Grade Heterogeneity in Small Renal Masses: Potential Implications for Renal Mass Biopsy

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Abbreviations and Acronyms

ccRCC = clear cell renal cell carcinoma

HG = high grade

LG = low grade

pRCC = papillary renal cell carcinoma

RCC = renal cell carcinoma

RMB = renal mass biopsy

SRM = small renal mass

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Purpose: Understanding the degree of phenotypic heterogeneity in a small renal mass may have implications for interpreting renal mass biopsy data. In this study we quantify nuclear grade heterogeneity in small renal masses.

Materials and Methods: Our institutional renal mass database was queried for patients with T1a (less than 4 cm) renal masses stratified by the criteria of imaging diameter less than 2 cm or 2 cm or greater, clear cell or papillary histology, low grade (Fuhrman 1-2) or high grade (Fuhrman 3-4) with tissue available for review. Four consecutive specimens were chosen from each of the 8 strata for a total of 32. All specimens were reanalyzed and the highest Fuhrman grade present in each 10× powered field was recorded. A case was classified as heterogeneous if multiple grades were present and as discordant if the highest Fuhrman grade was present in less than 50% of the specimen.

Results: A median of 5 slides (IQR 3.5–7.5) and 59, 10× powered fields (IQR 34–109) were examined per patient. Overall 26 samples (81.3%) were heterogeneous, including 15 of 16 (93.8%) high grade specimens. Among all cases 10 (31.3%) were discordant and of high grade specimens 4 (25%) were discordant. Median fraction of low grade tissue in high grade specimens was 38.9% (IQR 12.2–57.2).

Conclusions: The majority of small renal masses demonstrated considerable nuclear grade heterogeneity. The greatest degree of heterogeneity and discordance was observed in high grade tumors. One should consider these findings when interpreting renal mass biopsy data as the risk of under sampling high grade tumors may not be insignificant.

Key Words: carcinoma, renal cell; biopsy; risk; neoplasm grading

The incidence of kidney cancer has increased steadily during the last several decades, driven by the increasing incidental detection of small renal masses on cross-sectional imaging.[1] While 70% to 80% of SRMs are renal cell carcinoma, only 20% to 30% of malignant SRMs harbor potentially aggressive RCC.[2] Because of the need for improved preoperative risk stratification, there has been a resurgence of interest in renal mass biopsy to guide the treatment of SRMs.[3,4] While RMB has historically been limited by a high nondiagnostic rate and concerns about complications and biopsy tract seeding, recent series have demonstrated improved

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safety and diagnostic accuracy using RMB for the detection of malignancy and histological subtype. However, RMB continues to have poor accuracy in assessing Fuhrman grade.[5–10]

The Fuhrman grading system is the most commonly used nuclear grading system in RCC, designating a grade of 1 to 4 based on nuclear size, irregularity and nucleolar prominence.[11] Along with stage it is a key determinant of the biological potential of RCC and it is used in multiple prognostic models.[12–14] During pathological analysis tumors are assigned the highest Fuhrman grade found within them, even when it is only a small component. While multiple grades can exist in the same tumor, the grade distribution is not typically reported. Given the range of management options available for SRMs, knowledge regarding the distribution of Fuhrman grade in a tumor may prove helpful in understanding the implications of a RMB result. Therefore, in this study we characterize the intratumor distribution of Fuhrman grades in SRMs and define the amount of grade heterogeneity in these lesions.

METHODS

Our institutional review board approved renal mass database was queried for consecutive T1a renal masses (4 cm or less), stratified by the criteria of imaging diameter less than 2 cm or 2 cm or greater, clear cell or papillary histology, and low grade (Fuhrman 1-2) or high grade (Fuhrman 3-4). Four consecutive specimens were chosen from each stratum from the resultant $2 \times 2 \times 2$ table for a total of 32 specimens. All specimens corresponded to patients presenting with localized disease and treated surgically with negative margins.

The primary end point was the distribution of Fuhrman grade in each tumor. All archived pathology slides were reanalyzed by a single genitourinary pathologist. Each specimen had previously been sectioned per the institutional protocol and in accordance with established international guidelines,[10,15,16] ensuring that at least 1 representative section per cm tumor was analyzed, with a minimum of 3 sections per specimen. Additional slides were cut at the discretion of the grossing pathologist in areas suspicious for necrosis or fat invasion. Each slide containing tumor was analyzed in its entirety and divided into 10× powered fields. Each field was graded according to the Fuhrman grading system.[11,17] When more than 1 grade was present in a field, it was assigned the highest grade present in the field.

Specimens were classified as heterogeneous when more than 1 Fuhrman grade was present in the tumor. A specimen was designated as discordant when the highest Fuhrman grade was present in less than 50% of the specimen. The threshold for detecting the highest grade present in a specimen was calculated by summing the proportion of the specimen assigned a Fuhrman grade less than the overall grade of the specimen. Analyses were performed using a 4-tier and 2-tier grading system by combining Fuhrman grades 1-2 into a LG group and grades 3-4 into a HG group.[18] Analyses for the 2-tier grading system were restricted to HG tumors, since by definition no LG tumors contained HG components.

The data were characterized with descriptive statistics. Continuous variables were compared with the Mann-Whitney U test and categorical variables were compared with Fisher's exact test. All analysis was performed with Stata® 13 and 2-sided $p < 0.05$ was considered statistically significant.

RESULTS

From 32 specimens a total of 190 slides and 2,694 10× powered fields were examined. A median of 5 slides (IQR 3.5–7.5) and 59, 10× powered fields (IQR 34–108.5) were analyzed per specimen. Two specimens were up staged to pathological T3a on final pathology because of perinephric fat invasion. All other specimens were pathological T1a. There were no changes in histological subtype, final Fuhrman grade or pathological stage on rereview. Overall 26 samples (81.3%) were heterogeneous. Among HG specimens 15 of 16 (93.8%) were heterogeneous, with all 15 samples containing a LG component. Figure 1 illustrates grade heterogeneity in 2 representative patients. Heterogeneity was similar in pT1a and pT3a tumors (24 of 30 [80%] vs 2 of 2 [100%], $p = 1.0$). Discordance was observed in 10 of 32 (31.3%) cases, and was similar for histological types (papillary 25% vs clear cell 37.5%, $p = 0.446$) and size groups (less than 2 cm 25% vs 2 cm or greater 37.5%, $p = 0.446$). Among HG specimens 5 of 16 (31%) were discordant. Using a 2-tiered Fuhrman grading system, discordance was seen in 25% of specimens with no differences across size or histology strata. Table 1 summarizes heterogeneity and discordance as well as the threshold to detect the highest tumor grade across strata.

Among all specimens the median fraction of tissue that was assigned a Fuhrman grade less than the overall grade of the specimen was 36.8% (IQR 8.8–60.5). When limiting the analysis to only HG specimens, the median fraction of tissue that was assigned a Fuhrman grade less than the overall grade of the specimen increased to 40.6% (IQR 23.3–69.6). After combining grades 3-4 into a composite HG group, the median fraction of LG tissue in HG specimens was 38.9% (IQR 12.2–57.2). Figure 2 shows the grade distribution for each specimen.

With a median followup of 1 year, 1 patient had disease recurrence (distant metastasis) 22 months after surgery and died of disease at 26 months postoperatively. This patient had a 4 cm Fuhrman grade 4 pRCC tumor. The proportion of LG component in this tumor was 86%.

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