Growth Kinetics of Small Renal Masses on Active Surveillance: Variability and Results from the DISSRM Registry

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Purpose: Active surveillance is emerging as a safe and effective strategy for the management of small renal masses (4 cm or less). We characterized the growth rate and its pertinence to clinical outcomes in a prospective multi-institutional study of patients with small renal masses.

Materials and Methods: Since 2009, the DISSRM (Delayed Intervention and Surveillance for Small Renal Masses) prospective, multi-institutional registry of patients with small renal masses has enrolled patients who elect primary intervention or active surveillance. Patients who elect active surveillance received regularly scheduled imaging and those with 3 or more followup images were included in the current study to evaluate growth rates.

Results: We evaluated 318 patients who elected active surveillance, of whom 271 (85.2%) had 3 or more followup images available with a median imaging followup of 1.83 years. The overall mean ± SD small renal mass growth rate was 0.09 ± 1.51 cm per year (median 0.09) with no variables demonstrating statistically significant associations. The growth rate and variability decreased with longer followup (0.54 and 0.07 cm per year at less than 6 months and greater than 1 year, respectively). No patients had metastatic disease or died of kidney cancer. No statistically significant difference was noted in the growth rate in patients with biopsy demonstrated renal cell carcinoma or in those who died.

Conclusions: Small renal mass growth kinetics are highly variable early on active surveillance with growth rates and variability decreasing with time. Early in active surveillance, especially during the initial 6 to 12 months, the growth rate is variable and does not reliably predict death or adverse pathological features in the patient subset with available pathology findings. An elevated growth

Abbreviations and Acronyms

AS = active surveillance

CT = computerized tomography

DISSRM = Delayed Intervention and Surveillance for Small Renal Masses

GR = growth rate

MRI = magnetic resonance imaging

PI = primary intervention

RCC = renal cell carcinoma

SRM = small renal mass

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rate may indicate the need for further assessment with imaging or consideration of biopsy prior to progressing to treatment. Additional followup will inform the best clinical pathway for elevated growth rates.

Key Words: kidney neoplasms, watchful waiting, diagnostic imaging, prognosis, mortality

Approximately 40% of all newly diagnosed renal tumors are less than 4 cm.[1–3] The discovery of a SRM (4 cm or less) poses a considerable challenge to patients and care providers. AS with scheduled serial imaging and clinical followup is emerging as a safe treatment strategy in patients who decline initial surgery or ablative treatment due to reasons such as multiple comorbidities, increased age or personal preference.[3,4]

Previous studies suggest that less than 2% of SRMs progress to metastatic disease with monitoring with serial imaging.[4–6] The SRM GR has been proposed as an objective correlate of tumor aggressiveness to guide patient treatment and serve as a potential trigger for intervention. In some retrospective analyses of patients who received delayed intervention for SRMs RCC was associated with an increased GR.[7–9] However, a prospective study demonstrated that RCC histology was not associated with increased GR and another analysis showed that oncocytoma was associated with faster GR.[4,10] Therefore, while existing evidence supports AS as a safe management strategy in some cases, the clinical implications of SRM GR are not adequately understood.

The DISSRM prospective registry was established in 2009 as a multi-institutional collaboration to prospectively evaluate outcomes in patients with SRMs who elect PI or AS. The goals of the registry include determining comparative effectiveness, identifying optimal patient selection criteria for AS and establishing triggers for intervention (crossing over from AS to delayed intervention). In the current analysis we evaluated GR as a potential trigger for intervention by assessing factors associated with GR and the correlation to clinical outcomes. At the initiation of the registry we hypothesized that patients with a higher GR would more frequently cross over to delayed intervention, have potentially unfavorable histopathology and experience death.

METHODS

Patient Population and Study Design

Since January 1, 2009 the DISSRM registry has prospectively enrolled patients with SRMs who chose to undergo PI or AS. The registry is institutional review board approved and currently open at our 3 institutions. Study design, power calculations and protocol were previously reported.[4,11]

Patients were 18 years old or older with a clinically localized, solid, contrast enhancing SRM on axial imaging (CT or MRI). Patients elected to receive immediate surgical or ablative treatment (PI) or undergo AS. Five patients with a tumor greater than 4 cm were allowed to enroll in AS based on age and comorbidities. Regardless of the choice all patients were followed prospectively from the time of study entry until death or loss to followup. Study exclusion criteria included a prior RCC history, the presence of a renal mass concerning for metastatic disease and a RCC syndrome family history.

Surveillance Protocol

Patients generally underwent repeat axial imaging (contrast enhanced axial CT or MRI) within 6 months of entering the registry.[11] At the inception of the study patients were recommended to undergo repeat axial imaging every 4 to 6 months for the first 2 years. Approximately 2 years into the protocol ultrasound was allowed as an alternative imaging modality for surveillance and typically recommended to alternate with axial imaging.

All images taken for the duration of each patient followup were reviewed and interpreted by genitourinary radiologists. For patients who elected ultrasound immediate axial imaging was recommended if a significant change in tumor size or another characteristic was noted. Patients were recommended to undergo delayed intervention (cross over) if the SRM progressed. Progression was defined as GR greater than 0.5 cm per year, tumor diameter greater than 4 cm, the development of metastasis or the personal decision to cross over to delayed intervention. Patients could also choose to remain on AS despite having progressed. After patients crossed over they no longer received surveillance imaging but were followed at clinical visits.

Data Collection, Analysis and Outcomes

Patient data from 2009 to 2016 were compiled. Tumor interval GR was calculated as the difference in tumor size between 1 followup image and the immediately preceding image divided by the elapsed time between images. This formula yielded an interval GR in cm per year. The average of all interval GRs was designated as the overall tumor GR. This variable was considered the primary outcome. Secondary outcomes included progression, tumor histopathology in patients who underwent biopsy and overall survival.

The Student t-test and the chi-square test were used to compare differences in baseline and tumor GR characteristics. Linear regression was done to identify variables associated with tumor GR. Tumor GR was analyzed as a continuous variable and as a disjoint ordinal variable divided into 4 categories, including accelerated—0.5 or greater, slow—greater than 0 to less than 0.5, dormant—0

or regressed—less than 0 cm per year. Data were analyzed with STATA®, version 13.

RESULTS

Study Population

At the time of administrative censoring 615 patients were enrolled in DISSRM and data were available on 318 (51.7%) who elected AS. Four of these patients were excluded from analysis due to inadequate imaging or other data. A total of 43 patients were excluded because they had fewer than 3 observations at which a followup image was obtained. Therefore, 271 patients were included in study.

Patient Characteristics

Table 1 shows the baseline characteristics of the overall study population, patients who remained on AS and the 38 who crossed over to delayed intervention. Patient age was the only variable that significantly differed between patients who remained on AS and those who crossed over (70.7 vs 66.5 years, p = 0.03).

Growth Rate

Figure 1 shows SRM growth patterns in the patients. Patients who crossed over to delayed intervention had greater mean GR (0.31 vs 0.05 cm per year, p = 0.32) and a higher average maximum interval GR (1.19 vs 0.78 cm per year, p = 0.15), although this was not statistically significant. Among all patients GR was less than 0 cm per year in 96 (35.4%), 0 cm per year in 18 (6.6%), 0 to 0.5 cm per year in 111 (41.0%) and 0.5 cm per year or greater in 46 (17.0%) (fig. 2). The proportion of patients with a positive GR (0 cm per year or greater) was significantly greater in crossover patients than patients on AS (p <0.01). The mean GR in all patients with less than 6 months of followup, which was a group consisting of predominantly recent study participants, was 0.54 cm per year (table 2). Mean interval GR and GR variability decreased following the first 6 months in all patients, including a mean of 0.07 cm per year in patients on AS greater than 1 year. Figure 3 shows an approximately similar distribution of GRs above and below the 0 cm per year line.

Table 1. *Patient demographics in DISSRM registry*

	Overall	Active Surveillance	Crossovers	p Value
No. pts	271	233	38	
Mean ± SD age	—	70.7 ± 10.6	66.5 ± 11.1	0.03
No. male (%)	156 (57.6)	134 (57.5)	22 (57.9)	0.97
No. race (%):*				
White	213 (78.6)	179 (79.6)	34 (89.5)	0.61
Black	41 (15.1)	38 (17.2)	3 (7.9)	
Other	8 (0.03)	7 (3.04)	1 (2.6)	
No. Charlson comorbidity index (%):				
0	119 (43.9)	105 (45.1)	14 (36.8)	0.24
1	68 (25.1)	55 (23.6)	13 (34.2)	
2	42 (15.5)	40 (17.2)	2 (5.3)	
3	20 (7.4)	16 (6.9)	4 (10.5)	
4+	22 (8.1)	17 (7.3)	5 (13.2)	
No. smoking (%):				
Never	153 (56.5)	133 (57.1)	20 (52.6)	0.75
Active	21 (7.8)	17 (7.3)	4 (10.5)	
Former	97 (35.8)	83 (35.6)	14 (36.8)	
1st Imaging (%):				
CT	170 (62.7)	146 (62.7)	24 (63.2)	0.77
MRI	71 (26.2)	60 (25.8)	11 (29.0)	
Ultrasound	30 (11.1)	27 (11.6)	3 (7.9)	
Mean ± SD tumor size (cm):				
2 or Less	167 ± 61.6	143 ± 61.4	24 ± 63.2	0.62
Greater than 2—3	74 ± 27.3	66 ± 28.3	8 ± 21.1	
Greater than 3—4	23 ± 8.5	18 ± 7.7	5 ± 8.5	
Greater than 4	7 ± 2.6	6 ± 2.6	1 ± 2.6	

* Data available on 262 patients.

Factors Associated with Growth Rate, Biopsy Histology and Death

No patient specific variables or changes in imaging modalities during followup were significantly associated with GR (supplementary tables 1 and 2, http://jurology.com/). Furthermore, when GR was recoded as a binary variable (0.5 or greater and less than 0.5 cm per year), no variables were significantly associated with GR.

Table 2 shows the tumor characteristics of 33 patients with percutaneous biopsy data. Of these patients 24 remained on AS for the duration of followup while 9 crossed over. Although patients with biopsy demonstrated RCC had a higher GR than patients with oncocytoma, this difference was not statistically significant (p = 0.11).

In the study set 28 patients died but none died of kidney cancer or experienced metastasis. Mean GR was 0.41 cm per year in patients who died and 0.05 cm per year in survivors (p = 0.24).

DISCUSSION

In a prospective cohort of patients with SRMs on AS most tumors showed slow growth kinetics. Given that it is a recommended trigger to consider intervention, a greater proportion of patients with tumors showing growth crossed over to delayed intervention but mean GR did not differ between the groups. Additionally, GR was not significantly associated with patient characteristics, biopsy pathology or overall mortality.

While patients with RCC and those who experienced overall mortality appeared to have nonsignificantly increased GR, no patient experienced metastasis or death due to kidney cancer. Our data

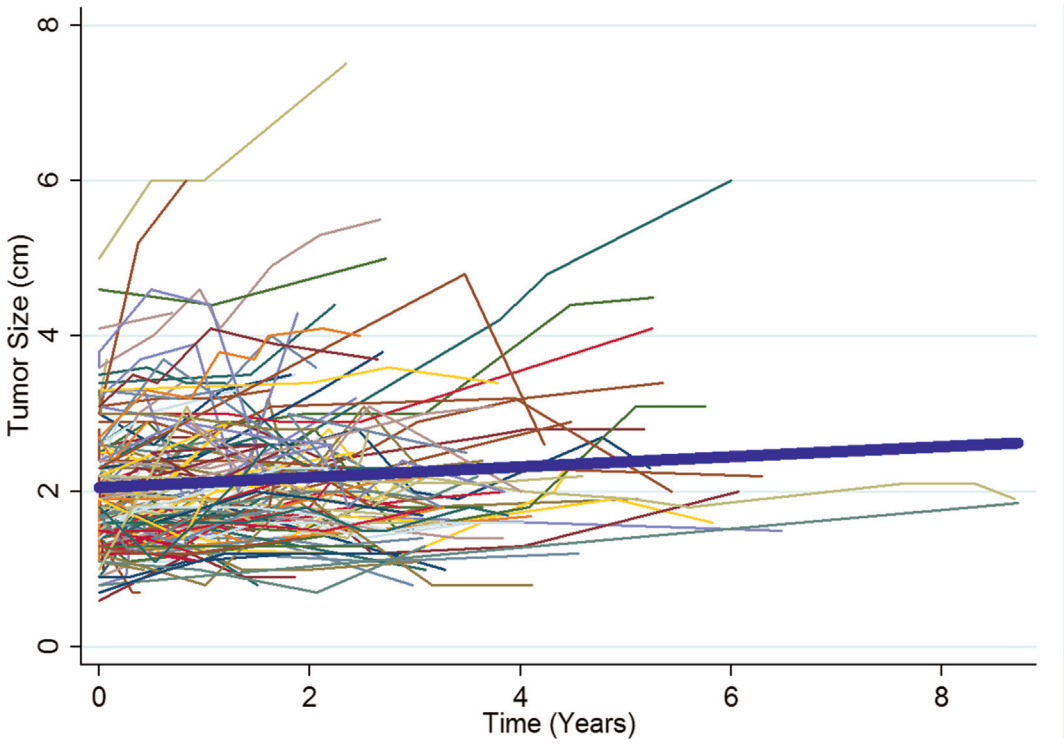

Figure 1. Growth pattern of small renal masses in patients undergoing active surveillance in DISSRM registry. Thick blue line represents linear regression of change in tumor size with time in all patients.

augment prior results in smaller cohorts and suggest at least in the short term that an absolute GR threshold might not be a reliable predictor of malignancy and metastatic potential.[6–10,12,13]

These data must be evaluated in the context of inclusion criteria for DISSRM. Patients in DISSRM have solid SRMs and biopsy is not mandated prior to enrollment. Therefore, the lack of clinical information gained by GR may reflect heterogeneity in tumor biology as there are certainly various benign, indolent and potentially aggressive tumors treated with AS. Importantly GR did not differ significantly between patients who remained on AS and those who crossed over or between patients who died and those who remained alive. Lastly, patient selection to offer AS was intentional and potentially demonstrates the ability to optimize outcomes with a regimented surveillance protocol.

Given the relatively small percent of crossover patients (14.0%), the dampening of tumor GR and variability seen with time cannot be attributable solely to crossover patients exiting the AS cohort. Variability was likely due to measurement error, which was thought to occur randomly, early in AS when there were few images with which to assess tumor size in a short interval. This would have resulted in mathematical artifacts resulting from extrapolation to longer times. It did not seem to reflect tumor biology and appeared evenly distributed above and below a line where GR equaled 0 cm per year. Most SRMs that demonstrate elevated GR within 6 months do not show elevated GR at interval followup or on repeat imaging.

Therefore, we recommend short interval repeat imaging or renal mass biopsy when an early elevated GR is encountered because a true elevated GR may indicate adverse biological behavior. Despite limitations with nondiagnostic results and under grading, biopsy could help in this scenario to avoid missing a dangerous, potentially fatal tumor demonstrating an “escape velocity” indicative of aggressive biological potential.[14,15] In general we believe that reflex intervention should be avoided in the first 6 months without additional evaluation, given the high tumor GR variability and the low metastatic potential of SRMs.[6]

Prior analyses have suggested elevated GR as predictor of adverse outcomes.[6–9] However, these studies were retrospective in nature, subject to retrospective biases and lacked strict inclusion criteria or regimented followup protocols characteristic of AS. One study suggested that faster growing tumors were more likely to be RCC but actually described no statistically significant difference in a cohort with clinical T1b or T2 disease in 34% of patients.[7] Two studies included small cohorts of patients with RCC but without strict inclusion

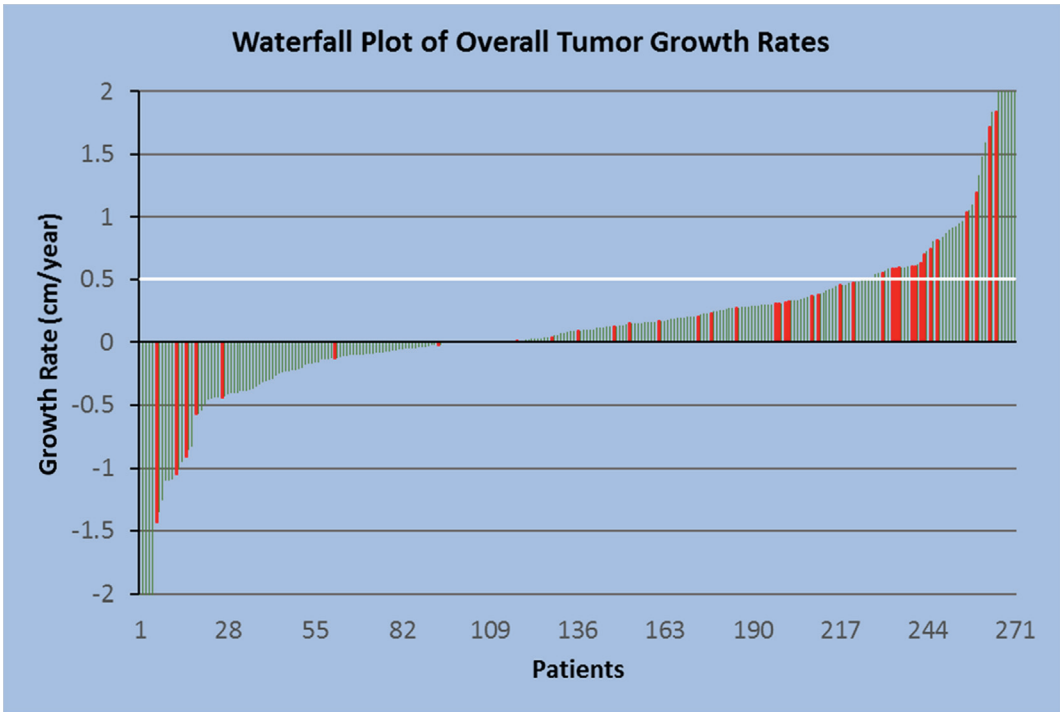

Figure 2. Waterfall plot of tumor growth rate distribution among all patients. Red bars indicate patients who crossed over to intervention. White horizontal line indicates 0.5 cm per year growth rate threshold.

criteria and showed a potential association of GR with tumor grade, although 1 cohort included 50% of patients with T1b, T2 or T3 disease.[8,9] There are minimal data comparing GRs among different histologies with a review concluding that GRs for RCC and benign oncocytomas are not distinguishable.[16] Notably our study included a uniform population of SRMs in which GR was not significantly

Table 2. *Tumor growth rates in DISSRM registry and tumor pathology in patients who underwent percutaneous renal biopsy*

		Overall Growth Rate (cm/yr)			
	No. Pts	Mean ± SD	Median	IQR	Range
Overall interval:	271	0.09 ± 1.51	0.09	−0.10—0.33	−14.75—8.42
Less than 180 days	31	0.54 ± 2.76	0	−0.46—0.87	−6.82—8.42
Greater than 180 days	240	0.03 ± 1.26	0.10	−0.08—0.33	−14.75—3.85
Greater than 1 yr	182	0.07 ± 0.59	0.09	−0.08—0.28	−5.52—1.84
Greater than 2 yrs	127	0.05 ± 0.64	0.09	−0.07—0.28	−5.52—1.72
Greater than 3 yrs	67	0.01 ± 0.37	0.03	−0.08—0.19	−1.35—0.84
Greater than 4 yrs	41	0.06 ± 0.30	0.03	−0.07—0.19	−1.1—0.84
Active surveillance	233	0.05 ± 1.60	0.03	−0.10—0.29	−14.75—8.42
Crossovers	38	0.31 ± 0.64	0.32	0.09—0.61	−1.43—1.84
Initial imaging modality:					
MRI	71	0.14 ± 1.14	0.03	−0.10—0.39	−3.72—7.93
CT	170	0.01 ± 1.62	0.12	−0.09—0.32	−14.75—6.28
Ultrasound	30	0.42 ± 1.61	0	−0.17—0.29	−0.91—8.42
Body mass index category:*					
Normal	59	0.51 ± 1.57	0.12	−0.04—0.48	−1.43—8.42
Overweight	98	−0.07 ± 1.82	0.03	−0.17—0.29	−14.75—6.28
Obese	92	0.06 ± 0.89	0.06	−0.12—0.32	−5.52—3.85
Imaging followup (days):					
Overall	233	824 ± 652	695	322—1,122	23—3,937
Crossovers	38	619 ± 483	558	285—841	64—1,921
Tumor subtype:					
RCC	13	0.63 ± 1.21	0.61	0—0.81	−1.05—3.85
Acute myeloid leukemia	1	0.23	—	—	—
Oncocytoma	14	0.07 ± 0.38	0.12	0—0.30	−1.09—0.48
Benign	3	0.08 ± 0.46	0.22	−0.44—0.45	−0.44—0.45
Nondiagnostic	2	−3.46 ± 4.78	−3.46	−6.84—−0.08	−6.84—−0.08

* Complete obesity data available in 251 patients with 2 underweight individuals excluded.

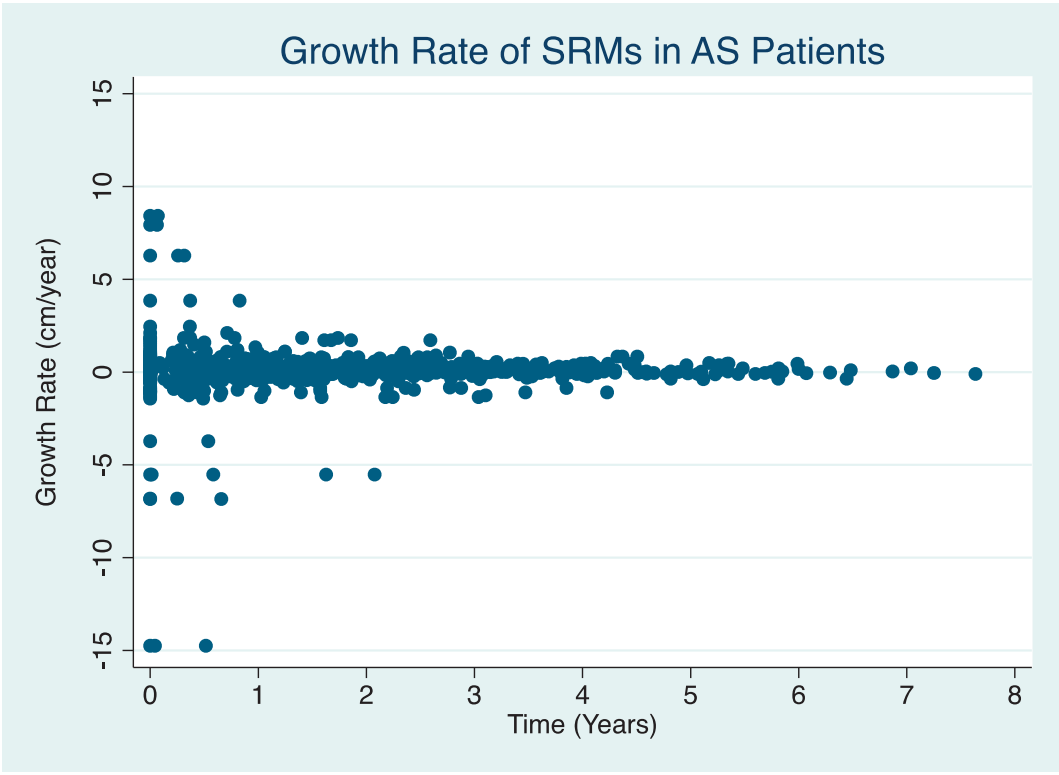

Figure 3. Tumor growth rate with time in patients undergoing active surveillance for small renal mass in DISSRM registry demonstrates large variability in year 1 and then decreased variability with time.

associated with adverse pathological findings on biopsy,

Another prospective AS experience in the literature, the Renal Cell Carcinoma Consortium of Canada, evaluated up to 169 patients but found no association of GR with any predictors of or progression to metastatic disease but was unable to evaluate any pathological outcomes.[12,13] DISSRM builds on this with additional data on delayed intervention, overall survival and biopsy outcomes in a larger prospective cohort of 271 evaluable patients. While GR greater than 0.5 cm per year is often a parameter to recommend intervention, not all patients in our study were treated according to this guideline and not all elevated GRs indicated adverse pathology. Furthermore, we recognize that tumor size has been shown to be the greatest predictor of malignant pathology and metastatic potential, and recommend intervention based on interval changes in overall tumor size.[4,17]

As mentioned, percutaneous renal biopsy is not uniformly performed in all patients at the time of study enrollment. Increasing evidence has suggested that an initial period of AS is safe for SRMs. Biopsy is associated with potential morbidity and does not change management in most cases because of an approximately 70% negative predictive value and the inability to reliably detect high grade disease due to grade heterogeneity.[14,18] We prefer baseline risk stratification on clinical variables predicting the risk of metastatic potential and death of competing causes.[11,19]

Biopsy is appropriate in patients in whom the findings may change treatment. For example, younger and healthier patients who can undergo minimally invasive partial nephrectomy should not be dissuaded from surgery based on a benign or low grade tumor due to the heterogeneity of SRMs.[18,20] At the time that the DISSRM registry was conceived neither the AUA (American Urological Association) nor EAU (European Association of Urology) had guidelines that addressed the use of percutaneous renal biopsy. Since its inception, the proportion of patients electing biopsy in DISSRM has increased from approximately 5% of patients per year to 20% in the most recent year of the registry. We expect to see that percent increase as understanding of the role of biopsy in management grows and with additional followup of DISSRM.

Finally, we considered that the variation in imaging modality could lead to significant changes in the calculated GR. The imaging modality used for the first image was not significantly associated with GR. However, there was a large degree of

variability in mean GR based on the initial imaging modality, which we believe was due to radiological artifact. The spatial resolution, interobserver variability and concordance with pathological specimens of each imaging modality, including ultrasound, are similar and on the order of 1 to 3 mm.[21–23] Patient characteristics such as obesity that make ultrasound challenging also make axial imaging less accurate. In our experience proficient ultrasound technologists and radiologists are able to target the index lesion and reliably obtain a maximal diameter. As the number of patients in the DISSRM registry grows, we will reexamine this assumption to ensure that it does not threaten the internal validity of the surveillance protocol as it is currently designed.

Additional limitations are that the study protocol of the DISSRM registry was designed for survival outcomes and not specifically powered to evaluate GRs. However, natural history and tumor kinetics were a planned secondary objective with continued enrollment of new patients with time. This also contributes to the relatively short followup. Additional followup will increase the sample size and the number of patients experiencing the outcomes of crossover, biopsy and death to better detect differences in GRs. Patient selection also impacts outcomes as patients with limited life expectancy have shorter exposure time to experience an outcome.

Lastly, the greater than 0.5 cm per year GR threshold was based on retrospective data. A more relevant biological cutoff may differ from this or a different clinical pathway could become the standard. A GR cutoff could trigger evaluation of a biopsy, biomarker or novel imaging modality parameter.

CONCLUSIONS

Among patients undergoing AS for SRMs tumor GRs varied significantly within the first 6 months of surveillance and did not reliably predict death or adverse pathological features in the subset with available pathology findings. Variations in tumor size within the first 6 months may not represent true tumor growth. Variability decreased with time and should not influence physicians to recommend treatment without additional evaluation. A high GR in less than 6 months should warrant reassessment and risk stratification using a shorter imaging interval or percutaneous renal biopsy as true elevated GR may indicate adverse biology. Additional followup will inform the best clinical pathway for elevated GRs, which may not involve setting an absolute threshold.

REFERENCES

1. National Cancer Institute Surveillance, Epidemiology and End Results Program: Cancer Stat Facts: Kidney and Renal Pelvis Cancer. Updated 2017. Available at https://seer.cancer.gov/statfacts/html/kidrp.html. Accessed February 15, 2017.
2. Chow WH, Dong LM and Devesa SS: Epidemiology and risk factors for kidney cancer. Nat Rev Urol 2010; **7:** 245.
3. Nguyen MM, Gill IS and Ellison LM: The evolving presentation of renal carcinoma in the United States: trends from the Surveillance, Epidemiology, and End Results Program. J Urol 2006; **176:** 2397.
4. Pierorazio PM, Johnson MH, Ball MW et al: Five-year analysis of a multi-institutional prospective clinical trial of delayed intervention and surveillance for small renal masses: the DISSRM registry. Eur Urol 2015; **68:** 408.
5. Jewett MA, Mattar K, Basiuk J et al: Active surveillance of small renal masses: progression patterns of early stage kidney cancer. Eur Urol 2011; **60:** 39.
6. Smaldone MC, Kutikov A, Egleston BL et al: Small renal masses progressing to metastases under active surveillance: a systematic review and pooled analysis. Cancer 2012; **118:** 997.
7. Zhang J, Kang SK, Wang L et al: Distribution of renal tumor growth rates determined by using serial volumetric CT measurements. Radiology 2009; **250:** 137.
8. Li XS, Yao L, Gong K et al: Growth pattern of renal cell carcinoma (RCC) in patients with delayed surgical intervention. J Cancer Res Clin Oncol 2012; **138:** 269.
9. Zhang L, Yin W, Yao L et al: Growth pattern of clear cell renal cell carcinoma in patients with delayed surgical intervention: fast growth rate correlates with high grade and may result in poor prognosis. Biomed Res Int 2015; **2015:** 598134.
10. Kawaguchi S, Fernandes KA, Finelli A et al: Most renal oncocytomas appear to grow: observations of tumor kinetics with active surveillance. J Urol 2011; **186:** 1218.
11. Pierorazio PM, Hyams ES, Mullins JK et al: Active surveillance for small renal masses. Rev Urol 2012; **14:** 13.
12. Mason RJ, Abdolell M, Trottier G et al: Growth kinetics of renal masses: analysis of a prospective cohort of patients undergoing active surveillance. Eur Urol 2011; **59:** 863.
13. Organ M, Jewett M, Basiuk J et al: Growth kinetics of small renal masses: a prospective analysis from the Renal Cell Carcinoma Consortium of Canada. Can Urol Assoc J 2014; **8:** 24.
14. Patel HD, Johnson MH, Pierorazio PM et al: Diagnostic accuracy and risks of biopsy in the diagnosis of a renal mass suspicious for localized renal cell carcinoma: systematic review of the literature. J Urol 2016; **195:** 1340.
15. Patel HD and Pierorazio PM: Kidney cancer: undertreatment of small renal masses by overuse of biopsy. Nat Rev Urol 2016; **13:** 701.
16. Chawla SN, Crispen PL, Hanlon AL et al: The natural history of observed enhancing renal masses: meta-analysis and review of the world literature. J Urol 2006; **175:** 425.
17. Pierorazio PM, Patel HD, Johnson MH et al: Distinguishing malignant and benign renal masses with composite models and nomograms: a systematic review and meta-analysis of clinically localized renal masses suspicious for malignancy. Cancer 2016; **122:** 3267.
18. Ball MW, Bezerra SM, Gorin MA et al: Grade heterogeneity in small renal masses: potential implications for renal mass biopsy. J Urol 2015; **193:** 36.

19. Patel HD, Kates M, Pierorazio PM et al: Balancing cardiovascular (CV) and cancer death among patients with small renal masses: modification by CV risk. BJU Int 2015; **115:** 58.

20. Pierorazio PM, Johnson MH, Patel HD et al: Management of renal masses and localized renal cancer: systematic review and meta-analysis. J Urol 2016; **196:** 989.

21. Punnen S, Haider MA, Lockwood G et al: Variability in size measurement of renal masses smaller than 4 cm on computerized tomography. J Urol 2006; **176:** 2386.

22. Mucksavage P, Kutikov A, Magerfleisch L et al: Comparison of radiographical imaging modalities for measuring the diameter of renal masses: is there a sizeable difference? BJU Int 2011; **108:** E232.

23. Mucksavage P, Ramchandani P, Malkowicz SB et al: Is ultrasound imaging inferior to computed tomography or magnetic resonance imaging in evaluating renal mass size? Urology 2012; **79:** 28.