original reports

Growth Rates of Genetically Defined Renal Tumors: Implications for Active Surveillance and Intervention

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abstract

PURPOSE Published series of growth rates of renal tumors on active surveillance largely consist of tumors without pathologic or genetic data. Growth kinetics of genetically defined renal tumors are not well known. Here, we evaluate the growth of genetically defined renal tumors and their association with patient clinical and genetic characteristics.

PATIENTS AND METHODS We evaluated patients with an inherited kidney cancer susceptibility syndrome as a result of a pathologic germline alteration of *VHL, MET, FLCN,* or *BAP1* with at least 1 solid renal mass managed with active surveillance at our institution. Tumor growth rates (GR) were calculated and patients were stratified by genetic alteration and other clinical and genetic factors to analyze differences in growth rates using linear regression and comparative statistics.

RESULTS A total of 292 patients with 435 genetically defined tumors were identified, including 286 *VHL*-deficient, 91 *FLCN*-deficient, 52 *MET*-activated, and 6 *BAP1*-deficient tumors. There were significant differences in GRs when stratified by genetic alteration. *BAP1*-deficient tumors had the fastest median GR (0.6 cm/y; interquartile range [IQR], 0.57-0.68 cm/y), followed by *VHL*-deficient tumors (GR, 0.37 cm/y; IQR, 0.25-0.57 cm/y), *FLCN*-deficient tumors (GR, 0.10 cm/y; IQR, 0.04-0.24 cm/y), and tumors with *MET* activation (GR, 0.15 cm/y; IQR, 0.053-0.32 cm/y; $P < .001$). Tumors from the same patient had similar GRs. Younger age was independently associated with higher GR ($P = .005$).

CONCLUSION In a cohort of genetically defined tumors, tumor growth rates varied in a clinically and statistically different manner according to genetic subtype. Rapid growth of *BAP1*-deficient tumors indicates that these patients should be managed with caution. The faster growth of tumors in younger patients may support more frequent imaging, whereas the slower growth of other tumors may support extended surveillance beyond annual imaging in some instances.

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INTRODUCTION

Active surveillance (AS) is an increasingly used management strategy for patients with small renal masses.[1,2] Potential triggers for intervention for patients on AS include both absolute tumor size and tumor growth kinetics, with a tumor growth rate (GR) of 0.5 cm per year or more designated as a threshold for intervention.[2] However, these parameters are applied broadly to renal tumors without regard for histology or genetic basis. Yet the cancers that arise in the kidney actually represent multiple diseases with different histologic subtypes, driven by different genetic alterations, and ultimately have different clinical courses that could benefit from more precise and specific treatments.[3] Currently, information on tumor GRs is derived from multiple series in which the majority of tumors are neither biopsied, surgically resected, nor genetically profiled, making it unclear if different histologies or different genetic alterations are associated with different growth kinetics (Appendix Table A1, online only).

At our institution, patients with hereditary kidney cancer are managed on the basis of their germline alteration. For example, patients with *VHL*-deficient, *MET*-activated, or *FLCN*-deficient tumors are managed with AS until the largest tumor reaches 3 cm, at which time tumors are resected on the basis of the observation of limited metastatic potential at this threshold.[4-7] Conversely, for patients with *FH*- or *SDH*-deficient tumors, AS is not recommended as even small tumors have the potential to spread.[8-10] For more recently described genetic alterations, such as *BAP1*-deficient tumors, the role of AS is currently unclear.[11] In contrast to most AS series, the majority of our patients on AS ultimately go on to have surgery, which enables us to correlate tumor growth kinetics with

ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

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genetic subtypes and clinicopathologic features. The purpose of the current study was to determine whether renal tumor growth during AS is influenced by genetic subtype of the tumor and if clinical or other factors influence tumor growth.

PATIENTS AND METHODS

Patient Cohort and Clinical Stratification

Patients with germline pathogenic variations in the *VHL* (patients with von Hippel-Lindau disease), *MET* (patients with hereditary papillary renal-cell carcinoma), *FLCN* (patients with Birt-Hogg-Dubé syndrome), and *BAP1* (patients with BAP1-tumor predisposition syndrome) genes with solid renal tumors managed with AS in a prospective fashion at the Urologic Oncology Branch of the National Cancer Institute were identified. All patients provided written, informed consent and were prospectively enrolled in a screening, treatment, and genetic analysis clinical protocol approved by the National Cancer Institute Institutional Review Board. Germline pathogenic variation analysis was performed using Clinical Laboratory Improvement Amendments–approved assays. Abdominal imaging was performed and we recorded maximum tumor diameter in any dimension for up to 5 solid index lesions. Cysts and mixed cystic–solid lesions were not included in the analysis. Demographic information, including sex, age at baseline tumor measurement, and baseline tumor size, was recorded. Patient follow-up interval, which varied from 6 months to 36 months, was individualized on the basis of current tumor size and previous GR of the largest solid tumors at each visit. Once the largest tumor reached the 3-cm threshold, partial nephrectomy for all lesions in the ipsilateral kidney was performed as previously described.[12,13]

GRs

Tumor GRs were calculated as the regression coefficient of a mixed-model linear regression of tumor size, measured as the largest single-dimension diameter in centimeters over follow-up time in years.

Genomic Stratification

Patients were stratified on the basis of their primary germline pathogenic variation into *VHL, FLCN, MET*, and *BAP1* cohorts. Each genetic subtype was then further stratified according to the criteria below. For patients with tumors carrying *VHL* alterations, mutations were divided into the following five categories: missense mutations and in-frame insertion/deletions, partial deletions (one or two exons), nonsense and frameshift mutations, complete deletions (all three exons), and splice-site alterations. *VHL* missense mutations were further classified by gene location, including exon, corresponding protein domain (α, amino acid [AA] 155-193; β, AA 63-155 and AA 193-204), or protein functional region (nuclear export, AA 114-155; elongin C binding, AA 155-166).[14] Partial and full gene deletions were further characterized by retention or deletion of the neighboring gene *BRK1* (formerly designated as *HSPC300*), as previous work has demonstrated that loss of both *VHL* and *BRK1* resulted in a lower prevalence of clear-cell renal carcinoma compared with other patients with only *VHL* loss.[15,16]

All mutations in patients with a germline *MET* alteration were missense. Patients were stratified on the basis of whether their mutation was classified as predisposing to early-onset disease (V1238I).[17] Tumors carrying *FLCN* alterations were stratified according to four mutation type categories. Mutations were categorized into missense and in-frame insertion/deletions, partial deletions, nonsense and frameshift mutations, and splice-site alterations. Because the number of *BAP1*-deficient tumors was small, no substratification was performed.

Statistical Analysis

We assessed the association of tumor GRs with clinical and genetic features by comparing subgroups with Wilcoxon-rank sum or Kruskal-Wallis tests. Univariable and multivariable linear regression was performed to quantify the impact of clinical and genetic variables on tumor GRs. Statistical analysis was performed with Stata 15 (StataCorp, College Station, TX) and GraphPad Prism 7.00 (GraphPad Software, La Jolla, CA). Two-sided P values $< .05$ were considered significant.

RESULTS

A total of 435 tumors in 292 patients with 2,213 tumor measurements were included for analysis. Of those, 286 were *VHL* deficient, 91 *FLCN* deficient, 52 *MET* activated, and 6 *BAP1* deficient. Appendix Table A2 (online only) provides the demographic of the patients in the study. Median follow up was 3.6 years (interquartile range [IQR], 2.0-5.6 years). Tumors had a median starting and ending diameter of 1.4 cm and 2.7 cm, respectively. Median imaging interval was 0.81 years (IQR, 0.73-1.14 years). Figure 1 illustrates representative cross-sectional imaging of genetically defined tumors. Histologically, all *VHL*- and *BAP1*-deficient tumors were clear-cell renal-cell carcinoma (RCC) and all *MET*-activated tumors were type 1 papillary, whereas *FLCN*-deficient tumors had multiple histologies, including hybrid oncocytic, chromophobe, clear-cell RCC, and papillary type 1 RCC, as seen in Figure 2. Median tumor GR for the entire cohort was 0.31 cm per year. When stratified by genetic alterations, there was a significant difference across the four genetic subtypes (Fig 3A). *BAP1*-deficient tumors had the fastest median GR (0.6 cm/y; IQR, 0.57-0.68 cm/y), followed by *VHL*-deficient tumors (GR, 0.37 cm/y; IQR, 0.25-0.57 cm/y), *MET*-activation tumors (GR, 0.15 cm/y; IQR, 0.053-0.32 cm/y), and *FLCN*-deficient tumors (GR, 0.11 cm/y; IQR, 0.04-0.24 cm/y; $P < .001$ across all groups). When stratifying all tumors by histologic subtype, clear-cell RCC exhibited significant GR

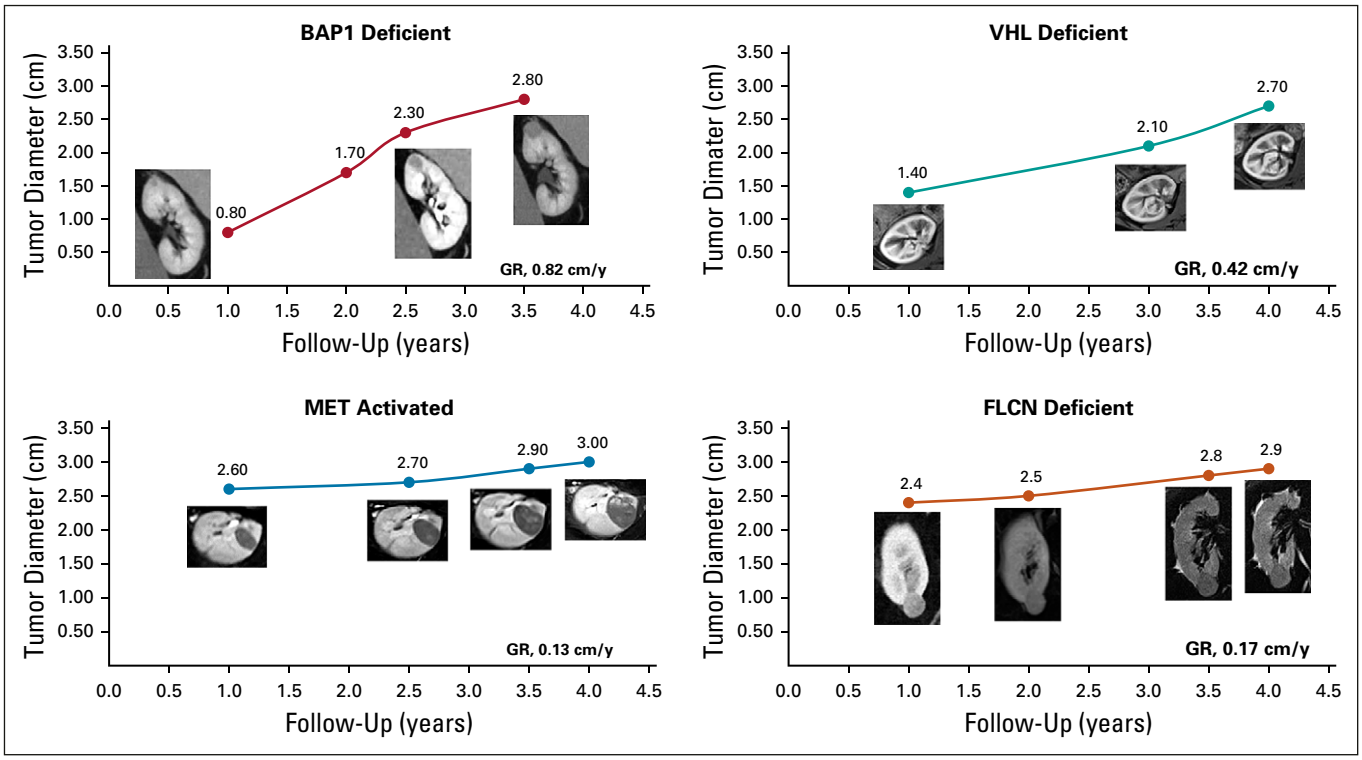

FIG 1. Representative patient examples of tumor growth rates (GRs) during active surveillance.

(0.37 cm/y), followed by papillary type 1 (0.15 cm/y), chromophobe (0.15 cm/y), and hybrid oncocytic tumors (0.11 cm/y; $P < .0001$ across all groups; Fig 3B).

Clinical Features

For all subsequent analyses, patients remained stratified by their primary genetic alteration. Table 1 lists the association of clinical factors with tumor GRs. There was no difference in GRs when stratified by sex, body mass index (BMI), or smoking status. To determine whether growth kinetics change as a function of starting tumor size, tumors were divided into three size groups on the basis of the tumor diameter at baseline: < 1 cm, 1-2 cm, and 2-3 cm. There was no difference in GRs by size group that indicated zero-order growth kinetics for this size range of tumors.

Among patients who had more than 1 index lesion, different tumors generally had similar GRs. Median standard deviation of the linear GR among all tumors from the same patient was 0.14 cm per year (IQR, 0.08-0.22 cm/y). The majority of patients with multiple tumors were a part of the VHL-deficient cohort.

To evaluate the effect of age, patients were stratified by their age at the beginning of AS and dichotomized by those younger than the median age and older than the median age for each genetic subtype. For patients with *VHL*-deficient tumors, younger patients had faster-growing tumors (0.40 cm/y *v* 0.34 cm/y; $P = .005$; Table 1). The difference in growth was more apparent when patients were stratified into age quartiles. Patients in the youngest quartiles (age < 42 years) had a median GR of 0.52 cm per year (IQR, 0.34-0.75 cm/y) versus the oldest cohort (age > 60 years) with a median GR of 0.32 cm per year (IQR, 0.22-0.49 cm/y; $P < .0001$; Fig 4). For patients with *FLCN*-deficient, *MET*-activated, and *BAP1*-deficient tumors, there was a trend that favored faster growth in younger versus older patients, although these comparisons did not meet statistical significance (data not shown).

To integrate potential genetic and environmental factors that may influence GRs, we performed univariable linear regression that included genetic alteration, sex, BMI, age, and smoking status (Appendix Table A3, online only). *VHL*-deficient and *BAP1*-deficient tumors had significantly faster GRs compared with the reference category of *FLCN*-deficient tumors. Age was negatively associated with growth, with each year increase in age associated with 0.0055-cm per year less growth. Sex, BMI, and smoking status were not associated with GRs. In a multivariable model that included genes and age, both remained independent predictors of GRs.

Genetic and Histologic Features

Association of GRs with genetic and histologic features is detailed in Table 2. For *VHL*-deficient tumors, there was no difference in GRs among the different types of *VHL* mutations. GRs of tumors with *VHL* missense mutations were independent of mutation location, whether stratified by exon, protein domain, or functional domain. For patients

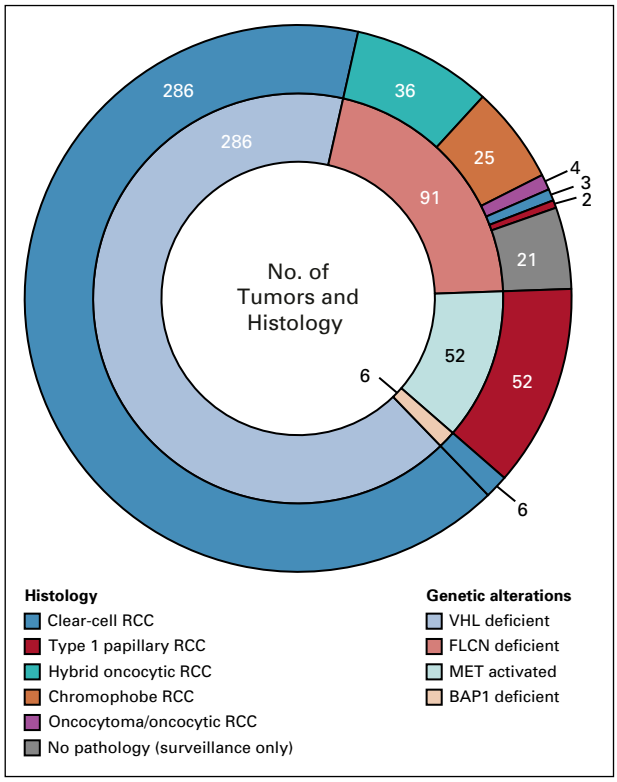

FIG 2. Layered pie chart of histology and genetic alteration. The outer layer represents histology and the inner layer represents genetic alterations. RCC, renal-cell carcinoma.

with a *VHL* deletion (partial or complete), no differences in GR were observed among tumors with retention or deletion of the adjacent gene *BRK1*.

For patients with *FLCN* germline mutation, there was no difference in GRs on the basis of mutation type or histologic subtype. For patients with *MET*-activating mutations, there was no difference in tumor GRs in patients with early-onset and later-onset mutations.

DISCUSSION

In AS cohorts of patients with sporadic RCCs, tumor GRs are often used as a criterion for progression and a trigger for intervention[2,18]; however, these cohorts often lack even histologic data, as the majority of masses observed on AS never have a tissue diagnosis. In fact, in reviewing the series of AS from which GRs are calculated, histologically proven RCCs account for less than 30% of tumors in all series (Appendix Table A1). Of previous studies, only the AS cohort from Fox Chase reports GR in more than 100 pathologically proven RCC cases.[19] In this study, we present one of the largest studies to date, to our knowledge, of renal tumor GRs in patients on AS and offer both histologic and genetic correlates. We found that there were significant differences in GRs stratified by genetic alteration, but within each gene the type of mutation did not affect GRs. Of note, *BAP1*-deficient tumors exhibited rapid GRs that exceeded 0.5 cm per year, which typically is used as a trigger for intervention. In addition, younger age was associated with faster GRs independent of genetic alterations. These findings have implications for guiding the development of AS schedules.

Whereas the current study evaluated patients with germline variants, these findings also have broader implications for patients with sporadic RCC. Alterations of *VHL* are present in more than 90% of patients with clear-cell

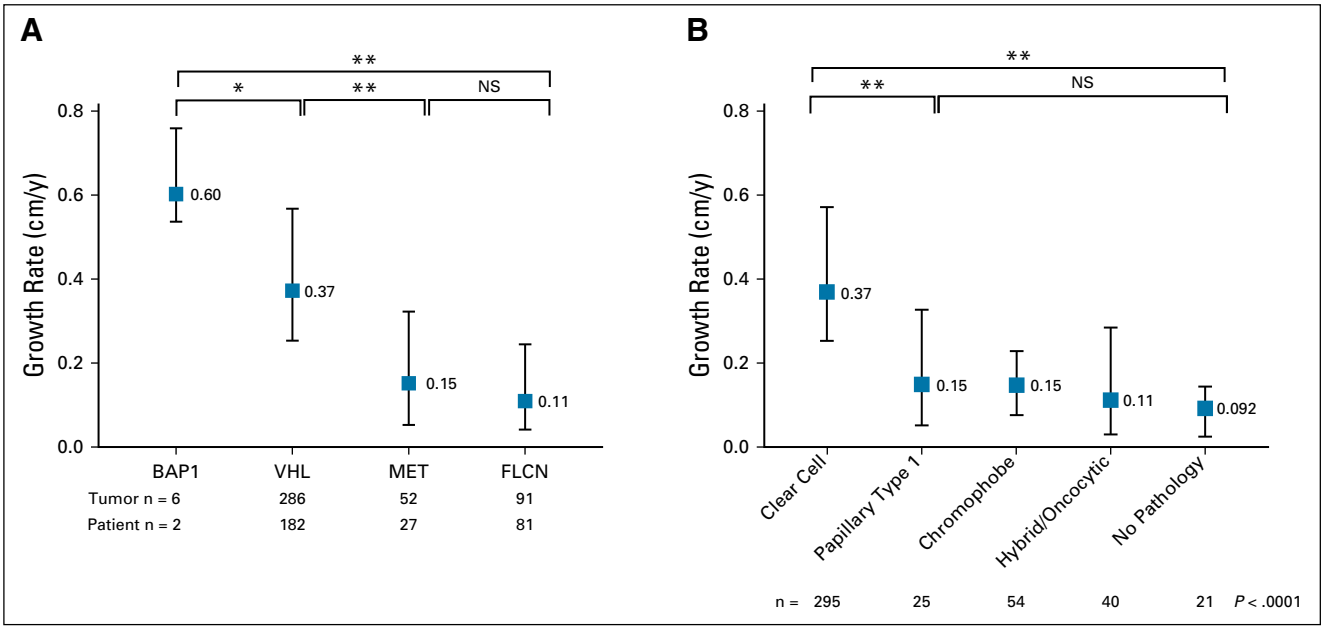

FIG 3. (A) Growth rates of genetically defined tumors stratified by gene. (B) Growth rates of renal tumors by histologic subtype. (*) $P < .05$. (**) $P < .0001$. NS, not significant.

TABLE 1. Growth Kinetics by Clinical Features

Clinical Feature	VHL	FLCN	MET	BAP1
Overall	0.37 (0.25-0.57)	0.10 (0.04-0.24)	0.15 (0.053-0.32)	0.60 (0.57-0.68)
Sex				
Women	0.35 (0.25-0.56)	0.13 (0.042-0.30)	0.12 (0.03-0.26)	0.0
Men	0.38 (0.26-0.59)	0.099 (0.037-0.18)	0.16 (0.07-0.35)	0.60 (0.57-0.68)
P	.2	.2	.2	
Age				
< Median age	0.40 (0.28-0.61)	0.13 (0.72-0.26)	0.16 (0.07-0.31)	0.78 (0.57-0.98)
≥ Median age	0.34 (0.25-0.51)	0.097 (0.024-0.18)	0.087 (0.034-0.33)	0.59 (0.50-0.65)
P	.005	.1	.2	.3
BMI				
< Median BMI	0.39 (0.27-0.58)	0.11 (0.031-0.18)	0.17 (0.71-0.33)	0.78 (0.58-0.98)
≥ Median BMI	0.36 (0.25-0.53)	0.12 (0.070-0.29)	0.13 (0.034-0.26)	0.56 (0.50-0.66)
P	.3	.2	.18	.3
Baseline size, cm				
< 1	0.37 (0.32-0.59)	0.12 (0.05-0.28)	0.17 (0.70-0.28)	0.68 (0.57-0.98)
1-2	0.37 (0.25-0.57)	0.11 (0.05-0.18)	0.15 (0.052-0.35)	0.56 (0.44-0.63)
2-3	0.33 (0.19-0.49)	0.08 (0.02-0.24)	0.13 (0.19-0.17)	N/A
P	.07	.5	.4	.1
Smoking status				
Smoker	0.37 (0.28-0.57)	0.14 (0.086-0.25)	0.17 (0.051-0.33)	N/A
Nonsmoker	0.40 (0.24-0.59)	0.097 (0.28-0.25)	0.15 (0.69-0.27)	0.60 (0.57-0.68)
Unknown	0.33 (0.25-0.45)	0.11 (0.72-0.15)	0.11 (0.13-0.29)	N/A
P	0.2	0.3	0.8	N/A

All measurements are GR(IQR), cm/y.
Abbreviations: BMI, body mass index; N/A, not applicable.

RCC,[20,21] and alteration of *VHL* is known to be an early, truncal event in sporadic RCC tumorigenesis.[22] In addition, somatic *BAP1* mutations were found in more than 10% of the Cancer Genome Atlas sporadic clear-cell RCC cohort.[21] Similarly, 17% of type 1 papillary RCCs in the Cancer Genome Atlas data set had activating *MET* mutations, and 81% had altered *MET* status—defined as mutation, splice variant, or gene fusion—or gain of chromosome 7.[23] Taken together, these data suggest that understanding the biology of hereditary kidney cancer informs our understanding of both the biology and clinical management of sporadic kidney cancer.

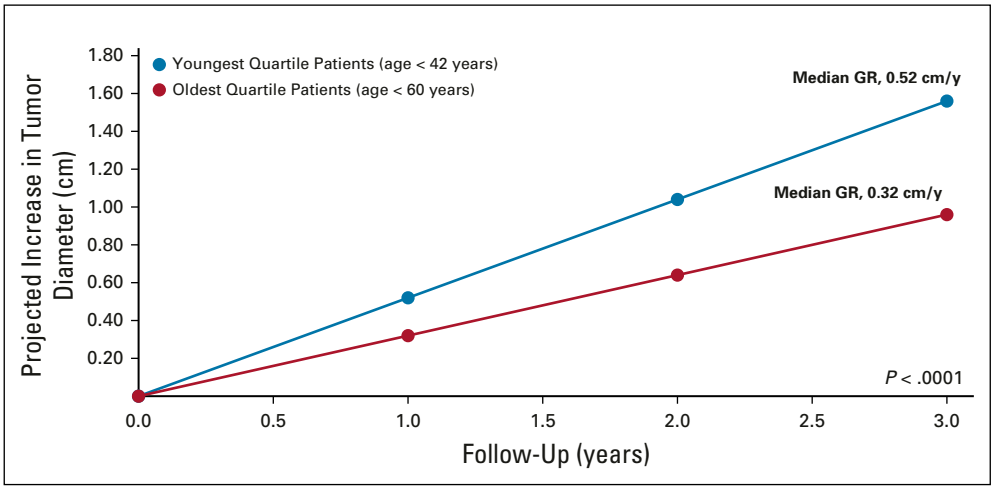

FIG 4. *VHL*-deficient tumor growth by age. GR, growth rate.

TABLE 2. Growth Rates of Tumors Stratified by Genetic Features and Histologies

Genetic Feature	GR (IQR), cm/y
VHL deficient	
Mutation type	
Missense/InDel	0.37 (0.24-0.57)
Partial deletion	0.36 (0.26-0.57)
Nonsense/frameshift	0.38 (0.28-.056)
Complete deletion	0.30 (0.025-0.034)
Splice site	0.37 (0.31-0.58)
P	.7
Protein domain (missense only)	
α (n = 44)	0.38 (0.20-0.53)
β (n = 84)	0.37 (0.25-0.059)
P	.4
Functional domain (missense only)	
Elongin C binding (n = 37)	0.40 (0.22-0.054)
Nuclear export (n = 28)	0.39 (0.25-0.063)
P	.4
Exon (missense only)	
1 (n = 64)	0.37 (0.25-0.56)
2 (n = 26)	0.39 (0.25-0.67)
3 (n = 51)	0.40 (0.23-0.53)
P	.9
BRK1 status	
Deleted (n = 6)	0.33 (0.24-0.56)
Retained (n = 77)	0.25 (0.25-0.53)
P	.9
FLCN deficient	
Mutation type	
Missense/InDel (n = 4)	0.40 (0.15-1.06)
Partial deletion (n = 7)	0.29 (0.04-0.39)
Splice (n = 18)	0.10 (0.05-0.22)
Frameshift/nonsense (n = 62)	0.11 (0.03-0.18)
P	.2
Histology	
Hybrid (n = 36)	0.11 (0.028-0.28)
Chromophobe (n = 25)	0.15 (0.083-0.22)
Oncocytoma/oncocytic (n = 4)	0.20 (0.13-0.33)
Clear cell (n = 3)	0.17 (0.062-1.56)
Papillary (n = 2)	0.43 (0.08-0.78)
No pathology (surveillance only; n = 21)	0.092 (0.03-0.12)
P	.3
MET amplified	
Early-onset mutation	0.12 (0.034-0.26)
Non–early-onset mutation	0.15 (0.054-0.33)
P	.4

Abbreviations: GR, growth rate; InDel, insertion/deletion; IQR, interquartile range.

The observation that older patients have slower growing tumors than younger patients has been noted previously[24]; however, it is unclear if this observation is a result of genetics, environmental effect, or selection bias. Other studies have demonstrated that younger men have been found to have increased cancer-specific mortality compared with older men, suggesting that there may be a hormonal effect.[25] Currently, AS is most often used in elderly or infirm patients, but there is increasing interest in expanding use to younger patients.[26] Whereas this observation will require additional investigation, it may suggest that if AS is used in a younger patient, a closer follow-up schedule may be considered.

Discovery of *BAP1*-deficient tumors is relatively recent,[11,27-29] and the safety of AS in these patients is unknown. We found that *BAP1*-deficient tumors are associated with rapid GRs. Previous work has demonstrated that somatic BAP1 alterations are associated with high-grade, high-stage, low-survival disease.[21] While the sample of BAP1 tumors in the current study was limited, taken together, these data suggest that *BAP1*-deficient renal tumors on AS may warrant increased caution.

These data may also affect the frequency of surveillance schedules. In two large prospective AS studies, surveillance imaging was performed every 3-6 months initially, followed by annual examination.[2,18] Our data suggest that in patients with *VHL*-deficient, *MET*-activated, or *FLCN*-deficient tumors, patients with smaller tumors may be surveyed less frequently than annually, depending on the size and location of tumors. Our institutional practice is to extend surveillance beyond 12 months in selected patients whose tumors are projected to be less than 3 cm during that interval.

GRs for RCC have been reported in several previously published AS series with reported rates from 0.06 to 0.86 cm per year (Appendix Table A1). The wide variation of GRs may be a reflection of a mixture of different RCC histologies and different genetic subtypes included within these cohorts. The three largest studies of AS reported GRs of 0.09 cm per year, 0.13 cm per year, 0.15 cm per year, and 0.19 cm per year,[2,18,19] which are significantly lower than our data report. However, these studies enrolled mostly older patients with a variety of benign lesions and multiple different RCC histologies. Mehrazin et al[30] reported a higher mean GR of 0.44 cm per year for larger T1b and T2 renal masses. Others studies with restricted pathologically proven RCC generally have higher GRs during AS, such as that by Kato et al,[31] that demonstrated a median GR of 0.42 cm per year.

Whereas no prior studies have compared different types of genetically defined tumors, two previous studies have evaluated *VHL*-deficient tumors. Zhang et al[32] analyzed 42 *VHL*-deficient tumors in 16 patients and reported a mean GR of 0.53 cm per year. Jilg and colleagues[33]

reported 96 tumors in 64 patients and reported a GR of 0.44 cm per year. In the latter study, the authors also evaluated germline mutation types and observed a similar lack of correlation between mutation type and growth kinetics.

Limitations of our study include the retrospective nature of our growth measurements. In addition, while all scans were read by board-certified radiologists, central radiology review was not performed. Furthermore, imaging intervals were not standardized. Strengths include the large number of tumors evaluated with corresponding pathologic and genetic data, which to our knowledge is the one of the largest reported in the literature for any renal AS cohort.

In conclusion, renal tumors have distinct growth patterns that reflect their genetic subtype. In addition, younger patients have faster growing tumors than older patients. Additional study is needed to determine the impact of somatic mutations on tumor development and growth kinetics and the role of somatic gene mutation analysis in the AS management of patients with sporadic RCC.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Growth Rates of Genetically Defined Renal Tumors: Implications for Active Surveillance and Intervention

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TABLE A1. Growth Rates From Previously Published Active Surveillance Cohorts

Series	Year	Tumor, No.	Patient, No.	Pathologic RCC, No.	Pathology Known, No.	Known Path, %	Mean Age, Years	Initial Diameter, cm	Mean GR, cm/y	Mean Follow Up, Months
Fujimoto et al: *Int J Urol* 2:71-6, 1995	1995	6	6	5	5	83.3	59.7	2.47	0.47	24.0
Bosniak et al: *Radiology* 197:589-597, 1995	1995	40	37	22	26	65.0	65.5	1.73	0.36	39.0
Oda et al: *Int J Urol* 10:13-8, 2003	2003	16	16	16	16	100.0	53.2	2.0 (median)	0.62	25.0
Volpe et al: *Cancer* 100:738-45, 2004	2004	32	29	8	9	28.1	71.0 (median)	2.48	0.1	39.0
Wehle et al: *Urology* 64:49-52, 2004	2004	29	29	3	4	13.8	70.5	1.83	0.12	32.0
Kato et al: *J Urol* 172:863-6, 2004	2004	18	18	18	18	100.0	56.5	2.0	0.42	27.0
Lamb et al: *Urology* 64:909-13, 2004	2004	36	36	23	23	63.9	76.1	7.2	0.39	27.7
Sowery et al *Can J Urol* 11:2407-10, 2004	2004	22	22	NR		0.0	77.0 (median)	4.08	0.86	26.0
Chawla et al: *J Urol* 175:425-31, 2006	2006	61	49	17	21	34.4	71.0	2.97	0.2	36.0
Abou Youssif et al: *Cancer* 110:1010-1014, 2007	2007	44	35	6	8	18.2	71.8	2.2	0.15	47.6
Kouba et al: *J Urol* 177:466-70; discussion 470, 2007	2007	46	43	12	14	30.4	67.0	2.92	0.7	32.8
Siu et al: *Urol Oncol* 25:115-9, 2007	2007	47	41	10	16	34.0	68.0	2.0	0.27	29.0
Fernando et al: *Int Urol Nephrol* 39:203-7, 2007	2007	13	13	0		0.0	80.4	5.0	0.17	38.4
Matsuzaki et al: *Hinyokika Kiyo* 53:207-11, 2007	2007	15	15	3	3	20.0	67.0	2.2	0.06	38.0
Lee et al: *Eur Radiol* 18:731-7, 2008	2008	30	30	30	30	100.0	65.5	2.6	0.59	12.6
Abouassaly R et al: *J Urol* 180:505-8; discussion 508-9, 2008	2008	110	110	2	4	3.6	81.0 (median)	2.5 (median)	0.26	24.0 (median)
Beisland et al: *Eur Urol* 55:1419-27, 2009	2009	65	63	15	18	27.7	76.3	4.3	0.66	33.0
Rosales et al: *J Urol* 183:1698-702, 2010	2010	223	212	32	40	17.9	71.0 (median)	2.8 (median)	0.34 (median)	35.0 (median)
Hwang et al: *Can J Urol* 17:5459-64, 2010	2010	58	46	10	15	25.9	64.3	2.1	0.21	22.0
Jewett et al: *Eur Urol* 60:39-44, 2011	2011	151	127	37	46	30.5	73.0	2.1	0.13	28.0
Li et al: *J Cancer Res Clin Oncol* 138:269-74, 2012	2012	32	32	32	32	100.0	52.2	2.14	0.8	46.0
Dorin et al: *Int Braz J Urol* 40:627-36, 2014	2014	131	114	12	15	11.5	69.1	2.1	0.17	
Schiavina et al: *Clin Genitourin Cancer* 13:e87-92, 2015	2015	72	70	16	18	25.0	76.0	2.1	0.5	92.7
Uzosike et al: *J Urol* 199:641-648, 2018	2018	271	271	13	22	8.1	70.7	NR	0.09	22.0 (median)
McIntosh et al: *Eur Urol* 74:157-164, 2018	2018	544	457	114	153	28.1	70.0	2.1	1.9	67.0
Overall		2,112	1,921	456	556	26.30	67.8	2.8	0.43	36.3

Abbreviations: GR, growth rate; NR, not recorded; RCC, renal-cell carcinoma.

TABLE A2. Patient and Tumor Characteristics

Characteristic	VHL	FLCN	MET	BAP1	Total
Tumors, No.	286	91	52	6	435
Tumor measurements	1,474	443	268	28	2,213
Patients, No.	182	81	27	2	292
Sex, No. (%)					
Women	85 (46.7)	38 (46.9)	15 (55.6)	2 (100.0)	138 (47.3)
Men	97 (53.3)	43 (53.1)	12 (44.4)	0	154 (52.7)
Median age, years (IQR)	51 (43.0-60.0)	60 (55.0-69.0)	57 (51.0-64.0)	65 (63.0-65.0)	55 (46.0-63.0)
Median size at beginning of study cm (IQR)	1.4 (1-1.8)	1.5 (1.0-2.0)	1.35 (0.9-1.7)	1.1 (0.8-1.3)	1.4 (1.0-1.8)
Median size at end of study, cm (IQR)	2.9 (2.5-3.2)	2.1 (1.6-2.8)	2.0 (1.5-2.5)	2.9 (2.5-3.2)	2.7 (2.1-3.1)
No. of tumors/patient					
1	88	76	19	0	
2	73	4	2	1	
≥ 3	21	1	6	1	
Median follow up, years (IQR)	3.2 (2.4-4.5)	3.8 (2.1-6.2)	3.2 (1.9-5.1)	2.8 (2.1-3.5)	3.6 (2.0-5.6)
Median BMI kg/m^2 (IQR)	27.1 (23.7-31.6)	28.0 (25.1-32.6)	26.6 (23.9-31.8)	32.0 (26.6-38)	27.6 (24.1-32.7)
Smoking status, No. (%)					
Smoker	60 (33.0)	23 (28.4)	9 (33.3)	0	92 (31.5)
Nonsmoker	85 (46.7)	54 (66.7)	11 (40.7)	2 (100.0)	152 (52.1)
Unknown	37 (20.3)	4 (4.9)	7 (25.9)	0	48 (16.4)

Abbreviations: BMI, body mass index; IQR, interquartile range; RCC, renal-cell carcinoma.

TABLE A3. Univariable and Multivariable Linear Regression Predictors of Tumor Growth Rates

Gene	Univariable, cm/y (IQR)	*P*	Multivariable, cm/y (IQR)	*P*
FLCN	Ref		Ref	
MET	0.005 (−0.063 to 0.073)	.8	−0.017 (−0.084 to 0.050)	.6
VHL	0.24 (0.18 to 0.30)	< .001	0.21 (0.15 to 0.27)	< .001
BAP1	0.46 (0.25 to 0.66)	< .001	0.48 (0.15 to 0.27)	< .001
Male Sex	0.032 (−0.019 to 0.083)	.2	Omitted	
BMI	0.00030 (−0.0041 to 0.0048)	.9	Omitted	
Age	−0.0055 (−0.0076 to −0.0034	< .001	−0.0041 (−0.0066 to −0.0016)	.001
Smoker	0.045 (−0.013 to 0.10)	.1	Omitted	

Abbreviations: BMI, body mass index; Ref, reference.