Estimated volume growth characteristics of renal tumors undergoing active surveillance

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Introduction: *The detection rate of incidental renal masses is increasing. Historically these masses have been treated with extirpative surgery. Hence, there is little information on the growth rate, metastatic potential, and natural history of renal tumors. Through active surveillance, we study the natural history of renal masses and determine their growth rate and risk for metastasis.*

Materials and methods: *From 1997 to 2007, active surveillance was offered to select patients with renal masses with no evidence of metastasis. Based on imaging studies from the initial diagnosis to the last follow up, tumor growth rates were determined.*

Results: *Forty-six patients were studied for a total of 58 masses. Mean age of patients at diagnosis was 64.3 years. Mean Charlson comorbidity score was 5.2 (median 5, range 2-13). Mean follow up period was 22 months (median 17, range 5-121). Mean initial tumor volume was 6.6 cm^3 (median 2.7, range 0.03-43.2). Mean growth rate was 1.9 cm^3/yr (median 0.1, range -3.8-27.9), and 6.8% had a volume doubling time of less than 1 year. No patient developed radiographic evidence of metastasis or died during follow up. Thirteen patients (15 masses) went onto operative intervention at a mean follow up of 19 months (median 18, range 4-36); 10/15 (67%) revealed renal cell carcinoma and 5/15 (33%) were benign.*

Conclusions: *In our cohort, negligible growth rates are observed in the vast majority of renal masses undergoing active surveillance, and thus, a carefully selected patient population may be safely managed with active surveillance with serial imaging.*

Key Words: active surveillance, renal cell carcinoma

Introduction

The incidence of renal tumors is growing in the United States due to the increase use of ultrasonography, computed tomography (CT) and magnetic resonance imaging (MRI) for medical evaluation, with most renal masses detected incidentally in asymptomatic patients.[1-3] In the United States, kidney cancer accounts for approximately 3% of all adult cancers.[2] Additionally, multiple studies have demonstrated an increased incidence of renal cell carcinoma (RCC) over the past several decades.[4-7] The probability of developing kidney cancer in a life-time among all races in the United States is 0.63%, and the probability of dying from these cancers is 0.17%, making mortality rates approximately 27%.[2] The 5 year and 10 year survival rates are 90% and 82% respectively.[2] However, patients who develop metastatic disease have a low median survival rate of 8 months from diagnosis.[8]

There is insufficient data about the natural history of renal masses, as most enhancing masses are surgically treated soon after the initial detection.[8] Previous studies have reported that at least 85% of contrast-enhancing renal masses greater than 1 cm in diameter are RCC.[9] Thus, the standard of care for treatment of these small renal tumors has been surgical extirpation, and more recently, renal tumor ablation. However, many of these small tumors are either benign or low

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grade RCC, with a slow growth pattern and low rate of metastasis.[10] In this context, an active surveillance protocol might be warranted in a high risk surgical population in which the risks of surgery outweigh the risks of interval tumor growth and metastasis.

Materials and methods

With the approval of the institutional review board at Emory University, we selected patients with renal tumors, starting in 1997, to undergo active surveillance based on either patient preference or being unfit for a surgical procedure. There were 46 patients, of whom 9 patients had multiple masses, either in the ipsilateral or contralateral renal unit; therefore, the cohort comprised of 58 masses from which we calculated the mean, median, and range of the tumor growth rate. The patients' tumors were initially detected using different imaging methods (CT and MRI). Subsequent imaging was CT or MRI, depending on surgeon and patient preference. All patients had undergone radiographic imaging and were clear of metastatic disease prior to enrolling in active surveillance. Tumor size measurements were initially obtained from radiology reports. A single radiologist re-measured the mass size when the radiology reports of the corresponding imaging studies recorded less than three dimensions in order to obtain measurements with the maximum number of dimensions.

To determine the growth rate (cm^3/yr), we calculated the slope of the regression line based on all the volume measurements taken for each mass versus follow up time, Figure 1. We used the start of the follow up period as the date the first image was taken and the end of the follow up period as the date the patient had his last radiological image taken. We excluded the masses with less than three follow up images. To estimate the volume, we made the assumption that each mass was ellipsoid in shape and used the equation 0.5326xyz, where x = length, y = width, and z = height. When radiology reports recorded fewer than three dimensions or no coronal images were available for direct measurement, we estimated the volume based on the following equations: if two dimensions were available, then the equation 0.5326xy ((1/2)x + (1/2)y) was used, and if only one dimension was measured, then $0.5326x^3$ was used. For consistency, we used the same number of dimensions to estimate the mass volume on all time points for each mass.

Statistical significance was determined using t-test for independent means and Mann-Whitney rank test. A p value < 0.05 was considered to be statistically significant.

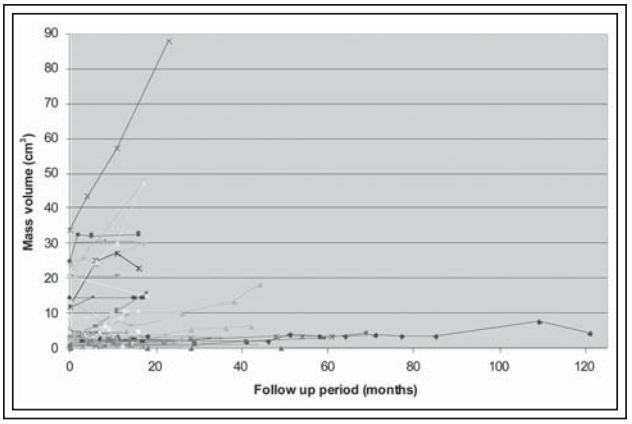

Figure 1. Graph depicting different growth rates for the renal masses in the study. For each mass, tumor volume (cm^3) was estimated in each imaging study during the follow up period and was plotted over time (months).

Results

The average age at initial diagnosis was 64.3 years old (median 67, range 35-89). Seventeen percent (8/46) of our patients were younger than 50 years of age at the time of diagnosis. Mean Charlson score was 5.2 (median 5, range 2-13). Seven patients had a baseline creatinine concentration of more than 1.5 mg/dL, and two patients had solitary kidneys due to either congenital abnormality or previous surgery unrelated to renal masses. None had genetic diseases associated with slow-growing renal carcinoma such as von Hippel-Lindau, hereditary leiomatosis and renal cell carcinoma, and Birt-Hogg-Dubé syndrome. Table 1 and 2 summarize the patient characteristics.

The average period of follow up imaging was 22 months (median 17, range 5-121). The average volume of the renal masses from the initial imaging study was

TABLE 1. **Patient characteristics**

Variable	Mean	Median	Range
Age at diagnosis (yr)	64.3	67	(35-89)
Follow-up (months)	22	17	(5-121)
Size at diagnosis (cm^3)	6.6	2.7	(0.03-43.2)
Growth rate (cm^3/yr)	1.9	0.1	(-3.8-27.9)
Male (27 masses)	2.4	0.2	(-3.8-18.4)
Female (31 masses)	1.4	0.1	(-1.8-27.9)
Charlson comorbidity index	5.2	5	(2-13)
Serum creatinine	1.6	1.2	(0.7-4.3)

TABLE 2. **Growth rate and tumor doubling time of less than 1 year**

Group	No. of tumors	Mean growth rate (cm^3/yr) (range)	No. of masses < 1 yr volume doubling time	p value
All masses	58	1.9 (-3.8-27.9)	4/58	
Age of patient				
< 50 yrs old	8	-0.1 (-1.8-1.3)	0/8	0.32
=> 50 yrs old	50	2.3 (-3.8-27.9)	4/50	
Type of mass				
Cystic mass	14	1.3 (-0.9-5.4)	1/14	0.32
Solid mass	44	2.1(-3.8-27.9)	3/44	
Initial size of tumor				
=> 40 mm	4	10.2 (-0.2-27.95)	0/4	0.15
< 40 mm	54	1.4 (-3.8-23.0)	4/54	

6.6 cm^3 (median 2.7, range 0.03-43.2). The average growth rate was 1.9 cm^3/yr (median 0.1, range -3.8-27.9). Of the 58 tumors, 4/58 (6.8%) had a volume doubling time of less than 1 year. Volume and growth rates for 31/58 (53%) masses were estimated using images with measurements in three dimensions, 19/58 (33%) masses in two dimensions, and 8/58 (14%) in one dimension.

Ninety-three percent (54/58) of the masses were classified as small (greatest diameter less than 4 cm). Of the 54 small renal masses, the average growth rate was 1.4 cm^3/yr (median 0.1, range -3.8-23.0), and the four large renal masses (≥ 4 cm) had a growth rate of 10.2 cm^3/yr (median 6.7, range -0.2-27.95) (p = 0.15). None of the larger masses had a volume doubling time of less than 1 year. Fourteen percent (8/58) of the masses were from patients younger than 50 years of age and had an average growth rate of -0.1 cm^3/yr (median 0.1, range -1.8-1.3). This was not statistically different from the 50 masses from patients who were at least 50 years old, in which the average growth rate was 2.3 cm^3/yr (median 0.1, range -3.8-27.9) (p =0.32). The growth rate of 44 solid masses was 2.1 cm^3/yr (median 0.1, range -3.8-27.9) and was not significantly different from the 14 cystic masses which had an average growth rate of 1.3 cm^3/yr (median 0.2, range 0.9-5.4) (p = 0.32).

By the end of our study period, no patient had died of RCC, and no patient had evidence of metastatic disease during follow up. Surgical intervention was undertaken in 13 patients (15 masses) and included: laparoscopic partial nephrectomy (5), cryoablation (4), radiofrequency ablation (2) and radical nephrectomy (2). Pathology revealed RCC in 10 (67%) of the tumors treated surgically, while the other five (33%) were benign. Histopathological subtypes included: clear cell (5), papillary (1), chromophobe (1), chromophobe versus oncocytoma (2), and unspecified (1). Seven of the 10 RCCs were low grade (Fuhrman I and II), 3 were unclassified, and none were high grade. The 15 masses had a median growth rate of 0.4 cm^3/yr (mean 3.5, range -3.8-27.9), and 2/15 (13%) had a volume doubling time of less than 1 year. Other than the mean size at diagnosis (14.7 cm^3 versus 5.3 cm^3), there were no significant differences in any characteristics between the patients that had surgical intervention versus those who continued with active surveillance during the study period as illustrated in Table 3.

TABLE 3. **Comparison of patients that continued on active surveillance versus those that had surgical intervention**

Variable	Patients continued on active surveillance (33)	Patients had surgical intervention (13)	p value
Mean age at diagnosis	66.0 yrs	59.2 yrs	0.28
Mean Charlson comorbidity score	5.2	5.1	0.97
Mean size at diagnosis	5.2 cm^3	14.7 cm^3	0.02
Mean growth rate	1.5 cm^3/yr	3.5 cm^3/yr	0.26
Mean follow up	23.4 mo	19.0 mo	0.59

Discussion

Invasive procedures such as partial or radical nephrectomy carry significant risks. Nephrectomy is a major surgical procedure, especially in the elderly with significant comorbidities, and has a high morbidity rate of between 11% to 40%.[2] Recent advancement in technology has introduced less invasive procedures such as laparoscopy and renal tumor ablation. However, these less invasive interventions are not without potential morbidity. Gill et al reported a perioperative complication rate of 21% in a series of 100 patients undergoing laparoscopic partial nephrectomy.[11] Additionally, Johnson et al reported a complication rate of 8.4% with one mortality in a multi-institutional study of patients undergoing renal tumor ablation.[12]

In addition, there have been numerous reports suggesting that small renal tumors have a higher rate of being benign, Table 4.[3,13-21] Frank et al observed that there is an inverse relationship between tumor size and likelihood of benign histology and low-grade compared to high grade malignancy.[4] Several studies reported that small renal masses occurring in asymptomatic patients have better survival outcomes.[6,7] Ozono et al concluded that the tumor doubling time was independent of the initial tumor volume and that the growth rate was significantly associated with the tumor size only when it was greater than 4 cm in diameter.[22] Thus, these small renal masses may be better suited with a protocol of active surveillance. However, even larger renal masses (greater than 4 cm diameter) in asymptomatic patients show a low likelihood to grow rapidly or metastasize. Lamb et al showed that large renal masses (mean diameter at diagnosis 7.2 cm) appeared to metastasize rarely, irrespective of size at presentation or growth rate.[8] The conservative management of their patients had little or no negative impact on life expectancy, and they proposed that the expectant management of larger masses is a reasonable and safe therapeutic option, especially for the elderly patients presenting with severe comorbidities.[8] Furthermore, a study by Kouba et al similarly found that the growth rate of masses did not correlate with initial size.[23] Our study confirmed that initial tumor size did not predict volume doubling time. Conversely, our study showed that masses larger than 4 cm did not have a significantly greater growth rate compared to the small tumors less than 4 cm ($p = 0.15$). Therefore, active surveillance in patients with renal masses, regardless of initial size, may be warranted, Figure 1.

In a published study,[8] the authors concluded that RCC in the elderly tended to be less aggressive than that observed in the younger population. Additionally, Kouba et al also found that age was perhaps the strongest predictor of tumor growth.[23] However, in our study, the mean growth rate of eight masses in patients younger than 50 years of age (average 42.6) was -0.1 cm^3/yr (range -1.8-1.3), which was not significantly different from the 50 masses in patients older than 50 years of age (average 67.8) with a mean growth rate of 2.3 cm^3/yr (range -3.8-27.9) ($p = 0.32$). Thus, while active surveillance is usually reserved for the elderly, even the younger patients with significant comorbidities on active surveillance do not appear

TABLE 4. **Comparison of this study to other published results**

	Total patients	Mean initial size (diameter or volume)	Average follow up (mo)	Mean overall growth rate	Mean age (yrs)
Bosniak et al[13]	37	< 3.5 cm	39	0.36 cm/yr	65.5
Rendon et al[18]	13	2.95 cm	42 median	1.32 cm^3/yr	69
Oda et al[17]	16	2 cm median	25.2 median	0.54 cm/yr	69 median
Wehle et al[3]	29	1.83 cm	32	0.12 cm/yr	70
Volpe et al[21]	32	< 4 cm	27.9 median	0.1 cm/yr	71
Sowery et al[19]	22	4.08 cm	26	0.86 cm/yr	77
Lamb et al[8]	36	6 cm median	24	0.39 cm/yr	76.1
Fernando et al[25]	13	5.0 cm	38.4	0.17 cm/yr	80.4
Matsuzaki et al[16]	15	2.2 cm	38	0.06 cm/yr	67
Kouba et al[23]	43	2.9 cm	35.8	0.7 cm/yr	67
This study	46	2.1 cm (6.6 cm^3 volume)	22	0.21 cm/yr (1.9 cm^3/yr)	64

to have adverse outcomes in our study. Of note, the decision to pursue active surveillance in this younger patient cohort was secondary to either patient choice or significant comorbidities, with an average Charlson comorbidity score of 2.7 (range 2-4).

Out of the thirteen patients (28%) who underwent surgery, none were secondary to patient or tumor characteristics. Patient age and Charlson comorbidity scores were similar to the group of patients that did not undergo surgery. Despite significantly larger mass size at diagnosis (14.7 cm^3 versus 5.3 cm^3), the growth rate for the surgery patients were not statistically different from those for non-surgery patients. Thus, the percentage of patients undergoing surgery is not reflective of the true proportion of masses unsuitable for watchful waiting. Tumors were surgically treated secondary to patient preference, surgeon preference, or both.

We do not implicate that kidney tumors without metastatic disease are insignificant. They can metastasize and also be fatal.[24,25] However, we believe that RCC associated with aggressive cancer is different from the ones we have observed. Rapidly enlarging masses on serial imaging studies warrant concern and possibly invasive treatment, but the growth rate at which intervention should occur has not been determined. Furthermore, more sensitive serologic markers are needed to aid in determining the progression of renal masses. Currently, serial image studies of the renal masses, Figure 2, and patients' presenting symptoms are the only reliable prognostic indicators available. Other markers currently in use for RCC progression such as intratumoral vessel density, MIB-1 score, DNA content, and expression of protein p53 are neither sensitive nor specific and require biopsy.[3]

There are several limitations to this study. First, this study was done with a small patient population and limited follow up in which outliers can significantly alter the mean. Thus, there may be results not reflective of the natural history of renal masses, especially in our smaller sub-groups. Next, due to unavailability of coronal images and MR images significantly degraded by motion in some cases, not all masses in this study were measured in three dimensions. Therefore, a follow up study with a larger cohort with longer follow up using only the three-dimensional measurements for all the masses is needed to confirm our results.

Conclusions

The incidence of RCC is growing, largely due to the increasing use of imaging. In our cohort, the growth rate of these tumors is slow and the risk of metastasis is low, regardless of patient age or initial tumor size.

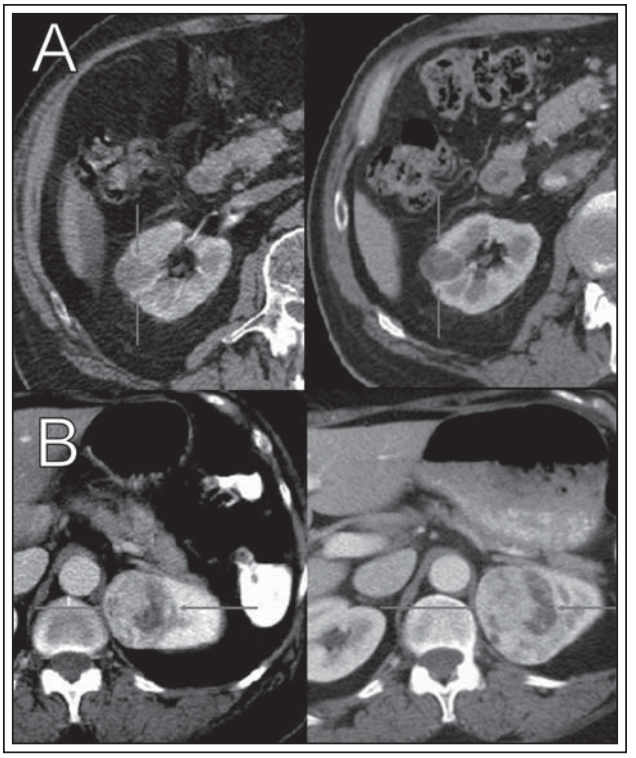

Figure 2. CT images depicting renal masses exhibiting different patterns of growth. (A) The images of a 73-year-old male patient's mass, one at diagnosis (top left) and another after 50 months of follow up (top right), show no change in mass size. The patient continued on active surveillance at the conclusion of this study. (B) The images of a 76-year-old female patient's mass, one at diagnosis (bottom left) and another after 27 months of follow up (bottom right) show increase in mass size. The patient subsequently underwent radical nephrectomy, and histopathologic study revealed renal cell carcinoma, clear cell subtype.

Of those who elect to go on to surgical therapy, tumors are found to be benign or of low grade. For patients for whom invasive therapy is not favored, expectant management with serial imaging may be a reasonable and safe option. □

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