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Original contribution

Prognostic significance of extensive necrosis in renal cell carcinoma☆

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Summary Few studies using the current classification of renal cell carcinoma (RCC) have looked at a large number of cases with near total necrosis. We identified 21 cases of resections of RCC with >90% necrosis from the archives of Johns Hopkins Hospital between 2000 and 2015. Patients' mean age was 59 years (43-77) with 16 men (76%); 12 cases (57%) were papillary RCC, 4 clear cell papillary RCC (19%), 4 clear cell RCC (19%), and 1 unclassified with sarcomatoid differentiation (5%). International Society of Urological Pathology (ISUP) nucleolar grade was grade 1 (9 cases) or grade 2 (9 cases). Two cases were ISUP nucleolar grade 3, and 1 case was grade 4. Pathological stage was low (pT1-2) in 20 (95%) with the unclassified RCC with sarcomatoid differentiation RCC stage pT3a. Mean tumor size was 6.3 cm (1.2-17). In 52% (11) of cases, it was difficult to identify viable tumor, requiring multiple sections; 4 cases of papillary RCC were diagnosed in part due to necrotic tumor "ghost" architecture. Follow-up was available in 17 cases (81%) with a mean follow-up of 59 months. Thirteen patients (62%) are alive without disease. The patient with unclassified carcinoma with sarcomatoid differentiation died of cancer, and 2 died due to causes unrelated to cancer. One patient (5%) with low-grade clear cell RCC developed metastases but had a contralateral RCC. In the setting of a low-grade RCC, extensive necrosis does not have an adverse prognosis. In summary, our data, together with a prior study from our institution, comprise one of the largest cohorts of extensively (>90%) necrotic RCCs and suggests that in the setting of a low-grade RCC, it portends a good prognosis (only 2/36 cases showing progression (6%) on follow-up). However, we did identify a single case of high-grade RCC with an adverse prognosis and therefore, careful attention to tumor grade and classification is critical. The presence of tumor necrosis as a prognosticator in RCCs is complex, and despite its well-accepted role as an indicator of poor prognosis, our data would suggest otherwise under specific conditions. Importantly, in diagnosing a renal mass with extensive cystic necrosis, careful and extensive sampling to identify small foci of viable tumor or "ghost" architecture may be necessary for classification. As such, evaluation of its presence should not only be quantitative, but critical attention should be made to tumor grade and stage, whereby in high-grade carcinomas, necrosis likely imparts a worse prognosis; however, in low-grade carcinomas with extensive necrosis, the histological subtype, grade, and stage drive prognosis.

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1. Introduction

The presence of histologic tumor necrosis is a well-accepted independent prognostic factor for patients with renal cell carcinomas, particularly clear cell renal cell carcinoma (CCRCC) [1-6] In CCRCC, tumor necrosis has been shown to be associated with higher grade and worse prognosis, and has been utilized clinically in scoring systems for quantifying the risk of metastasis as well as in algorithms for triaging patients for clinical trials using adjuvant therapy [7-10]. However, the literature has shown conflicting data with respect to its prognostic implications. It has been shown in several studies that necrosis in papillary renal cell carcinoma (PRCC) appears to have no association with a worse prognosis [4,11,12]. In other more recent larger studies, a statistically significant independent association has been found between tumor necrosis and adverse prognosis in PRCC [13,14]. There are numerous limitations amongst these studies, including small sample size, population selection and most importantly, reproducible assessment and quantification of tumor necrosis. Together these limitations have collectively contributed to the lack of cohesive and consistent findings.

In an earlier study from our institution, Brinker et al showed that when stratifying tumors by percent necrosis, there appeared to be an association between overall survival and extensive near total tumor necrosis. Cases with >99% renal cell carcinoma tumor necrosis had only rare disease progression relative to those patients with less extensive (>50%) necrosis [15]. Several follow-up studies appeared to corroborate this correlation between extensive necrosis and decreased overall disease-free survival relative to less necrotic or non-necrotic renal cell carcinomas [9,16]. Few studies have looked at a large number of renal cell carcinoma cases with near total necrosis containing only rare viable tumor clusters. Many of the earlier studies on this topic preceded the current classification of renal cell carcinoma, which has undergone a significant evolution over the last decade. Herein, we set out to evaluate extensive subtotal tumor necrosis and its association with tumor grade, subtype of renal cell carcinoma, and prognosis.

2. Materials and methods

We conducted a computer-based search to retrospectively identify all cases diagnosed as renal cell carcinoma with the terms “cystic” or “necrotic” or “cystically necrotic” from the archives of Johns Hopkins Hospital between 2000 and 2014 to screen for renal cell carcinoma with >90% necrosis. The study was approved by our institutional IRB. Available cases were reviewed and classified according to 2016 World Health Organization (WHO) system based on the consensus conference of the International Society of Urological Pathology (ISUP) [17]. Tumors were assigned an ISUP nucleolar grade [18]. Tumor staging was based on the seventh edition of American Joint Committee on Cancer (AJCC) cancer staging [19]. Other tumor characteristics were noted upon review, including size, difficulty of identifiable viable tumor, presence of calcifications including psammoma bodies, foamy macrophages, “ghost” (necrotic but architecturally intact) tumor cells, and any additional lesions.

Tumor necrosis was defined as the presence of microscopic coagulative tumor cell necrosis, characterized by homogeneous clusters and sheets of degenerating and dead cells (Fig. 1). Histologic changes such as cystic transformation, hyalinization, and fibrosis were not considered to represent necrosis. Necrosis was quantitatively assessed by “eyeball” estimation, and only nephrectomy specimens with >90% necrosis were included for the purposes of this study. As most cases were from consults, we could not rely on the gross findings and sampling, such that necrosis was assessed based on the histological sections.

Immunohistochemical (IHC) staining for cytokeratins (AE1/3, cytokeratin 7 [CK7]), CA IX, and racemase was performed in a limited number of cases for diagnosis and definitive classification.

A previous history of a needle biopsy was investigated for all cases. Survival data were retrieved and defined as the time (in months) from date of surgery to death. Patients with unavailable clinical follow-up from previous hospitals were searched on the Social Security Database Index for their reported death [20].

3. Results

Between 2000 and 2014, 37 cases were identified with 26 available for review. One case was a biopsy and was excluded. Of the remaining 25 cases, only 21 cases (84%) showed central necrosis involving >90% of the specimen and were included in the study. Patients ranged in age from 43 to 77 years (mean 58.5).

Central necrosis was characterized by necrotic debris, calcifications, fibrin, cholesterol clefts, and in a few cases ghost of tumor cells (Fig. 1A). Twelve cases (57%) were classified as PRCC (4 solid variant), 4 clear cell papillary renal cell carcinoma (CCPRCC) (19%), 4 clear cell renal cell carcinoma (CCRCC) (19%), and 1 unclassified renal cell carcinoma with sarcomatoid differentiation (5%) (Table 1, Fig. 1B-E, respectively). ISUP nucleolar grade was low in 18 (86%) cases, either grade 1 (9 cases) or grade 2 (9 cases). Two cases were ISUP nucleolar grade 3, and 1 case was grade 4 (Tables 1, 2). Tumor stage was low (1-2) in 20 (95%) cases with the unclassified renal cell carcinoma with sarcomatoid differentiation presenting at stage 3a (Table 1, Fig. 1B-D). Mean tumor size was 6.3 cm (range, 1.2-17 cm) (Table 1). Four PRCCs (19%) were diagnosed, in part, due to the presence of necrotic tumor “ghost” architecture (Fig. 2A and B). Five (24%) cases showed tumor calcifications with only 2 showing psammoma bodies (Fig. 1B). Tumors lacked a significant lymphoid response around the tumor. In 52% (11) of the tumors, it was