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Original Article

Renal tumor growth rate in patients with previously normal CT scan: Analysis of the initial stage of growth

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ABSTRACT

Objective: Most of the studies regarding natural history of renal masses are based on active surveillance series and suggest that the renal masses have a slow growth rate. Nevertheless, only a few studies report the time between a normal computed tomography (CT) scan to the first detection of a tumor. We aimed to analyze the growth rate in newly diagnosed kidney tumors.

Material and methods: We analyzed patients with enhancing renal masses that developed after a normal CT scan, which was performed at most 12 months earlier. Variables examined included patient age, gender, tumor size, volume, tumor linear growth rate (LGR). All cases were surgically treated. Mann–Whitney U test was used to compare variables. A $p<0.05$ was considered as statistically significant.

Results: We found 31 patients with 33 lesions. Male to female ratio was 1.58 (19/12). The average age was 59.2 years (standard deviation [SD]±12.1), and the mean tumor size was 4.27 cm (SD±4.3). Tumor LGR was 0.87 cm/month (range: 0.28–1.66) and presumed to be 10.4 cm at 1 year (range: 3.36-19.9). Tumor LGR for time detection at <6 month or ≥6 months were 1.1 cm/month and 0.68 cm/month (range: 0.27–1.08 and 0.88–1.76, respectively; p=0.0004), respectively. Tumor LGRs for low- and high-grade tumors were 0.89 cm/month and 0.83 cm/month (p=0.65), respectively. Median volume was 36.1 cm^3 (range: 2.61–143.7), and for low and high grade the median volumes were 27.9 cm^3 and 47.6 cm^3, respectively (p=0.54). Malignant pathology was present in 93.9 % (31 of 33) of masses (lesions).

Conclusion: We found differences in tumor LGR in tumors detected before and after 6 months. We did not find any correlation between tumor growth rate and Fuhrman grade system, gender, histology, or age. We found the highest LGR published up to date.

Keyword: Active surveillance; natural history; renal tumor.

Introduction

Renal cell carcinoma (RCC) is the most common solid lesion in the kidney. In the last decades, its incidence has increased by an average of 2–3% annually. The widespread use of abdominal imaging has led to detect incidentally enhancing renal masses <4 cm in maximal diameter: small renal masses (SRM).[1-4]

The natural history of renal masses has not been adequately researched, given that most patients are surgically treated right after diagnosis. Historically, RCC has been considered to have a slow growth rate, that is, 1 to 10 mm/year.[5,6] Today, most of the studies regarding natural history of renal masses are based on active surveillance (AS) series and suggest a slow rate of metastasis.[6-9] Nevertheless, only a few studies report the time between a normal computed tomography (CT) scan to the first detection of a tumor. Therefore, growth pattern is still controversial.

Our aim is to analyze the growth rate in newly diagnosed renal masses and attempt a better approach to understand the natural history of the disease.

Material and methods

After institutional review board approval, a retrospective review of institutionally confined kidney renal mass databases was performed

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from January 2010 to December 2017 for patients in whom a new enhancing renal mass developed. All patients had a normal CT scan of the kidneys at most 12 months earlier and then another CT scan that showed renal masses. The differences between the two CT scans were noted. Tumor diameter for all lesions at the time of the normal CT was considered 0 cm.

Variables examined included demographics, indication for imaging, radiographic tumor features, tumor size, volume, growth, histopathology, and follow-up. Tumor size was measured as the maximal diameter in any dimension. Tumor volume was calculated using the maximal tumor diameter, using the ellipsoid equation (V=0.5236xyz) where V represents volume and x, y, and z represent major tumor dimensions in the x, y, and z axes. Tumor linear growth rate (LGR) was calculated by the relation between the size of the tumor at detection and the time of the CT scan in which the tumor was detected. All cases were surgically treated after tumor detection, and AS was not performed. Cases without histopathological confirmation were excluded. All CT scans included were reviewed by the treating urologist.

Statistical analysis

Descriptive statistics of samples were expressed as mean and standard deviation or median and interquartile range (IQR). Growth rates were compared by low-grade (Fuhrman Grade I–II) and high-grade (Fuhrman Grade III–IV) tumors, histology (clear cell carcinoma or other malignancy), gender, presence of symptoms at detection, age (60 year or older), and time at detection (6 months or more) using Mann–Whitney U test and were expressed as median (range). Frequencies were compared using chi-square test. Stata® version 13 was used to perform the analyses. A $p<0.05$ was considered as statistically significant.

Results

All 863 patients diagnosed of having renal masses were operated in this period, and we identified 31 patients with 33 lesions who met the inclusion criteria. Table 1 shows patient demographics and radiographic tumor features at the time of the first CT scan demonstrating renal mass. One patient presented synchronous bilateral tumor, and another patient presented two tumors in the same renal unit. No patient presented familiar history of RCC.

Main Points:

- We found the highest tumor growth rate published up to date.
- We found differences in tumor LGR in tumor detected before and after 6 months.
- We did not find any correlation between tumor growth rate and Fuhrman grade system, gender, histology, or age.
- This study can add further useful information about the natural history of renal cancer, especially about the first stage of tumor growth.

Male to female ratio was 1.58 (19/12), and the average age was 59.2 years (SD±12.1). Mean tumor size was 4.27 cm (SD±4.3). The median time between zero time and the first CT scan demonstrating a renal tumor was 5.4 months (IQR: 3–11).

Median tumor LGR was 0.87 cm/month (range: 0.28–1.66) and presumed to be 10.4 cm (range: 3.3–19.9) at 1 year. Tumor LGR for low- and high-grade tumors were 0.89 cm/month and 0.83 cm/month (p=0.65), respectively. LGR for time detection at <6 month and ≥6 months were 1.1 cm/month and 0.68 cm/month (range: 0.27–1.08 and 0.88–1.76, respectively; p=0.0004), respectively. Median volume was 36.1 cm^3 (range: 2.61–143.7). Median volumes for low- and high-grade tumors were 27.9 cm^3 and 47.6 cm^3, respectively, (p=0.54) (Table 2 and 3).

Carcinoma was present in 93.9% (31 of 33) of treated renal masses (lesions). Histology showed clear cell carcinoma (n=25, 75.7%), chromophobe (n=2, 6.1%), papillary renal cell cancer type 1 (n=2, 6.1%), papillary renal cell cancer type 2 (n=1,

Table 1. Demographic characteristics

Characteristics	**n=31**
% Gender: Female/Male	12/19
Age (Mean, SD)	59.2 (12.1)
Charlson index (n)	
≥2	9
1	22
DBT (n, %)	2 (6.4)
AH (n, %)	4 (12.9)
BMI (kg/m^2, SD)	26.1 (6.4)
Indication for CT (n, %)	
Follow-up RCC	15 (45.4)
Lithiasis	1 (3.0)
Other oncologic	3 (9.2)
Symptoms	4 (12.1)
Other	10 (30.3)
% Radiographic (solid/cystic)	31/2 (94/6) %
Side (n, %)	
Left	13 (39.4)
Right	20 (60.6)

SD: standard deviation; DBT: diabetes; AH: hypertension; BMI: body mass index; CT: computed tomography; RCC: renal cell carcinoma.

Table 2. Comparison of diameter, LGR, and volume by Mann–Whitney U test

Characteristics	Median	Range	p
Tumor diameter (cm)	4.1	1.7–6.5	
Tumor diameter FI–II (cm)	3.7	2.4–6.5	0.60
Tumor diameter FIII–IV (cm)	4.6	1.7–6.5	
Female (cm)	4.0	1.7–6.2	0.54
Male (cm)	4.2	2.7–6.5	
Time at detection <6 months (cm)	3.6	1.7–5.3	0.10
Time at detection ≥6 months (cm)	4.5	2.2–6.5	
History of RCC (cm)	4.3	1.7–4.9	0.84
Non-history of RCC (cm)	4.1	3.3–6.5	
Clear cell carcinoma (cm)	4.2	3.7–4.9	0.94
Not clear cell carcinoma (cm)	4.1	1.7–6.5	
Age ≤60 (cm)	3.6	3.2–6.5	0.20
Age >60 (cm)	4.4	1.7–6.5	
Symptoms at detection (cm)	5.6	3.5–6.5	0.08
No symptoms at detection (cm)	4.1	1.7–6.2	
LGR (cm/month)	0.87	0.28–1.66	
LGR FI–II (cm/month)	0.89	0.3–1.66	0.65
LGR FIII–IV (cm/month)	0.83	0.28–1.08	
Female (cm/month)	0.96	0.28–1.25	0.62
Male (cm/month)	0.75	0.3–1.66	
Time at detection <6 months (cm/month)	1.1	0.75–1.66	0.00
Time at detection ≥6 months (cm/month)	0.68	0.28–1.1	
History of RCC (cm/month)	0.88	0.28–1.66	0.76
Non-history of RCC (cm/month)	0.83	0.6–1.1	
Clear cell carcinoma (cm/month)	0.96	0.7–1.1	0.18
Not clear cell carcinoma (cm/month)	0.62	0.28–1.66	
Age ≤60 (cm/month)	0.75	0.4–1.65	0.32
Age >60 (cm/month)	0.96	0.28–1.66	
Symptoms at detection (cm/month)	0.96	0.72–1.08	0.19
No symptoms at detection (cm/month)	0.75	0.28–1.66	
Tumor volume (cm^3)	36.1	2.6–143.7	
Tumor volume FI–II (cm^3)	27.9	7.2–143.4	0.54
Tumor volume FIII–IV (cm^3)	47.6	2.6–143.7	
Female (cm^3)	33.5	2.6–124.3	0.66
Male (cm^3)	38.7	7.2–143.7	
Time at detection <6 months (cm^3)	22.4	7.2–80.9	0.12
Time at detection ≥6 months (cm^3)	47.6	2.6–143.7	
History of RCC (cm^3)	41.6	2.6–61.6	0.81
Non-history of RCC (cm^3)	36.1	18.8–143.7	
Clear cell carcinoma (cm^3)	38.7	26.5–61.6	0.72
Not clear cell carcinoma (cm^3)	36.1	2.6–143.7	
Age ≤60 (cm^3)	22.4	14.1–143.7	0.28
Age >60 (cm^3)	43.2	2.6–143.7	
Symptoms at detection (cm^3)	98.9	22.4–143.7	0.05
No symptoms at detection (cm^3)	33.3	2.6–143.4	

Statistically significant p values are in bold. LGR: linear growth rate; RCC: renal cell carcinoma; F: Fuhrman

3.0%), carcinoma sarcomatoid (n=1, 3.0%), angiomyolipoma (n=1, 3.0%), and oncocytoma (n=1, 3.0%).

Fuhrman grading system had the following grades: Grade I (n=10, 34.5%), Grade II (n=12, 41.3%), and Grade III (n=7, 24.2%). According to TNM score the stages were as follows: 1a (n=10), 1b (n=17), 2a (n=1), 3a (n=2), and 3b (n=1).

A total of 41.9% (13 of 31) of lesions had a history of RCC with complete resection at least 5 years before and were evaluated for other conditions. Symptoms potentially attributable to a renal tumor, hematuria or flank pain, were the indications for radiographic imaging (n=4). Symptoms at detection were hematuria (n=2), paraneoplastic syndrome (n=1), metastatic, and related pain (n=1), whereas some patients were asymptomatic (n=27). At detection, 48.5% (16 of 33) of tumors were smaller than 4 cm. Median follow-up was 48.6 months (IQR: 34.2–96.3). Of 29 patients with malignant lesions, six cases (6/29, 20.7%) presented recurrence during follow-up. Three (3/29, 1.3%) patients died during follow-up because of disease dissemination despite chemotherapy treatment.

Discussion

Genome of clear cell carcinoma (CCR), the most common subtype of renal cancer, is distinctive. The early development of CCR follows strongly preferred evolutionary trajectories. Chromosome 3p loss encompasses tumor suppressor genes such as *VHL*, *PBRM1*, *BAP1*, and *SETD2*. This is found in more than 90% of patients, arising in childhood or adolescence, even though cancer may not be diagnosed for another 30–50 years.[10]

Most RCC grow slowly, with average LGR ranging from 0.09 cm/year to 0.86 cm/year.[11] These studies are based on AS of patients, and this is the main reason for not treating them. On the other hand, approximately 2 % of patients under AS present progression to metastatic disease over a median of 3 years and is associated with rapid primary tumor growth during AS.[12] In a review including 36,495 patients older than 70 years with SRM, conversion to active treatment for 4–26% of patients until 91 months of follow-up was seen.[13]

Turk J Urol 2021; 47(1): 9–13
10.5152/tud.2020.20201

Table 3. Comparison of demographic and histopathologic variables by time at diagnosis

Characteristics	Detected <6 months (n=13)	Detected ≥6 months (n=20)	p
Female %	6/13 (46.1%)	6/20 (30.0%)	** 0.34
Age (median, range)	60.5 (31–82)	58.8 (34–80)	* 0.69
T1a	5	5	
T1b	5	12	
T2a	0	1	
T3a	2	0	
T3b	1	0	
Benign	0	2	
FI–II	8	14	** 0.75
FIII–IV	3	4	
Recurrence, %	15.3 (2/13)	22.2 (4/18)	** 0.63
Necrosis (Yes), %	23.1 (3/13)	27.7 (5/18)	** 0.41

*Mann–Whitney U test; **Chi-square test. F: Fuhrman.

Zhang et al.[14] in a review of small renal masses in AS, found tumor LGR of 0.33 cm/year and mean volumetric growth rate of 9.48 cm^3/year.[1] Kunkle et al.[15] described a case series of AS of 106 masses of average size of 2 cm and a median follow-up of 29 months and found an LGR of 0.3 cm/year in 67% of lesions. Kato et al.,[16] in a series with 18 patients with a mean presentation size of 2.0 cm and a median follow-up of 22.5 months in tumors <4 cm in size, found growth rate of 0.42 cm/year. Haramis et al.[17] evaluated AS for 5 years in a series of 44 patients with 51 tumors, where mean size at presentation was 2.7 cm and mean follow-up was 6.4 years. The average growth rate was 0.15 cm/year and in tumors larger than 4 cm it was 0.31 cm/year.[17]

On the other hand, other studies showed that patients in AS presented phases of high growth rate until 4.74 cm/year.[14] Mues et al.[18] calculated the LGR in kidney tumors larger than 4 cm, stages T1bN0M0 and T2N0M0, in a series of 36 patients, with a mean size of 7.13 cm (4–13.7 cm) and a mean follow-up of 36 months (range: 6–96 months) found a growth rate and progression rate of 0.57 (range: 0–5.9) cm/year and 5.9%, respectively.

Crispen et al.[19] compared observed and presumed growth rate of kidney tumors of 2.3 cm (range: 1–5) in patients with previously normal CT scan and observed a large difference (0.71 cm/year vs 0.039 cm/year, p=0.028) between the two. The average time to diagnosis was 40.3 months. This could justify this difference in LGR because in our study, time to diagnosis was 5.4 months. Another difference is that they only had 66% of histopathology samples.

These studies suggest that an initial explosive phase, in some cases later, would coincide with a form of growth in peaks, which could present stages of slow growth rate alternated with stages of rapid growth.

We found that although there was a large variation in the growth rates, most grew fast. In our series of 33 lesions, we found a median presumed growth rate of 8.06 cm/year with a maximum of 19 cm/year, the highest published to date. This is probably due to the design of the study. We also found a significant difference of 0.42 cm/month or 38.2% in tumor detected before 6 months. This finding may support the Gompertzian's growth theory that suggests that tumor growth is exponential before it is clinically detectable and decreases once the tumor is larger and clinically detectable.[20]

Most of the AS studies are retrospective with limited strength. Present lack of pathological confirmation and growth rate are estimated during AS period, not recorded over time.[14] In this study, we had a 100% pathological confirmation.

There is controversy in the role of histological type and grade in tumor growth. Kato et al.[16] found that RCC with Fuhrman Grade III grew faster than those with Fuhrman Grade I and II. Li et al.[21] in a study involving 32 confirmed RCC after delayed surgery of at least 12 months found that the LGR of Fuhrman Grade I tumors was 0.36 cm/year, slower than Fuhrman Grade II (0.88 cm/year) and Grade III tumors (1.04 cm/year). On the other hand, Oda et al.[22] found no correlation between growth rate and tumor grade.

Tumor growth is believed to be influenced by multiple factors such as tumor size, number and type of genetic mutations, blood supply, and host immune system. High tumor grade and clear cell RCC may have aggressive potential,[14] but no definite predictor is defined at present.

In this study, while comparing by histology, grade, age, gender, and symptoms at detection, we did not find statistical differences in size or growth rate.

This study has several limitations, mostly related to its retrospective nature. It was a single-institution data set and as all patients were surgically treated, we could not affirm if was is passive for later AS. We estimated the tumor might have started growing after the last CT scan showed normal results. As we did not have diagnostic information from this point until first visit, we assumed a very conservative growth rate, from last normal scan, although the actual growth rate could have been faster, i.e. the tumor could have started growing shortly before the control visit.

In conclusion, we calculated the initial stage of growing of renal masses. We found differences in LGR in tumors detected be-

fore and after 6 months. We did not find any correlation between tumor LGR and Fuhrman grade system, gender, histology, or age. We found the highest tumor LGR published up to date. This study can add further useful information about the natural history of renal cancer, especially regarding the first stage of tumor growing.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Hospital Alemán of Buenos Aires (protocol number 0026-2018).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – C.A., L.B.; Design – L.B.; Supervision – L.B.; Materials – C.A., H.R.P., G.V.; Data Collection and/or Processing – C.A., L.B.; Analysis and/or Interpretation – L.B.; Literature Search – L.B.; Writing Manuscript – L.B.; Critical Review – L.B.

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