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Original article

Is anatomic complexity associated with renal tumor growth kinetics under active surveillance?

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Abstract

Introduction: Linear growth rate (LGR) is the most commonly employed trigger for definitive intervention in patients with renal masses managed with an initial period of active surveillance (AS). Using our institutional cohort, we explored the association between tumor anatomic complexity at presentation and LGR in patients managed with AS.

Methods and materials: Enhancing renal masses managed expectantly for at least 6 months were included for analysis. The association between Nephrometry Score and LGR was assessed using generalized estimating equations, adjusting for the age, Charlson score, race, sex, and initial tumor size.

Results: Overall, 346 patients (401 masses) met the inclusion criteria (18% $\geq$ cT1b), with a median follow-up of 37 months (range: 6–169). Of these, 44% patients showed progression to definitive intervention with a median duration of 27 months (range: 6–130). On comparing patients managed expectantly to those requiring intervention, no difference was seen in median tumor size at presentation (2.2 vs. 2.2 cm), whereas significant differences in median age (74 vs. 65 y, $P < 0.001$), Charlson comorbidity score (3 vs. 2, $P < 0.001$), and average LGR (0.23 vs. 0.49 cm/y, $P < 0.001$) were observed between groups. Following adjustment, for each 1-point increase in Nephrometry Score sum, the average tumor LGR increased by 0.037 cm/y ($P = 0.002$). Of the entire cohort, 6 patients (1.7%) showed progression to metastatic disease.

Conclusions: The demonstrated association between anatomic tumor complexity at presentation and renal masses of LGR of clinical stage 1 under AS may afford a clinically useful cue to tailor individual patient radiographic surveillance schedules and warrants further evaluation.

Keywords: Active surveillance; Renal cell carcinoma; Nephrometry Score; Tumor complexity; Growth kinetics; Renal tumor

1. Introduction

The management of small renal masses (SRMs) has dramatically evolved over the past 2 decades. Clinically localized stage I SRMs represent a heterogeneous entity, with 20% being benign masses, 60% indolent cancer, and 20% to 25% representing potentially aggressive cancers [1,2]. Although surgical excision is the standard of care for localized renal tumors [3], there is growing recognition that

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surgical intervention in the elderly and comorbid may not demonstrate significant improvement in overall survival and cancer-specific survival [4,5]. As a result, an initial period of active surveillance (AS) has emerged as an attractive alternative management strategy in patients with substantial competing risks to mortality who are poor candidates for definitive intervention.

The cumulative literature supporting AS is still in its infancy [6–8] and consists largely of institutional retrospective experiences. In the absence of standardized AS algorithms, tumor growth kinetics (predominantly linear growth rate [LGR]) is often used to guide the frequency of surveillance imaging and the need for definitive intervention [7,9–13]. To date, no radiographic characteristics at presentation have been identified that are associated with LGR. However, there is emerging evidence to suggest that anatomic complexity features of enhancing renal masses are associated with malignant and high-grade pathology at the time of surgical resection [14–16]. Our aim in this study was to examine the association between tumor anatomic complexity defined by Nephrometry Score (NS) at initial presentation and LGR in patients managed with an initial period of AS.

2. Methods and materials

2.1. Patient selection

Our institutional, prospectively maintained, kidney cancer database at Fox Chase Cancer Center was queried to identify enhancing solid and cystic renal masses managed expectantly from 2000 to 2013. Hereditary disease, biopsy-proven non–renal cell lesions, and urothelial cell carcinomas were excluded from analysis. Only localized tumors managed expectantly with a minimum of 2 imaging studies over a 6-month interval were included for analysis.

2.2. Surveillance protocol

Patients were stratified by absolute, relative, and elective indications for AS, as previously described [11]. Surveillance imaging was performed per institutional preference: 3- to 6-month intervals following initial diagnosis and then the restaging interval was increased to every 6 to 12 months, once stable growth kinetics were established [3]. NS was assigned and size comparisons were performed by the treating uro-oncologist using a consistent radiographic characteristic (maximum tumor diameter) across studies, while paying close attention to the cross-sectional cut from which the data were obtained [11]. Tumor LGR was defined as net change in diameter per year. Indications for delayed intervention included patient preference, change in tumor growth kinetics, change or improvement of comorbidity status, or development of tumor-related symptoms. Intervention was categorized as radical (open or laparoscopic approach) or nephron-sparing surgery (NSS) (open, laparoscopic, robotic-assisted laparoscopic approach, or ablative techniques).

2.3. Covariates and clinical outcomes

The patient and clinical characteristics examined included age (y), gender, Charlson comorbidity index (CCI), indication for AS, tumor size at presentation (cm), duration of AS (mo), radiographic tumor characteristics (solid vs. cystic), presence of multifocal renal tumors, LGR, surgical pathology, type and reason for intervention, NS [17], and progression to metastatic disease. Multifocal disease was defined as multiple tumors in 1 kidney or the presence of bilateral enhancing renal tumors.

2.4. Statistical analysis

The associations between categorical and continuous variables and tumor growth rate were assessed using the Wilcoxon rank sum and the Kruskal-Wallis tests. Categorical variables were analyzed using the chi-square test. Logistic regression was used to evaluate the association between clinical characteristics and progression to definitive intervention. The association between anatomic complexity (both individual components and summary score) and LGR was assessed using linear regression estimated by generalized estimating equations after controlling for the age, Charlson score, race, sex, and initial tumor size. generalized estimating equations was used to account for patients with more than 1 renal lesion under AS. Nominal $P = 0.05$ were used as the criterion for statistical significance. Analyses were conducted using the STATA software package (version 12; Stata Corporation, College State, TX).

3. Results

Of the 461 patients managed with AS in our institutional database, 346 (401 masses) were identified with renal tumors managed expectantly for at least 6 months. It was seen that 18% of the masses were larger than 4.0 cm (cT1b or larger). The patient demographic information and tumor characteristics are presented in Table 1. Indications for AS were categorized as elective (30%), relative (41%), and absolute (29%). Overall, 357 (89%) were solid lesions, and the remaining 11% were classified as Bosniak IIF, III, or IV cystic lesions. Additionally, 7 patients (2%) had a solitary affected kidney, 34 patients (10%) had bilateral renal tumors, and 24 (7%) had multifocal lesions. The median age was 71 years (mean = 67.8 ± 12.8; range: 40–94), 61% were men, and the median CCI was 2 (mean = 2.6 ± 2.0; range: 0–11). The median tumor size at presentation was 2.2 cm (mean = 2.6 ± 1.6; range: 0.5–13.7), and the median NS sum was 7 (mean = 6.9 ± 2.0, range: 4–12). The median number of images obtained during the length of AS was 4 (mean = 4.2 ± 2.4, range: 2–14).