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Kidney Cancer

Small Renal Mass Surveillance: Histology-specific Growth Rates in a Biopsy-characterized Cohort

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Abstract

Background: Most reports of active surveillance (AS) of small renal masses (SRMs) lack biopsy confirmation, and therefore include benign tumors and different subtypes of renal cell carcinoma (RCC).
Objective: We compared the growth rates and progression of different histologic subtypes of RCC SRMs (SRM^{RCC}) in the largest cohort of patients with biopsy-characterized SRMs on AS.
Design, setting, and participants: Data from patients in a multicenter Canadian trial and a Princess Margaret cohort were combined to include 136 biopsy-proven SRM^{RCC} lesions managed by AS, with treatment deferred until progression or patient/surgeon decision.
Outcome measurements and statistical analysis: Growth curves were estimated from serial tumor size measures. Tumor progression was defined by sustained size $\geq$4 cm or volume doubling within 1 yr.
Results and limitations: Median follow-up for patients who remained on AS was 5.8 yr (interquartile range 3.4–7.5 yr). Clear cell RCC SRMs (SRM^{ccRCC}) grew faster than papillary type 1 SRMs (0.25 and 0.02 cm/yr on average, respectively, $p = 0.0003$). Overall, 60 SRM^{RCC} lesions progressed: 49 (82%) by rapid growth (volume doubling), seven (12%) increasing to $\geq$4 cm, and four (6.7%) by both criteria. Six patients developed metastases, and all were of clear cell RCC histology. Limitations include the use of different imaging modalities and a lack of central imaging review.
Conclusions: Tumor growth varies between histologic subtypes of SRM^{RCC} and among SRM^{ccRCC}, which likely reflects individual host and tumor biology. Without validated

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biomarkers that predict this variation, initial follow-up of histologically characterized SRMs can inform personalized treatment for patients on AS.
Patient summary: Many small kidney cancers are suitable for surveillance and can be monitored over time for change. We demonstrate that different types of kidney cancers grow at different rates and are at different risks of progression. These results may guide better personalized treatment.

1. Introduction

Most small renal masses (SRMs), defined as enhancing solid tumors <4 cm in diameter without metastases [1,2], are renal cell carcinomas (75%; SRM^{RCC}) and at a low risk of cancer-specific mortality [3–6].

Although SRMs comprise a heterogeneous group of diseases, most grow slowly with limited metastatic potential, including biopsy-proven SRM^{RCC} [7,8]. Initial active surveillance (AS) has therefore become an attractive management option and has been incorporated into treatment guidelines [9–12]. However, the evidence to date surrounding the natural history of SRMs managed by AS has not been informed by their histologic subtype [4,13–19]. The growth and progression patterns for different histologic SRM^{RCC} lesions remain poorly understood.

In the absence of validated prognostic markers [20,21], better understanding of biopsy-characterized renal cell carcinoma (RCC) tumor kinetics may allow for improved individualized treatment recommendations. We thus report the histology-specific growth and progression of the largest cohort of biopsy-confirmed SRM^{RCC} managed by initial AS.

2. Patients and methods

Eight centers across Canada (Renal Cell Carcinoma Consortium of Canada [RC^4]) prospectively enrolled patients with an incidental SRM diagnosis between August 2004 and December 2015 in a phase 2 trial of initial AS with treatment after progression [4]. Eligibility criteria included a clinical T1aN0M0 renal mass in patients who elected not to have immediate treatment. All patients were asked to undergo percutaneous needle core renal mass biopsy (RMB) for pathologic diagnosis. We pooled the RC^4 cohort with our Princess Margaret Cancer Centre (PM) AS cohort identified retrospectively for the same period. These patients had been started on AS after biopsy but not enrolled in the RC^4 trial (usually because their SRM was detected >12 mo before they were seen).

Patients were ineligible if they had an estimated life expectancy of <2 yr, were on concurrent systemic therapy for malignancy, had a hereditary renal cancer syndrome, and/or had a nondiagnostic or benign biopsy. One patient with a single image was excluded. These eligibility and exclusion criteria were the same irrespective of whether they were in the prospective trial or the retrospective cohort. This research was approved by the University Health Network Research Ethics and completed with anonymized data.

Serial imaging with computed tomography (CT), magnetic resonance imaging (MRI), or ultrasound (U/S) was performed at 3, 6, and 12 mo, and annually thereafter. Tumor size was measured by maximal axial diameter. Tumor volume was calculated depending on the number of measurements available ($\frac{\pi}{6}[x \times y \times z]$ if all three measurements were available [52% of the time], $\frac{\pi}{6}\left[x \times y \times \frac{1}{2}\{x+y\}\right]$ if two measurements were available [25%], and $\frac{\pi}{6}[x^3]$ if only one measurement was available [23%]) [22]. Baseline chest imaging became mandatory midway through accrual and, thus, was not available in 40% of individuals. The technique for core biopsy has been reported previously [5,23]. A 17-gauge guiding cannula and an 18-gauge core needle were used in multiple passes, and the core specimens were placed in 10% formalin solution for pathology. The number of cores was left to the operator's discretion.

Tumor progression was defined by (1) large size (sustained maximum diameter >4 cm in at least two measurements within 15 mo) and/or (2) rapid growth (doubling of tumor volume within 1 yr). These criteria for local progression have been reported previously [4] and represent conservative expert opinion as triggers for treatment consideration. Once patients reached these criterion thresholds, it was standard practice at our institutions to recommend treatment, although the ultimate decision was made in a patient-centric fashion.

2.1. Statistical analysis

The primary study outcomes were tumor growth rate and progression. A Kaplan-Meier survival curve was used to estimate the probability of progression at 5-yr follow-up, and Cox proportional hazard modeling was used to estimate the hazard ratio (HR) comparing the risk of progression between cohorts. Follow-up time was measured from the first image until progression or the last image without progression for censored patients.

Axial diameter and volumetric growth rates were modeled using linear mixed effect models (clustered by lesion), which included time (year) as a linear term and both random intercept and random slope terms. Data were log transformed to stabilize the variance since the growth of the mass is exponential. Differences in growth rates between the retrospective and prospective cohorts and between different histologic subtypes were tested by including, respectively, main effects and interaction terms between year and cohort or between year and histologic subtype. All analyses were completed using R version 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was assessed at $p <$ 0.05 for two-sided comparison.

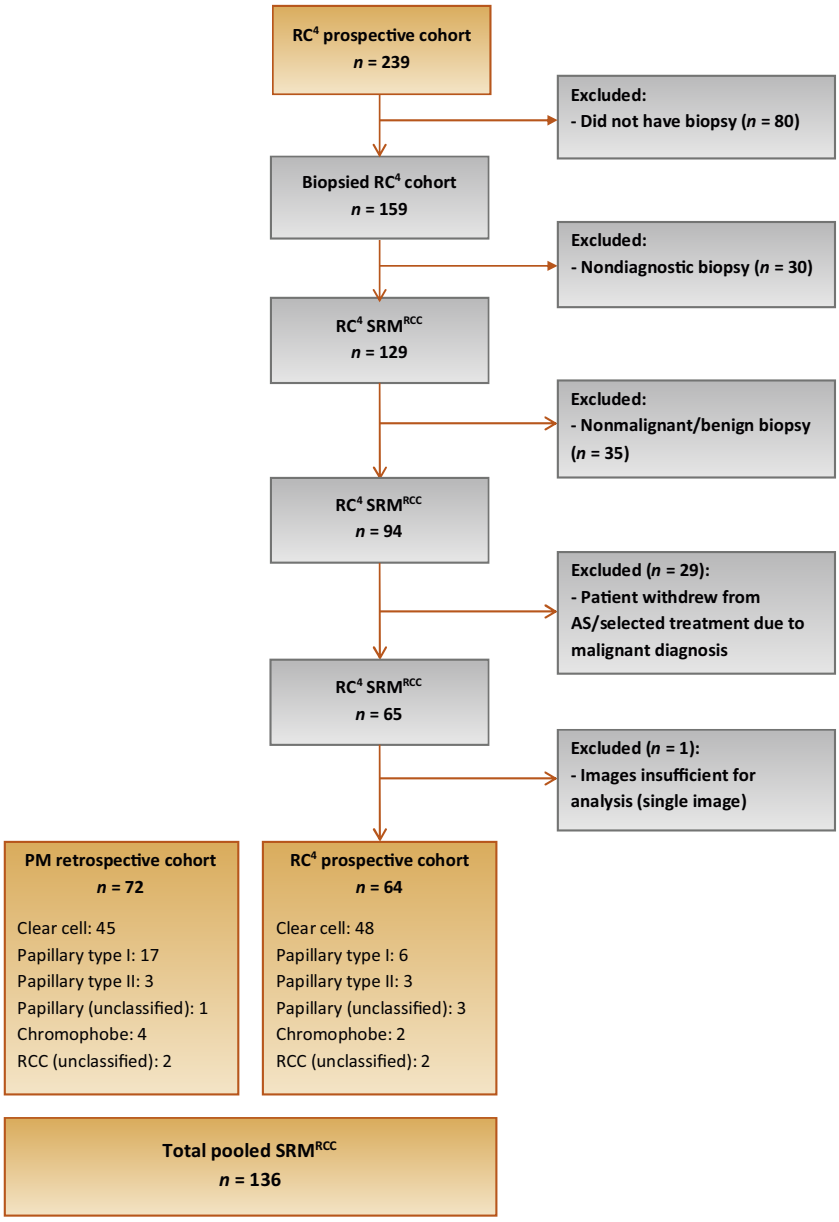

Fig. 1 – CONSORT diagram of the cohorts of patients with SRMs managed by active surveillance.
AS = active surveillance; PM = Princess Margaret Cancer Centre; RC[4] = Renal Cell Carcinoma Consortium of Canada; RCC = renal cell carcinoma; SRM = small renal mass.

3. Results

The prospective RC[4] trial included 239 patients with SRMs, of whom 159 were biopsied. Among 94 patients with proven RCCs (SRM[RCC]), 62 (with 64 tumors) were eligible (Fig. 1). An additional 72 patients (with 72 SRM[RCC] lesions) at PM were included. There was no significant difference in growth rate (interaction $p = 0.8$; Supplementary Fig. 1) or progression rate (HR: 1.04, 95% confidence interval [CI]: 0.62–1.73, $p = 0.9$ for retrospective vs prospective cohort) between the groups, and the patients were pooled for a combined cohort of 134 patients with 136 SRM[RCC] lesions.

The median age at the first image was 70 (range 41–87) yr and median diameter was 2.3 (IQR 1.8–2.9) cm. For patients still on AS (49 lesions at the end of follow-up) as a surrogate for the total duration of observation, their median time of follow-up was 5.8 (IQR 3.4–7.5) yr. Of the patients, 17% were followed for at least 7 yr. Within follow-up, 963 images and their modalities were identified, of which 482 (50%) were imaged with CT, 425 (44%) with U/S, and 56 (6%) with MRI. Imaging modality did not demonstrate an association with tumor diameter or volume. Pathologic characteristics of the lesions are shown in Table 1.

Table 1 – Characteristics of SRMs (n = 136 lesions).

Variable	Categories		RC[4] (N = 64)	PM (N = 72)
Histology, n (%)	Chromophobe		2 (3.1)	4 (5.6)
	Clear cell		48 (75)	45 (63)
	Papillary, type I		6 (9.4)	17 (24)
	Papillary, type II		3 (4.7)	3 (4.2)
	Papillary, unclass		3 (4.7)	1 (1.4)
	RCC, unclass		2 (3.1)	2 (2.8)
Grade (clear cell only), n (%)	I		22 (46)	17 (38)
	II		17 (35)	23 (51)
	III		3 (6.2)	5 (11)
	Unknown		6 (13)	0 (0)
Imaging appearance, n (%)	Cystic		4 (6.2)	3 (4.2)
	Solid		50 (78)	69 (96)
	Solid and cystic		1 (1.6)	0 (0)
	Unknown		9 (14.1)	0 (0)
Baseline volume	Median (25–75%)	7.2 (4.7–11)		3.6 (1.8–7.5)
Baseline axial diameter	Median (25–75%)	2.5 (2.2–3)		2 (1.5–2.7)
Time between first and last image (yr)	Median (25–75%)	2.6 (1.2–5.3)		3.9 (2.2–6.5)
Treatment, n (%)	Received treatment before end of follow-up		30 (47)	23 (32)
Type of treatment, n (%)	Partial nephrectomy		8 (27) [a]	9 (39)
	Radical nephrectomy		3 (10)	5 (22)
	Nephrectomy		1 (3.3)	0 (0)
	Ablation		9 (30)	7 (30)
	Embolization		0 (0)	1 (4.3)
	Type unknown		9 (30)	1 (4.3)

PM = Princess Margaret Cancer Centre; RC[4] = Renal Cell Carcinoma Consortium of Canada; RCC = renal cell carcinoma; SRM = small renal mass; unclass. = unclassified.
[a] Percentage of total patients treated.

The probability of progression at 5 yr was 54% (95% CI: 43–64%). Sixty lesions had progressed according to large size or rapid growth by the last follow-up, of which the majority (73%) had clear cell histology. Of these, 49 (82%) progressed by rapid growth with volume doubling within 1 yr, seven (12%) increased to ≥4 cm, and four (6.7%) progressed by both criteria. The individual growth patterns are available in Supplementary Fig. 2.

The average growth rate in maximal tumor diameter was 8%/yr (0.17 cm/yr in the 1st year, 0.19 cm/yr over the first 3 yr, and a predicted growth of 0.28 cm/yr over 12 yr). The average increase in volume was 1.1 cm^3 in the 1st year and 1.3 cm^3/yr over the first 3 yr, and predicted to be 4.2cm^3/yr over 12 yr.

By histology, there was a significant difference in the diameter growth rate between clear cell (SRM^{ccRCC}) and papillary type 1 (SRM^{p1RCC}) RCC SRMs ($p < 0.001$; Fig. 2A). The predicted growth rates for diameter and volume for SRM^{ccRCC} over 3 yr were 0.28 cm/yr and 2.4 cm^3/yr, respectively. The growth rates in diameter for SRM^{ccRCC} over 3 yr were heterogeneous and ranged from −0.03 to 1.0 cm/yr (IQR 0.15–0.41 cm/yr). Of these, 14 lesions (15%) had a diameter growth rate of ≥0.5 cm/yr. In contrast, the average diameter- and volume-predicted growth rates for SRM^{p1RCC} remained essentially unchanged over the same period (0.017 cm/yr and −0.006 cm^3/yr, respectively). The growth rates are depicted in waterfall plots, clustered by histology (Fig. 2B) and cumulatively overlaid (Fig. 2C).

In prolonged follow-up, 46 SRM^{ccRCC} lesions were followed for >3 yr. Interestingly, of 21 (46%) SRMs that showed rapid local growth, eight (38%) did not demonstrate sustained growth on repeat measurement, highlighting the substantial measurement variation and/or stochastic growth that exists in serial measurements of SRMs.

Where pathology reports were available (ie, nephrectomy), nine patients had lesions with a pathologic grade of ≥3, three patients had evidence of tumor necrosis (including 1/9 with grade 3+), and no patients on final pathology had evidence of sarcomatoid or rhabdoid features. Metastases occurred in six SRM^{RCC} patients (4%), and all of them had clear cell histology. One patient with minimal growth was diagnosed with chest metastases on the first chest x-ray at 6 mo with no pre-AS x-ray. Another patient was found to have bone metastases after 2 yr on AS without local progression. Two patients experienced rapid local growth within the 1st and 2nd years of AS, which triggered surgery, but progressed to metastases in follow-up. Finally, two patients developed metastases after having been placed on watchful waiting: they experienced local growth on AS initially, but refused or were unfit for treatment by that time (before eventually developing metastases at a final diameter of 5 and 7 cm at 50 and 90 mo, respectively). Therefore, of the six patients progressing to metastases, only one was managed exclusively by AS (two cases occurring after definitive surgical management, one with rapid progression <6 mo in the setting of incomplete staging, and two on eventual watchful waiting). Twenty-nine patients died by the end of follow-up: three as a result of renal cancer metastases, 23 from causes unrelated to renal cancer, and

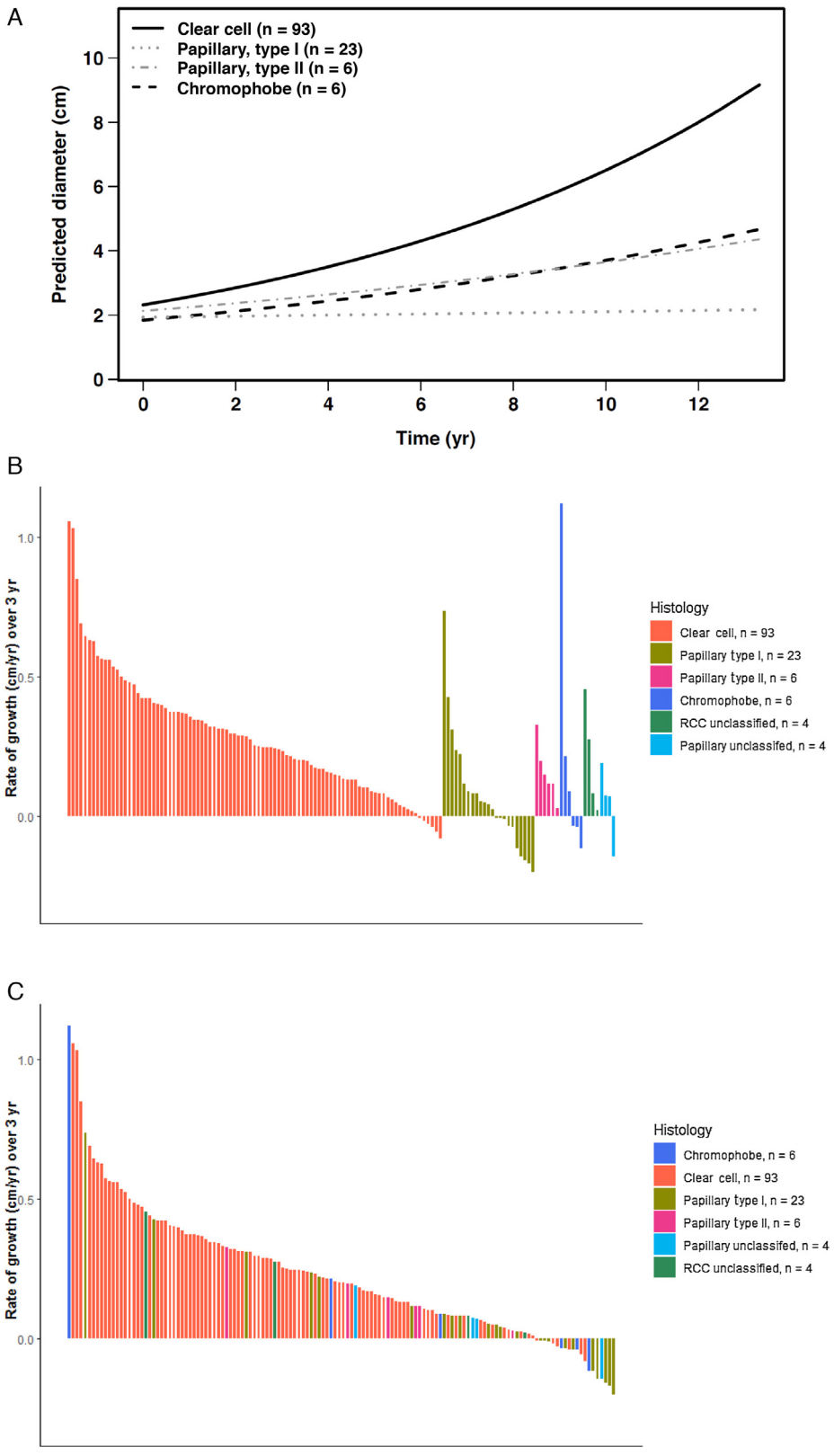

Fig. 2 – (A) Average SRM growth rates (maximum average diameter in cm) by histological subtype. The growth rate for clear cell renal cell carcinoma SRM was significantly higher than for papillary type 1 RCC ($p = 0.0003$). Growth rates for log-transformed diameter were modeled using linear mixed effect models (clustered by lesion), including both random intercept and random slope terms. Growth rates were compared between histological subtypes by including histological subtype as a main effect and an interaction term between year and subtype in the linear mixed model. Waterfall plots of individual growth rates (cm/yr) based on predicted growth over 3 yr within individuals (annualized): (B) clustered by histology and (C) subtypes overlaid.
RCC = renal cell carcinoma; SRM = small renal mass.

three from unknown causes. Six patients were lost to follow-up.

4. Discussion

Optimal management of newly diagnosed SRMs is controversial, and there are no validated prognostic markers for progression. Local growth can impact treatment options and metastatic disease is usually incurable. Published AS cohorts are not histologically defined, and given that up to 30% of SRMs are not RCC, study cohorts have been heterogeneous and do not reflect malignant tumor behavior alone [24,25]. Furthermore, follow-up has generally been short across studies due to treatment or competing risks of mortality. This is a critical issue, as SRM growth is usually slow and metastases are infrequent.

In this study, we present the largest cohort of biopsy-confirmed SRM^{RCC} managed by initial AS. RMB has not been adopted widely by urologists, but we routinely biopsy all SRMs before treatment decision [5,26,27], which has enabled us to generate natural history data for SRM^{RCC} by histology. This report is an update of our prospective multicenter phase 2 clinical trial of AS for SRMs [4] and has several main findings.

First, SRM^{RCC} overall have a slow growth rate of 0.19 cm/yr (diameter) or 1.3 cm^3/yr (volume) over a 3-yr follow-up period, in line with rates presented previously by McIntosh et al [6]. However, given the unique biopsy-proven nature of our cohort, we were able to observe notable differences between and within histologic subtypes. For the most frequent subtype SRM^{ccRCC}, these lesions displayed substantial heterogeneity: most demonstrated stable or little growth for years, while a small subset (15%) exhibited growth of $\geq$0.5 cm/yr. Strikingly, all metastases had clear cell histology. Thus, there is a clear need for better personalized markers and an understanding of the underlying tumor biology (eg, clear cell RCC vs clear cell papillary RCC [28]) to differentiate the heterogeneous potential in what appear to be similar SRM^{ccRCC}. In contrast, SRM^{p1RCC} lesions remained stable throughout observation, exhibiting near zero growth, and had no documented metastases. These findings re-emphasize the safety of AS in these histologic-proven patients. Therefore, for the time being, an initial histologic-driven strategy of AS to allow an SRM to declare its potential for progression/necessity for treatment may be appropriate. Furthermore, considering the few cases of metastatic progression and renal cancer–specific mortality observed in our cohort, this strategy may be particularly appealing in comorbid patients where treatment portends a greater risk.

Second, the definition of progression and the way it is measured varies widely in practice. This is particularly apparent when individual tumor growth is evaluated as a clinician would in the clinic from visit to visit (Supplementary Fig. 2). Some SRMs demonstrate little growth initially, but may accelerate at a later date, as evidenced in the case of 46 SRM^{ccRCC} lesions followed over 3 yr. This emphasizes the need for continued AS despite an initial suggestion of indolence, and may reflect ongoing genomic/biological evolution in the tumor and host. Equally important, disparities in tumor measurement exist between images: in numerous cases, tumors that appeared to be growing or >4 cm were stable in subsequent observations. These may reflect inter- and intraobserver variability, or stochasticity in growth [29]. By reviewing the imaging (and its growth trajectory) and reimaging (sometimes after a 2–3-mo interval), there was less difference and apparent progression had not occurred. We attribute most of these observations to measurement variation. Therefore, it appears that clinical decisions should be delayed until sustained growth is confirmed through axial imaging.

Lastly, while it is generally believed that SRM growth predicts the risk for metastases, this is not always the case and we have observed metastatic progression in the absence of local growth (specifically, one case after 2 yr of AS). Other cases included one patient with metastatic progression at 6 mo (likely representing incomplete staging), two cases with metastatic progression years after local treatment (unclear whether the treatment window had been missed or they were destined to have metastases), and two cases with metachronous metastases where the patient refused or was unable to safely undergo treatment when the tumor reached 4 cm. Taken together, the risk of metastases remains low in a well-selected population: only one patient was managed exclusively by AS (1%), with a total metastatic progression of 4%. However, for this one case, tumor diameter and volume did not reflect biological risk accurately.

Notably, while our study was focused on patients with malignant histologies, in real-world practice, there are nondiagnostic and benign biopsies. In this context, we have previously reported that repeat RMB is diagnostic in an additional 80–83% of cases, yielding a cumulative diagnostic rate of 91–94% in single- and multi-institutional series [5,30]. Similarly, in a meta-analysis completed by Marconi et al [31], the median diagnostic biopsy rate across 57 studies and 5228 patients was 92%. Furthermore, although the outcome of patients with benign histologies was not the focus of this work, we have already reported on the growth rates for oncocytoma (0.14 cm/yr) and angiomyolipoma (0.002–0.02 cm/yr) for comparison [24,25,32]. Thus, our study highlights the potential value of biopsy to inform histology-specific SRM management in malignant cases.

A recent study by Ball et al [33] reported variation in the growth rates of SRMs based on genetic alterations and histology in patients with an inherited kidney cancer syndrome. However, hereditary SRMs are likely very different from the more common sporadic RCC, and less generalizable to the general population. Indeed, once stratified by histology, this was reflected in the limited number of clear cell and papillary patients in the hereditary cohort, and limits the direct comparison of any growth rates beyond description. In both cases, significant heterogeneity in the growth rates between and within histologies was observed, and must be characterized accurately when managing these patients.

This study has certain limitations. Different imaging modalities and indications (off-protocol) between patients may have affected the consistency of the measurements. This is unavoidable in the real-world clinical setting, but likely accounts for some of the heterogeneity within this study. As a result of considerable variation between images, we now recommend short-term follow-up with axial imaging after initial progression before commencing any treatment.

Notably, this variation may also have exacerbated the impact of rapid growth: in our study, the vast majority of patients who progressed did so for rapid growth (volume doubling within 1 yr), which may reflect a limitation in this outcome definition. In particular, smaller lesions are more susceptible to volume doubling despite minimal absolute change to their axial diameter (as radius is cubed for volumetric calculations). These changes in diameter may then represent true growth or measurement error. Regardless of the source, however, these may inflate the percentage of patients achieving this progression endpoint versus that in clinical practice. A lack of central imaging review is another important limitation, but is reflective of real-world practice.

In addition, we pooled data from a prospectively enrolled trial and our own retrospective database, which may introduce a selection bias. Although we attempted to identify homogenous patients (both cohorts had the same inclusion and exclusion criteria, and all patients elected not to have immediate treatment), the main difference is that the trial patients were newly diagnosed patients, whereas those in the retrospective cohort were usually detected >12 mo before being seen. This may introduce a bias toward patients who are slower to progress and more indolent in the retrospective cohort, although this was not seen when we pooled the data. However, while growth and progression rates were similar between cohorts, small differences remain in the histology, imaging, and treatment characteristics of the cohorts. Furthermore, small subgroup sizes for papillary type II and chromophobe histologies limit their interpretation, but have been described in previous work, including chromophobe and oncocytic tumors [25].

Despite these issues, the strength of this study relates to the unique biopsy-characterized RCC cohort, which is the largest in the literature and allows for a subgroup analysis without the heterogeneity present in other studies. This is the first study to show different progression and growth rates among different sporadic RCC subtypes, and provides useful additional support for RMB in managing small incidental RCCs.

5. Conclusions

This is the largest cohort of biopsy-proven sporadic SRM^{RCC} patients followed with AS. The growth rate of SRM^{RCC} is slower than previously reported and likely reflects the heterogeneity of these lesions. There is significant difference in growth and progression among different RCC subtypes. Pathology from an RMB will become important in counseling patients and personalizing the management of SRMs until non–tissue-based markers are developed.

***Author contributions*:** Antonio Finelli 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: Finelli, Jewett, Morash, Pautler, Siemens, Tanguay, Rendon, Gleave, Drachenberg, Chin, Fleshner.
Acquisition of data: Finelli, Jewett, Haider, Kachura, Fleshner, Al-Matar.
Analysis and interpretation of data: Sykes, Jewett, Finelli, Cheung.
Drafting of the manuscript: Jewett, Finelli.
Critical revision of the manuscript for important intellectual content: Jewett, Finelli, Morash, Pautler, Siemens, Tanguay, Rendon, Gleave, Drachenberg, Chin, Fleshner, Evans, Cheung.
Statistical analysis: Sykes.
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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eururo.2020.06.053.

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