Evaluation of Tumor Pseudocapsule Status and its Prognostic Significance in Renal Cell Carcinoma

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Purpose: We determined whether tumor pseudocapsule status, including the extent of invasion by cancer and lack of a pseudocapsule, has prognostic value in renal cell carcinoma.

Materials and Methods: We retrospectively reviewed the records of 1,577 patients with different stages of renal cell carcinoma who underwent nephrectomy at our institution, of whom 1,307 (82.9%) were eligible for analysis. Presented pseudocapsules were classified as grade 0—completely intact, grade 1—merely involved and grade 2—penetrated. We studied overall and progression-free survival using the Kaplan-Meier method and a Cox regression model.

Results: Of the 1,307 patients 1,244 (95.2%) presented with a pseudocapsule, including 350 (28.1%), 643 (51.7%) and 251 (20.2%) with a grade 0, 1 and 2 pseudocapsule invasion extent, respectively. Kaplan-Meier curves revealed great losses in overall and progression-free survival for an increased extent of invasion and pseudocapsule absence. On multivariate analyses we identified significant overall and progression-free survival harms for grade 2 pseudocapsules (HR 2.12 and 2.66, each $p < 0.0001$) and lack of a pseudocapsule (HR 1.95, $p = 0.0248$ and HR 2.54, $p = 0.0007$, respectively) compared to grade 0 pseudocapsules. A change in statistical risk from grade 1 to 0 was only detected for progression-free survival. The prognostic value of pseudocapsule status was shown by a higher HR on multivariable analyses in individuals with localized renal cell carcinoma.

Conclusions: Our findings suggest that pseudocapsule status has good prognostic implications in renal cell carcinoma. Lack of a pseudocapsule certainly had a remarkably adverse impact on the patient outcome. Accessibility in use and cost makes pseudocapsule status a potential cost-effective parameter in clinical practice.

Key Words: kidney; carcinoma, renal cell; neoplasm invasiveness; fascia; mortality

Abbreviations and Acronyms

MVI = microvascular invasion
OS = overall survival
PFS = progression-free survival
PS = pseudocapsule
RCC = renal cell carcinoma

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THE relationship between the cancer mass and the surrounding fibrous barriers to a great extent defines disease severity. In kidney cancer breaking through the renal capsule and through Gerota's fascia are crucial events in malignancy progression, resulting in notably poorer survival. Even mere invasion of the renal capsule without penetration has a remarkably adverse impact.[1–4] Curiously, when characterized by a fibrous capsule that delimits cancer from renal parenchyma,

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RCC has been little described in the literature in regard to whether and how the first capsule (PS) impacts patient outcome, although PS involvement was frequent.[5]

In 2014 Minervini et al noted in a cohort mainly composed of localized RCC cases that PS involvement was not an independent prognostic feature.[6] In contrast, in 2016 Volpe et al found a remarkably increased risk of cancer specific death for an involved capsule.[7] These studies had a limited number of patients, mainly focused on localized stage and differed in capsule classification. In addition, a small subset of RCC tumors lacking PS was observed early but whether they resulted in a different clinical outcome was never answered.

In this study we sought to determine whether and how PS status, including the extent of PS invasion and a lack of PS, had prognostic implications for RCC in a large cohort at a single institution in Shanghai, China.

MATERIALS AND METHODS

We reviewed the records of 1,577 patients who underwent radical, partial or cytoreductive nephrectomy at our institution between 2006 and 2011. No metastatectomy or enucleation was performed. Partial surgery was done with approximately 5 mm or more normal tissue at the edge. All removed masses were pathologically verified to be RCC with negative margins. A total of 270 patients (17.1%) were excluded from analysis due to inadequate pathological/followup data on 241 and receipt of tyrosine kinase inhibitor therapy in 29, leaving 1,307 eligible for analysis. The Zhongshan Hospital Clinical Research Ethics Committee approved this study.

Clinicopathological data were collected from archived records. TNM stage was determined by the 2010 AJCC (American Joint Committee on Cancer) TNM classification. According to the experience of previous studies[5,8] PS status was assessed and finally affirmed by 1 senior genitourinary pathologist. The extent of PS invasion was classified into 3 grades, including grade 0—completely intact PS, grade 1—PS involved but not penetrated and grade 2—completely penetrated PS (supplementary fig. 1, http://jurology.com/). Sometimes the "jumping phenomenon of tumor nest" could be observed. PS thickness was determined as the mean of at least 3 PS images for each tumor. Of note, to ensure that the PS was being studied all assessments were done with parenchyma on the other side.

For localized disease abdominal imaging and chest radiography were performed twice annually for the first 3 years and once annually thereafter. For locally advanced disease the schedule was every 3 months for year 1 and twice annually for another 2 years before shifting to once per year. Metastatic disease was monitored every 4 to 6 weeks. In each individual the schedule may have temporarily been enhanced for a specific reason such as a new complaint.

The main study end points were OS and PFS calculated from the day of surgery. Progression was determined by computerized tomography or magnetic resonance imaging.

For statistical analyses we used the chi-square test, the Student t-test and ANOVA to evaluate associations among the listed variables. Thickness was compared by the Mann-Whitney test. The Kaplan-Meier method and the log rank test were used to determine survival rates and differences among groups. With the Cox proportional hazards model univariate and multivariate analyses were performed to determine the HR and the corresponding 95% CI. We considered $p < 0.05$ to be significant. All analyses were done in the R, version 3.3.2 (https://www.r-project.org/) statistical environment.

RESULTS

Of the 1,307 cases 964 (73.8%) were localized (TNM I + II) and the other 343 (26.2%) were advanced (TNM III + IV), including 38 cases with initial metastases (M1). The clear cell phenotype dominated, noted in 82.6% of cases. Mean patient age was 55 years and mean followup was 71 months. Supplementary table 1 (http://jurology.com/) lists the clinical and pathological features of the cohort.

A total of 1,244 patients (95.2%) presented with PS, including 350 (28.1%), 643 (51.7%) and 251 (20.2%) with grade 0, 1 and 2 PS invasion, respectively. Average thickness was 0.46 mm. It was obvious that a thin PS was less resistant to cancer involvement (supplementary fig. 2, http://jurology.com/). PS invasion reached the highest level in chromophobe tumors, followed by papillary and clear cell tumors. A significant association of PS invasion was also detected with TNM stage, tumor size, MVI and necrosis. Specifically there was a remarkably unbalanced distribution of PS invasion with respect to venous thrombus and regional lymph node involvement (supplementary table 2, http://jurology.com/). The proportion of grade 2 PS doubled in pN1 cases compared to the remainder (40.9% vs 19.8%). Also, half of cases with venous tumor thrombus showed grade 2 PS with no case of grade 0. The incidence was 19.8% and 28.5%, respectively, in contrasting populations.

In 63 patients (4.8%) there was a microscopic lack of PS. It was found most in chromophobe tumors. Of cases of absent PS 25.4% were Fuhrman grade 4, 19.0% were Fuhrman grade 3 and 55.6% were Fuhrman grade 1 + 2, markedly different from cases with PS (9.5%, 22.6% and 68.0%, respectively, $p = 0.008$). Absent PS was also associated with TNM stage and MVI but not with necrosis, tumor size, venous thrombus or pN stage (supplementary tables 2 and 3, http://jurology.com/). Notably we noted absent PS in more females than males (6.6% vs 4.0%, $p = 0.0469$).