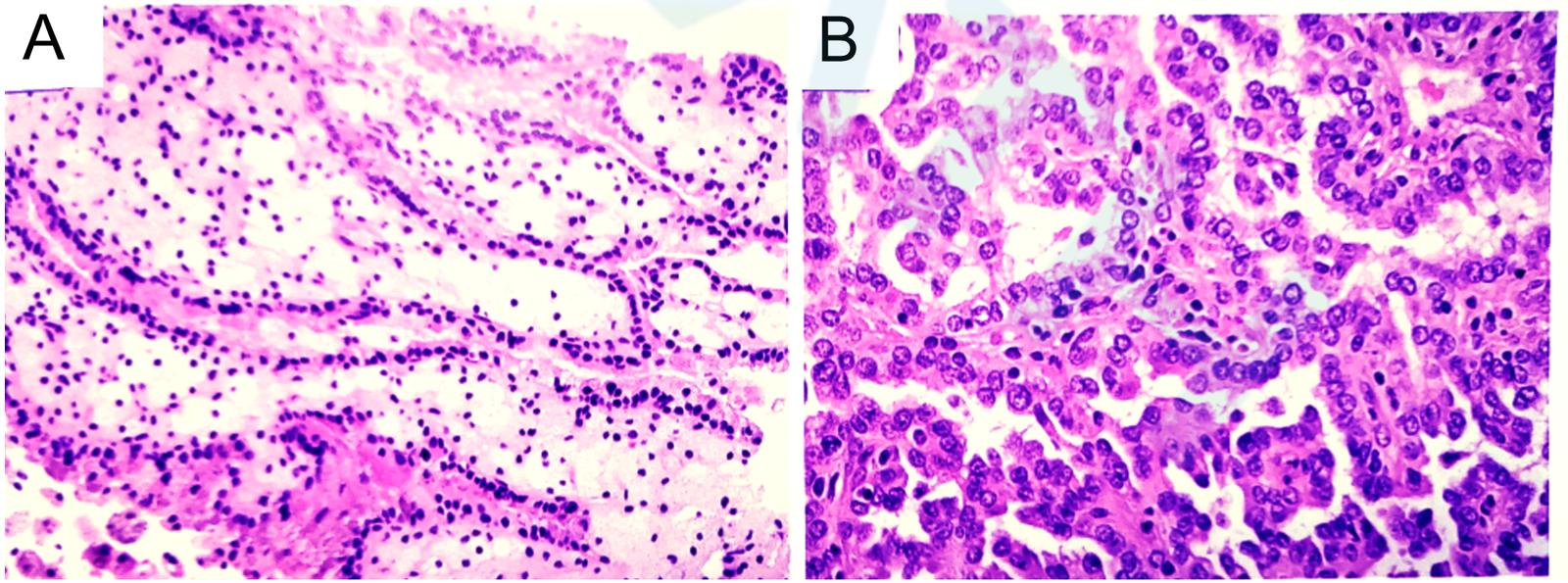
- 乳头状肾细胞癌（PRCC）最初是在1976年由Mancilla-Jimenez等描述的，是第二大常见的RCC类型
- 分为1型和2型
- 孤立或者多发
- 双侧和多灶在PRCC中更常见
- 淋巴结转移常见，肾静脉侵犯较ccRCC少见

Renal cell tumours	
Clear cell renal cell carcinoma	8310/3
Multilocular cystic renal neoplasm of low malignant potential	8316/1
Papillary renal cell carcinoma	8255/1
Hereditary leiomyomatosis and renal cell carcinoma (HLRCC)-associated renal cell carcinoma	8311/3*
Chromophobe renal cell carcinoma	8317/3
Collecting duct carcinoma	8319/3
Renal medullary carcinoma	8510/3
MiT Family translocation carcinomas	8311/3
Succinate dehydrogenase (SDH)-deficient renal carcinoma	8312/3
Mucinous tubular and spindle cell carcinoma	8480/3
Tubulocystic renal cell carcinoma	8316/3
Acquired cystic disease associated renal cell carcinoma	8316/3
Clear cell papillary renal cell carcinoma	8323/1
Renal cell carcinoma, unclassified	8312/3
Papillary adenoma	8260/0
Oncocytoma	8290/0


A
B
C
D
cm 1 2 3 4 5

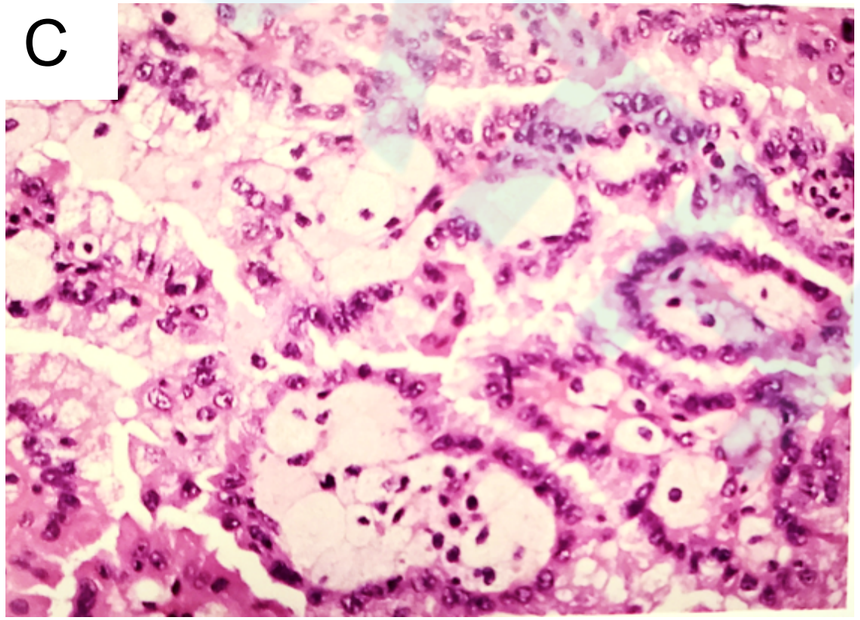
BACKGROUND

- Type 1 PRCCs are composed mostly of small basophilic cuboidal cells arranged in a single layer. Cells tend to have a small, uniform, round to oval nuclei with inconspicuous nucleoli.

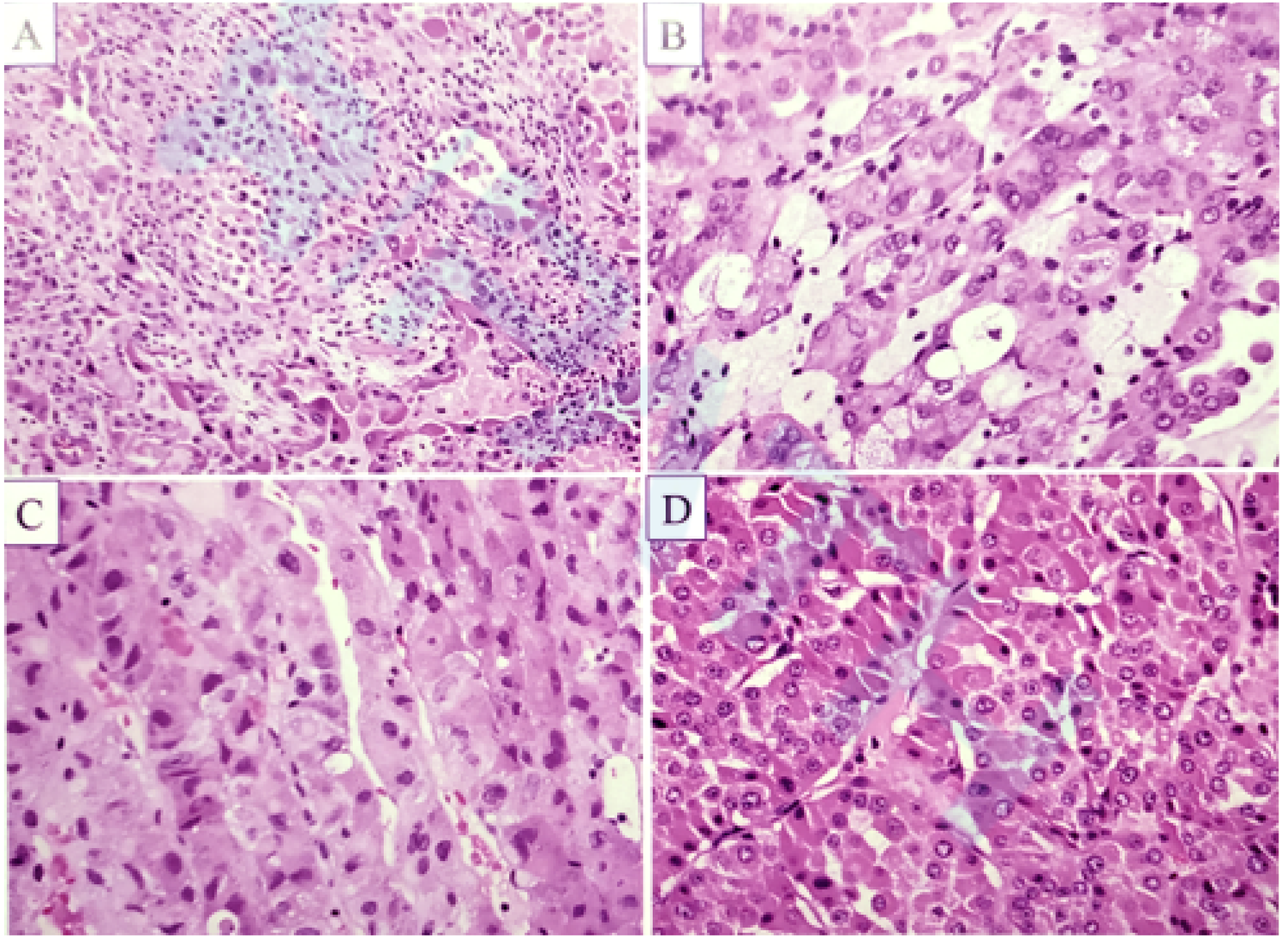


BACKGROUND

- In contrast, pseudostratified layers of cells with a copious amount of eosinophilic cytoplasm and atypical nuclei showing prominent nucleoli are the hallmark features of type 2 PRCCs.



囊性/腺样生长



巨噬细胞

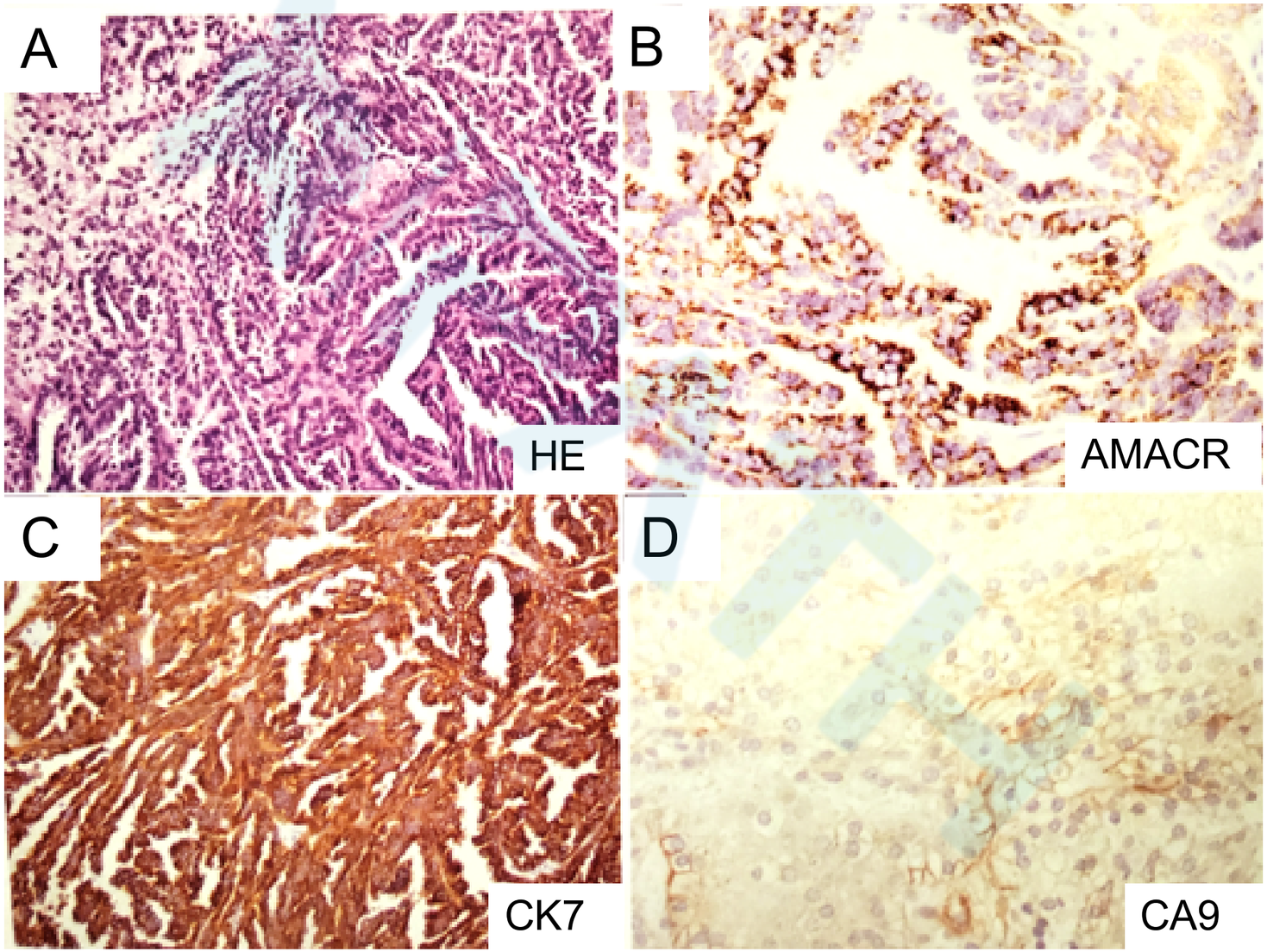
梁索状

巢团状

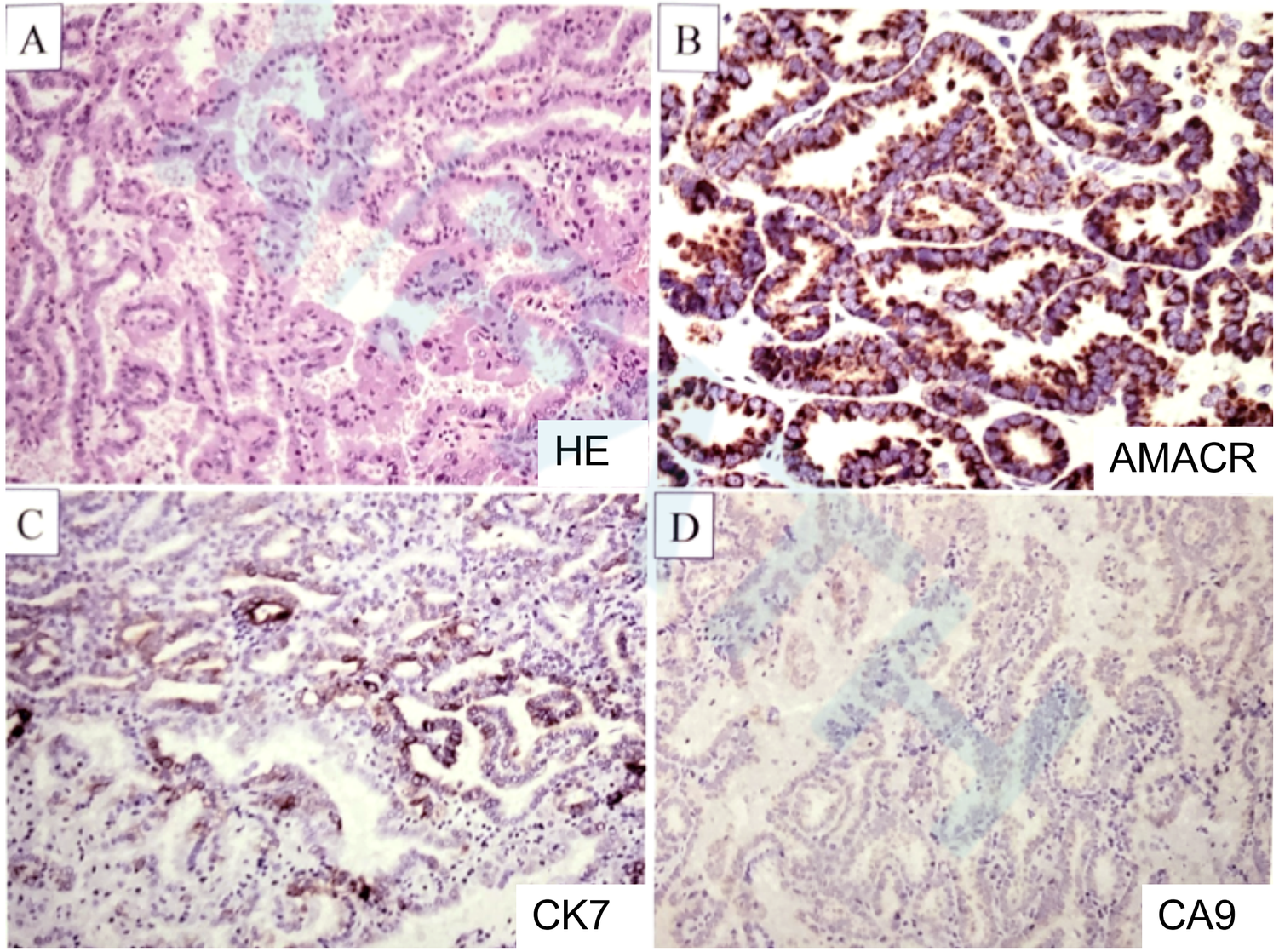
PRCC的级别和亚型的比较

分型	1型	2型
级别	低级别	高级别
ISUP核分级	1级和2级	3级和4级
大小	小	大
基因学	低级别不同于高级别	
生物学行为	惰性	侵袭性
胞质	较少（似嗜碱）	丰富，嗜酸性
泡沫细胞	常见	不太常见
细胞层数	单层	单层或假复层
核级别	常为低级别	常为高级别
生物学行为	绝大多是惰性	绝大多是侵袭性

免疫组织化学



免疫组织化学



分子检测

- 染色体7、17三倍体是最常见的细胞遗传学发现
- 家族性PRCC具有Met突变或延胡索酸水化酶基因的改变，散发性PRCC中这些基因的突变率非常低

BACKGROUND

- College of American Pathologists (CAP) guidelines require reporting the presence of WHO/ISUP grade, tumor necrosis, lymphovascular invasion (LVI), and rhabdoid or sarcomatoid histology have been well-esatablished to be associated with aggressive disease behavior.
- Other features, such as the presence of foamy macrophages, hemosiderin-laden macrophages, psammomatous calcification have also been proposed to have a prognostic impact.

BACKGROUND

- However, unfavorable histologic findings in tumors with papillary architecture from other anatomic sites have not been thoroughly evaluated in PRCCs.
- Specifically, solid and hobnail architecture are seen in papillary thyroid carcinoma, and the micropapillary architecture observed in urothelial carcinoma have not been described in the PRCC literature.
- The goal of our study was to evaluate the prognostic significance of PRCC typing, WHO/ISUP grade, and novel solid, micropapillary, and hobnail architecture in a large cohort of patients with clinical follow-up.

Materials and Methods

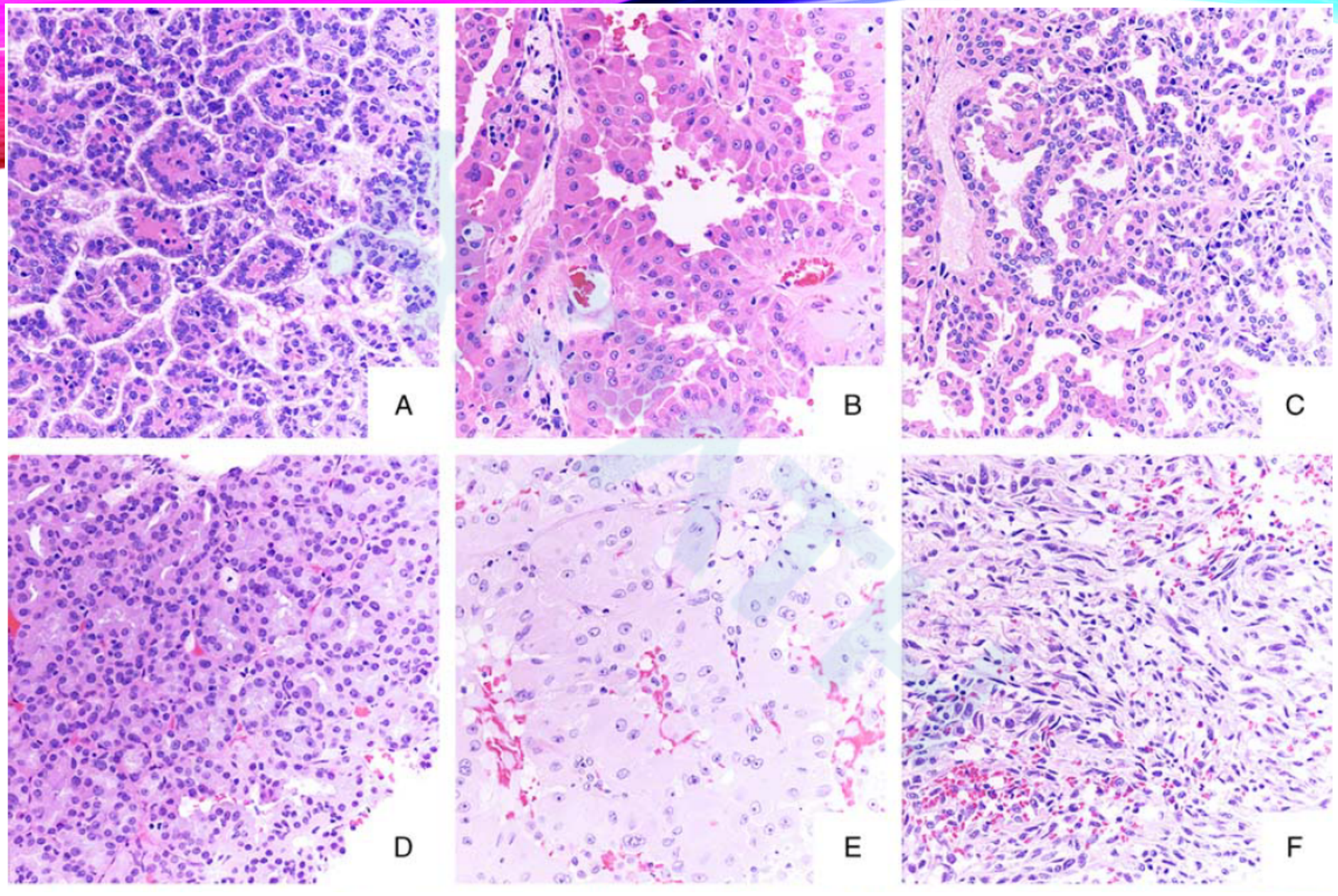
- The surgical pathology archives from the Department of Pathology were searched for partial and radical nephrectomies performed between the years 1996 and 2017 with the final or main differential diagnosis of PRCC.
- All archived hematoxylin and eosin and immunohistochemistry stained slides were retrieved and reviewed by 2 genitourinary pathologists blinded to the clinical outcome.

Materials and Methods

- A total of 185 cases were confirmed as PRCC and were included in our analysis. Clinical information and follow-up data were extracted from the electronic medical records.
- Primary tumor size and pathologic stage were recorded from the initial surgical pathology report.

Materials and Methods

- All slides were reviewed for the following features:
- type 1 versus type 2 histology;
- tumor grade (WHO/ISUP grading scheme);
- tumor necrosis;
- LVI;
- special architecture (solid, micropapillary, and hobnail);
- special cytology (oncocytoma-like cytologic features, papillary thyroid carcinoma–like nuclear features, clear/flocculent cytoplasm; hemosiderinrich cytoplasm);
- percentage of macrophages.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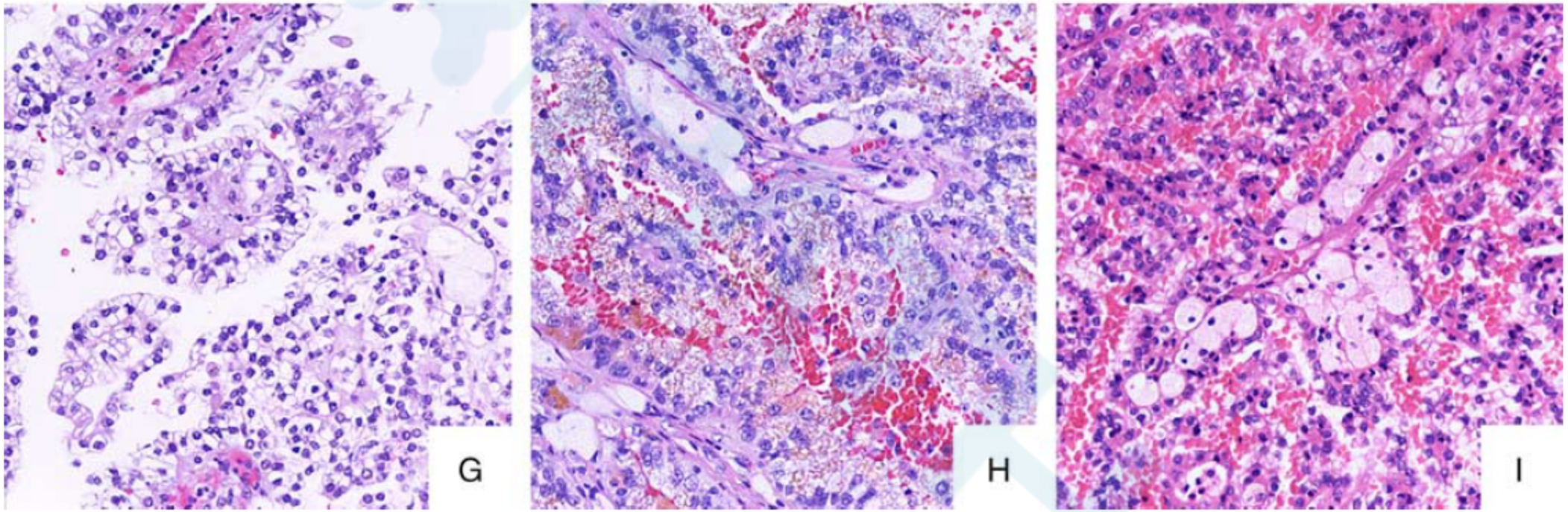
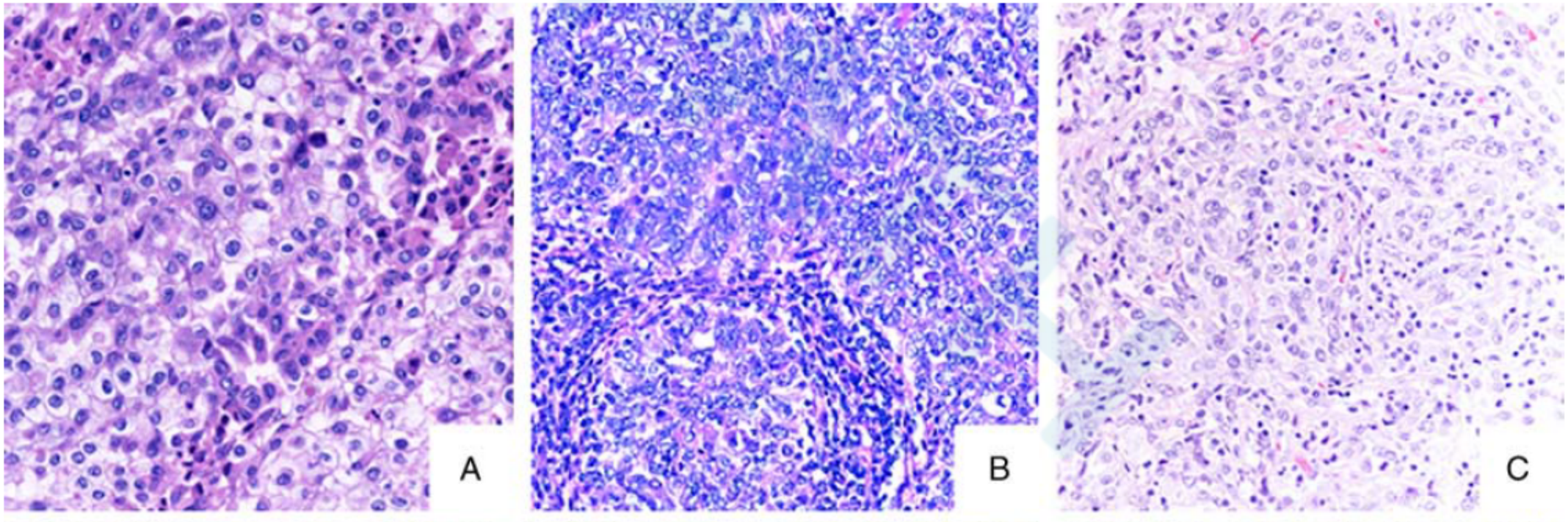


FIGURE 1. Morphologic spectrum seen in PRCC.

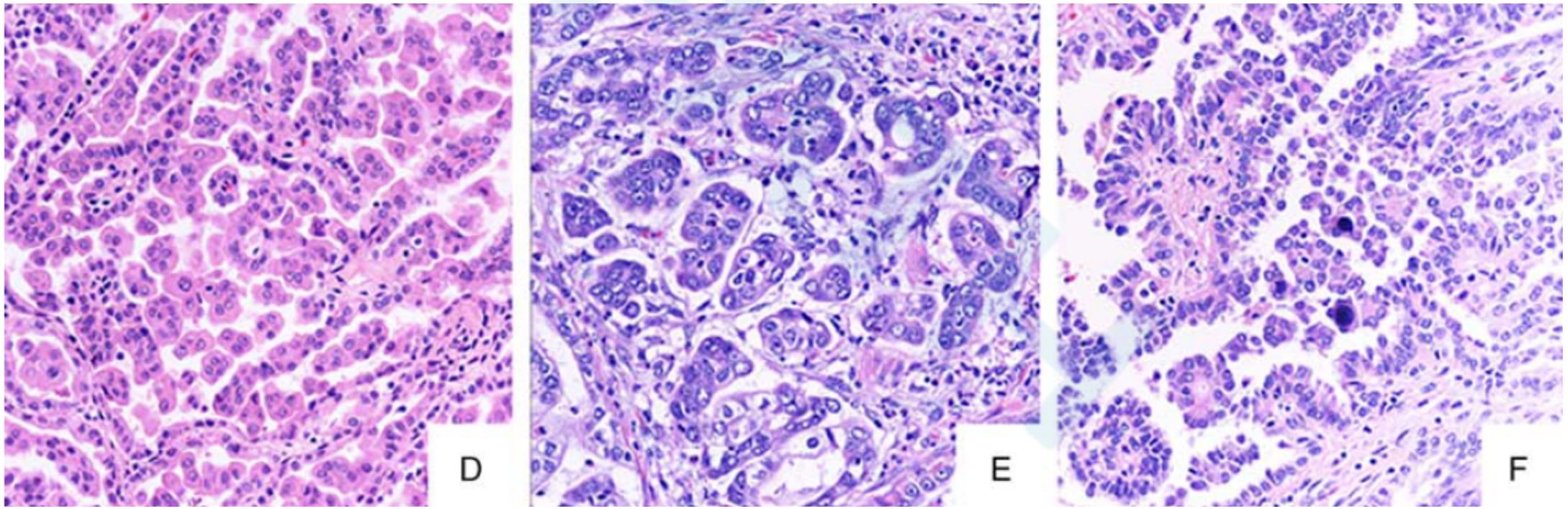
Materials and Methods

- strict definitions to classify the 3 special architectures (Fig. 2)
- for solid



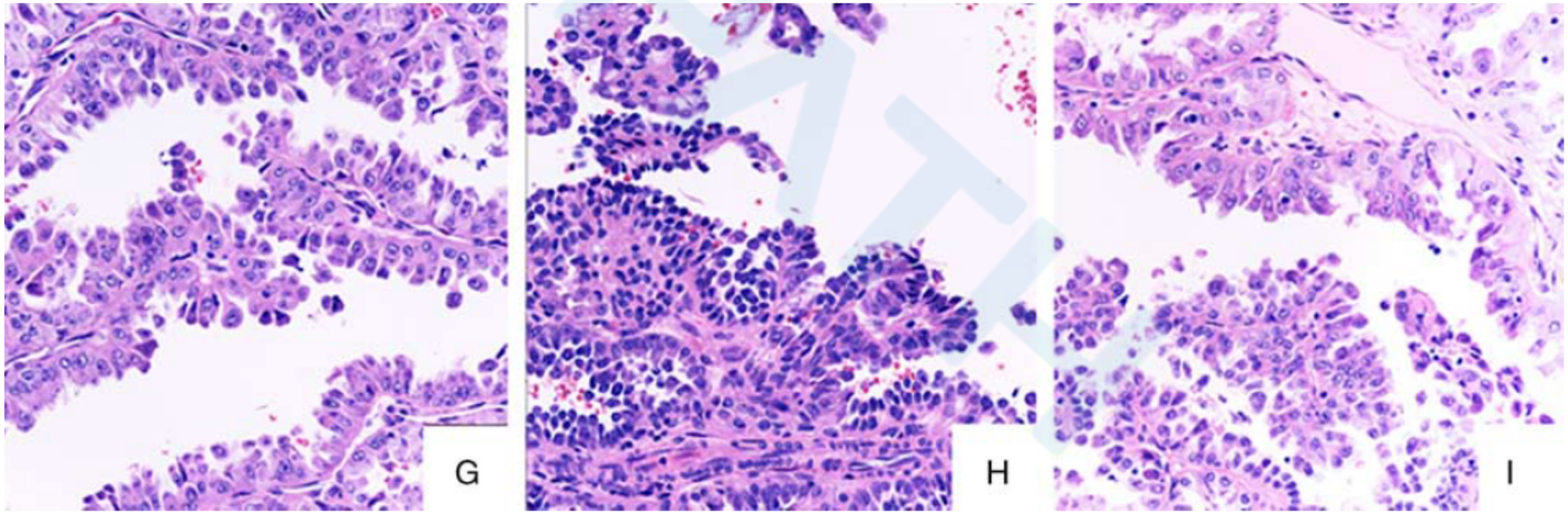
Materials and Methods

- strict definitions to classify the 3 special architectures (Fig. 2)
- for micropapillary



Materials and Methods

- strict definitions to classify the 3 special architectures (Fig. 2)
- for hobnail architecture



Materials and Methods

- Relationships between the different variables were examined using Kruskal-Wallis tests, Mann-Whitney U tests, $\chi 2$ tests, and Cox proportional hazards regression analyses.

Results—Clinical Characteristics

TABLE 1. Patient Demographics and Tumor Characteristics

Characteristics	Cases, n (%)
Patients	
Male	147 (79.5)
Female	38 (20.5)
Age (y)	
Mean	59
Median	60
Range	11-89
Ethnicity	
White	125 (67.6)
Black	51 (27.6)
Other	9 (4.9)
Laterality	
Left	94 (50.8)
Right	89 (48.1)
Bilateral	1 (0.5)
Allograft	1 (0.5)
Treatment	
Radical nephrectomy	73 (39.5)
Partial nephrectomy	112 (60.5)

Results—Clinical Characteristics

Tumor size (cm)	
Mean	4.3
Median	3.5
Range	1.5-18.0
Tumor type	
Type 1	117 (63.2)
Type 2	45 (24.3)
Mixed types 1 and 2	11 (5.9)
Other	12 (6.5)
WHO/ISUP grade	
Grade 1	6 (3.2)
Grade 2	116 (62.7)
Grade 3	61 (33.0)
Grade 4	2 (1.1)
AJCC staging (eighth edition)	
Stage I	152 (82.6)
Stage II	20 (10.9)
Stage III	12 (6.5)
Stage IV	0 (0)
Follow-up (mo)	
Mean	74
Median	59
Range	0.1-241
Metastasis	
Yes	11 (5.9)
No	174 (94.1)

Results—Histologic Characteristics

- Coagulative tumor necrosis was seen in 26 cases (14.1%)
- Sarcomatoid differentiation and LVI were seen only in 1 case (0.5%) each
- The solid architecture was observed in 3 cases (1.6%)
- Micropapillary architecture was present in 10 cases (5.4%)
- Hobnail architecture was seen in 9 cases (4.9%)
- Clear/flocculent cytoplasm was identified in 110 cases (59.5%)
- Hemosiderin was present in tumor cells in 60 cases (32.4%)
- Macrophages were also frequently seen, present in 125 cases (67.6%)
- 8 cases (4.3%) of OPRCC and 6 cases (3.2%) of PRCC demonstrating papillary thyroid carcinoma–like features (PTCPRCC) were identified

Results—
Survival and Analysis of Prognostic Parameters

TABLE 2. Univariate Analysis of DFS and OS Prognostic Parameters

Prognostic Factors	DFS HR	DFS 95% CI	DFS *P*	OS HR	OS 95% CI	OS *P*
Age (n)						
<60 y (90)	1			1		
≥60 y (95)	1.12	0.34-3.70	0.84	1.70	0.80-3.62	0.17
Sex (n)						
Female (38)	1			1		
Male (147)	0.64	0.17-2.42	0.51	0.84	0.34-2.06	0.70
WHO/ISUP grade	9.74	2.95-32.19	**<0.01**	4.07	2.01-8.21	**<0.01**
AJCC stage (eighth edition)	5.45	2.76-1075	**<0.01**	3.03	1.98-4.62	**<0.01**
Multifocality						
Unifocal (169)	1			1		
Multifocal (16)	0.00	0.00-4.62	0.97	0.29	0.04-2.12	0.22
Tumor size (n)						
<4 cm (107)	1			1		
≥4 cm (78)	14.92	1.91-116.66	**0.01**	2.99	1.39-6.45	**<0.01**
Solid (n)						
No (182)	1			1		
Yes (3)	20.56	4.25-99.44	**<0.01**	17.84	5.06-62.83	**<0.01**
Micropapillary (n)						
No (175)	1			1		
Yes (10)	16.43	5.01-53.95	**<0.01**	5.23	2.12-12.88	**<0.01**
Hobnail (n)						
No (176)	1			1		
Yes (9)	14.84	4.33-50.90	**<0.01**	4.03	1.40-11.61	**<0.01**
Necrosis (n)						
No (159)	1			1		
Yes (26)	2.68	0.71-10.12	0.15	3.68	1.67-8.12	**<0.01**
Clear/flocculent cytoplasm (n)						
No (75)	1			1		
Yes (110)	1.85	0.49-6.98	0.36	1.17	0.55-2.47	0.69
Hemosiderin (n)						
No (125)	1			1		
Yes (60)	1.27	0.37-4.36	0.70	1.68	0.80-3.54	0.17
Macrophages (n)						
No (60)	1			1		
Yes (125)	0.53	0.16-1.73	0.29	0.56	0.27-1.18	0.13
PRCC subtype (n)						
Type 1 (117)	1			1		
Type 2 (45)	1.14	0.29-4.43	0.85	1.12	0.46-2.69	0.80
Types 1 and 2 (11)	1.23	0.43-3.51	0.70	0.75	0.28-2.07	0.58

Results—
Survival and Analysis of Prognostic Parameters

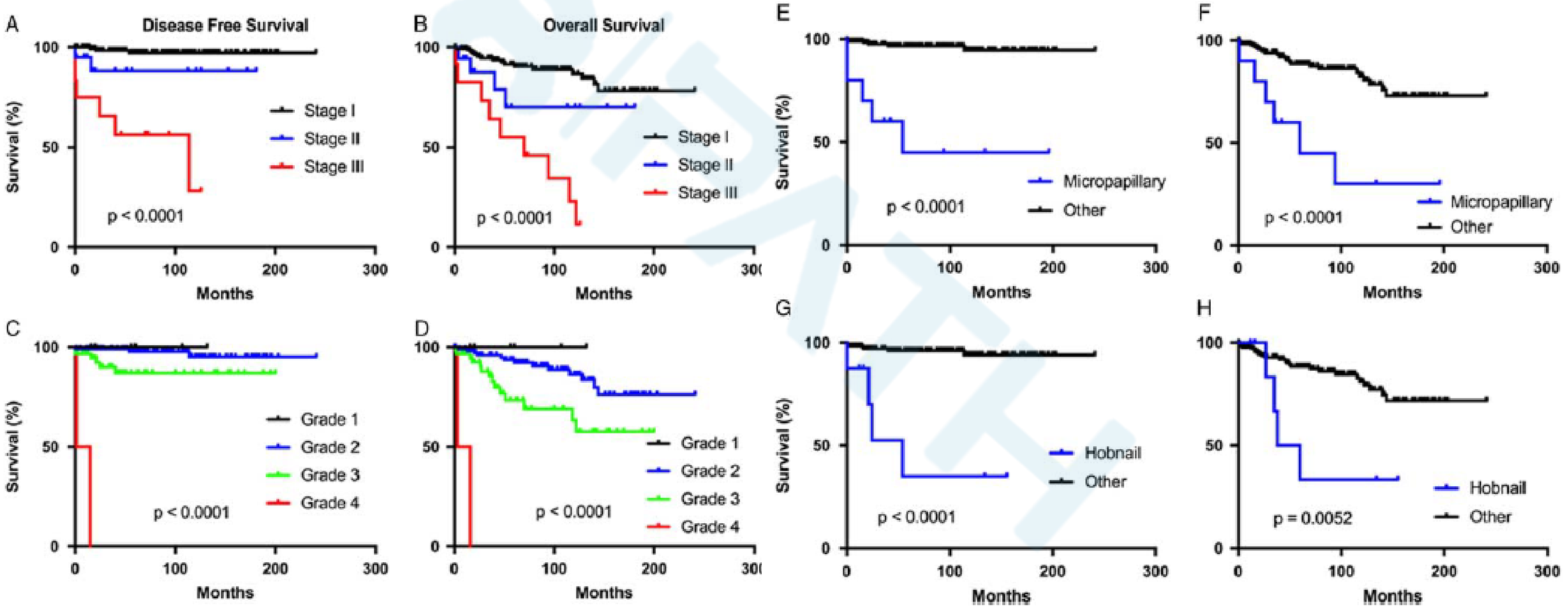


FIGURE 3. Kaplan-Meier curves showing parameters affecting the DFS and OS of PRCC patients.

Results—
Survival and Analysis of Prognostic Parameters

TABLE 3. Multivariate Analysis of DFS and OS Prognostic Parameters

	DFS			OS		
Prognostic Factors	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Age (≥60 y)	0.70	0.13-3.90	0.68	1.01	0.42-2.42	0.98
Sex (male)	0.35	0.06-2.10	0.25	0.94	0.33-2.70	0.91
Tumor size (≥4 cm)	5.51	0.57-53.05	0.14	1.48	0.55-3.99	0.43
AJCC stage (eighth edition)	4.39	1.55-11.84	**<0.01**	1.88	1.01-3.50	**<0.05**
Subtype (type 2)	0.52	0.09-3.03	0.47	0.32	0.11-0.98	**<0.05**
WHO/ISUP grade	7.00	1.52-32.20	**0.01**	5.08	2.09-12.36	**<0.01**
Solid	2.59	0.07-90.69	0.60	2.48	0.29-20.98	0.41
Micropapillary	6.30	0.75-52.65	0.09	4.21	1.15-15.45	**0.03**
Hobnail	6.61	0.37-117.60	0.19	0.76	0.14-3.00	0.74
Necrosis	0.48	0.03-6.65	0.58	2.15	0.70-6.58	0.18
Macrophages	0.81	0.07-9.62	0.87	0.66	0.23-1.88	0.43

Bold values indicate statistical significance.
CI indicates confidence interval; HR, hazard ratio.

Results—
Survival and Analysis of Prognostic Parameters

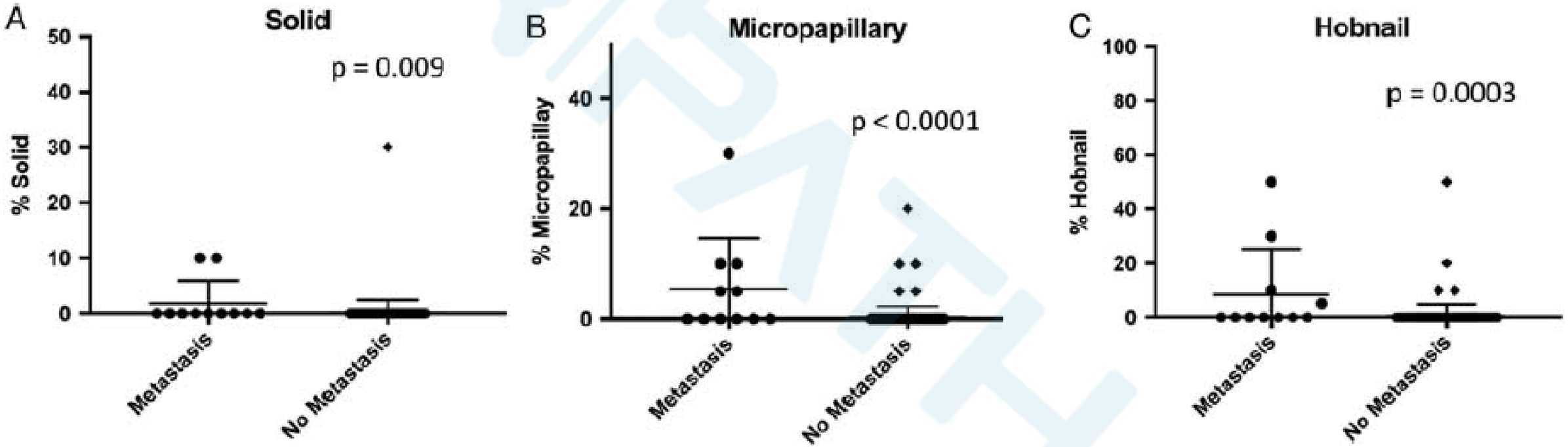


FIGURE 4. Comparison of cases with and without recurrence/ metastasis.

DISCUSSION

- The classification of kidney epithelial neoplasms has undergone significant transformation in the past few decades.
- Our results in a large single-institutional study highlight histopathologic features relevant to prognosis in PRCCs. We identified WHO/ISUP grade and novel solid, micropapillary, and hobnail growth patterns, rather than PRCC type as being correlated with worse prognosis in our cohort of patients.

DISCUSSION

- We utilized the WHO/ISUP grading scheme in our study and showed that WHO/ISUP grade is the only other parameter, aside from the pathologic stage, to show statistical significance in predicting DFS and OS (Table 3). Of the 11 cases with metastatic disease, 8 (72.7%) were WHO/ISUP grade 3 and 4 PRCCs.

DISCUSSION

- Despite the major role of tumor architecture evaluation in the grading of many malignancies, scant data exist for unfavorable growth patterns in PRCCs.
- Given the resemblance in the histology of PRCC to papillary thyroid carcinoma, we hypothesized that these similar architectures might also carry a poor prognosis in PRCCs.
- We found that all 3 architectural patterns were associated with worse DFS and OS on univariate survival analysis (Table 2). Only micropapillary architecture was shown to be statistically significant as an adverse prognostic factor of OS in multivariate analysis (Table 3).

DISCUSSION

- Studies in the literature h… …logic var…

风险比率，正式的英文名称是Hazard Ratio。风险比率是两个风险率（Hazard Rate）的比值。它反映了单位时间内的相对风险，是相对风险在单位时间内的一种反映。

- In… …logic studies with… …d ratios (HRs)… …g on DFS and OS, respectively.

DISCUSSION

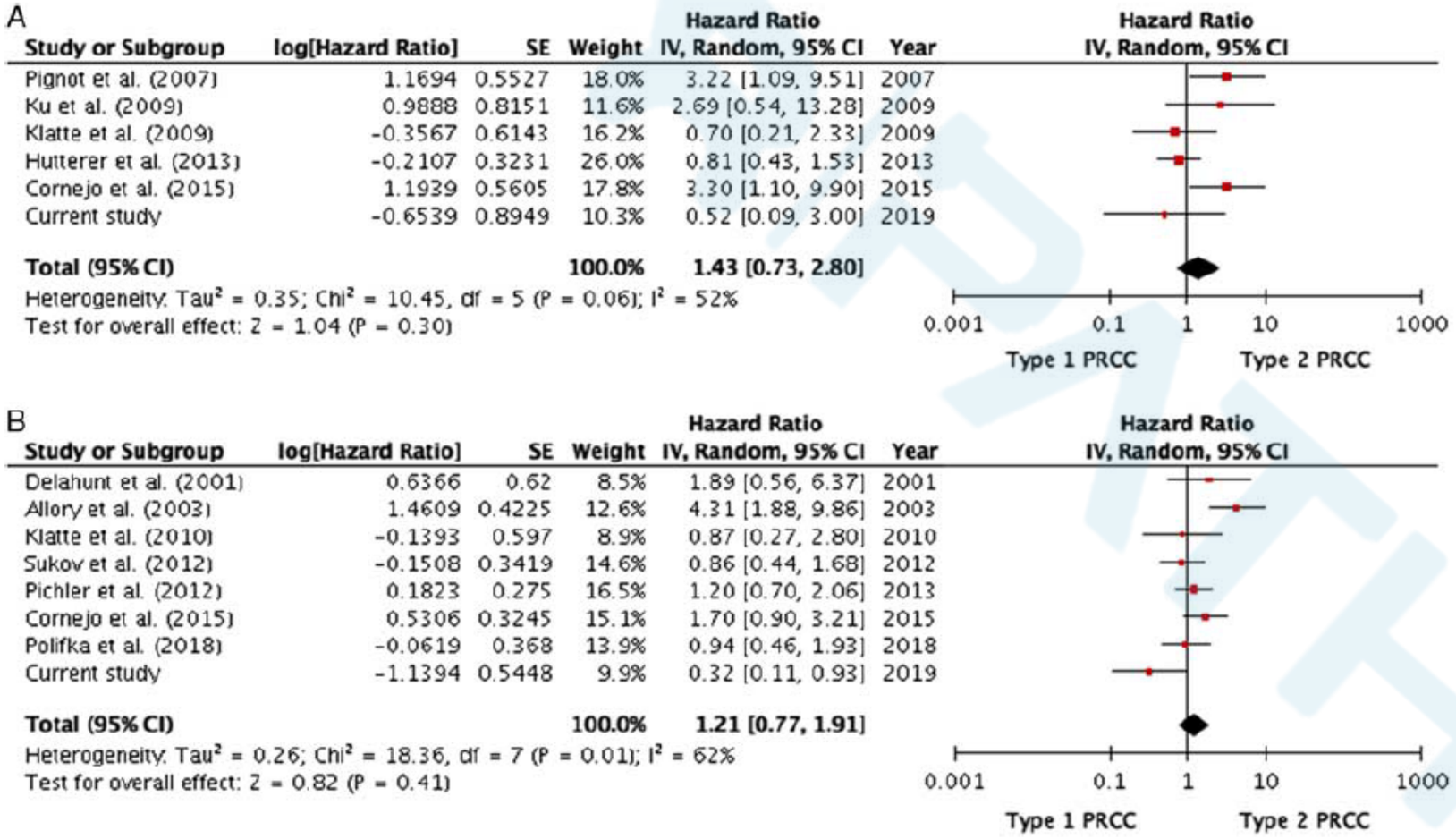


FIGURE 5. Forest plot comparing the HR of reports in the literature of type 2 versus type 1 PRCC in predicting DFS (A) and OS (B), respectively.

OPRCC
oncocytic papillary renal cell carcinoma
（嗜酸性乳头状肾细胞癌）

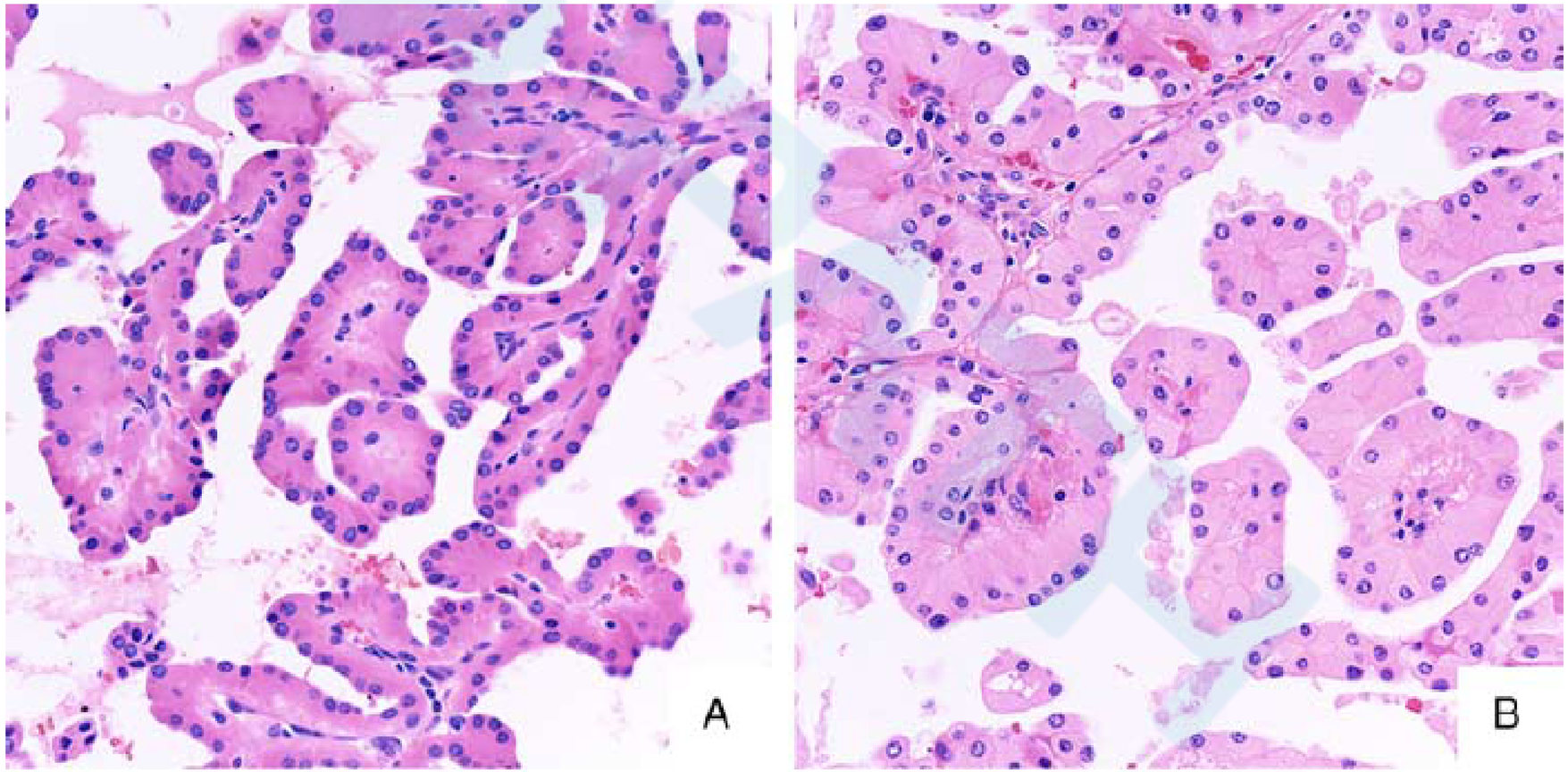


FIGURE 6. PRCCs with special cytologic features.

PTCRCC
papillary thyroid carcinoma–like features RCC
（甲状腺乳头状癌样特征的RCC）

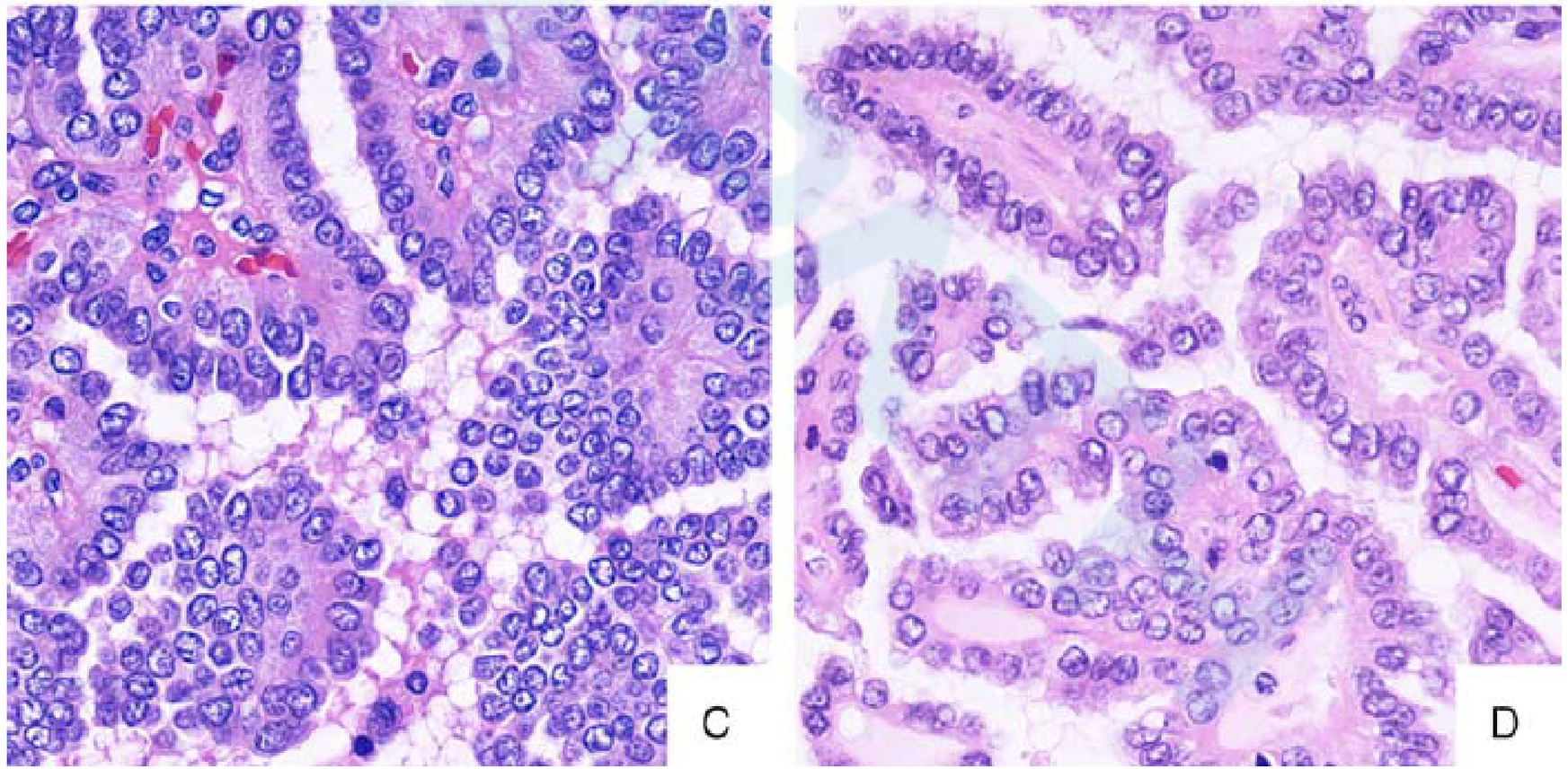


FIGURE 6. PRCCs with special cytologic features.

ESCRCC
eosinophilic solid and cystic renal cell carcinoma
（嗜酸性实性和囊性肾细胞癌）

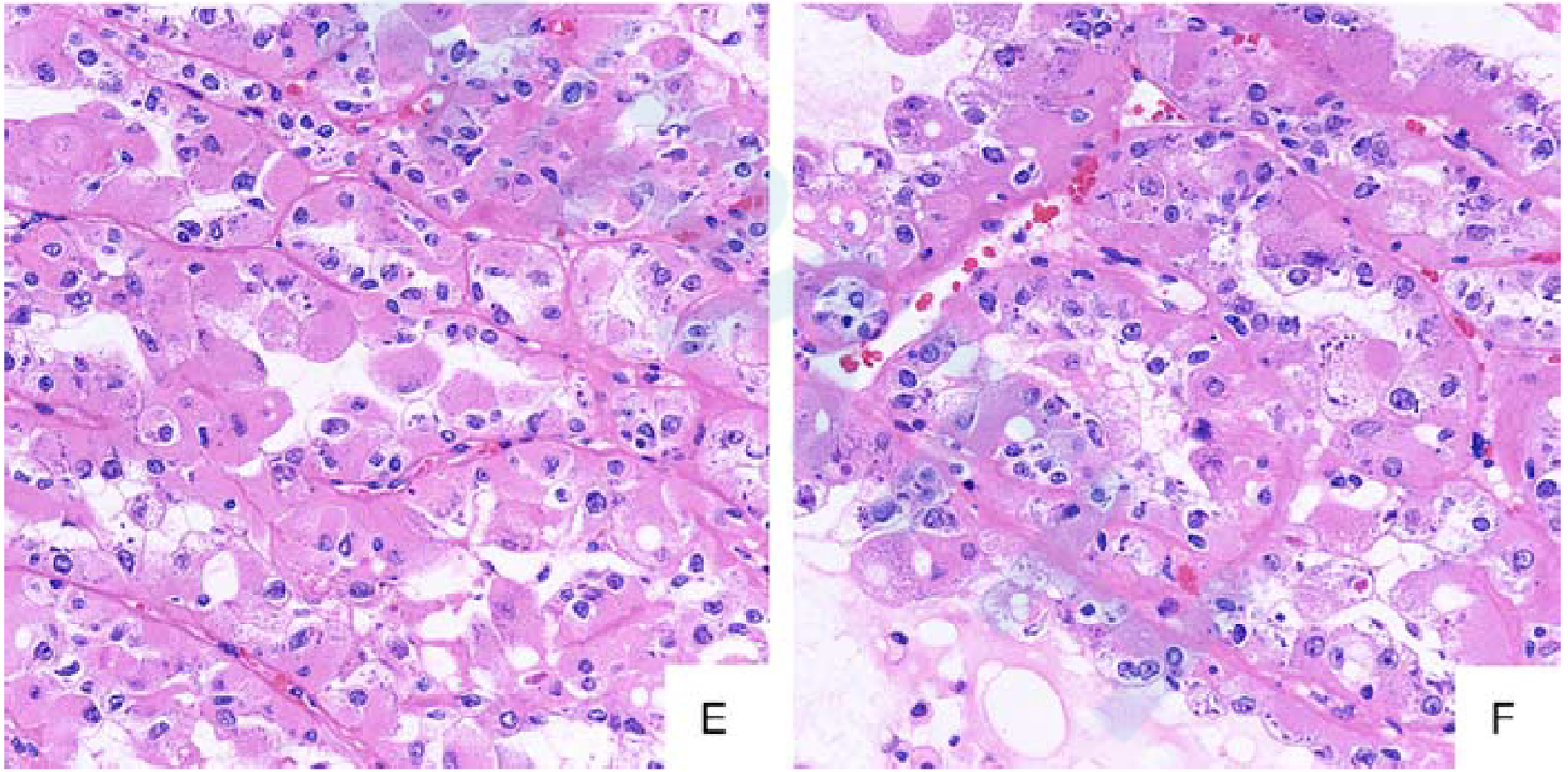


FIGURE 6. PRCCs with special cytologic features.

DISCUSSION

- First, our study was retrospective in design and was limited by the inherent bias associated with any investigation of this nature.
- Second, all our cases originated from a single institution and was inevitably influenced by the patient population represented in this geographic region.
- Third, our study has a limited number of cases with special histology (solid, micropapillary, and hobnail) due to the relatively low prevalence. A prospective and large multi-institutional study would be necessary to address the above issues.
- Finally, the low number of progression events (metastasis) is a limitation of this study in the multivariate analysis, but this is a reflection of the relatively indolent nature of PRCC.

DISCUSSION

- The architecture of clear cell RCC has recently been shown to be of prognostic significance.
- The analysis presented here is the first to comprehensively evaluate WHO/ISUP grade and new histopathologic (micropapillary, hobnail, or solid) architectures in a large cohort of PRCCs.

DISCUSSION

- Parameters associated with worse DFS and OS in the univariate analysis included WHO/ISUP grade, pathologic stage, tumor size, and solid, micropapillary, or hobnail architecture.
- On multivariate analysis, tumor pathologic stage and WHO/ISUP grade, and not PRCC type, show statistically significant association with DFS and OS.
- These unfavorable features should be documented on routine histologic evaluation to provide additional information to help physicians to better risk-stratify patients for therapy or surveillance.

THANKS