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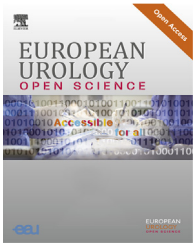

European Association of Urology

Kidney Cancer

Evaluation of Growth Rates for Small Renal Masses in Elderly Patients Undergoing Active Surveillance

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Abstract

Background: As the adoption of active surveillance (AS) for small renal masses (SRMs) grows, the number of elderly patients enrolled for a prolonged period of time will increase. However, our understanding of comparative growth rates (GRs) in aging patients with SRMs remains poor.
Objective: To examine whether particular age cutoffs are associated with an increased GR for patients undergoing AS for SRMs.
Design, setting, and participants: We identified all patients with SRMs enrolled in the multi-institutional, prospective Delayed Intervention and Surveillance for Small Renal Masses (DISSRM) registry since 2009 who elected for AS.
Outcome measurements and statistical analysis: Two definitions of GR were examined: GR from the initial image (GR_i) and GR from the prior image (GR_p). Image measurements were dichotomized based on patient age at the time of imaging. Multiple age cutoffs were examined: 65, 70, 75, and 80 yr. Mixed-effect linear regression examined the associations between age and GR, with controlling to account for multiple measurements from the same individual.
Results and limitations: We examined 2542 measurements from 571 patients. The median age at enrollment was 70.9 yr (interquartile range [IQR] 63.2–77.4) with a median tumor diameter of 1.8 cm (IQR 1.4–2.5). As a continuous variable, age was not associated with GR_i (–0.0001 cm/yr, 95% confidence interval [CI] –0.007 to 0.007, $p = 0.97$) or GR_p (0.008 cm/yr, 95% CI –0.004 to 0.020, $p = 0.17$) after adjustment. The only age thresholds associated with an increased GR were 65 yr for GR_i and 70 yr for GR_p. Limitations include the one-dimensional nature of the measurements used.

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Conclusions: Increased age for patients on AS for SRMs is not associated with increased GRs.
Patient summary: We examined whether patients undergoing active surveillance (AS) exhibited accelerated growth of their small renal masses (SRMs) after a certain age. No demonstrable change was seen, suggesting that AS is a safe and durable management option for aging patients with SRMs.

1. Introduction

The American Urological Association guidelines state that active surveillance (AS) is a reasonable management option for appropriately counseled patients harboring a small renal mass (SRM) [1]. The European Association of Urology takes a more conservative approach, only weakly recommending the use of AS in frail or comorbid patients [2]. Nevertheless, close monitoring is recommended to assess for interval growth, but no clear triggers for intervention have clearly been defined. While prior studies have recommended growth rates (GRs) in excess of 0.5 cm/yr as a threshold to convert from AS to delayed intervention (DI), this criterion has not been evaluated in a prospective manner [1,3]. While both tumor- and patient-related factors play a crucial role in counseling patients with SRMs, our understanding of tumor growth kinetics and factors influencing GRs in SRMs remains poor.

Recent data have suggested that tumor microenvironments may differ among patients based on age, which may conceivably influence growth kinetics of SRMs [4,5]. In particular, older patients may harbor features such as a suppressed immune system, which make them susceptible to accelerated tumor growth compared with their younger counterparts. As the adoption of AS for SRMs grows, there is an ever-growing list of patients who have elected AS for a prolonged period of time [6]. As surgical candidacy for elderly patients may be limited due to comorbidities or frailty, clinicians are often faced with the challenge of how to manage the growing SRMs in elderly patients. Comparative SRM GR dynamics in elderly patients are not well defined, however. Thus, it remains unclear whether intervention on SRMs before a certain age—while patients remain candidates for active treatment strategies—would be prudent to avoid sudden accelerations in growth or metastatic potential.

We sought to examine the correlation between age and GR among patients enrolled in a large, prospective, multi-institutional AS program for SRMs. Specifically, we describe whether accelerated growth is observed after particular age cutoffs to determine the safety of AS in elderly patients.

2. Patients and methods

Since January 1, 2009, the institutional review board–approved Delayed Intervention and Surveillance for Small Renal Masses (DISSRM) registry has prospectively enrolled patients with SRMs who elected to undergo primary intervention or AS across multiple institutions (NCT02346435). The design and protocol of DISSRM have previously been described in detail [3,7]. In brief, patients with clinical stage T1a renal masses (≤4.0 cm) are given the option to pursue immediate intervention or undergo AS after individualized counseling. Patients who choose AS follow a predefined protocol that involves imaging at 6-mo intervals for the first 2 yr and yearly thereafter. Initial imaging is performed with a contrast-enhanced computed tomography scan, and follow-up images can be obtained using ultrasound as a means to reduce radiation exposure. Although this may raise concerns about accurately measuring SRMs, we have previously demonstrated that our highly trained ultrasound technologists and radiologists are able to interpret images with reliability [8,9]. Patients with masses that exceed 4.0 cm in size or a GR of >0.5 cm/yr are counseled to undergo DI. Patients may also choose to convert from AS to DI at their discretion.

We identified patients enrolled in DISSRM who elected for AS for their SRMs. SRM measurements taken at enrollment and during follow-up were tracked and linked to the appropriate patient. A GR was calculated as the change in size divided by the change in time. Two definitions of GR were examined: GR from the initial baseline image (GR_i) and GR from the prior image (GR_p). We elected to analyze both these measures of GRs as SRM growth may not be linear with time, and any change in the growth trajectory would be better captured by GR_p, while GR_i would capture overall growth. Age was examined as both a continuous and a categorical variable. For the categorical age component, image measurements were dichotomized based on patient age at the time of imaging. Multiple age cutoffs were examined: 65, 70, 75, and 80 yr. Mixed-effect linear regression was used to examine associations between age and GR, with controlling to account for multiple measurements from the same individual. Additional regression models were constructed to adjust for the effects of other variables (sex, race, comorbidities, body mass index, and initial tumor diameter) on GRs. While tumor measurements were obtained to the tenths digit, GRs were reported to the thousandths digit to clearly illustrate the small differences among groups. All analyses were performed using Stata 17.0, and statistical significance was set at $\alpha = 0.05$.

3. Results

We examined 2542 measurements obtained from 571 patients. The median age of patients at enrollment was 70.9 yr (interquartile range [IQR] 63.2–77.4), with a median tumor diameter of 1.8 cm (IQR 1.4–2.5; Table 1). The median follow-up time was 2.8 yr (IQR 1.4–5.2). The majority of patients were White (77.4%) and male (58.8%). There were 80 deaths (14.0%), of which all but one were due to causes other than renal cell carcinoma (RCC). The one patient who died of RCC was noted to have evidence of metastatic disease that was missed on initial presentation. Each patient had an average of 4.4 measurements taken. The tumor size, GR_i, and GR_p for each patient over time are depicted in Figure 1A. The median GR_i and GR_p of all mea-

Table 1 – Baseline clinicodemographic characteristics of patients initially enrolled in active surveillance, stratified by the final disposition of the patient at last follow-up

Characteristics at enrollment	Patient cohort (n = 571)	Active surveillance (n = 485)	Delayed intervention (n = 86)	p value
Age (yr), median (IQR)	70.9 (63.2–77.4)	71.2 (63.2–78.1)	69.6 (62.5–74.2)	0.02
Male, n (%)	336 (58.8)	285 (58.8)	51 (59.3)	0.93
Race, n (%)				0.11
White	442 (77.4)	368 (75.9)	74 (86.1)	
Black	94 (16.5)	86 (17.7)	8 (9.3)	
Other	35 (6.1)	31 (6.4)	4 (4.7)	
Charlson Comorbidity Index, n (%)				0.69
0	247 (43.3)	212 (43.7)	35 (40.7)	
1	123 (21.5)	102 (21.0)	21 (24.4)	
2	110 (19.3)	96 (19.8)	14 (16.3)	
≥3	91 (15.9)	75 (15.5)	16 (18.6)	
Cerebrovascular accident, n (%)	23 (4.0)	19 (3.9)	4 (4.7)	0.94
Chronic kidney disease, n (%)	50 (8.8)	46 (9.5)	4 (4.7)	0.34
Congestive heart failure, n (%)	24 (4.2)	20 (4.1)	4 (4.7)	0.96
Diabetes mellitus, n (%)	140 (24.5)	115 (23.7)	25 (29.1)	0.56
Hyperlipidemia, n (%)	181 (31.7)	148 (30.5)	33 (38.4)	0.35
Hypertension, n (%)	364 (63.8)	308 (63.5)	56 (65.1)	0.96
Myocardial infarction, n (%)	47 (8.2)	39 (8.0)	8 (9.3)	0.87
Peripheral vascular disease, n (%)	25 (4.4)	21 (4.3)	4 (4.7)	0.97
Body mass index (kg/m^2), median (IQR)	28.2 (24.9–32.1)	28.2 (24.8–31.9)	28.8 (25.2–33.0)	0.30
Tumor diameter (cm), median (IQR)	1.8 (1.4–2.5)	1.8 (1.3–2.5)	2.1 (1.5–2.8)	0.005

IQR = interquartile range.

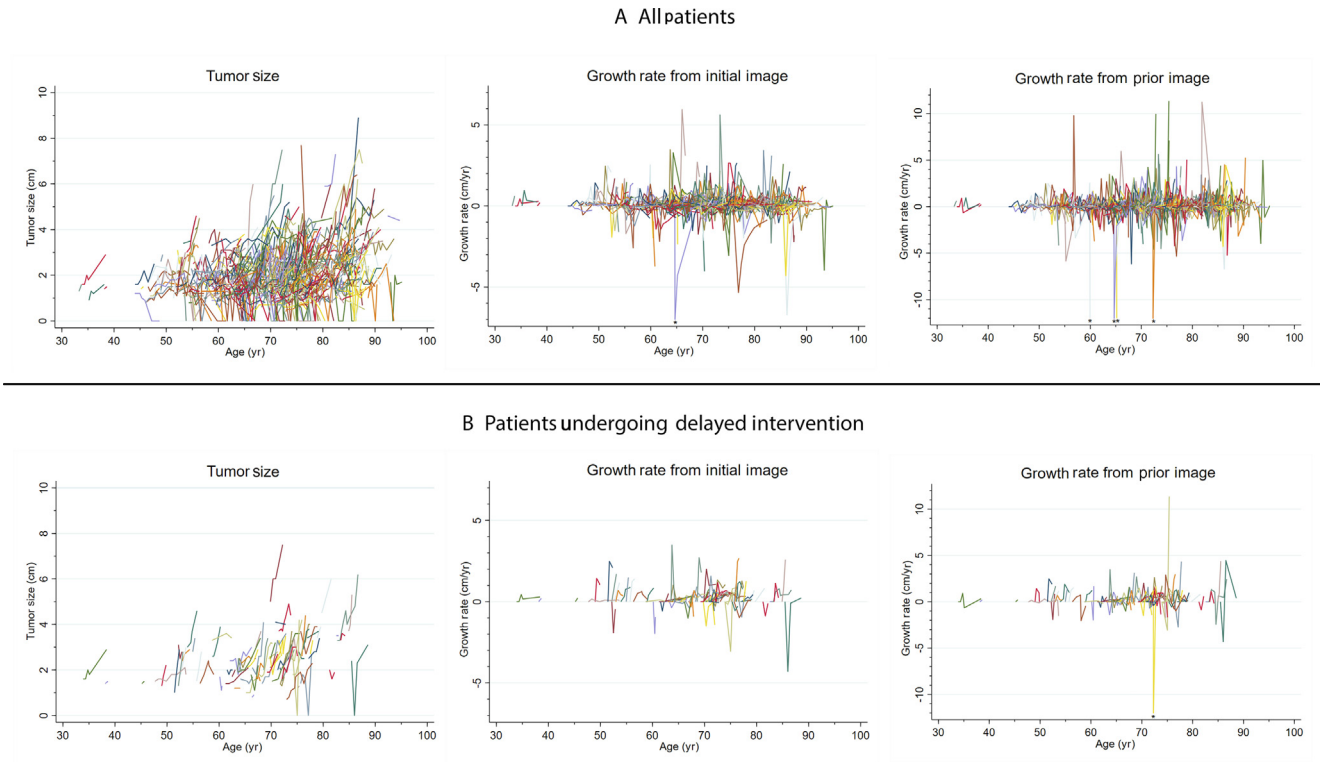

Fig. 1 – Tumor size, GR_i, and GR_p of (A) all patients and (B) patients who underwent delayed intervention. Asterisks (*) are indicative of values that extend beyond the boundaries of the graph. GR_i = growth rate from the initial image; GR_p = growth rate from the prior image.

surements recorded were 0.094 cm/yr (IQR –0.036 to 0.313) and 0.090 cm/yr (IQR –0.201 to 0.499), respectively.

When examined as a continuous variable, age was not associated with GR_i (–0.001 cm/yr, 95% confidence interval [CI] –0.008 to 0.005, p = 0.69; Table 2). Notably, Black patients had a significantly lower GR_i than White patients (–0.229 cm/yr, 95% CI –0.416 to –0.042, p = 0.02). Even in the multivariable model, this association proved significant (–0.283 cm/yr, 95% CI –0.479 to –0.088, p = 0.005), whereas none of the other factors demonstrated associations with GR_i. For the analysis of GR_p, age as a continuous variable was again not a significant factor (0.007 cm/yr, 95% CI –

Table 2 – Mixed-effect linear regression demonstrating associations between clinicodemographic characteristics and GR_i and GR_p

Characteristics	Univariable		Multivariable	
	Difference, cm/yr (95% CI)	*p* value	Difference, cm/yr (95% CI)	*p* value
Growth rate from initial image (GR_i)				
Age (yr)	−0.001 (−0.008 to 0.005)	0.69	−0.0001 (−0.007 to 0.007)	0.97
Male	0.002 (−0.137 to 0.142)	0.98	−0.038 (−0.184 to 0.108)	0.61
Race				
White	Reference	–	Reference	–
Black	−0.229 (−0.416 to −0.042)	0.02	−0.283 (−0.479 to −0.088)	0.005
Other	0.105 (−0.215 to 0.426)	0.52	0.096 (−0.227 to 0.419)	0.56
Baseline Charlson		–		
Comorbidity Index				
0	Reference	0.12	Reference	–
1	0.145 (−0.036 to 0.326)	0.26	0.158 (−0.031 to 0.347)	0.10
2	0.108 (−0.082 to 0.299)	0.25	0.103 (−0.093 to 0.299)	0.30
≥3	0.118 (−0.083 to 0.318)		0.173 (−0.037 to 0.382)	0.11
Baseline body mass index (kg/m^2)	0.003 (−0.007 to 0.014)	0.51	0.004 (−0.007 to 0.015)	0.45
Baseline tumor diameter (cm)	−0.039 (−0.115 to 0.038)	0.32	−0.047 (−0.130 to 0.036)	0.27
Growth rate from prior image (GR_p)				
Age (yr)	0.007 (−0.003 to 0.017)	0.18	0.008 (−0.004 to 0.020)	0.17
Male	0.097 (−0.120 to 0.313)	0.38	0.047 (−0.184 to 0.278)	0.69
Race				
White	Reference	–	Reference	–
Black	−0.091 (−0.386 to 0.204)	0.55	−0.103 (−0.417 to 0.211)	0.52
Other	−1.189 (−1.706 to −0.672)	<0.001	−1.192 (−1.720 to −0.664)	<0.001
Baseline Charlson		–		
Comorbidity Index				
0	Reference	0.42	Reference	–
1	0.113 (−0.161 to 0.388)	0.11	0.149 (−0.145 to 0.442)	0.32
2	0.247 (−0.054 to 0.548)	0.13	0.213 (−0.102 to 0.528)	0.19
≥3	0.251 (−0.070 to 0.573)		0.281 (−0.058 to 0.621)	0.11
Baseline body mass index (kg/m^2)	−0.002 (−0.019 to 0.014)	0.79	−0.0007 (−0.019 to 0.017)	0.93
Baseline tumor diameter (cm)	−0.002 (−0.118 to 0.115)	0.98	−0.038 (−0.167 to 0.091)	0.56

CI = confidence interval; GR_i = growth rate from the initial image; GR_p = growth rate from the prior image.

0.003 to 0.017, p = 0.18; Table 2). Race was significantly associated with GR_p in the multivariable model; none of the other factors were significantly associated with GR_p.

The numbers of measurements stratified by the predefined age cutoffs are listed in Table 3. Prior to adjustment for other variables, no statistically significant association was observed between age and GR_i at any of the age cutoffs. Upon adjustment, patients aged ≥65 yr demonstrated an increased GR_i compared with those aged <65 yr (0.151 cm/yr, 95% CI 0.002–0.300, p = 0.05). None of the other age cutoffs were significantly associated with GR_i after adjustment.

Similar to GR_i, no statistically significant association was observed between age and GR_p at any of the age cutoffs. Upon adjustment, patients aged ≥70 yr demonstrated an increased GR_p compared with those aged <70 yr (0.243 cm/yr, 95% CI 0.004–0.481, p = 0.05). The other age cutoffs were not significantly associated with GR_p after adjustment.

There were 86 patients (15.1%) who converted from AS to DI. There were 43 patients (50.0%) who converted to DI with a GR_i of >0.5 cm/yr, all of whom also had a GR_p of >0.5 cm/yr. There were an additional 18 patients (20.9%) who converted to DI on the basis of a GR_p of >0.5 cm/yr alone. Patients who converted were younger (69.6 vs 71.2 yr, p = 0.02) and had larger tumors at the initial scan (2.1 vs 1.8 cm, p = 0.005) than those who remained on AS (Table 1). Among those who converted, DI was selected after an average of 3.6 measurements. The median GR_i and GR_p of all measurements in patients who underwent DI were 0.323 cm/yr (IQR 0.085–0.623) and 0.326 cm/yr (IQR 0–0.951), respectively (Fig. 1B).

Compared with patients who remained on AS, those who converted to DI had an increased GR_i of 0.293 cm/yr (95% CI 0.097–0.489, p = 0.003), which remained significant after adjustment (0.282 cm/yr, 95% CI 0.078–0.487, p = 0.007; Table 4). The GR_p was not significantly increased in the DI group on unadjusted (0.308 cm/yr, 95% CI −0.019 to 0.636, p = 0.07) or adjusted (0.319 cm/yr, 95% CI −0.032 to 0.670, p = 0.07) analysis.

4. Discussion

As our understanding of cancer immunology grows, there are data to suggest that elderly patients with cancer may harbor features in the tumor microenvironment that allow for more rapid growth compared with younger patients [4]. These findings are particularly relevant to patients who choose to forego immediate intervention to avoid the side effects and potential complications of treatment. To this end, we demonstrate using a large, prospective, multi-institutional registry that there is no clear evidence of accelerating tumor growth in aging patients who chose to undergo AS for SRMs. Hence, our data suggest that "prophylactic" intervention on an aging patient with an SRM need not be pursued routinely by a certain age for fear of sudden acceleration in growth or metastatic potential.

Interpretations of progression can vary based on the definition of GR being used (ie, GR_i vs GR_p). Although GR is widely used as one of the metrics to evaluate for progression, there appear to be inconsistencies within the literature as to how a GR should be defined. Most studies, in fact, do not offer a clear definition [3,10–12]. For the few studies

Table 3 – Associations between dichotomized age groups and both definitions of GR

Age at measurement (yr)	Number of measurements	Number of patients	Median GR_i (IQR)	*p* value	GR_i unadjusted	*p* value	GR_i adjusted	*p* value	Median GR_p (IQR)	*p* value	GR_p unadjusted	*p* value	GR_p adjusted	*p* value
<80	1953	471	0.095 (−0.021 to 0.323)	0.11	Reference	0.79	Reference	0.99	0.088 (−0.199 to 0.485)	0.91	Reference	0.31	Reference	0.29
≥80	589	157	0.090 (−0.060 to 0.299)		−0.019		−0.001		0.097 (−0.240 to 0.571)		0.127		0.149	
<75	1523	379	0.098 (−0.014 to 0.335)	0.06	Reference	0.52	Reference	0.66	0.089 (−0.201 to 0.492)	0.95	Reference	0.11	Reference	0.09
≥75	1019	264	0.090 (−0.053 to 0.293)		−0.040		−0.029		0.089 (−0.213 to 0.519)		0.174		0.209	
<70	1030	263	0.095 (0–0.312)	0.72	Reference	0.90	Reference	0.80	0.070 (−0.199 to 0.464)	0.61	Reference	0.07	Reference	0.05
≥70	1512	371	0.093 (−0.044 to 0.314)		0.008		0.017		0.095 (−0.209 to 0.514)		0.199		0.243	
<65	654	177	0.095 (0–0.297)	0.84	Reference	0.07	Reference	0.05	0 (−0.196 to 0.402)	0.18	Reference	0.28	Reference	0.28
≥65	1888	448	0.094 (−0.043 to 0.319)		0.130		0.151		0.100 (−0.202 to 0.524)		0.137		0.148	

GR = growth rate; GR_i = growth rate from the initial image; GR_p = growth rate from the prior image; IQR = interquartile range.
GR_i and GR_p were measured in units of cm/yr.

Table 4 – Associations between final patient disposition and both definitions of GR

Final disposition	Number of measurements	Number of patients	Median GR_i (IQR)	*p* value	GR_i unadjusted	*p* value	GR_i adjusted	*p* value	Median GR_p (IQR)	*p* value	GR_p unadjusted	*p* value	GR_p adjusted	*P*-value
Active surveillance	2222	485	0.077 (−0.052 to 0.277)	<0.001	Reference	0.003	Reference	0.007	0 (−0.215 to 0.431)	<0.001	Reference	0.07	Reference	0.07
Delayed intervention	320	86	0.323 (0.085–0.623)		0.293		0.282		0.326 (0–0.951)		0.308		0.319	

GR = growth rate; GR_i = growth rate from the initial image; GR_p = growth rate from the prior image; IQR = interquartile range.
GR_i and GR_p were measured in units of cm/yr.

that define a GR, there is a mix between GR_i and GR_p [13,14]. Others have devised a system in which an "overall GR" is defined as the average of all GR_p values, but this calculation is highly susceptible to skewed data points, which runs the risk of overestimating the true GR [15–17]. Radiologists typically use two consecutive images to evaluate for interval developments, but as data from the initial image may not always be available readily, GR_p is the more accessible definition in the clinical setting. Certainly, the DISSRM experience appears to reflect this theory, as there were no patients who underwent DI on the basis of GR_i alone. This would suggest that any single GR_p is more susceptible than the GR_i to variations that exceed the threshold for intervention. Indeed, this is consistent with a previous analysis of the DISSRM cohort, which demonstrated that variability in GRs decreased with an increase in the number of data points for any given patient [8]. As such, while GR_i may be more cumbersome to calculate, it likely paints a more accurate picture of tumor growth over time.

Nevertheless, regardless of the definition used, we found no consistent association between age and GR. Although our results suggest that patients aged ≥65 yr demonstrate an increased adjusted GR_i compared with patients aged <65 yr, this observation does not hold at higher age cutoffs. Furthermore, only the 70-yr age cutoff demonstrated a significant difference in adjusted GR_p. This suggests that tumor velocity is likely highest between ages 65 and 75 yr. However, these statistically significant findings likely do not translate to clinical relevance since the differences in GR_i and GR_p fall below the conventional 0.5 cm/yr threshold. A prior study of 89 octogenarians with cT1 disease (≤7.0 cm) undergoing AS revealed a GR of 0.20 cm/yr [18]. Although slightly higher than our finding of 0.09 cm/yr among octogenarians, our study includes only patients with cT1a (≤4.0 cm) disease, which has been shown to demonstrate the lowest GRs of all renal mass stages [10]. Regardless, no acceleration in GRs appears to be present in elderly populations, which is reassuring for those who choose to pursue AS into old age. Instead, race appeared to play a more significant role, with Black and other race patients exhibiting decreased GR_i and GR_p, respectively. Although outside the scope of our study, this could be indicative of biological or socioeconomic differences among races and may warrant future investigation [19].

When examining patients who underwent DI, we found that this patient cohort experienced an increased GR_i compared with those who remained on AS. This is consistent with a prior meta-analysis of six studies that also demonstrated similar findings (0.38 cm/yr for the DI group vs 0.24 cm/yr for the AS group) [20]. This narrow difference between the DI and AS groups likely reflects an appropriate overabundance of caution to intervene while the cancer remains in a curable stage. Indeed, the same meta-analysis found that patients who progressed to metastatic disease while on AS demonstrated a larger difference in GRs than those who did not progress to metastatic disease (0.80 vs 0.30 cm/yr) [20]. This is further corroborated by the octogenarian study, in which the GR for those with metastatic progression was 1.28 cm/yr versus 0.18 cm/yr for those without [18]. Since no patients in our study experienced progression from localized to metastatic disease, we are unable to directly confirm these findings, but our reported GRs reassuringly fall in line with those of patients who did not experience metastasis. Furthermore, a prior investigation comparing AS with primary intervention confirms that no difference in overall mortality is seen among elderly patients aged 75 yr or older [21]. This, in conjunction with a lack of a GR increase with age, suggests that AS is a safe management strategy into old age. Notably, however, GR_p did not significantly differ between patients who underwent DI and those who continued on AS, suggesting that GR_i is a more stable indicator of true growth than GR_p. Nevertheless, the triggers to pursue DI remain fairly complex, with a variety of patient- and tumor-related factors often driving these decisions [22].

There are several limitations that should be noted. First, with a median age of 70.9 yr, our patient population may be too young to demonstrate true changes to their immune system and tumor microenvironment. Furthermore, patients in DISSRM represent a unique cohort of patients who are potential surgical candidates who have deferred immediate intervention and therefore may be potentially too healthy to demonstrate detriments in their immune system, especially when compared with individuals who undergo watchful waiting. With further maturation of the dataset, it may be possible to detect changes in GRs by following patients over an extended period of time (ie, >30 yr). Next, renal mass biopsy is not a requirement for enrollment in our AS program; as such, it was not possible to histologically characterize all SRMs. In light of recent evidence demonstrating differential GRs across different subtypes of RCC, a renal mass biopsy may provide a rough benchmark as to the expected GR for certain RCC subtypes [23]. Finally, the concept of tracking GRs may not be a fruitful metric for predicting tumor biology, as no prospective data have linked a GR to high-grade or high-stage disease. Still, in the absence of reliable biomarkers, a GR continues to be widely used as a trigger for intervention among patients in AS.

5. Conclusions

Leveraging a large, multi-institutional, prospective registry, we show that patients with SRMs on AS do not exhibit a clear association between tumor GRs and patient age. Tumor velocity appears to be the highest between 65 and 75 yr, but the GR still falls below the conventional threshold of 0.5 cm/yr to prompt an intervention. At older ages, there is little to no acceleration of tumor growth, suggesting that AS is a safe and durable management option for aging patients with SRMs.

Author contributions: Nirmish Singla had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Singla.
Acquisition of data: Wlajnitz, Yerrapragada, Chang, Wagner, McKiernan, Pierorazio, Allaf, Singla.

Analysis and interpretation of data: Alam, Yerrapragada, Watts, Pallauf, Enikeev, Chang, Wagner, McKiernan, Pierorazio, Allaf, Singla.
Drafting of the manuscript: Alam, Singla.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Alam.
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Supervision: Singla.
Other: None.

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