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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 NS and LGR was assessed using generalized estimating equations, adjusting for age, Charlson score, race, sex, and initial tumor size.

Results—346 patients (401 masses) met inclusion criteria (18% cT1b), with a median follow-up of 37 months (range: 6-169). 44% of patients progressed to definitive intervention with a median duration of 27 months (range: 6-130). Comparing patients managed expectantly to those requiring intervention, no difference was seen in median tumor size at presentation (2.2 vs. 2.2 cm), while significant differences in median age (74 vs. 65 years, $p<0.001$), Charlson co-morbidity score (3 vs. 2, $p<0.001$), and average LGR (0.23 vs. 0.49 cm/year, $p<0.001$) were observed between groups. Following adjustment, for each 1-point increase in NS sum, the average tumor LGR increased by 0.037 cm/year ($p=0.002$). Of the entire cohort, 6 patients (1.7%) progressed to metastatic disease.

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Conclusions—The demonstrated association between anatomic tumor complexity at presentation and LGR of clinical stage 1 renal masses 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

Introduction

The management of small renal masses (SRM's) has dramatically evolved over the past two decades. Clinically localized stage I SRMs represent a heterogeneous entity, with 20% being benign masses, 60% indolent cancer, and 20-25% representing potentially aggressive cancers.^{1, 2} Although surgical excision is the standard of care for localized renal tumors³ there is growing recognition that surgical intervention in the elderly and co-morbid may not demonstrate significant improvement in overall (OS) and cancer specific survival (CSS).^{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 that 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)) are often used to guide the frequency of surveillance imaging as well as 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.

Methods and Materials

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 two imaging studies over a six-month interval were included for analysis.

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

6-12 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 was 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).

Covariates and Clinical Outcomes

Patient and clinical characteristics examined included age (years), gender, Charlson comorbidity index (CCI), indication for AS, tumor size at presentation (cm), duration of AS (months), radiographic tumor characteristics (solid versus 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 one kidney or the presence of bilateral enhancing renal tumors.

Statistical Analysis

The associations between categorical and continuous variables and tumor growth rate were assessed using the Wilcoxon rank sum and Kruskal-Wallis tests. Categorical variables were analyzed using chi-square tests. 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 (GEE), controlling for age, Charlson score, race, sex, and initial tumor size. GEE was used to account for patients with more than one renal lesion under AS. Nominal *p* values of 0.05 were used as the criterion for statistical significance. Analyses were conducted using the STATA software package (version 12; Stata Corporation, College Station, Texas).

Results

Of 461 patients managed with AS in our institutional database, 346 patients (401 masses) were identified with renal tumors managed expectantly for at least 6 months. Eighteen percent of the masses were larger than 4.0 cm (cT1b or larger). Patient demographic information and tumor characteristics are presented in table 1. Indications for AS were categorized as elective (30%), relative (41%), and absolute (29%). 357 (89%) were solid lesions while the remaining 11% were classified as Bosniak IIF, III or IV cystic lesions. Seven patients (2%) had a solitary kidney, 34 patients (10%) had bilateral renal tumors, and 24 (7%) had multifocal lesions. The median age was 71 (mean 67.8 ±12.8; range, 40-94), 61% were male, and the median CCI was 2 (mean, 2.6±2.0; range, 0-11). 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). Median number of images obtained during the length of AS was 4 (mean, 4.2±2.4, range 2-14). During a median follow up of 37 months (mean 44± 32,

range 6-169), the median linear growth rate was 0.24 (mean 0.36 ± 0.35 , range 1.2-2.2) cm/year and 19% of renal masses demonstrated no growth over time.

Total of 194 patients (56.1%) were managed solely with AS, while 152 (43.9%) patients (183 masses) progressed to definitive intervention at a median duration of 27 (35 ± 26) months. Indications for progressing to definitive intervention were patient choice (55%), interval tumor growth (37%), medical clearance (5%), and development of tumor related symptoms (1 patient). Pre-surveillance biopsy was performed on 57 (16.5%) of the renal masses. Pathology results from needle core biopsy revealed clear cell RCC in 41 (72%), oncocytoma in 9 (16%), papillary in 5 (9%) and chromophobe in 2 (3%) patients respectively. Of patients progressing to definitive intervention, 87% underwent NSS (partial nephrectomy [$n=132$] or ablation [$n=27$]), and 63% were treated with a minimally invasive surgery approach. 1 patient underwent simultaneous RN at the time of esophagectomy for esophageal carcinoma. Malignant renal cell carcinoma was confirmed in 73% (133/183), while oncocytoma (13%), benign cortical cyst (8%), and lipid poor angiomyolipoma (5%) were documented in those with benign lesions (Table 2). Among those managed solely with AS, a total of 21 patients (10%) were deceased at the last follow-up, all of other causes. In the entire cohort, a total of 6 patients (1.7%) progressed to metastatic disease, of which one was after surgical intervention.

Comparing patients who remained on AS to those requiring surgical intervention, no difference was seen in median tumor size at presentation (2.2 vs. 2.2 cm), while significant differences in median age (74 vs. 65 years, $p<0.001$), CCI (3 vs. 2, $p<0.001$), and median LGR (0.16 vs. 0.43 cm/year, $p<0.001$) were observed between the two groups (Table 1). Although overall anatomic complexity, quantified by the NS, was not different between the two cohorts (7 vs. 7, $p=0.7$), masses which underwent delayed intervention were more likely to be abutting the hilar vessels ($p=0.010$), and closer to the collecting system ($p=0.002$) compared to those managed expectantly (Table 3).

Sub-analysis restricted to localized tumors greater than 4.0 cm (68 patients (18%); 72 tumors) showed that overall cT1b/T2 masses have a slightly faster growth rate, compared to cT1a masses (0.44 vs. 0.33 cm/year, $p=0.068$). The mean LGR for cT1b/T2 masses significantly differed between patients managed expectantly and those progressed to intervention (0.37 vs. 0.73 cm/year, $p=0.020$). 14.7% of cT1b/T2 masses demonstrated zero growth over time. Out of 68 patients, 23 (34%) progressed to definitive intervention. 31% of cT1b/T2 masses were biopsied during the course of management, and despite a period of AS, 65% underwent a NSS and 52% were treated with a MIS approach.¹³

Following adjustment, younger age (OR=0.98, 95% CI: 0.96-0.99, $p<0.0001$), fewer comorbidities (OR=0.86, CI: 0.79-0.93, $p<0.0001$), faster LGR (OR= 4.71, CI: 3.17-6.97, $p<0.0001$), and African American race (OR=1.53, CI: 1.09-2.14, $p=0.013$), demonstrated significant associations with receipt of delayed intervention (Table 4). In separate analyses evaluating the association between individual nephrometry score components and LGR, "R"adius ($p=0.002$), "E"xo/"E"ndophyticity ($p=0.047$), and "N"earness of tumor to the collecting system ($p<0.0001$) were each associated with increased LGR (Table 5). Following

adjustment, for each 1-point increase in NS sum, the average tumor LGR increased by 0.037 cm/year ($p=0.002$, Figure 1).

Discussion

Active surveillance of SRMs has been incorporated into existing management algorithms¹⁸ and has favorable outcomes with intermediate follow up.¹² However, AS schedules are not standardized and are largely at the discretion of the individual physician, and the decision to intervene versus continue expectant management can be challenging. Current recommendations suggest cross sectional imaging at defined intervals (3-6 months), which may increase and transition to renal ultrasound as stability of the lesion is demonstrated.¹⁹ Although some clinicians advocate the use of percutaneous biopsy in the majority of patients for risk stratification, others selectively use renal biopsy in patients with absolute or relative indications or specific circumstances where nephron preservation is paramount such as synchronous bilateral lesions.²⁰

LGR is one of the more readily measured variable for patients with SRMs under AS undergoing repeat imaging. Available data indicates that LGR over time is the radiographic characteristic that has demonstrated the strongest association with progression to definitive intervention and there is empiric evidence to suggest an association with progression to metastases.¹² Similar to our prior reports,^{11, 13} the rationale for intervention in this series was predominantly rapid growth kinetics with approximately 44% of patients were ultimately managed surgically with a median delay to treatment of 27 months. Although there was a considerable variation (0-1.65 cm/year), when comparing tumor characteristics between lesions managed solely with AS and those that were not, those that progressed to definitive intervention demonstrated more rapid growth kinetics. As pooled data analysis have suggested,¹² the risk of progression to metastasis in our cohort while under observation was low (1.7%) but not negligible. Among these patients, the mean initial observed tumor size was 3.7 cm and demonstrated mean LGR of 0.88 cm/year. As associations between tumor size and metastatic potential have been reported²¹ and there is no evidence supporting that renal tumors with sequential growth metastasize while on AS,¹² those lesions demonstrating more rapid kinetics should either be managed by biopsy (for risk stratification) or surgical intervention.

Efforts have been made to harness radiographic tumor characteristics to help predict pathology and hence biology of disease. Even though no standardized definition of “exophytic” was provided, studies have suggested that “highly exophytic” tumors, when compared with central lesions, are more likely to be low grade²² and non-clear cell tumors.²³ Kutikov et al.,¹⁶ using a large institutional cohort, reported that all individual anatomic descriptor components of NS, with the exception of the anterior/posterior (A) designation, significantly differed between high and low grade disease as well as tumor histology groups. Furthermore, large series have demonstrated the correlation between increase in tumor diameter and presence of high-grade disease.^{24, 25} To date, no radiographic characteristics at the time of diagnosis have been identified that predict tumor growth rate. In our large contemporary institutional AS series, our results demonstrate that patients presenting with anatomically complex tumors are more likely to demonstrate rapid

growth kinetics when followed over time. Tomaszewski et al.²⁶ illustrated that compared with patients who underwent immediate surgical treatment, patients selected for AS had overall lower NS with tumor that were smaller, more often polar, further away from the urothelium, and less hilar. In lines with this hypothesis, when evaluating the association between individual NS components and LGR, “R”adius, “E”xo/“E”ndophyticity, and “N”earness of tumor to the collecting system were associated with increased LGR during the course of AS, suggesting for every point increase in NS the average tumor LGR increased by 0.037 cm/year.

While our results require external validation, our data suggest that tumor complexity at presentation may be useful in determining the optimal timing of surveillance imaging. For instance, in a patient with absolute indication for AS who has a biopsy proven low-grade and anatomically simple renal mass, it may be possible to increase the duration between imaging studies. Furthermore, imaging characteristics can be a clinically useful tool that can help in determining the initial course of management at the time of diagnosis, as a more anatomically complex lesion may influence clinician's decision to proceed with biopsy versus immediate treatment.

Although our findings suggest that tumor anatomic complexity is associated with observed growth kinetics, there are several limitations that warrant consideration. We report that tumor anatomic complexity is associated with receipt of delayed intervention; however, there maybe confounding factors which may limit generalization of our findings. The presented data is based on a single institution retrospective study and findings cannot be generalized without an external validation. Histology of majority of masses that were managed expectantly is unknown and biopsy was underutilized. Also, LGR was used as a continuous variable and tumor growth rates over discrete periods were not evaluated. In addition, individual urologic oncologists at our institution did not have a consistent criteria for enrollment into or termination of AS during the entirety of this study period. Despite these limitations, as part of multi-institutional efforts to standardize AS protocols for SRM's, our findings should be evaluated prospectively.

Conclusions

Our findings add to the growing literature that AS is safe as an initial short term management to define growth kinetics and assess risk. Our finding that NS is associated with LGR is novel, and supports the emerging consensus that anatomic complexity may be associated with malignant potential.

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Figure 1. Association between renal mass's anatomic complexity assessed by NS and linear growth rate.

Table 1
Patient Demographic Information & Tumor Characteristics

Patient Characteristics	Overall (%)	AS (%)	Surgical Intervention (%)	p- value
No. Patients	346	194 (56)	152 (44)	-
No. Tumors	401	218 (54)	183 (46)	-
Male Gender	210 (61)	116 (60)	94 (62)	0.74
Age (Median, Mean±SD, range)	71, 67.8±12.8, 40-94	74, 70.8±12.4, 40-94	65, 63.9±12.3, 40-87	<0.001
CCI (Median, Mean±SD, range)	2, 2.6 ± 2.0, 0-11	3, 3.0 ± 2.0, 0-11	2, 2.0 ± 1.8, 0-10	<0.001
Months of FU (Median, Mean±SD, range)	37, 44±32, 6-169	45.6, 57±35, 9-169	27, 35 ±26, 6-130	<0.001
Indication for AS:				<0.001
Elective	104 (30)	41 (21)	61 (40)	
Relative	142 (41)	85 (44)	56 (37)	
Absolute	100 (29)	68 (35)	35 (23)	

Tumor Characteristics	Overall (%)	AS (%)	Surgical Intervention (%)	p- value
Tumor Type (%):				.19
Solid	357 (89)	190 (87)	167 (91)	
Bosniak IIF, III or IV cyst	44 (11)	28 (13)	16 (9)	
Tumor Size on Presentation (cm)				
(Median, Mean ±SD, range)	2.2, 2.6±1.6, 0.5-13.7	2.2, 2.6±1.6, 0.5-9.7	2.2, 2.5±1.6, 0.6-13.7	0.93
Tumor Size at Last FU/Surgery (cm)				
(Median, Mean ±SD, range)	2.8, 3.3 ±1.9, 0.7-15.0	2.8, 3.3±2.0, 0.7-10.3	2.8, 3.2±1.9, 0.8-15.0	0.93
Nephrometry Score				
(Median, Mean ±SD, range)	7, 6.9 ±2.0, 4-12	7, 6.8 ±2.1, 4-12	7, 7.0 ±1.9, 4-11	0.66
No. Images During AS				<0.001
(Median, Mean ±SD, range)	4, 4.2±2.4, 2-14	4, 4.7±2.6, 2-14	3, 3.6±2.0, 2-14	
Linear Growth Rate				<0.001
(Median, Mean ±SD, range)				
Monthly (cm/month)	0.02, 0.03 ± 0.04, 0-0.18	0.01, 0.02 ± 0.02, 0-0.14	0.04, 0.04 ± 0.03, 0-0.18	
Annually (cm/year)	0.24, 0.36 ± 0.38, -1.2-2.2	0.16, 0.23 ± 0.28, -0.49-1.68	0.43, 0.49 ± 0.40, -0.91-2.2	
Zero Growth	76 (19)	59 (27)	26 (14)	
Clinical Stage:				0.06
cT1a	329 (82)	169 (78)	160 (87)	
cT1b	65 (16)	43 (20)	22 (12)	
cT2a	5 (1)	5 (1)	0	
cT2b	2 (1)	1 (1)	1 (1)	

Table 2
Pathologic Assessment in 183 patients who had delayed intervention

Pathology	No. (%)
Benign	50 (27)
Cortical Cyst	15 (8)
Oncocytoma	23 (13)
Angiomyolipoma	10 (5)
Fibroma/Adenoma	2 (1)
Malignant	133(73)
Clear Cell	79 (43)
Papillary	45 (25)
Chromophobe	9 (5)
Stage	
T0	15 (8)
T1a	136 (74)
T1b	16 (9)
T2a	2 (1)
T2b	2 (1)
T3a	12 (7)
Nuclear grade	
1	42 (23)
2	41 (22)
3	26 (14)
4	49 (27)
Unknown	25 (14)
Type of Surgery	
OPNx	65 (36)
ONx	2 (1)
LPNx	13 (6)
RALPNx	54 (30)
LNx	22 (12)
Ablation	27 (15)

OPNx: open partial nephrectomy; ONx: Open nephrectomy; LPNx: Laparoscopic Partial Nephrectomy; RALPNx: Robotic-Assisted Laparoscopic Partial Nephrectomy; LNx: Laparoscopic Radical Nephrectomy.

Table 3

Comparison of R.E.N.A.L. Nephrometry Scores between patients remained on AS vs. those underwent delayed intervention.

	Overall (n=401)	AS Patients (n=218)	Surgical Patients (n=183)	p-value
(R)adius				0.419
1	321 (80.3%)	171 (78.4%)	151 (82.5%)	
2	63 (15.7%)	37 (17.0%)	26 (14.2%)	
3	17 (4.0%)	10 (4.6%)	6 (3.3%)	
(E)xo/Endophytic				0.858
1	148 (36.9%)	73 (33.5%)	75 (41.0%)	
2	180 (44.9%)	107 (49.1%)	73 (39.9%)	
3	73 (18.2%)	38 (17.4%)	35 (19.1%)	
(N)earness of the tumor to the collecting system				0.002
1	167 (41.7%)	102 (46.8%)	65 (35.5%)	
2	68 (17.0%)	36 (16.5%)	32 (17.5%)	
3	166 (41.4%)	80 (36.7%)	86 (47.0%)	
(A)nterior/Posterior				0.529
A	187 (46.6%)	100 (45.9%)	87 (47.5%)	
P	165 (41.2%)	88 (40.4%)	77 (42.1%)	
X	49 (12.2%)	30 (13.8%)	19 (10.4%)	
(L)ocation relative to the polar lines				0.300
1	171 (42.6%)	98 (45.0%)	73 (39.9%)	
2	125 (31.2%)	62 (28.4%)	63 (34.4%)	
3	105 (26.2%)	58 (26.6%)	47 (25.7%)	
"H"ilar location (abutting main artery or vein)	31 (7.7%)	11 (5.1%)	20 (10.9%)	0.010

Table 4
Factors Associated with Receipt of Delayed Intervention

	OR (95% CI)	p Value
Tumor Growth Rate	4.71 (3.17-6.97)	<0.001
Charlson Comorbidity Index	0.86 (0.79-0.93)	<0.001
Age at presentation	0.98 (0.96-0.99)	<0.001
Race (Caucasian as reference)		
African American	1.53 (1.09-2.14)	0.013
Other	0.44 (0.9-2.21)	0.320
Initial Tumor Size on Presentation	1.01 (0.90-1.1)	0.853
Tumor Anatomic Complexity	0.83 (0.74-0.93)	0.042
Gender	1.08 (0.75-1.53)	0.676

Table 5
Association between R.E.N.A.L. Nephrometry Score variables and tumor linear growth rate

NS Variable:	Overall Cohort	
	Effect on LGR (cm/yr) Mean $\pm$ range, Median	p Value
(R)adius:		0.002
1	0.31 $\pm$ 0.30, 0.22	
2	0.53 $\pm$ 0.53, 0.37	
3	0.50 $\pm$ 0.50, 0.37	
(E)xo/Endophytic		0.047
1	0.30 $\pm$ 0.29, 0.23	
2	0.38 $\pm$ 0.41, 0.23	
3	0.38 $\pm$ 0.38, 0.32	
(N)earnes Tumor to Collecting System		<0.0001
1	0.26 $\pm$ 0.27, 0.18	
2	0.38 $\pm$ 0.37, 0.31	
3	0.43 $\pm$ 0.43, 0.34	
(A)nt/Posterior		0.21
A	0.37 $\pm$ 0.39, 0.27	
P	0.35 $\pm$ 0.37, 0.23	
X	0.28 $\pm$ 0.26, 0.22	
(L)ocation relative to Polar Line		0.28
1	0.32 $\pm$ 0.36, 0.20	
2	0.38 $\pm$ 0.36, 0.32	
3	0.36 $\pm$ 0.38, 0.26	
“H”ilar location (abutting main artery or vein)		0.058
Yes	0.49 $\pm$ 0.42, 0.46	
No	0.34 $\pm$ 0.36, 0.23	