Classification of Histologic Patterns of Pseudocapsular Invasion in Organ-Confined Renal Cell Carcinoma

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Abstract

A standardized histologic definition and classification of the patterns of renal tumor pseudocapsular invasion (RTPI) in renal cell carcinoma (RCC) is not available. We classified RTPI into 2 main histologic patterns: expansive and infiltrative RTPI. Patients with organ-confined RCC and infiltrative RTPI had a greater risk of cancer-specific death and might require stricter postoperative surveillance strategies.

Introduction: A standardized histologic definition and classification of patterns of renal tumor pseudocapsular invasion (RTPI) in renal cell carcinoma (RCC) is not available. The aim of the present study was to propose a classification of RTPI patterns and assess their correlation with other pathologic features and prognosis. **Patients and Methods:** The renal tumor pseudocapsule was assessed by 2 expert genitourinary pathologists on the histologic slides of 190 specimens from radical nephrectomy performed for organ-confined (pT1-pT2) RCC. The histologic patterns of RTPI were classified and described. The association between the RTPI patterns and other pathologic features was assessed. The Kaplan-Meier method was used to calculate the survival functions, and Cox regression models were used to assess the predictors of cancer-specific survival. **Results:** RTPI was classified into 2 main histologic patterns (expansive and infiltrative). Expansive and infiltrative RTPI was observed in 39.5% and 51.6% of cases, respectively. A significant association between the RTPI pattern and Fuhrman grade ($P = .006$) and RCC histologic subtype ($P = .034$) was detected. Patients with infiltrative pseudocapsular invasion had significantly poorer 5- and 10-year cancer-specific survival rates than patients with expansive invasion or no invasion (93.6% vs. 98.9% and 84.9% vs. 93%, respectively; $P = .039$). The presence of infiltrative pseudocapsular invasion was a significant predictor of cancer-specific survival (hazard ratio 4.38, 95% confidence interval 1.04-20.27). **Conclusion:** An expansive and an infiltrative RTPI pattern can be described. In our study, patients with organ-confined RCC and an infiltrative RTPI pattern had a greater risk of cancer-specific death and might require stricter postoperative surveillance strategies.

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Introduction

The incidence of renal cell carcinoma (RCC) has been increasing in the past decades.[1] Although most RCCs are organ confined at diagnosis, about 20% of patients undergoing nephrectomy will progress to metastatic disease during the follow-up period. In the past few years, the identification of the predictors of tumor progression after surgery has become important to allow tailoring follow-up strategies and select patients for adjuvant treatment in clinical trials.

TNM stage and Fuhrman grade are known as the most powerful prognostic factors of cancer-specific survival (CSS) after surgical

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treatment of RCC.[2-4] Other histologic characteristics have been studied for their prognostic impact, including tumor histologic subtype, coagulative necrosis, microvascular invasion, sarcomatoid differentiation, and invasion of the renal capsule on the perinephric side.[5,6]

In contrast, limited information is available on the prognostic role of tumor invasion of the fibrous pseudocapsule that completely surrounds renal neoplasms.[7,8] Different histologic variants of renal tumor pseudocapsular invasion (RTPI) have been observed, which might potentially predict different biologic and clinical behavior of RCC. However, a standardized histologic definition and classification of RTPI patterns is not currently available.

In the present study, we reviewed the pathologic slides and the clinical information from a consecutive cohort of patients who had undergone radical nephrectomy (RN) for organ-confined RCC with the aim of describing and classifying the histologic patterns of RTPI and evaluating their correlation with other histologic features and prognosis.

Patients and Methods

Study Population

We retrospectively reviewed the records of 308 patients who had undergone open or laparoscopic RN at 2 academic centers from January 2000 to April 2010. Patients with organ-confined (pT1-pT2), pathologically confirmed RCC according to the 2002 American Joint Committee on Cancer (AJCC) TNM classification were considered eligible for the present study.[9] Patients were excluded if the histologic slides were missing, lost, or not suitable for pathologic review. The histologic material was considered insufficient when < 3 slides with tumor surrounded by the pseudocapsule were available. When the tumor size was < 25 mm, < 3 slides were considered sufficient if the whole lesion was included in the slide. Patients were not eligible if the pathologic revision identified a benign tumor, venous invasion, or infiltration of the perinephric or sinus fat, Gerota fascia, adrenal gland, regional lymph nodes, or surrounding organs. All patients preoperatively underwent chest radiography and abdominal computed tomography (CT). Patients with evidence of distant metastatic disease at diagnosis were excluded. The oncologic follow-up protocol included abdominal imaging (CT scan or ultrasonography) and chest radiography every 6 months for 3 years and yearly thereafter.

Overall, 190 patients were considered eligible for the study and included in the analysis. The study was performed in accordance with the principles of the Declaration of Helsinki. For each patient, the demographic, clinical, and pathologic data were collected into a dedicated database.

Pathologic Assessment

At nephrectomy, all specimens were fixed in 4% formaldehyde, and representative tumor fragments were embedded in paraffin and stained according to standard methods (hematoxylin-eosin). Two expert genitourinary pathologists (E.B., C.B.) reviewed all pathologic specimens. The following traditional histologic variables were assessed: histologic subtype according to the World Health Organization 2004 classification,[10] tumor grade according to the Fuhrman classification,[11] presence of intratumoral necrosis, and presence of sarcomatoid differentiation. When the results were not concordant, the 2 reviewers reached a consensus after further examination of the slides.

The tumor pseudocapsule was thoroughly evaluated in all cases and the presence of RTPI assessed. After collegial discussion, a classification of RTPI patterns was defined, and the histologic features of the different variants were carefully described.

Statistical Analysis

The association between RTPI and the available clinical and pathologic features was assessed using the χ^2, Fisher's exact, and Kruskal-Wallis tests for categorical and continuous variables, as appropriate. For this purpose, RTPI was classified into 3 groups: no RTPI, expansive RTPI, and infiltrative RTPI.

The cause of death was determined by the treating physician, a review of the medical records corroborated by the death certificate, or from the death certificate alone. The Kaplan-Meier method was used to calculate survival functions, and differences were assessed using the log-rank test. Patients alive and disease free were censored. Univariable Cox regression models were used to assess the predictors of CSS after RN. Statistical significance was set at $P \leq .05$. All reported P values are 2-sided. Statistical analysis was performed using SPSS statistics, version 20 (SPSS Inc, Chicago, IL).

Results

Patient and Tumor Characteristics

The patient and tumor characteristics are listed in Table 1. RN was performed using a laparoscopic approach in 94 patients (49.5%) and an open approach in the remainder. RCC was stage pT1 in 148 patients (77.9%) and low-grade (Fuhrman grade I-II) in 155 patients (81.6%). Most RCCs (82.1%) had a clear cell histotype. Coagulative necrosis was observed in 60 cases (31.6%) and sarcomatoid differentiation in only 1 case.

Pathologic Assessment and Classification of RTPI Patterns

A tumor pseudocapsule completely surrounded all the tumors and was a dense and continuous layer of connective tissue. RTPI was considered absent when the pseudocapsule was regular and continuous, with homogeneous thickness and an absence of tumor spikes (Figure 1A). Two main patterns of RTPI were defined: expansive RTPI (Figure 1B,C) and infiltrative RTPI (Figure 1D-H). Expansive RTPI was characterized by the presence of tumor cells that abutted the pseudocapsule, which, however, remained regular, well defined, and without breaks. In such cases, the pseudocapsule could be thinned (Figure 1B) or show undulations (Figure 1C). Infiltrative RTPI was characterized by the presence of tumor cells penetrating into the pseudocapsule with spikes that reached varying depths. Different variants of infiltrative RTPI could be described. These included as follows: a pseudocapsule of variable thickness with irregular undulations or erosions (Figure 1D); the presence of neoplastic spikes that penetrated the pseudocapsule perpendicularly without breaking it (Figure 1E); the presence of neoplastic spikes that penetrated the pseudocapsule horizontally without breaking it (Figure 1F); the presence of tumor cells almost completely penetrating the pseudocapsule (Figure 1G); and the presence of tumor cells completely penetrating the pseudocapsule (Figure 1H). Expansive or infiltrative RTPI using these defined histologic criteria was observed in 39.5% and 51.6% of the cases, respectively.