



Prognostic significance of pseudocapsule status in patients with metastatic renal cell carcinoma treated with tyrosine kinase inhibitors

Wei Xi^{1#}, Yingyong Hou^{2#}, Xiaoyi Hu^{1#}, Yu Xia¹, Shuai Jiang¹, Hang Wang¹, Qi Bai¹, Jun Hou², Jianming Guo¹

¹Department of Urology, Zhongshan Hospital, Fudan University, Shanghai, China; ²Department of Pathology, Zhongshan Hospital, Fudan University, Shanghai, China

Contributions: (I) Conception and design: J Guo, W Xi; (II) Administrative support: J Guo; (III) Provision of study materials or patients: Y Hou, X Hu; (IV) Collection and assembly of data: X Hu, Y Xia, S Jiang; (V) Data analysis and interpretation: W Xi, Y Hou, X Hu, H Wang, Q Bai, J Hou; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Jianming Guo, Department of Urology, Zhongshan Hospital, Fudan University, Shanghai 200032, China.

Email: guo.jianming@zs-hospital.sh.cn.

Background: We sought to determine whether pseudocapsule (PS) features have prognostic implications in patients with metastatic renal cell carcinoma (mRCC).

Methods: We retrospectively reviewed 231 patients diagnosed with mRCC and treated with tyrosine kinase inhibitors; 188 patients with data available regarding the tumor-parenchyma interfacial PS of the primary tumor were enrolled for analysis. PS status was evaluated as intact (grade 0), merely involved (grade 1), penetrated (grade 2), and absent (grade 3). We applied the Kaplan-Meier method and Cox regression model to assess the survival impact.

Results: Of the 188 patients, 19 (10.1%), 61 (32.4%), 96 (51.1%) and 12 (6.4%) had grade 0, 1, 2 and 3 PS, respectively. PS status was significantly associated with histology ($P=0.0206$), venous tumor embolus ($P=0.0511$), microvascular invasion ($P=0.0108$) and microsatellite formation ($P=0.0097$). Patients without a PS had the worst overall survival (OS), with a 3-year OS rate of 12.7%, whereas the OS rates for grades 0, 1 and 2 were 78.8%, 50.8% and 43.6%, respectively. Adjusted by other variables, grade 3 and grade 2 PS gave rise to a much higher risk of death across the cohort [hazard ratio (HR) =5.217, $P=0.0182$; HR =3.765, $P=0.0281$, respectively]. Sarcomatoid change was also an independent factor for OS (HR =2.932, $P=0.0075$). In contrast, microsatellite formation was not associated with survival in the cohort.

Conclusions: PS status has prognostic implications for OS in metastatic renal cancer. The absence of the PS and sarcomatoid change are two pathological features related to an extremely poor prognosis.

Keywords: Metastatic renal cell carcinoma (mRCC); tumor-parenchyma interface (TPI); pseudocapsule (PS); prognosis; tyrosine kinase inhibitors (TKIs)

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Introduction

Metastatic renal cell carcinoma (mRCC) has a dismal but heterogeneous prognosis (1). Laboratory indicators have been identified to greatly impact prognosis. Mainly based on

these indicators, several prognostic models were developed in succession [e.g., Memorial Sloan Kettering Cancer Center (MSKCC), International Metastatic RCC Database Consortium (IMDC)], but recent models have not shown

much improvement in predictive accuracy, indicating that a ceiling has been reached (2,3). In the literature, traditional clinicopathologic factors of the primary tumor, such as pT stage, Fuhrman grade and sarcomatoid change, have been consistently reported to have an impact on clinical outcome even after metastasis (4–6). However, pathological parameters at the tumor-parenchyma interface (TPI) have not been well studied.

The pseudocapsule (PS) of the TPI is a common phenomenon in malignancies (7–9). An infiltrative pattern of the PS has been frequently observed. In kidney cancer, 10–33% patients were reported to have a penetrated PS, and this rate is much higher than renal capsule (10–14). In addition, the extent of PS invasion could reflect the burden of cancer cells entering the circulation, and venous tumor thrombus (VTT) and microvascular invasion (MVI) are remarkably more frequent when the PS is penetrated or absent (15). Consequently, PS penetration and absence indicate a significantly increased risk of death and progression (15,16). In recent years, a study reported the pathological impact of axitinib therapy and found a significantly strengthened PS at the TPI, suggesting plasticity of the anatomic structure (17). However, studies of PS status in mRCC patients remain rare. The hypothesis of the study was that the PS at the TPI has prognostic implications in mRCC. We sought to assess this hypothesis by analyzing a cohort of mRCC patients treated with tyrosine kinase inhibitors (TKIs). We present the following article in accordance with the REMARK reporting checklist (available at <https://dx.doi.org/10.21037/tau-21-429>).

Methods

The retrospective cohort study was carried out at Zhongshan Hospital, Fudan University. With archived data from our institution, the inclusion criteria were as follows: patients received kidney surgery (partial, radical or cytoreductive nephrectomy) between 2004 and 2017 at our institution and were pathologically diagnosed with renal cell carcinoma (RCC); M1 stage was reached at or after surgery; patients received sunitinib or sorafenib as first-line therapy; no history of other malignancies. The exclusion criteria were as follows: inadequate clinical or pathological data or unevaluable PS. Finally, 188 out of 231 cases were included in the analyses. Second-line treatment included other TKIs, cytokine therapy, traditional Chinese medicine and supportive treatment. No programmed cell death protein 1 (PD-1)/programmed death ligand 1 (PD-L1) inhibitors

were used. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Zhongshan Hospital Clinical Research Ethics Committee (No. B2016-158) and individual consent for this retrospective analysis was waived.

We collected clinicopathological data from archived records. Tumors were staged according to the 2010 American Joint Committee on Cancer (AJCC) TNM classification. Tumor Fuhrman grade was determined according to the World Health Organisation (WHO)/International Society of Urologic Pathologists (ISUP) 2016 criteria. The PS status of primary tumors was classified into four categories as we previously reported (15): grade 0 for intact PS, grade 1 for involved but not penetrated PS, grade 2 for penetrated PS with renal parenchyma involvement, and grade 3 for PS absence (*Figure 1*). To ensure that it was PS being assessed (rather than the renal capsule or perirenal capsule), assessment was only carried out when the parenchyma was observed on the other side.

The main endpoints were overall survival (OS) and progression-free survival (PFS), calculated from TKI treatment initiation. All patients underwent computed tomography scans to evaluate the response to TKI treatment according to the Revised Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1) (18).

Statistical analysis

The chi-square test and ANOVA were used to evaluate the associations among variables. The Kaplan-Meier method and log-rank test were applied to determine the survival difference. The hazard ratio (HR) and corresponding 95% confidence interval (CI) were calculated with a Cox proportional model. P less than 0.05 was considered to be significant. Analyses were done with the R environment (version 3.3.2).

Results

Basic clinical characteristics

The characteristics of the 188 patients are summarized in *Table 1*. Clear cell, papillary and chromophobe cases accounted for 86.2%, 7.4% and 6.4%, respectively. As many as 39.9% of tumors were initially localized at diagnosis but progressed to M1 after surgery; 29.3% were simultaneously metastatic at surgery. According to the IMDC criteria, 18.6%, 65.4% and 16.0% of patients were classified into

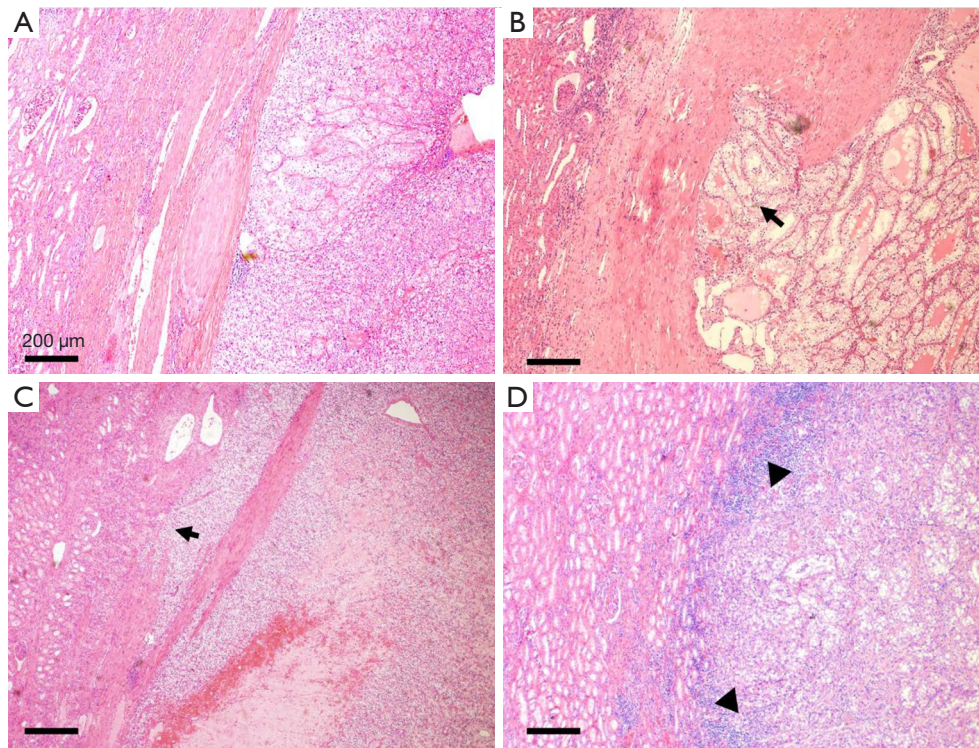


Figure 1 Representative pictures of PS status. (A) Grade 0 for intact PS (hematoxylin-eosin, original magnification $\times 40$); (B) grade 1 for merely involved but not penetrated PS (hematoxylin-eosin, original magnification $\times 40$); (C) grade 2 for penetrated PS with renal parenchyma involved (hematoxylin-eosin, original magnification $\times 40$); (D) grade 3 for PS absence (hematoxylin-eosin, original magnification $\times 40$). Black arrows indicate where cancer invades or penetrates PS. Enhanced inflammation could be observed in (D) as indicated with black arrowheads. PS, pseudocapsule.

the favorable, intermediate and unfavorable risk groups, respectively. Fifty-nine-point-six percent and 40.4% of the patients were treated with sunitinib and sorafenib, respectively. The median follow-up time was 30.9 months after TKI therapy initiation.

Associations with clinicopathological parameters

There is a high rate of PS involvement in mRCC. In total, 19 (10.1%), 61 (32.4%), 96 (51.1%) and 12 (6.4%) tumors had grade 0, 1, 2 and 3 PS status, respectively. Compared to those with clear cell subtype, patients with non-clear cell histology had a lower rate of PS absence (4.9% vs. 15.4%, $P=0.0206$). The rates of MVI significantly increased with PS grade ($P=0.0108$) and tumor embolus increased had the similar association with marginal significance ($P=0.0511$). The MVI and embolus rates in tumors with grade 2/3 PS were 83% and 73%, respectively. PS was not associated with nuclear grade ($P=0.0975$), initial stage ($P=0.3202$) or IMDC

risk stratification ($P=0.3132$). In addition, 20.2% of tumors had at least one site of microsatellite formation, which was associated with higher PS grade (grade 2 and 3, $P=0.0097$) (Table 1).

Prognostic value of PS status

During follow-up, a total of 118 patients (62.8%) experienced progression and 96 (51.1%) died. PS status was not associated with PFS (Figure 2A, $P=0.376$) or therapy response ($P=0.596$, Table S1), but it stratified OS well (Figure 2B, $P=0.0117$). The 1.5-year and 3-year survival rates of patients with grade 3 PS were the lowest (38.1% and 12.7%) compared to those with grade 0 (78.8% and 78.8%), grade 1 (70.9% and 50.8%) and grade 2 PS (61.0% and 43.6%). Microsatellite formation was not associated with survival ($P=0.6120$). Sarcomatoid change resulted in an increased risk of death with marginal significance ($P=0.0632$). IMDC, MVI, nuclear grade and lung metastasis were also

Table 1 Basic characteristics and relations of PS status with other variables

Variable	Total, n (%)	PS status, n (%)				P
		Grade 0	Grade 1	Grade 2	Grade 3	
Age, years*						0.2502
≤58	94 (50.0)	11 (11.7)	30 (31.9)	44 (46.8)	9 (9.6)	
>58	94 (50.0)	8 (8.5)	31 (33.0)	52 (55.3)	3 (3.2)	
Gender						0.7271
Male	139 (73.9)	12 (8.6)	46 (33.1)	72 (51.8)	9 (6.5)	
Female	49 (26.1)	7 (14.3)	15 (30.6)	24 (49.0)	3 (6.1)	
Fuhrman grade						0.0975
2	97 (51.6)	10 (10.3)	39 (40.2)	45 (46.4)	3 (3.1)	
3	73 (38.8)	8 (11.0)	19 (26.0)	40 (54.8)	6 (8.2)	
4	18 (9.6)	1 (5.6)	3 (16.7)	11 (61.1)	3 (16.7)	
Histology						0.0206
Clear cell	162 (86.2)	16 (9.9)	58 (35.8)	80 (49.4)	8 (4.9)	
Non-clear cell	26 (13.8)	3 (11.5)	3 (11.5)	16 (61.5)	4 (15.4)	
Venous tumour embolus						0.0511
Yes	37 (19.7)	1 (2.7)	9 (24.3)	22 (59.5)	5 (13.5)	
No	151 (80.3)	18 (11.9)	52 (34.4)	74 (49.0)	7 (4.6)	
With MVI						0.0108
Yes	24 (12.8)	0	4 (16.7)	16 (66.7)	4 (16.7)	
No	164 (87.2)	19 (11.6)	57 (34.8)	80 (48.8)	8 (4.9)	
With necrosis						0.2797
Yes	57 (30.3)	6 (10.5)	13 (22.8)	33 (57.9)	5 (8.8)	
No	131 (69.7)	13 (9.9)	48 (36.6)	63 (48.1)	7 (5.3)	
With sarcomatoid change						0.1953
Yes	13 (6.9)	3 (23.1)	2 (15.4)	8 (61.5)	0	
No	175 (93.1)	16 (9.1)	59 (33.7)	88 (50.3)	12 (6.9)	
With microsatellite formation						0.0097
Yes	38 (20.2)	1 (2.6)	7 (18.4)	25 (65.8)	5 (13.2)	
No	150 (79.8)	18 (12.0)	54 (36.0)	71 (47.3)	7 (4.7)	
Lung involvement						0.9040
Yes	115 (61.2)	11 (9.6)	39 (33.9)	57 (49.6)	8 (7.0)	
No	73 (38.8)	8 (11.0)	22 (30.1)	39 (53.4)	4 (5.5)	
Number of metastatic sites						0.5770
1	126 (67.0)	14 (11.1)	41 (32.5)	65 (51.6)	6 (4.8)	
≥2	62 (33.0)	5 (8.1)	20 (32.3)	31 (50.0)	6 (9.7)	

Table 1 (continued)

Table 1 (continued)

Variable	Total, n (%)	PS status, n (%)				P
		Grade 0	Grade 1	Grade 2	Grade 3	
IMDC risk group						0.3132
Favorable	35 (18.6)	5 (14.3)	12 (34.3)	18 (51.4)	0	
Intermediate	123 (65.4)	13 (10.6)	41 (33.3)	61 (49.6)	8 (6.5)	
Unfavorable	30 (16.0)	1 (3.3)	8 (26.7)	17 (56.7)	4 (13.3)	
Initial stage at surgery						0.3202
Localized	75 (39.9)	8 (10.7)	28 (37.3)	38 (50.7)	1 (1.3)	
Advanced	58 (30.9)	5 (8.6)	18 (31.0)	29 (50.0)	6 (10.3)	
Metastatic	55 (29.3)	6 (10.9)	15 (27.3)	29 (52.7)	5 (9.1)	

*, split at median value. PS, pseudocapsule; MVI, microvascular invasion; IMDC, International Metastatic Renal Cancer Database Consortium.

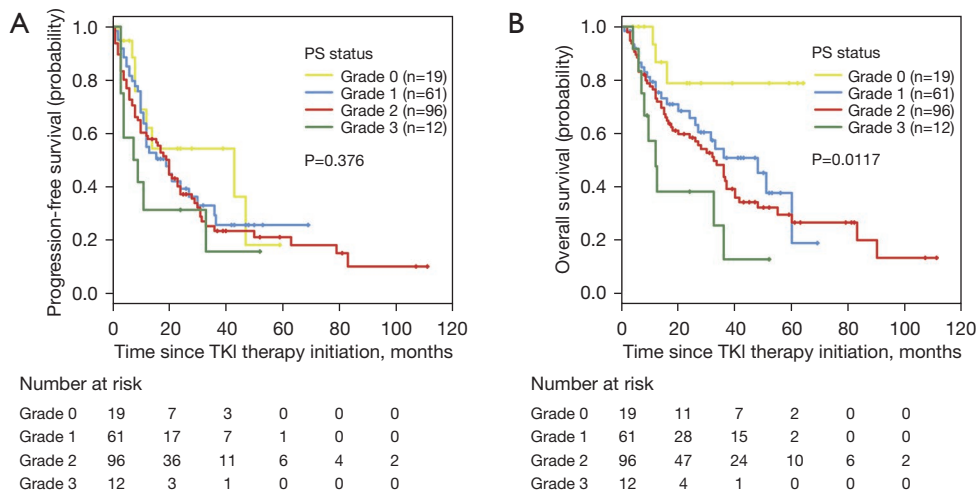


Figure 2 Kaplan-Meier curves of survival according to time after therapy initiation and PS status in mRCC. (A) PFS; (B) OS. mRCC, metastatic renal cell carcinoma; PS, pseudocapsule; PFS, progression-free survival; OS, overall survival; TKI, tyrosine kinase inhibitor.

significant in the univariate analysis (Table 2). In multivariate analysis, PS status and sarcomatoid change persisted to be two pathological prognostic parameters (Table 3). The absence and penetration of PS resulted in a 4.2- and 2.7-fold higher risk of death to grade 0 PS, respectively (HR =5.217, P=0.0182; HR =3.765, P=0.0281). The survival benefit of grade 1 to 0 was marginal (P=0.0524). Nuclear grade lost the influence on OS in multivariate analysis.

Although PS absence and sarcomatoid change were only observed in 13.3% of all cases (n=25), they were related to remarkably poor survival. Patients with one of the features

made those in favorable or intermediate risk group have clinical outcomes as poor as those in the unfavorable risk group (Figure S1). Integrating PS status into the IMDC model increased the C-index for survival from 0.64 to 0.73 across the cohort.

Discussion

There are few studies on PS status in renal cancer and even fewer studies in mRCC. The present study demonstrated that PS status in mRCC was far different from that in

Table 2 Univariable analyses for OS

Variable	HR	95% CI	P
Age, year (>58 vs. ≤58)	1.083	0.724–1.620	0.6970
Gender (female vs. male)	0.889	0.556–1.423	0.6250
Histology (non-clear cell vs. clear cell)	1.358	0.793–2.325	0.2660
MVI (with vs. without)	1.746	1.005–3.037	0.0480
Necrosis (with vs. without)	1.430	0.929–2.202	0.1040
Sarcomatoid change (with vs. without)	2.004	0.962–4.173	0.0632
Fuhrman grade (3+4 vs. 2)	1.582	1.057–2.368	0.0259
Systematic therapy (sunitinib vs. sorafenib)	0.9454	0.615–1.454	0.7980
Lung involvement (with vs. without)	1.797	1.159–2.787	0.0087
Bone involvement (with vs. without)	1.149	0.732–1.804	0.5450
Liver involvement (with vs. without)	1.307	0.694–2.463	0.4070
Number of involved organs (≥2 vs. 1)	1.213	0.796–1.847	0.3690
Initial stage at surgery			
Localized	Reference		
Advanced	1.223	0.744–2.008	0.4271
Metastatic	1.519	0.934–2.468	0.0917
IMDC risk group			
Favorable	Reference		
Intermediate	1.717	0.900–3.276	0.1008
Unfavorable	4.072	1.991–8.326	0.0001
PS status			
Grade 0	Reference		
Grade 1	3.111	0.941–10.290	0.0628
Grade 2	3.866	1.210–12.350	0.0225
Lack of PS	7.130	1.924–26.420	0.0032
Microsatellite formation (with vs. without)	1.139	0.688–1.885	0.6120

CI, confidence interval; HR, hazard ratio; IMDC, International Metastatic Renal Cancer Database Consortium.; MVI, microvascular invasion; MVI, microvascular invasion; OS, overall survival; PS, pseudocapsule.

patients without metastasis and was significantly associated with survival. Although PS absence was only observed in a small proportion of samples, it resulted in remarkable survival loss. Thus, the treatment and monitoring of patients with unfavorable clinicopathological features (PS absence or sarcomatoid change) should follow a stricter approach.

The PS is the fibrous interface between the tumor and renal parenchyma. It has been found to be frequently

invaded and penetrated by cancer cells. In early stage of RCC (p/cT1–2), the penetration ratio reaches 10–33% (10–14). In a large cohort from our institution, 20% of nonmetastatic tumors and 18% of localized tumors penetrated the PS. The proportion reached nearly 50% in mRCC in the present cohort (15). Of note, all assessments were based on pathology specimens after surgery, indicating that the extent of potential aggressiveness could be revealed as early as the time of surgery. This could also be

Table 3 Multivariable analyses for OS

Variable	HR	95% CI	P
MVI (with vs. without)	1.412	0.785–2.538	0.2488
Sarcomatoid change (with vs. without)	2.932	1.332–6.455	0.0075
Fuhrman grade (3+4 vs. 2)	1.196	0.770–1.859	0.4251
Lung involvement (with vs. without)	2.057	1.292–3.275	0.0023
IMDC risk group			
Favorable	Reference		
Intermediate	1.749	0.891–3.433	0.1042
Unfavorable	3.387	1.595–7.190	0.0014
PS status			
Grade 0	Reference		
Grade 1	3.318	0.987–11.153	0.0524
Grade 2	3.765	1.153–12.292	0.0281
Lack of PS	5.217	1.324–20.558	0.0182

CI, confidence interval; HR, hazard ratio; IMDC, International Metastatic Renal Cancer Database Consortium.; MVI, microvascular invasion; MVI, microvascular invasion; OS, overall survival; PS, pseudocapsule.

complemented by the comparable distribution of PS status in different initial stage groups ($P=0.32$). PS penetration in different initial stage groups was the same (~50%). The only exception was that patients with a higher initial stage had higher rates of PS absence (initial nonlocalized *vs.* localized: 9.7% *vs.* 1.3%, $P=0.04$).

Although the prognostic assessment of mRCC mostly depends on laboratory indicators, anatomic or traditional factors of the primary lesion could be useful. Kim *et al.* (4) found that initial pT stage is an independent factor for cancer-specific survival in mRCC. Its prognostic value was stronger than that of any molecular marker discussed in the report [carbonic anhydrase 9 (CA9), phosphatase and tensin homolog (PTEN), p53, vimentin]. Combining clinical and molecular markers achieved the best predictive accuracy. In another study, Tosco *et al.* (5) investigated the role of initial clinical factors in mRCC patients who underwent nephrectomy and at least one metastasectomy. He proved that T stage ≥ 3 and Fuhrman grade ≥ 3 separately led to a 2.3–2.8 higher risk of cancer-specific death. A model purely based on clinical factors (including T stage and Fuhrman grade) was efficient [area under the curve (AUC) at 5-year =0.88]. In contrast, Leibovich *et al.* (6) did not detect any influential role of T stage or Fuhrman grade but revealed a good predictive role of sarcomatoid change, which was

also verified by other reports (19). In the present study, we did not find prognostic capability of initial TNM stage. Survival decreased with increasing Fuhrman grade, but it was nonsignificant in multivariate analysis. Only PS status and sarcomatoid change were pathological factors of prognostic value.

The prognostic significance of PS status was also reported in the liver metastases of gastrointestinal cancer. Patients with a thin PS or without a PS had significantly decreased survival (20). Here, we provided the first evidence of the relationship between PS status and oncological outcome in mRCC. Specifically, patients without a PS experienced extremely poor survival, with a median survival time of only 10.7 months. Notably, the PS of the primary tumor rather than metastatic lesion was assessed because metastases from RCC had nearly no PS (figure not shown).

PS is associated not only with prognosis but also with plasticity with treatment. In a cohort of 74 patients with soft tissue sarcoma, O'Donnell *et al.* (21) found that neoadjuvant chemotherapy before surgery contributed to the development of a PS. A similar finding was also reported for the liver metastasis of colorectal cancer (22). In kidney cancer, a recent study with 46 clear cell RCC patients discussed pathological changes at TPI after axitinib treatment (17). Compared with the control group

(n=23, surgery alone), the group with neoadjuvant axitinib treatment (5 mg for up to 12 weeks) had significantly higher PS grade, whereas the degree of glomerulosclerosis, arteriosclerosis and nephrosclerosis remained unchanged (n=23). This phenomenon indicated that the PS could be reconstructed in a short period of time. We wondered whether PS was associated with the TKI response, which was denied by the results (Table S1). Generally, the current efficient models or indicators are more related to OS (2). In this study, the phenomenon also applies to PS status.

Three percent of RCC cases are observed to have sarcomatoid change. The presence of this feature may be one of the most influential prognostic variables for clinical outcome (19). The majority of series report a median survival of 4–9 months (23–25). The median survival in the present study was 4 months. We verified that patients without a PS also had rather dismal outcomes. The two features could help to distinguish a small group of patients with high risk whatever the status of other indicators. Meanwhile, we also found that patients with sarcomatoid change all had a PS at TPI, which was contradictory to the intuition. Given the limited cases, more studies are needed to verify our findings.

The PS could be an important means by which cancer cells spread. We previously found that the incidence of venous embolus and MVI, direct evidence of cancer cells entering the circulation, rises dramatically with increasing PS grade (15). The phenomenon was also found in this study. A total of 18.5% of patients with grade 2/3 PS had MVI, whereas the rate was only 5% in the grade 0/1 group. The association with tumor venous embolus was similar (Table 1). Invasive tumors could have a small subgroup of cancer cells that can collectively invade new regions through cell-cell and cell-matrix interactions, thus facilitating metastasis (26). In several other non-metastatic clear cell RCC cases, we observed that the PS area and the close peri-PS area contained the most abundant veins with large diameters (long diameter >200 μm). They went diagonally through the PS, which further increased the size of the tumor-facing surface. In many situations, the leading-edge cancer cells were only separated by a thin layer of endotheliocytes from large veins (Figure S2). CD44, the indicator of invasion ability, was mainly distributed along the boundary between PS and tumors. They were further enriched surrounding large vessels (Figure S3, another case). Therefore, cancer cells near the PS are more aggressive, and the vasculature of the PS potentially provides a pathway for cancer cells to escape the primary

site. Targeting these vessels could have therapeutic effects. In fact, Kawakami *et al.*'s report to some degree verified that these vessels of PS are undeniable targets during axitinib therapy (17). But initial PS status was not associated with TKI response or PFS, but significantly associated with OS, indicating that treatment response is complicated which might be determined by many unknown factors.

Microsatellite formation was also discussed in malignancies. In a study involving 278 hepatocellular carcinoma (HCC) patients (27), both PS and microsatellite formation had a survival impact, although the latter lost significance in multivariate analysis. Patients with microsatellite formation had a median disease-free survival (DFS) time of only 6.3 months, whereas other patients had a median DFS time of 14.9 months ($P=0.0006$). Similar findings were observed in two other studies in HCC (20,28). In the present study, we detected a close relationship between PS status and microsatellite formation in renal cancer, but the latter did not effectively stratify patients according to prognosis ($P=0.6120$).

Metastatic site and number of metastatic lesions could impact survival greatly. Motzer *et al.* found that liver metastasis and increased metastatic number indicated deteriorated outcomes (29). In another report enrolled 113 mRCC patients with the intermediate risk group, bone and brain metastasis had a negative effect on OS (30). However, we in the present study found that patients with lung metastasis on the contrary experienced worse survival than those with other metastatic sites. This could be influenced by the factor that in our study patients with lung metastasis had more metastatic sites, indicating increased tumor burden in these patients. The finding was previously reported with a smaller cohort from our institution (31), suggesting a stable phenomenon.

The main limitations of this study are its retrospective nature and relatively small sample size. All assessments relied on preserved slides, and the exclusion criteria could lead to potential selection bias. Although strict follow-up made the cohort typical, the findings in the study still need to be verified by other institutions with a large cohort, especially with more cases without a PS. In addition, we did not include patients treated with other TKIs (such as pazopanib) because they were unavailable at that time. Given the huge survival difference among patients treated with different TKIs, the prognostic value of PS status in these patients needs to be further studied.

In conclusion, we found that PS status has prognostic implications for OS in metastatic renal cancer. The absence

of the PS and sarcomatoid change are two pathological features related to an extremely poor prognosis.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Zhongshan Hospital Clinical Research Ethics Committee (No. B2016-158) and individual consent for this retrospective analysis was waived.

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