Histopathological Validation of the Safe Margin for Nephron – Sparing Surgery Based on Individual Tumor Growth Pattern

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Research

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Abstract

Background

To evaluate the clinicopathologic value of morphological growth patterns of small renal cell carcinoma (sRCC) and define the real demand to take a rim of healthy parenchyma to avoid positive SM.

Methods

Data was collected from 560 sRCC patients who underwent surgery from May 2010 to October 2017. 149 cases had nephron-sparing surgery (NSS) and others had radical nephrectomy (RN). All specimens were analyzed separately by two uropathologists and identified three morphological growth patterns. The presence of pseudocapsule (PC), surgical margins (SM) and other routinely variables were recorded. The relationship between growth patterns and included variables was measured by χ^2 test and Fisher's exact probability test. Survival outcomes were evaluated by Kaplan-Meier method and log-rank test.

Results

Median age of patients was 63.2 years and mean tumor diameter was 3.0 cm. 480 (85.7%) patients were clear cell RCC and 541 (96.6%) cases were pT1a stage. Peritumoral PC was detected in 512 (92.5%) specimens and the ratio of tumor invasion in PC in infiltration pattern increased obviously than other growth patterns. Similarly, the pT stage was significantly correlated with infiltration pattern as well. 149 patients underwent NSS and 3 (2.0%) of them had positive SM after operation. Statistical differences of 5-year overall survival (OS) and cancer-specific survival (CSS) existed among different morphological growth patterns, PC status and pT stages.

Conclusions

Morphological growth patterns of sRCC might be used as a potential biomarker to help operating NSS to avoid the risk of positive SM. How to distinguish different morphological growth patterns before operation and the effectiveness of growth pattern as a novel proposed parameter to direct NSS in sRCC patients deserves further exploration.

Background

RCC is one of the most malignant tumors of genitourinary disease and significant progress in treatments has been made during the last 20 years. NSS has been widely confirmed as an effective measure for sRCC(1, 2), and the number of sRCC patients who accepted NSS has increased significantly in recent years. Nevertheless, no research had clarified the histopathological and clinical features of different kinds of morphological growth patterns of sRCC. Considering this, a more practicable classification and

treatment strategy that could be utilized for choosing proper therapeutic methods for sRCC patients is necessary. A better understanding of the diverse growth patterns of sRCC, including their intricate characteristic, might bring about novel prognostic and therapeutic prospects.

Generally, the growth of tumor can be broadly divided into two groups according to the morphology of tumor and parenchyma relationship: an expansive growth pattern and infiltrative pattern(3). Relevant studies have shown that the layers of connective fibrous tissue which has been termed tumor PC located at the interface between the tumor and adjacent renal parenchyma(1, 4), and in some cases the presence of tumor PC invasion has been considered poor prognostic outcome for RCC(5, 6). In the last few years, several studies have indicated reduction of the thickness of safety margins that should be excised with tumor to avoid local recurrence, while some researchers considered the thickness of resection margin is irrelevant with disease progression(7, 8). Nevertheless, the existence of tumor PC is not a standard parameter for pathological analysis so far.

In the present study, we analyzed 560 patients with sRCC (no cystic RCC included) and identified three major sRCC morphological growth patterns based on the growth types and features of peritumoral PC, indicating biological and oncological differences: a single nodular pattern (SNP), a multinodular fusion pattern (MFP) and an infiltration pattern (IP).

The objective of this retrospective study was to evaluate the clinicopathologic value of different histological growth patterns, with the purpose of charactering peritumoral PC in sRCC and defining the optimal resection margin of healthy parenchyma individually to avoid the risk of positive SM.

Patients And Methods

Patients

This multi-institutional retrospective study included 560 consecutive patients (416 men and 144 women) diagnosed with sRCC and underwent kidney surgery from May 2010 to October 2017 (Patients of hereditary RCC were not enrolled in this work). As shown in Table 1, the median age of them was 63.2 ± 11.1 years (range: 17–85). The major clinical symptoms of 37 patients were gross hematuria, 96 were microscopic hematuria, 55 were renal area pain and other 338 cases had no obvious symptoms (Table not shown). All patients in our research underwent preoperative computed tomography (CT) or magnetic resonance imaging (MRI) of the abdomen, a chest x-ray, and ultrasonography of urinary system. 4 patients were examined multiple lesions in lung and diagnosed as RCC lung metastasis. The mean tumor diameter was 3.0 ± 0.6 cm (range: 0.5-4.0 cm), 46 cases were < 2.0 cm, 123 were 2.0–3.0 cm and 391 were 3.1–4.0 cm, respectively. Overall, 149 (26.6%) cases had NSS and the other 411 (73.4%) had RN. The decision to proceed NSS or RN depended on the patients' preoperative imaging result, medical history, age, patient preference and physician counseling comprehensively.

Table 1
– Clinicopathologic Characteristics

Charateristic	*Value*
No. of patients	560
Age (years)	
Range	17–85
Median	63.2
Sex	
Male	416 (74.3%)
Female	144 (25.7%)
sRCC subtype	
Clear cell	480 (85.7%)
Chromofobe	38 (6.8%)
Papillary	26 (4.6%)
Others	16 (2.9%)
Growth pattern	
SNP	438 (78.2%)
MFP	58 (10.4%)
IP	64 (11.4%)
pT stage	
1a	541 (96.6%)
3a	19 (3.4%)
Fuhrman grade	
1	137 (24.5%)
2	370 (66.1%)
3	42 (7.5%)
4	11 (1.9%)
PC	
Absent	48 (7.5%)
Present	512 (92.5%)

Charateristic	*Value*

sRCC, small renal cell carcinoma; SNP, a single nodular pattern; MFP, a multinodular fusion pattern; IP, an infiltration pattern; pT, pathologic tumor; PC, pseudocapsule.

Histological Assessment

The tumor size, integrity of peritumoral PC and infiltration status of renal parenchyma were observed by morphological examination and then fixed in a 10% formalin solution. The growth pattern of the tumor was assessed on archival 4μm HE-stained tissue sections cut from formalin-fixed paraffin-embedded specimens from the tumor-kidney boundary. In order to standardize the material, only the tissue section with the highest representation of the interface was examined. All specimens were analyzed separately by two dedicated uropathologists and cases of doubt were judged by consensus review.

Statistical analysis

The $\chi 2$ test and Fisher's exact probability test were utilized to compare the relationship between growth patterns and clinical or pathological variables. A p-value < 0.05 was considered statistically significant. The statistical calculations were performed using SPSS version 22.0 (SPSS, Chicago, IL). For survival statistics, Kaplan-Meier method was used to estimate 5-year OS and CSS, and log-rank tests were conducted to compare the groups of patients with respect to pT stage, growth patterns and PC invasion. The survival curves were performed by Graphpad Prism 8.0.1.

Results

Characteristics of tumor growth patterns

The whole 560 renal tumor specimens are classified into three different growth patterns and examples of them are shown in Fig. 1. We defined the three growth patterns of sRCC as follows: (□) SNP, in which only one entire tumor lesion exists in the kidney and the margin between tumor and renal parenchyma is clearly visible. Intact peritumoral PC could be observed in most of this type of sRCC (Fig. 1A, 1B and 1C). (□) MFP, in which several masses fuse into a large, well-defined, irregularly shaped mass and these masses usually separate from each other with connective fibrous tissue, most of MFP tumors have complete peritumoral PC (Fig. 1D, 1E and 1F). And (□) IP, in which the tumor involves with poorly circumscribed margins with cancer cells extensively infiltrating and unequivocally entrapping normal kidney parenchyma, or the presence of normal renal tissue in the tumor, regardless of tumor circumscription (Fig. 1G, 1H and 1I). The peritumoral PC was defined as a band of fibrous connective tissue located at the interface between the tumor and adjacent parenchyma or adjacent tumors. Positive SM was defined as tumor reaching the edge of the specimen that was removed in the case of invasive tumor that was within 1 mm of the edge of the specimen. The tumor size, pathological subtype, tumor stage, Fuhrman grade, depth of tumor invasion and other variables all were also assessed entirely.

Classification of PC

The specimen which had no obvious peritumoral PC was shown in Fig. 2A. PC status could be further divided into three categories: PC intact and free from invasion (Invasion(-), Fig. 2B); PC with neoplastic infiltration on the parenchymal kidney with no invasion beyond it (Invasion(+), Fig. 2C); and PC with neoplastic infiltration and invasion beyond it (Invasion(++), Fig. 2D).

Baseline clinicaopathologic characteristics

The descriptive clinicopathologic statistics for this study are provided in Table 1. Overall, there are 560 patients included and the median age is 63.2 range from 17 to 85. 416 (74.3%) patients are male and others are female. The histopathologic evaluation based on the 2004 WHO classification revealed that 480 (85.7%) patients were clear cell RCC, 38 (6.8%) were chromophobe RCC, 26 (4,6%) were papillary RCC and 16 (2.9%) were other RCC subtypes. The SNP of tumors was found in 78.2% patients (n = 438), the MFP in 10.4% (n = 58) and IP in 11.4% (n = 64) of all cases.

The post-operative pathological analysis based on the TNM classification showed that 96.6% (n = 541) of tumors were pT1a and 3.4% (n = 19) were pT3a stage owing to the perirenal adipose was infiltrated by tumor cells. According to the Fuhrman nuclear grading, 24.5% (n = 137) of the tumors were grade Ⅰ, 66.1% (n = 370)were grade Ⅱ, 7.5% (n = 42) were grade Ⅲ and 1.9% (n = 11) were grade Ⅳ. The presence of peritumoral PC was detected in 512 (92.5%) cases, and the rest of 48 (7.5%) patients had no obvious PC.

Distribution of growth patterns in sRCC subtypes

Table 2 revealed the distribution of three growth patterns in different sRCC subtypes and no statistical difference was found in such a situation (p = 0.941). The results showed that the distribution of three growth patterns are SNP (69.2%-81.3%) > MFP(6.2%-15.4%) > IP(10.5%-15.4%) in all sRCC subtypes.

Table 2
The Distribution of Three Growth Patterns in Different sRCC Subtypes.

	Growth Patterns			
sRCC subtype	SNP	MFP	IP	p value
Clear cell	378 (78.8%)	48 (10.0%)	54 (11.2%)	0.922
Chromofobe	29 (76.3%)	5 (13.2%)	4 (10.5%)	
Papillary	18 (69.2%)	4 (15.4%)	4 (15.4%)	
Others	13 (81.3%)	1 (6.2%)	2 (12.5%)	
sRCC, small renal cell carcinoma; SNP, a single nodular pattern; MFP, a multinodular fusion pattern; IP, an infiltration pattern				

Relationship of PC, PC invasion, pT stage, SM and different growth patterns

Our results showed that the presence of PC was significantly correlated with different morphological growth patterns ($p < 0.001$) and the absence of PC in IP (43.8%) was obviously frequent than other two patterns (Table 3). PC status was also statistically associated with different growth patterns ($p < 0.001$) (Table 3), the situation of invasion (++) in IP was significantly higher than SNP ($p < 0.001$) and MFP ($p < 0.001$) (Table not shown). In all specimens of Invasion(++), the mean depth of tumor invasion in renal parenchyma was 1.06 mm (SD: 0.22; median: 1.11; range: 0.30–2.6 mm), the infiltrative depth in more than 95% cases was limited in 2 mm and 100% in 3 mm beyond the surface of peritimoral PC.

Table 3 - The Relationship of PC, PC Invasion, pT stage, SM and Different Growth Patterns

Growth Pattern		SNP	MFP	IP
PC	*Absent*	17 (3.9%)	3(5.2%)	28 (43.8%)
	Present	421 (96.1%)	55(94.8%)	36 (56.2%)
p value		< 0.001		
PC Invasion	*Invasion(-)*	325 (77.2%)	35(63.6%)	0 (0%)
	Invasion(+)	90 (21.4%)	16(29.1%)	8 (22.2%)
	Invasion(++)	6 (1.4%)	4(7.3%)	28 (77.8%)
p value		< 0.001		
pT stage	*T1a*	436 (99.5%)	55(94.8%)	50 (78.1%)
	T3a	2 (0.5%)	3(5.2%)	14 (21.9%)
p value		< 0.001		
SM	*(+)*	0 (0%)	1(3.8%)	2 (5.9%)
	(-)	89 (100%)	25(96.2%)	32 (94.1%)
p value		0.088		

PC, pseudocapsule; SNP, a single nodular pattern; MFP, a multinodular fusion pattern; IP, an infiltration pattern; Invasion(-), PC intact and free from invasion; Invasion(+), PC with neoplastic infiltration on the parenchymal kidney with no invasion beyond it; Invasion(++), PC with neoplastic infiltration and invasion beyond it.pT, pathologic tumor; SM: surgical margins

A total of 19 patients were diagnosed pT3a through post-operative pathological examination, among them 14 were found in IP cases. Table 3 showed that pT3a stage was statistically related to IP ($p < 0.001$) and the ratio of such stage in IP was significantly higher than SNP ($p < 0.001$) and MFP ($p = 0.007$). In our cohort, a total of 149 sRCC patients underwent NSS eventually and 3 (2.0%) of them had positive SM in the following pathological findings (Table 3), 1 was found in MFP and 2 was in IP. No significant differences of SM (+) were discovered between SNP and MFP ($p = 0.226$) or between SNP and IP ($p =$

0.075). The situation of SM did not seem to vary across the three growth patterns (p = 0.088), while these data were only available for 149 cases and only 3 patients were SM (+).

Survival Outcomes

The median follow-up time was 62.7 months, and there were 64 deaths and 57 cancer-specific deaths. We calculated and compared 5-year OS and CSS in different morphological growth patterns, PC status and pT stage. For morphological growth patterns, 5-year OS were 90.2%, 87.9% and 73.4% in SNP, MFP and IP (Fig. 3A), and 5-year CSS were 91.5%, 91.4% and 76.2% respectively (Fig. 3B). There were statistical differences of 5-year OS (p = 0.0002) and 5-year CSS (p = 0.0003) between three different growth patterns. 5-year OS (p < 0.0001) and CSS (p < 0.0001) in SNP were significantly higher than that in IP (Table not shown). For PC status, 5-year OS were 93.1%, 85.1% and 73.7% in invasion (-), invasion (+) and invasion (++) (Fig. 3C), and 5-year CSS were 94.1%, 86.8% and 76.2% respectively (Fig. 3D). There were statistical differences of 5-year OS (p < 0.0001) and 5-year CSS (p < 0.0001) between PC status. 5-year OS and CSS in invasion (++) and invasion (+) were significantly higher than that in invasion (-) (Table not shown). For pT stage, 5-year OS were 89.1% and 57.9% in pT1a and PT3a (Fig. 3E), and 5-year CSS were 90.7% and 62.7% respectively (Fig. 3F). There were statistical differences of them between pT1a and pT3a stages.

Discussion

At present, sRCC (≤ 4 cm) is comprehensively considered to be well differentiated, with low clinical stage and better prognosis. Several studies have shown that NSS could provide equally effective local control and oncologic safety when compared with RN for treating sRCC(9, 10). In addition, some reports have also revealed that NSS could offer local tumor control equivalent to RN even for RCC of more than 4cm(11–13). One meta-analysis indicated that compared with RN, NSS reduced the incidence of post-operative renal complication by 61% and reduced mortality of patients by 19%(14). These advantages make NSS become the primary treatment for sRCC currently. Nevertheless, some sRCC masses with an infiltrative growth pattern has an aggressive clinical course and high tendency for distant metastasis. It's extremely important to systematically study the histological characteristics of sRCC and to investigate the appropriate operational manner.

Akitoshi F et al reported that growth pattern could be a predictive parameter for small clear cell RCC(15), moreover, in their subsequent study they demonstrated that infiltrative growth pattern was an independent risk factor for disease-free survival (DFS) and CSS even in advanced cases (3). In our study, we divided the growth patterns of sRCC into three groups: SNP, MFP, and IP, and we found most tumors (78.2%) were consisting of a single mass. Peritumoral PC is mainly composed of connective fibrous tissue with the mean thickness was 0.39 mm (SD: 0.33; median: 0.58; range: 0.2-1.0 mm) in our report, some authors supposed that it was a kind of protective manner to confine tumor growth and proliferation because inflammatory layer consisted of lymphocytes and plasmocytes sometimes could also be found between PC and normal parenchyma(16). Minervini A et al analysed 90 cases of pT1 stage RCC tumors

which underwent enucleation and found complete PC was present in 67% of tumors, and incomplete PC or PC infiltrated by cancer cells was detected in the rest of samples(17). Our research showed that 360 (64.3%) cases had intact PC and the total proportion of PC invaded by tumor cells in IP (100%) was remarkably higher than other two growth patterns. Accordingly, tumor enucleation is not recommended in sRCC of IP owing to the high risk of incomplete excision and extending the scope of resection around tumor is very essential.

To prevent the risk of local recurrence, the excision of a minimal and visible margin of normal-appearing parenchyma around the tumor is regarded the optimal surgical technique of NSS. However, whether or not to excise a rim of healthy parenchyma, theoretically adequate to avoid a positive SM and local recurrence, is still controversial. Marco B et al reviewed articles published from January 2002 to May 2012 and discovered the overall incidence of positive SM ranges from 0–7%,with no significant differences in open, laparoscopic, and robot-assisted techniques(18). What we found in our report came up with very similar result, with the incidence of positive SM was 2.0%. Although no statistical differences of positive SM were discovered across the three growth patterns, we realized the probability of positive SM in MFP and IP was evidently higher than in SNP. The pathological stage of 19 (3.4%) patients who were diagnosed pT1a stage before operation increased to pT3a stage after surgery due to the perirenal adipose tissue was invaded with tumor cells. This reminded us NSS might lead to positive SM of sRCC, though most neoplasms were limited in PC. Seongyub Oh reported that perirenal fat infiltration was an independent prognostic factor for predicting DFS in patients with tumors of 7 cm or less in size and the presence of perirenal fat infiltration requires stricter follow-up planning, even in small renal cell carcinoma(19). Considering this, it’s necessary to routinely excise the perirenal adipose tissue to reduce the possibility of local recurrence when undergoing NSS.

By all accounts, we recommend that the surgical margin (SM) could be proceeded along the peritumoral PC in cases of SNP sRCC because most of SNP tumors were surrounded by complete PC. Tumor enucleation is also an available treatment for this kind of patients. 63.6% of MFP tumors have intact peritumoral PC, even if they are inclined to grow in an irregular or polymorphy manner. For this pattern, tumor enucleation ought to be particularly choosy and a NSS margin with thickness of 1–3 mm of renal parenchyma around the mass should be acceptable. Tumor enucleation is not suitable in IP sRCC in which almost all tumors possess no PC or uncomplete PC infiltrated with cancer cells. Owing to the infiltrative depth of all tumors were confined in the range of 3mm away from the peritumoral PC in this report, we advise the optimal resection distance of NSS in IP sRCC is better to extend more than 3mm around tumor surface to acquire a histologic tumor-free margin. As for some infrequent cases, such as tumor cells invade deeply in normal kidney parenchyma over PC and sRCC with the presence of tumor multifocality or satellite lesions(20, 21), this recommended surgical measure of NSS is not appropriate anymore and radical nephrectomy should be taken into account. Our study also proved that prognostic outcome of SNP and MFP was significantly better than that in IP, and the infiltration level of PC invasion was closly related to 5-year OS and CSS.

There are also some limitations of our study. First and uppermost, no reliable method could precisely distinguish different growth patterns before operation at present. This confines the application of growth patterns in clinic. Second, the study was a retrospective, nonrandomized design which decreased the level of evidence. Third, pathologic data were collected from multiple institutions over a long period and the procedures for handling specimens were not uniform. Last, there are an inherent bias for the quality of specimens operated by distinct surgical manners that can affect the SM. Nevertheless, we believe that recognition of different growth patterns is useful for preoperative decision making in the future. Large-scale studies are warranted to validate our growth pattern classification to determine the optimal resection range.

Conclusion

According to our study, the growth pattern of sRCC could be divided into three morphological subtypes: SNP, MFP and IP, and we showed that uncomplete peritumoral PC, pT stage, and positive SM were statistically correlated with IP. This study indicates morphological growth patterns, if validated externally in a lager cohort, could be used as a valuable biomarker to help operating NSS in sRCC patients to avoid the risk of positive SM. The effectiveness of growth pattern as a novel proposed parameter to direct NSS in sRCC patients deserves further exploration.

Abbreviations

sRCC: mall renal cell carcinoma

NSS: nephron-sparing surgery

RN: radical nephrectomy

PC: pseudocapsule; SM, surgical margin

RCC: renal cell carcinoma; SNP, single nodular pattern

MFP: multinodular fusion pattern

IP: infiltration pattern

OS: overall survival

CSS: cancer-specific survival

DFS: disease-free survival

Declarations

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

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Author Contributions

GL, YYY, KRW designed the study and edited the manuscript. RYZ and CZY collected the data and wrote the manuscript. AXW, GL and KRW collected and analyzed the data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The Institutional Review Board of Tianjin Medical University approved the study.

Informed consent was obtained from all these patients or their guardians.

Consent for publication

The written consent is available for review by the chief editor.

Competing interests

The authors declare that they have no competing interests.

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Figures

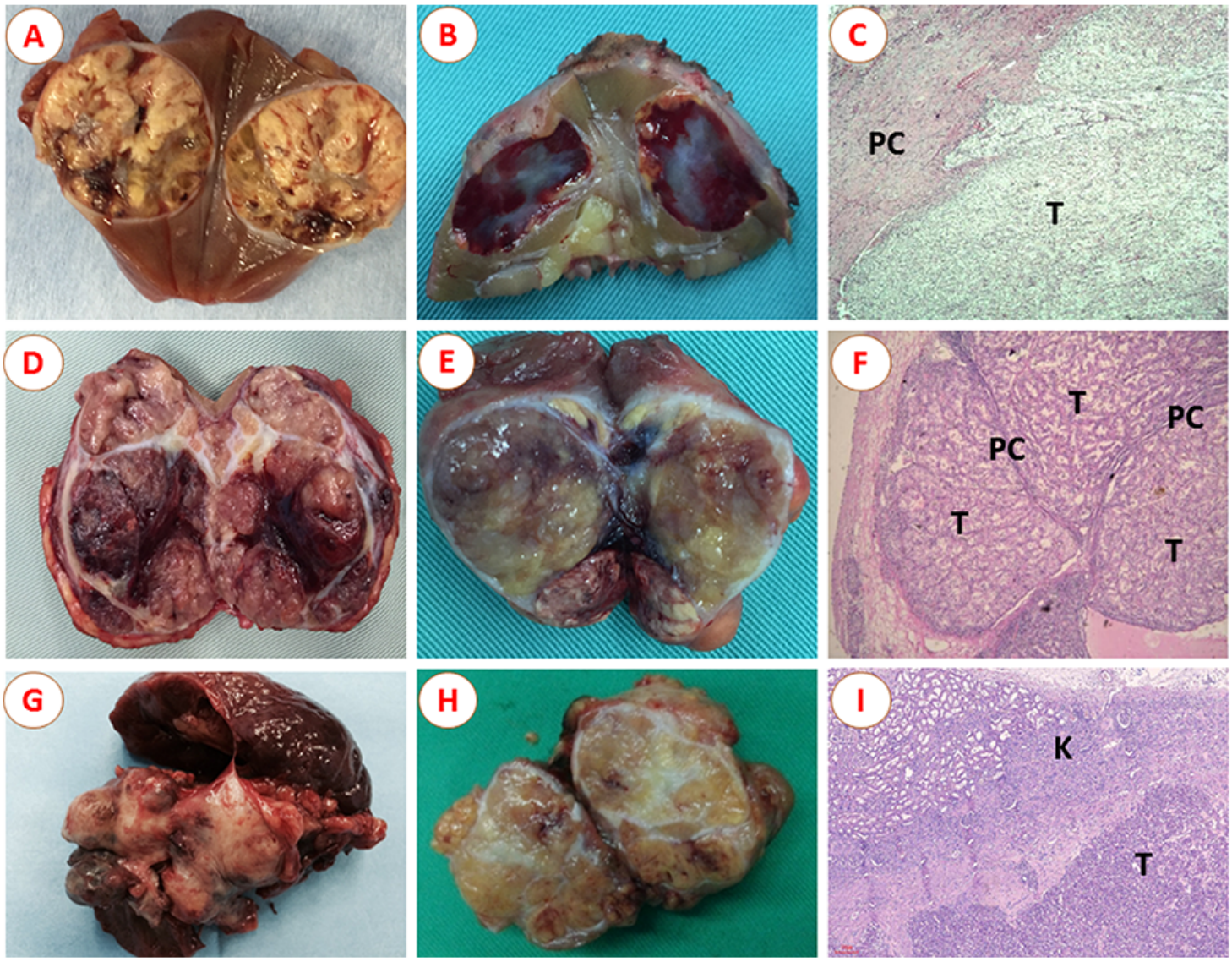

Figure 1

Different morphological subtypes of small renal cell carcinoma (sRCC) after nephron-sparing surgery: (A and B) Single nodular growth pattern of sRCC and the H-E staining pathological specimen (C); (D and E) Multinodular fusion growth pattern of sRCC and the H-E staining pathological specimen (F); (G and H) Infiltration growth pattern of sRCC and the H-E staining pathological specimen (I). Abbreviations: T, tumor; PC, pseudocapsule; K, kidney.

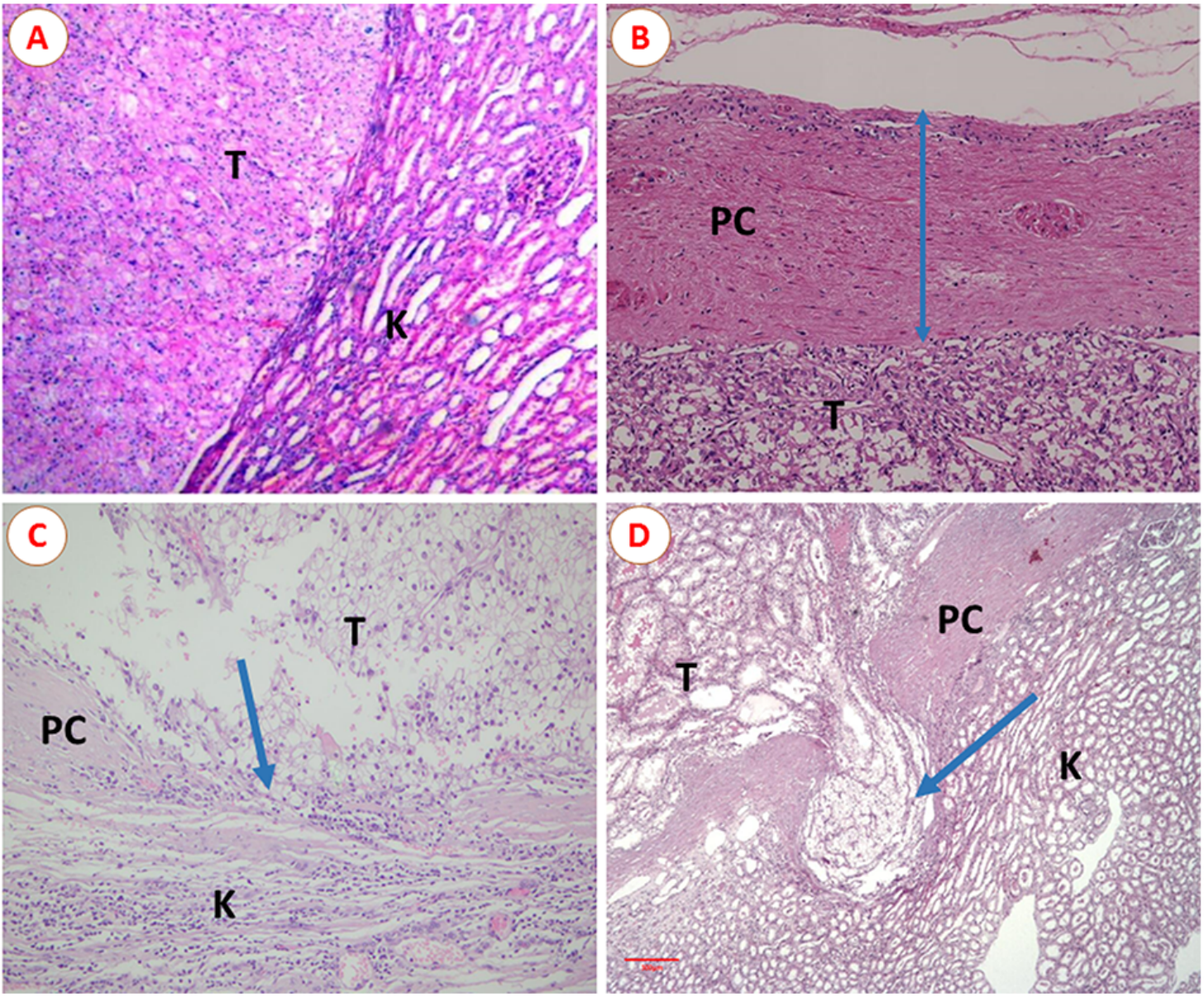

Figure 2

(A) no pseudocapsule between tumor and renal parenchyma; (B) pseudocapsule (PC) intact and without infiltration of tumor cells (Invasion(-)); (C) PC infiltrated by tumor cells but no invasion beyond it (Invasion(+)); (D) PC with neoplastic infiltration beyond it (Invasion(++)), and the depth of tumor invasion was about 14mm (the scale bar: 300 μm). Abbreviations: T, tumor; K, kidney.

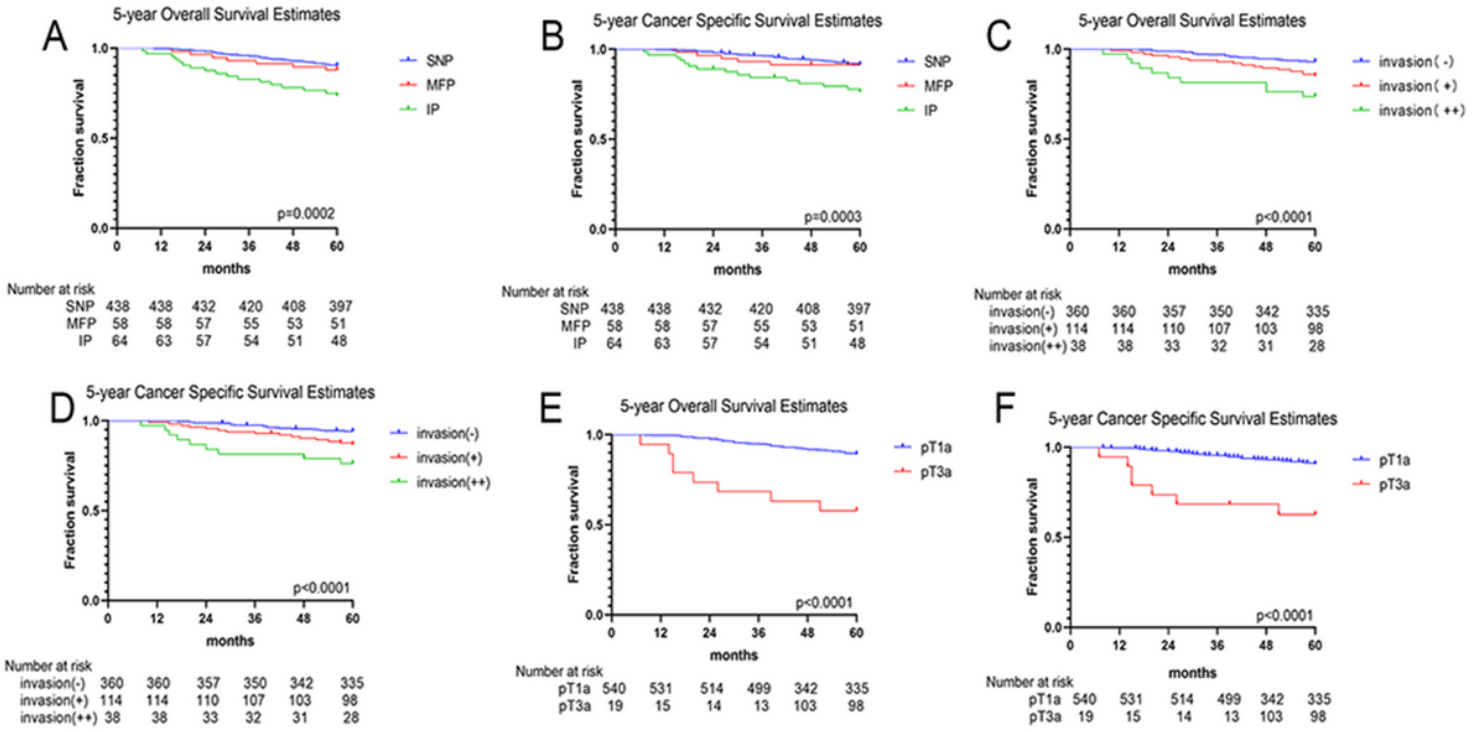

Figure 3

5-year OS and CSS among different morphological growth patterns (A), PC status (B) and pT stages (C). Abbreviations: OS, overall survival; CSS, cancer-specific survival; PC, pseudocapsule