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Use of delayed intervention for small renal masses initially managed with active surveillance

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Abstract

Introduction: A number of patients who elect active surveillance of their small renal masses (≤ 4 cm) subsequently pursue delayed intervention (DI). The indications, timing, and rates of DI have not been well determined prospectively.

Materials and methods: Data from Delayed Intervention and Surveillance for Small Renal Masses, a prospective, multi-institutional registry was utilized to evaluate factors associated with DI between 2009 and 2018.

Results: Of 371 patients enrolled in AS, 46 (12.4%) pursued DI. Patients who pursued DI spent a median 12 months on surveillance (inter-quartile range 5.5−23.6), had better functional status ($P < 0.01$), and had greater median growth rate vs. those who remained on surveillance (0.38 vs. 0.05, $P < 0.001$). Indications for intervention included growth rate > 0.5 cm/y for 23 (50%) patients, patient preference for 22 (47.8%) patients, and qualification for renal transplant in 1 (2.2%) patient. Thirty-two patients (69.6%) underwent nephron-sparing surgery, 5 (10.9%) underwent radical nephrectomy, and 9 (19.6%) underwent percutaneous cryoablation. Renal mass biopsy was utilized in 37 (11.4%) and 15 (32.7%) patients in the AS and DI arms, respectively ($P = 0.04$). No patients experienced metastatic progression or died of kidney cancer.

Conclusions: As nearly 50% of patients pursue DI secondary to anxiety in the absence of clinical progression, comprehensive counseling is essential to determine if patients are suitable for a surveillance protocol. AS remains a safe initial management option for many patients but may not be a durable strategy for patients who are acceptable surgical candidates with an extended life expectancy. DI does not compromise oncologic outcomes or limit treatment options. © 2018 Elsevier Inc. All rights reserved.

Keywords: Active surveillance; Kidney neoplasms; Carcinoma, Renal cell; Renal cancer

1. Introduction

While surgical excision remains the cornerstone of management for patients with small renal masses (SRMs; renal masses ≤ 4 cm suspicious for cT1a renal cell carcinoma [RCC]), active surveillance (AS) has emerged as a safe initial management strategy for many patients, including those with decreased life expectancy, significant competing medical comorbidities, or very SRMs [1−3].

AS has gained acceptance in part from an increased understanding of the natural history of SRMs. While their tumor biology and growth rates (GRs) are heterogeneous, multiple prospective and retrospective studies have found that the majority of SRMs on AS demonstrate low rates of metastatic potential [3−7]. Prospective data of 178 patients

from the Renal Cell Carcinoma Consortium of Canada identified a metastatic progression rate of 1.1% over a mean follow-up of 28 months, and a meta-analysis by Chawla et al. of 9 recent AS series observed metastatic progression in 3 of 286 lesions (1%) on AS over a 32-month median follow-up [8,9]. Data from our registry have similarly demonstrated no metastatic progression for patients on AS with up to 5 years of prospective follow-up [10]. There is also growing recognition that surgical excision may not improve overall survival for all patients with SRMs, and contemporary studies indicate that patients over the age of 75 are more likely to die of cardiovascular and other noncancerous comorbidities than of their SRM [11−13].

A guiding principle of AS, however, is the use of timely intervention without compromise of oncologic outcomes. As a result, a subset of patients managed with AS will subsequently crossover to definitive treatment. The indications, timing, and rates of delayed intervention, however, have not been well determined prospectively. We present results from a prospective, multi-institutional AS registry with a specific focus on clinical and pathologic outcomes of patients undergoing definitive therapy following a period of AS.

2. Methods

2.1. Patient population and study design

The Delayed Intervention and Surveillance for Small Renal Masses (DISSRM) registry is a prospective study for patients with SRM undergoing AS or primary intervention. The registry is institutional review board-approved, and since January 2009, has been enrolling patients at the Johns Hopkins Hospital, Columbia University Medical Center, and Beth Israel Deaconess Medical Center. Study design, power calculations, inclusion/exclusion criteria, and protocol have been previously reported [10,14].

2.2. Active surveillance protocol and delayed interventions

All patients underwent axial imaging (computed tomography or magnetic resonance imaging) within 6 months of enrolling in the registry [10]. Contrast imaging was utilized in patients with acceptable renal function. The DISSRM protocol recommends serial imaging every 6 months for 2 years, and annually thereafter. Time intervals can be modified based on clinical parameters, and alternating ultrasound and axial imaging modalities are preferred. For patients who elect surveillance with ultrasound, axial imaging is prompted by any significant discrepancy in tumor size or GR, or if ultrasound images were of poor quality (i.e., isoechoic lesions). DI was recommended for renal masses with GR > 0.5 cm/y or if the tumor diameter progressed to >4.0 cm in diameter. During follow-up, patients could choose to pursue DI at any time, regardless

of changes on imaging, or to continue on AS despite radiographic evidence of disease progression. All patients were counseled regarding the respective risks and benefits of AS, percutaneous renal mass biopsy (RMB), and surgical and percutaneous intervention options at the time of enrollment into DISSRM and at subsequent visits.

2.3. Data collection, analysis, and outcomes

Clinical and pathologic data for patients enrolled in AS between 2009 and 2018 were collected for analysis. Indications, timing, and rates of DI were prospectively captured. Tumor GR was calculated as the difference between tumor diameter at the time of enrollment and tumor diameter on the most recent imaging study divided by the elapsed time between images. This formula yielded an interval GR in cm per year. Rates of disease progression, tumor histopathology in patients who underwent DI and RMB, and modality of interventions were also analyzed.

Student t test and chi-square tests were utilized to compare differences in baseline clinical and tumor characteristics. Linear regression was performed to identify differences in tumor GRs between the AS and DI cohorts. Freedom from intervention analysis was performed using the Kaplan-Meier method. All P values were 2-sided, and $P < 0.05$ was considered statistically significant. Data analyses were performed using Stata, Version 13 (StataCorp LP, College Station, TX).

3. Results

3.1. Study population and patient characteristics

At the time of administrative censoring, 727 patients were enrolled in DISSRM, and 371 (51.0%) patients that initially elected AS were included in the study. Forty-six (12.4%) patients subsequently pursued DI. Table 1 outlines baseline characteristics of the AS, DI, and overall study cohorts. Patient functional status, as gauged by ECOG score, was the only baseline variable that significantly differed between patients who remained on AS and those who pursued DI ($P < 0.01$). Median follow-up time for all patients was 23.6 (9.0−43.4) months.

3.2. Growth rates and factors associated with use of delayed intervention

Patients who pursued DI had a greater median GR compared to those who remained in AS (0.38 vs. 0.05 cm/y, $P < 0.001$; Table 2). The proportion of patients with a mean GR > 0.5 cm/y was also higher in the DI arm (32.7% vs. 10.8%, $P < 0.001$; Fig. 1).

Indications for intervention included a GR > 0.5 cm/y during surveillance intervals or radiographic evidence of stage progression in 23 patients (50.0%), patient preference or anxiety in the setting of a GR < 0.5 cm/y in 22 patients

Table 1
Demographic and clinical characteristics of study cohorts

	Total	Active surveillance	Delayed intervention	P value
N	371	325 (87.6%)	46 (12.4%)	
Age (y)	71.0 (63.1−78.0)	71.3 (63.1−78.2)	69.3 (63.5−74.9)	0.17
Gender				0.38
Female	163 (43.9%)	140 (43.1%)	23 (50%)	
Male	208 (56.1%)	185 (56.9%)	23 (50%)	
Race				0.37
White	288 (77.6%)	249 (76.6%)	39 (84.8%)	
Black	58 (15.6%)	54 (16.6%)	4 (8.7%)	
Other	25 (6.7%)	22 (6.8%)	3 (6.5%)	
Education				0.62
Incomplete	11 (7.0%)	10 (7.8%)	1 (3.4%)	
High school (or equivalent)	66 (42.0%)	54 (42.2%)	12 (41.4%)	
Bachelors degree (or equivalent)	49 (31.2%)	41 (32.0%)	8 (27.6%)	
Professional degree	31 (19.7%)	23 (18.0%)	8 (27.6%)	
(masters, Ph.D., M.D., D.D.S., J.D.)				
Marital status				0.52
Married	97 (75.8%)	89 (76.1%)	8 (72.7%)	
Divorced	5 (3.9%)	4 (3.4%)	1 (9.1%)	
Separated	1 (0.8%)	1 (0.9%)	0 (0.0%)	
Single	12 (9.4%)	11 (9.4%)	1 (9.1%)	
Widowed	10 (7.8%)	10 (8.5%)	0 (0.0%)	
Unknown	3 (2.3%)	2 (1.7%)	1 (9.1%)	
BMI (kg/m^2)	28.2 (24.9−31.9)	28.0 (24.9−31.6)	29.5 (24.6−33.5)	0.24
Obesity				0.091
Underweight (BMI < 18.5)	4 (1.2%)	4 (1.3%)	0 (0.0%)	
Normal (BMI 18.5−24.9)	79 (23.2%)	66 (22.2%)	13 (30.2)	
Overweight (BMI 25.0−29.9)	133 (39.1%)	124 (41.8%)	9 (20.9%)	
Obese (BMI 30.0−34.9)	77 (22.6%)	66 (22.2%)	11 (25.6%)	
Severe obesity (BMI 35.0−39.9)	25 (7.4%)	19 (6.4%)	6 (14.0%)	
Morbid Obesity (BMI > 40.0)	22 (6.5%)	18 (6.1%)	4 (9.3%)	
ECOG Score				< 0.01
0		227 (78.8%)	39 (88.6%)	
1		48 (16.7%)	0 (0.0%)	
2		4 (1.4%)	3 (6.8%)	
3		6 (2.1%)	2 (4.5%)	
4		3 (1.0%)	0 (0.0%)	
Charlson comorbidity index				0.49
0		150 (46.0%)	17 (37.0%)	
1−3		155 (47.5%)	25 (54.3%)	
4+		21 (6.4%)	4 (8.7%)	
Comorbidities				
Cerebrovascular disease		10 (3.1%)	1 (2.2%)	0.73
Chronic kidney disease		29 (8.9%)	3 (6.5%)	0.84
Chronic obstructive pulmonary disease		24 (7.4%)	4 (8.7%)	0.76
Congestive heart failure		13 (4.0%)	3 (6.5%)	0.44
Diabetes mellitus		72 (22.6%)	17 (36.7%)	0.053
Dementia		4 (1.2%)	1 (2.2%)	0.61
Hypertension		209 (63.4%)	27 (58.7%)	0.43
Myocardial infarction		26 (8.0%)	5 (10.9%)	0.53
Peripheral vascular disease		15 (4.6%)	4 (8.7%)	0.25
Liver disease		9 (2.8%)	2 (4.3%)	0.83
Smoking, active		27 (8.3%)	4 (8.7%)	0.79
Solid organ tumor, within 5 y		64 (20.0%)	5 (10.9%)	0.24
Metastatic progression	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Deaths				0.80
Secondary to RCC	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Secondary to other causes		31 (9.5%)	2 (4.3%)	

BMI = body mass index; ECOG = Eastern Cooperative Oncology Group; RCC = renal cell carcinoma.

Data are present as *n* (%) or median (interquartile range).

Table 2
Tumor characteristics of renal masses on active surveillance vs. delayed intervention

	All patients ($n = 371$)	Active surveillance ($n = 325$)	Delayed intervention ($n = 46$)	P value
Median initial tumor diameter (cm)	1.8 (1.3−2.5)	1.7 (1.3−2.4)	1.95 (1.4−2.6)	0.32
Overall growth rate (cm/y)				
Mean growth rate (cm ± SD)	0.18 ± 1.39	0.12 ± 1.43	0.56 ± 1.07	0.06
Median growth rate (cm)	0.09	0.05	0.38	< 0.001
IQR	−0.05−0.34	−0.0−0.30	0.018−0.73	
Range	−9.70−16.86	−9.70−6.86	−2.44−2.20	
Median follow-up (mo)	23.6 (9.0−43.4)	22.3 (7.9−37.2)	43.2 (23.3−62.0)	< 0.001
Number of patients with GR > 0.5 cm/y	50 (13.8%)	35 (10.8%)	15 (32.7%)	< 0.001
Local progression > cT1a while on AS	18 (5.9%)	14 (4.6%)	4 (8.9%)	0.22
Percutaneous renal biopsy	52 (14.0%)	37 (11.4%)	15 (32.7%)	0.04
Biopsy histology				
Oncocytoma/oncocytic cells	21 (40.4%)	19 (51.4%)	2 (13.3%)	
Renal cell carcinoma	25 (48.1%)	12 (32.4%)	13 (86.7%)	
Angiomyolipoma	1 (1.9%)	1 (2.7%)	0 (0.0%)	
Benign, other	3 (5.8%)	3 (8.1%)	0 (0.0%)	
Nondiagnostic	2 (3.8%)	2 (5.4%)	0 (0.0%)	
Pathological tumor characteristics (surgical DI only)				
Histology				
Renal cell carcinoma			29 (78.4%)	
Clear cell			20 (54.1%)	
Papillary			7 (18.9%)	
Chromophobe			2 (5.4%)	
Oncocytoma			3 (8.1%)	
Angiomyolipoma		4 (10.8%)		
Benign cyst		1 (2.7%)		
Fuhrman grade				
1−2			23 (79.3%)	
3			6 (20.7%)	
4			0 (0.0%)	
Pathologic stage				
pT1a			31 (83.8%)	
pT1b			4 (10.8%)	
pT3a			2 (5.4%)	
Median tumor diameter (cm) on pathology			2.5 (1.8−3.4)	
Disease recurrence after DI			0 (0.0%)	

DI = delayed intervention; GR = growth rate; IQR = interquartile range; SD = standard deviation.

(47.8%), and need for local treatment in order to qualify for renal transplantation in 1 patient (2.2%; Table 3). Patients spent a median of 12 months (interquartile range 5.5−23.6) on AS before electing DI. Freedom from intervention was 78.1% at 5 years (95% confidence interval 0.70−0.84; Fig. 2).

Subset analysis yielded no statistically significant differences in patient age, functional status, year of enrollment in DISSRM, or indication for intervention between patients who proceeded to DI within 1 year of initiating AS vs. those who waited longer. There were also no differences in pathologic outcomes based on indication for DI.

Of patients undergoing delayed therapy, minimally invasive surgery was utilized in 33 cases (71.7%; Table 3). Thirty-two patients (69.6%) underwent nephron-sparing surgery, 5 (10.9%) underwent radical nephrectomy, and 9 (19.6%) underwent percutaneous cryoablation. Histopathology from patients who underwent surgical excision

demonstrated pT1a, pT1b, and pT3a disease in 31 (83.3%), 4 (10.8%), and 2 (5.4%) patients, respectively. Median tumor diameter on surgical pathology was 2.5 cm (1.8 −3.4). Of the 2 lesions upstaged to pT3a, one grew from 3.4 cm to 4.1 cm (GR 0.77 cm/y), and the other from 3.0 cm to 3.7 cm (GR 0.19 cm/y). The majority of tumors (23 patients, 79.3%) were low-grade (Fuhrman grade 1−2). Unfavorable pathology (high-grade or pT3) was present in 7 patients (18.9%); there were no episodes, however, of disease recurrence following surgery in the DI cohort. Fifteen patients (32.7%) demonstrated GR > 0.5 cm/y; these patients did not demonstrate statistically significant higher rates of RCC, high-grade disease, or pathologic upstaging compared to patients who did not demonstrate elevated GR (data not shown).

In the study, there were no deaths secondary to RCC. Thirty-one patients (9.5%) and 2 patients (4.3%) died in the AS and DI groups, respectively, secondary to
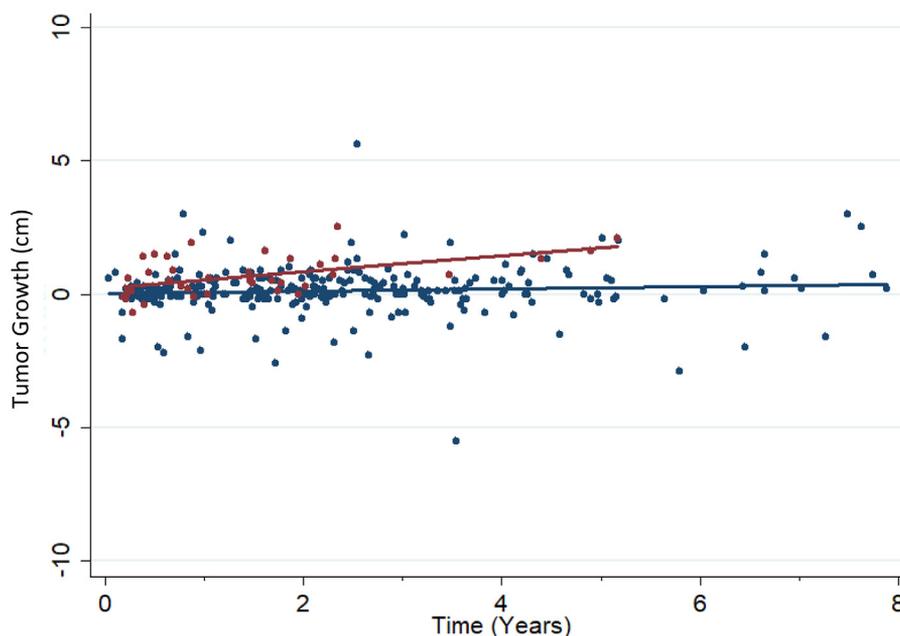
Fig. 1. Growth rates of small renal masses over time since enrolling in active surveillance. Dots represent individual masses, and lines represent linear regression of change in tumor size with time. Red data points represent patients who underwent delayed intervention, and blue data points represent patients who remained in the active surveillance cohort.

non−RCC-related causes ($P = 0.8$). Median follow-up time for patients after undergoing DI was 23.9 months (interquartile range 4.2−46.0); the overall follow-up time for patients in the DI cohort was 43.2 months (23.3−62.0).

3.3. Use of renal mass biopsy

RMB was utilized in 37 (11.4%) patients in the AS arm and in 15 (32.7%) patients in the DI arm ($P = 0.04$) prior to intervention (Table 2). Of those undergoing RMB in the DI arm, 6 were performed due to GR > 0.5 cm/y, and 9 were performed secondary to patient request in the absence of elevated GR. Two (3.8%) biopsies demonstrated nondiagnostic findings. The majority of patients who pursued DI had RCC on biopsy (13 patients, 86.7%). Biopsies demonstrated oncocytic neoplasm, low-grade RCC, and benign/nondiagnostic histology in 19 (51.4%), 12 (32.4%), and 5 (16.2%) patients who remained on AS, respectively.

Table 3
Indications and modalities of treatment pursued by patients electing delayed intervention

	Delayed intervention ($n = 46$)
Indications for delayed intervention	
GR > 0.5 cm/y or stage progression	23 (50.0%)
GR > 0.5 cm/y	19 (41.3%)
Stage progression	4 (8.7%)
Patient preference or anxiety, GR < 0.5 cm/y	22 (47.8%)
Qualification for renal transplantation	1 (2.2%)
Median time on AS prior to delayed intervention (mo)	12.0 (5.5−23.6)
Intervention modality	
Partial nephrectomy	32 (69.6%)
MIS	28 (60.1%)
Open	4 (8.7%)
Radical nephrectomy	5 (10.9%)
MIS	5 (10.9%)
Open	0 (0.0%)
Cryoablation, percutaneous	9 (19.6%)

AS = active surveillance; GR = growth rate; MIS = minimally invasive surgery.
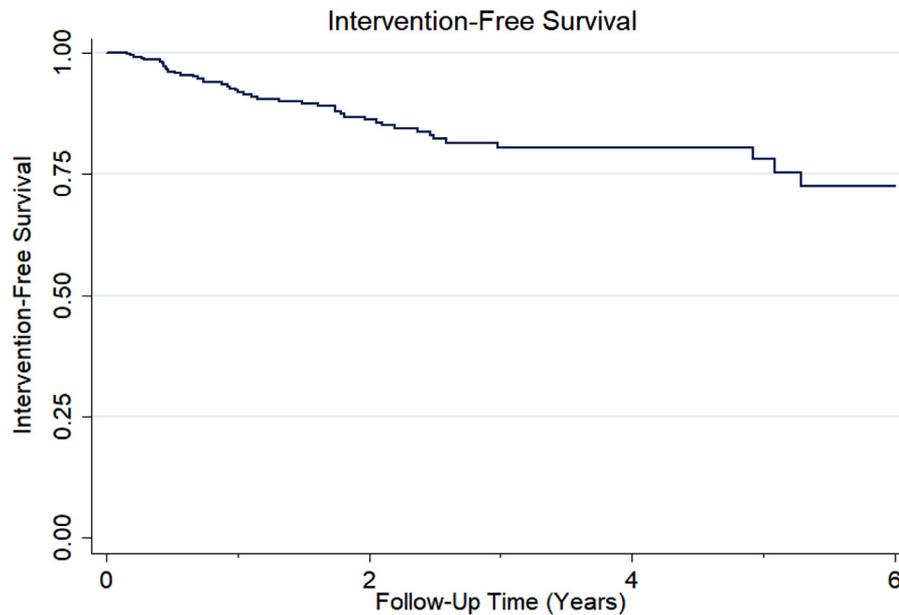
Fig. 2. Intervention-free survival for patients undergoing active surveillance in the Delayed Intervention and Surveillance for Small Renal Mass (DISSRM) registry.

4. Discussion

The use of AS of SRMs has emerged as a safe management option to select patients with significant competing comorbidities or with very small masses, as reflected by current guideline statements [1,2,15,16]. Prospective findings from this study corroborate these statements and support the safety of AS as an initial management strategy in these patients: no patient has died of RCC, and nearly 10% of patients in the AS cohort died of non−RCC-related causes over a median follow-up of 22.3 months. In addition, 12% of patients undergoing AS underwent DI without compromise of oncologic outcomes. There are a number of important implications of these data.

First, the only significant baseline difference identified between patients who pursued intervention compared to those who remained on AS was their functional status ($P < 0.01$). This suggests that patients with satisfactory performance status may be more inclined to pursue DI as they may be able to accept risks associated with surgery despite advanced age. AS is consequently most suitable as an alternative to definitive therapy in patients with limited life expectancies or competing health risks. Furthermore, urologists should not dissuade functional, elderly patients from primary intervention based solely on their age.

Second, comprehensive patient counseling is essential to determine the suitability and durability of AS for a patient with a newly diagnosed SRM. Only 50% of patients undergoing DI did so for clinical progression (elevated GR or tumor size > 4 cm). Conversely, nearly 50% of patients pursued DI secondary to anxiety

in the absence of GR > 0.5 cm or evidence of clinical progression. Given the absence of curative treatment options for patients with metastatic RCC, patients and physicians who elect AS must accept a calculated risk of metastasis during or after AS [3,17]. The Damoclean risk of disease progression and of potential limitations on treatment options in the future, however, can cause significant anxiety and influence a patient's decision to terminate AS. Based on our data and prior AS cohorts, patients should be counseled and reassured that survival data supports the safety of AS for SRMs in the short-term with minimal oncologic risks [8]. If patients are unwilling to accept these risks, they may not be appropriate candidates for AS and are likely to terminate surveillance in the future. While the median time to DI was 1 year in our study, the median follow-up of the DI cohort was significantly longer, thus indicating that a significant number of DI patients enrolled very early in our experience with DISSRM. The choice for early DI (within a year) may consequently reflect poor patient selection, inadequate counseling, or lack of confidence with the AS protocol—all of which have improved with experience. Quality-of-life surveys from DISSRM also indicate that mental component scores (including anxiety and depression) improve in patients undergoing (and remaining) on AS, thus supporting the notion that well-selected, well-counseled patients may experience an improvement in quality of life (QOL) over time [18].

Third, our study also supports recent evidence that DI following a period of AS does not limit the feasibility of nephron-sparing or minimally invasive surgery, or adversely affect pathologic outcomes [5,19,20]. Only 18.9% of

DI patients demonstrated adverse pathological features (high grade or stage), no patient developed metastatic disease or died of the disease in either cohort, and no differences were observed in pathological outcomes between those electing DI based on preference or GR.

The majority of contemporary, retrospective AS cohorts report rates of DI between 20% and 30% [3,6,21]. Indications for DI, however, are neither uniform nor well-defined and are often based on tumor growth kinetics [3]. In DISSRM, median tumor GR was significantly higher in patients who underwent DI compared with those who remained on surveillance (0.38 vs. 0.05 cm/y, $P < 0.001$), and more patients electing DI had GR > 0.5 cm/y (32.7% vs. 10.8%, $P < 0.001$). This supports the notion that tumor growth kinetics can weigh heavily upon physicians' and patients' decision to pursue DI. Recent analyses, however, demonstrate that tumor growth kinetics for SRMs can be variable and do not always gauge tumor biology [4,15]. Kunkle et al. found similar rates of malignancy among renal tumors that demonstrate growth and those do not [22]. Furthermore, Jewett et al. demonstrated that histologically proven benign tumors (e.g., angiomyolipomas and oncocytomas) can grow at the same rates as malignant tumors [9]. Despite these findings, GR remains a worrisome clinical feature: retrospective AS data indicate that patients developing metastases had 3 cm to 4 cm tumors with dramatic growth during follow-up, and recent evidence indicates that patients with multiple time periods of tumor growth maybe more likely to harbor unfavorable pathology [15,23,24].

While the low rate of DI in our study reflects increased contemporary experience and physician comfort with AS as a management modality, it is also likely secondary to the presence of regimented thresholds for DI in our surveillance protocol. The structured DISSRM protocol provides reassurance to patients that their SRM is being closely monitored and also affords valuable information to clinicians regarding tumor growth kinetics. Recent evaluation of this data demonstrates that early in AS, especially during the initial 6 to 12 months, tumor GRs are variable and do not reliably predict death or adverse pathology following intervention [4]. We consequently recommend short interval repeat imaging or RMB—as opposed to reflex intervention —when an early elevated GR is encountered given the low short-term metastatic potential of SRMs and since GR may reflect heterogeneity in tumor biology. We do recognize, however, that overall tumor size has been shown to be the greatest predictor of malignant pathology and metastatic potential, and we consequently recommend DI if a patient's tumor diameter progresses to > 4.0 cm in diameter [4,10,25].

At present, American Urological Association and European guidelines advise utility-based use of RMB and do not require RMB for older or frail patients who will be managed conservatively independent of RMB findings [1,16]. While all patients entering DISSRM are offered a RMB, biopsy is recommended only when uncertainty exists regarding the most suitable management option and is consequently highest in patients undergoing DI [10,26]. During initial consultation, we acknowledge that our patients most likely harbor a low-grade, indolent RCC, and due to the significant negative predictive value and low specificity for high-grade disease, do not mandate RMB at enrollment [1,4,27,28]. Instead, we reserve RMB for patients in whom the management choice is unclear, radical nephrectomy is required due to tumor complexity, a SRM demonstrates elevated growth on AS, and, recognizing the safety of current RMB techniques, for patients who want histologic information to guide their treatment decision. In our cohort, patients who utilized RMB were more likely to undergo DI compared to those who remained on AS (32.4% vs. 11.4%, $P = 0.04$). Notably, 9 of 15 patients in the DI pursued RMB in the absence of elevated GR; these patients likely used their biopsy findings to warrant use of DI despite the low-grade, indolent nature of most SRMs. As its role in the management of SRM becomes clearer, we expect to see an increased utilization of RMB.

There are limitations of our study. All the sites currently participating in DISSRM are large academic hospital systems and consequently may not represent the global experience with SRMs. Current analyses of DISSRM also do not capture the financial costs of serial imaging or the potential risks of cumulative radiation exposure over time for patients enrolled in AS—factors which can affect the feasibility of any management strategy. Finally, due to active enrollment in this prospective registry, the median follow-up for our cohort remains relatively short while the maximum follow-up time increases (25% of patients have greater than 5 years of follow-up). As the registry matures, however, long-term data will provide not only additional oncologic outcomes but will also validate our surveillance protocol, determine the optimal frequency of follow-up imaging for SRMs, and establish compelling indications for DI. We anticipate that the future incorporation of reliable biomarkers and advanced imaging modalities will also improve our ability to select patients for AS.

5. Conclusions

While AS of SRMs has emerged as a safe option for select patients, a notable number of patients will pursue DI after a period of surveillance. Patient preference and anxiety is a common indication for DI in many patients, and comprehensive counseling at enrollment and follow-up is consequently essential to the durability of an AS plan. Based on observed differences in functional status, AS may not be a durable management strategy for patients who are acceptable surgical candidates or who have extended life expectancies. Additional follow-up will establish true rates of disease progression and inform clinical pathways for pursuing DI.

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Supplementary materials

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