Distribution of Renal Tumor Growth Rates Determined by Using Serial Volumetric CT Measurements[1]

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Purpose: To retrospectively determine the distribution of growth rates across different sizes and subtypes of renal cortical tumors by assessing tumor volume and maximum tumor diameter at serial volumetric computed tomographic (CT) examinations.

Materials and Methods: The institutional review board approved this retrospective, HIPAA-compliant study. Fifty-three of 2304 patients (34 men, 19 women; mean age, 67 years ± 10 [standard deviation; range, 39–88 years) who underwent nephrectomy from 1989 to 2006 did not receive preoperative chemotherapy or radiation therapy and underwent at least two preoperative contrast material–enhanced CT examinations (at least 3 months apart) with identical section thickness that was no more than one-fifth of longitudinal tumor diameter. Tumor volume and maximum diameter were measured on CT scans. Reciprocal of doubling time (DT) (RDT) was calculated. Analysis of variance and Student *t* tests were performed.

Results: Thirty-two clear cell carcinomas, 10 papillary carcinomas, six chromophobe carcinomas, four oncocytomas, and one angiomyolipoma were analyzed. Median tumor size was 2.9 cm (range, 1–12 cm). Seven tumors did not increase in volume. DT ranged from −248 to 72 days (mean, 474 days; median, 811 days). Growth rate determined by using maximum diameter ranged from −10.8 to 33.2 mm/y (mean, 5.1 mm/y; median, 3.5 mm/y). Faster-growing tumors were more likely to be clear cell carcinomas, those of higher grade had higher growth rates. No significant correlation was found between RDT and tumor initial volume, subtype, or grade. Small renal tumors (≤3.5 cm) were similar to larger tumors in subtype and growth rate. Age at diagnosis correlated negatively with renal tumor growth rate ($P = .03$).

Conclusion: Growth rates in renal tumors of different sizes, subtypes, and grades represent a wide range and overlap substantially. Small renal tumors appear to be similar to larger ones in nature.

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Kidney cancers account for about 3% of all cancer cases and deaths in the United States, with 38 890 new diagnoses and 12 840 deaths in 2006 (1). It is estimated that approximately $1.9 billion is spent in the United States each year on treatment of kidney cancer (2). The incidence of kidney cancers has been increasing at a rate of about 2% per year for the past 30 years (3). The overall mortality rate from kidney cancers has slightly increased over the past 2 decades, but not as rapidly as the incidence rate. This is a result of improvement in 5-year survival (4). Newer radiographic techniques help detect renal tumors more frequently and at an earlier disease stage, when tumors can be resected for cure (5–13). However, it appears that not all incidentally found malignant renal tumors undergo clinically important active growth (6–8). In addition, the long-term renal health of patients with renal tumors has become an important clinical consideration for the following reasons: *(a)* Renal cortical tumors may be bilateral and multifocal in both hereditary and nonfamilial forms; *(b)* a large number of these tumors carry a low metastatic potential and a good long-term prognosis (14); and *(c)* as the patients age, they are at risk for development of added intrinsic renal damage from common diseases such as diabetes, hypertension, and glomerulonephritis (15). Therefore, "watchful waiting" has been proposed as a reasonable approach in selected cases (6,7), especially in patients who are elderly or poor surgical candidates.

Over the last decade, it has become clear that renal cortical tumors are a family of neoplasms with distinctly different histopathologic features, malignant potential, and patterns of disease progression (16–25). For example, conventional clear cell carcinomas carry a greater metastatic potential than do papillary and chromophobe carcinomas (25). The overall 5-year survival rates for the papillary and chromophobe subtypes (80%–90%) are much higher than those for conventional renal cell carcinoma (50%–60%) (26–28).

A few studies have estimated the growth rates of kidney cancers by using imaging findings (6–8,29–35). However, these studies were limited by relatively small sample sizes and lack of pathologic correlation in all tumors. Better knowledge of the growth rates of renal cancer overall and in different subtypes may help in the formulation of clinical recommendations for CT observation or surgical treatment. At our medical center (Memorial Sloan-Kettering Cancer Center, New York, NY), many patients with renal tumors are referred from outside institutions and may have undergone serial CT examinations before treatment. Therefore, we undertook this study to retrospectively determine the distribution of growth rates across different sizes and subtypes of renal cortical tumors by assessing tumor volume and maximum tumor diameter at serial volumetric CT examinations.

Advances in Knowledge

- The ranges of the growth rates of renal tumors of different sizes, subtypes, and grades are wide and overlap substantially.
- Tumor growth rates do not correlate with initial tumor volume and the distribution of histologic subtypes and growth rates among small renal tumors is similar to that among larger tumors.
- Age at diagnosis is negatively correlated with renal tumor growth rate.
- Some pathologically proved cancers decrease in volume between the initial and final CT examinations.

Implication for Patient Care

- Because tumor growth rates vary widely, surveillance of small renal masses, if selected as the clinical management approach, must be vigorous.

Materials and Methods

Patients

Approval for this retrospective study was obtained from our institutional review board, which waived the requirement for informed consent. This study was compliant with the Health Insurance Portability and Accountability Act.

We searched the electronic database from the Department of Urology for clinical information on all patients who had undergone nephrectomy (excluding nephroureterectomy for upper-tract urothelial carcinoma) and who did not receive preoperative antitumor chemotherapy or radiation therapy from April 1989 to January 2006; 2304 patients were identified. Subsequently, we searched for all patients who had undergone at least two preoperative contrast material–enhanced CT examinations, with the initial and follow-up CT examinations at least 3 months apart, and excluded patients who did not receive contrast material for these scans. This search yielded 121 patients. CT studies that demonstrated noticeable motion artifact, in which the entire tumor either was not imaged or could not be delineated, were excluded. Furthermore, to minimize measurement bias related to varying CT section thicknesses (36), we restricted our analyses to patients who had undergone two CT examinations with the same section

Published online
10.1148/radiol.2501071712

Radiology 2009; 250:137–144

Abbreviations:
DT = doubling time
RDT = reciprocal of DT

Author contributions:
Guarantors of integrity of entire study, J.Z., S.K.K.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; literature research, J.Z., S.K.K., A.T.; clinical studies, J.Z., S.K.K., A.T.; statistical analysis, J.Z., S.K.K., L.W.; and manuscript editing, J.Z., S.K.K., A.T., H.H.

Authors stated no financial relationship to disclose.

thickness that were at least 3 months apart. To minimize the partial volume effect, we restricted our measurements to renal tumors that were present on five or more sections. CT studies that demonstrated noticeable motion artifact, in which the entire tumor either was not imaged or could not be delineated, were excluded. The remaining 53 patients were included in the analysis. Documented information included patient age at diagnosis, date of surgery, renal tumor location, size, type, pathologic stage, and type of surgery. Clear cell carcinoma grades were also recorded. The criteria for grading papillary carcinomas had changed over time and therefore were not included in the analysis. Chromophobe carcinomas are generally not graded at our institution. For the CT examinations included in the study, the examination date, section thickness, and section increment were recorded.

CT Technique and Image Analysis

All examinations were performed with a CT scanner (GE Healthcare, Milwaukee, Wis) by using an automated power injector. CT images were reviewed with a three-dimensional multiplanar reformatting interactive mode used on an integrated workstation (Advanced Workstation; GE Healthcare) suite of our enterprise-wide picture archiving and communication system workstations. The integrated workstation suite allows the reader to draw lines and regions of interest and automatically calculates the line length and the area enclosed by the region of interest.

For each patient, the first and last CT examinations among those that qualified were identified and displayed in random order. Only two sets of measurements were obtained per patient, regardless of how many serial scans were obtained. The renal tumor was classified according to the surgical pathologic report. Two investigators (S.K.K. and J.Z.) measured the maximum tumor diameters and the tumor volume in consensus without knowing the type of renal tumor. One investigator (S.K.K.) obtained the initial measurements and saved them with the digital images. The second investigator (J.Z.) subsequently reviewed the measurements and discussed with the other to reach consensus when necessary. The greatest axial diameters, greatest perpendicular diameters, and greatest longitudinal diameters were measured and recorded. The tumor contour was then traced manually on every axial image by using the integrated workstation on the picture archiving and communication system, which automatically calculates the cross-sectional area size. Tumor volume was then calculated by multiplying the sum of all cross-sectional areas by the section thickness.

Data Analyses

The tumor doubling time (DT), measured in days, was calculated by using the following equation: $DT = t \cdot \log 2 / (\log V - \log V_0)$, where t is the time between two measurements and V_0 and V denote the tumor volume at the initial and last CT examinations, respectively (31).

The DT was also converted to the linear function 365/DT − RDT for data analyses, where RDT is reciprocal of DT (37).

The growth rate in the maximum cross-sectional dimension was calculated by using the following equation: $R = (D - D_0)/(T - T_0)$, where R is the growth rate and D_0 and D indicate the maximum cross-sectional diameters at the initial and last CT examinations, respectively (31).

Statistical Analyses

To assess the relationship between tumor growth and tumor volume at the baseline level, we fit overall simple linear regression models with RDT as the dependent variable and volume at baseline as the independent variable, and the Pearson correlation coefficient was calculated. Age at diagnosis was also correlated with RDT and initial tumor volume by using the Pearson coefficient. The age of male and female patients at diagnosis was compared by using the Wilcoxon rank sum test. To test for differences in the distributions of DT and growth rates across histologic subtypes and grades, we used analysis of variance. We divided tumors into slow- and fast-growing groups (by using quartiles of RDT) and evaluated the distribution of histologic subtypes. Two-sample Student t test with unequal variance was performed to compare the RDT in small (≤3.5 cm) and large renal tumors. All analyses were performed with software (Stata, version 9.2 for Windows; Stata, College Station, Tex).

Results

A total of 53 patients with 53 renal tumors were included in this study (Table 1, Fig 1). There were 34 men and 19 women, with a median age of 68 years (mean age, 67 years ± 10 [standard deviation]; range, 39–88 years). The men had a median age of 70 years (mean age, 68 years ± 10; range, 47–88 years), and the women had a median age of 68 years (mean age, 66 years ± 12; range, 39–85 years). There was no significant difference in age by using sex in this group

Table 1

Patient and Lesion Characteristics

Characteristic	No. of Patients (n = 53)
Sex	
Male	34 (64)
Female	19 (36)
Age (y)*	68 (39–88)
Lesion data	
Pathologic stage	
T1a	35 (66)
T1b	8 (15)
T2	3 (6)
T3a	5 (9)
T3b	2 (4)
Histologic outcome	
Clear cell	32 (60)
Papillary	10 (19)
Chromophobe	6 (11)
Oncocytoma	4 (8)
Angiomyolipoma	1 (2)
Location	
Left side	25 (48)
Right side	28 (52)

Note.—Unless otherwise noted, numbers in parentheses are percentages.

* Data are medians; numbers in parentheses are the range.

of patients. Of 53 lesions, 32 (60%) were clear cell renal carcinomas, 10 (19%) were papillary, six (11%) were chromophobe, four (8%) were oncocytomas, and one (2%) was a lipid-poor angiomyolipoma. Of the 32 clear cell carcinomas, five (16%) were Furhman grade 1, 19 (60%) were grade 2, and eight (25%) were grade 3. In terms of primary tumor stage, 35 (66%) of 53 patients had stage T1a disease, eight (15%) had stage T1b disease, and 10 (19%) had stage T2 disease or above at the time of surgery.

The median interval between the initial and final CT examinations was 245 days (range, 93–2984 days) (Table 2). The mean section width was 4.8 mm (range, 2–7.5 mm). Tumor dimensions were measured for 976 CT sections. The median tumor volume was 10 495 mL (mean, 48 351.24 mL; range, 477–662 746 mL) at initial and 13 291 mL (mean, 65 744 mL; range, 684–688 209 mL) at final CT examinations (Fig 2). At surgical pathologic review, the maximum tumor diameter ranged from 1.0 to 12.0 cm, with a median maximum diameter of 2.9 cm (mean, 3.7 cm ± 2.4).

Median percentage change in tumor volume between the initial and final CT examinations was 27% (mean, 67%; range, −36% to 633%).

Seven (13.2%) of 53 tumors did not increase in volume between the initial and final CT examinations (Table 3).

Renal Tumor Growth

The median RDT of all renal tumors was 0.45, corresponding to a DT of 811 days, with a mean RDT of 0.77, corresponding to a DT of 474 days. The RDT range was −1.47 to 5.06, corresponding to a DT range of −248 to 72 days. Twenty-one (40%) of 53 tumors demonstrated a DT of more than 730 days (RDT < 0.5) (Fig 3). Growth rate by using maximum cross-sectional diameter between the initial and final CT examinations was also calculated, showing a range of −10.8 to 33.2 mm/y (mean, 5.1 mm/y; median, 3.5 mm/y).

Figure 1

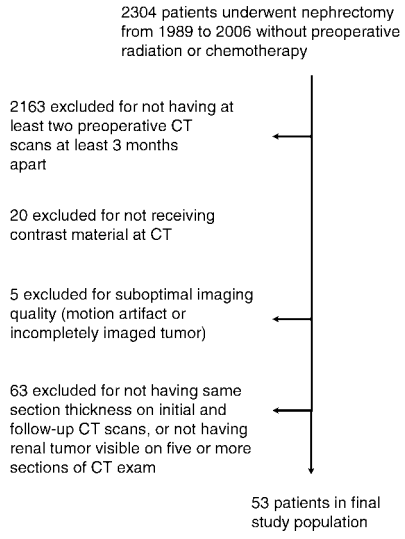

Figure 1: Flowchart of patient accrual and exclusion.

Figure 2

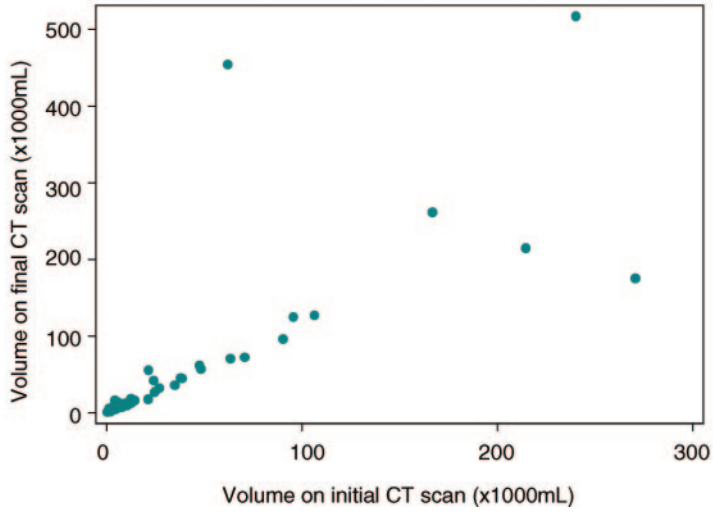

Figure 2: Tumor volume seen at initial and final CT examinations. One patient with tumor volume of 662 745 mL on initial scan and volume of 668 209 mL on final scan is not shown on scatterplot owing to extremely large size compared with other tumors.

Table 2

Time between Initial and Final Scans and Maximum Tumor Diameter at Surgical Pathologic Review

Characteristic	All (n = 53)	Renal Tumor Subtype: Clear Cell (n = 32)	Papillary (n = 10)	Chromophobe (n = 6)	Oncocytoma (n = 4)	Angiomyolipoma (n = 1)
Time between initial and final scans (d)	245 (93–2984)	224 (97–738)	282 (93–2984)	393 (159–749)	1298 (189–2039)	144
Maximum tumor diameter at pathologic review (cm)	2.9 (0.9–12)	3.5 (0.9–12)	2.8 (1.4–7.5)	2.0 (1.1–5)	1.6 (1.1–3)	2.8

Note.—Data are the medians; numbers in parentheses are the ranges.

There was no significant correlation between age at diagnosis and initial tumor volume ($P = .13$). However, age at diagnosis was negatively correlated with RDT ($P = .03$). Each 1-year increase in age at diagnosis was associated with a 3% decrease in RDT.

Tumor Size and Growth Rate

There was no significant correlation between RDT and initial tumor volume ($P = .42$) (Fig 4). Pearson correlation coefficient was −0.11.

Thirty-three (62%) of 53 renal tumors were 3.5 cm or less in maximum diameter at pathologic examination and met the definition of small renal tumors. Seventeen (52%) of those 33 were clear cell carcinomas, seven (21%) were papillary carcinomas, four (12%) were chromophobe, four (12%) were oncocytomas, and one (3%) was a fat-poor angiomyolipoma. The mean RDT in this group was 0.88 (corresponding to a DT of 415 days), with a median of 0.52 (corresponding to a DT of 702 days) and a range of −1.47 to 5.06. There was no significant difference between the RDT of the 33 small tumors and the RDT of the 21 larger ones ($P = .3$). In the small renal tumors, the mean growth rate in the maximum cross-sectional diameter between the initial and final CT examinations was 0.37 cm/y (median, 0.28 cm/y; range, −0.34 to 1.37 cm/y).

Tumor Histologic Subtype, Grade, and Growth Rate

There was no significant difference in RDT ($P = .56$) among the histologic subtypes (Table 4). The proportion of clear cell carcinomas in the slowest-growing tumor group (four of 13, 31%) was much lower than those in the faster-growing tumor groups (eight of 13, 62%; nine of 13, 69%; and 11 of 14, 79%) (Table 5).

Among clear cell carcinomas, there was an apparent trend of RDT increasing with tumor grade, with the respective median and range of RDT for each Fhurman grade as follows: grade 1, 0.18 and −0.42 to 2.63; grade 2, 0.55 and −0.90 to 3.24; and grade 3, 1.39 and 0.19–3.54. However, owing to the wide range of growth rates in each group and the substantial overlap in growth rates among the groups, no significant difference in RDT ($P = .25$) was shown among the tumors of different Fuhrman grades.

Table 3

Characteristics of the Renal Tumors That Did Not Demonstrate Growth between Initial and Final CT Examinations

Tumor No.	Tumor Type	Initial Volume (mL)	Final Volume (mL)	Interval between CT Examinations (d)	Volume Change (%)
1	Chromophobe	2050	1315.5	150	−35.8
2	Clear cell	270 823.5	174 971.8	525	−35.4
3	Clear cell	21 393.25	17 517.25	120	−18.1
4	Papillary	10 494.6	9593.75	330	−8.6
5	Oncocytoma	7680.4	7203.75	540	−6.2
6	Oncocytoma	4462.2	4269	1080	−4.3
7	Papillary	214 818.8	214 441.5	195	−0.2

Discussion

Little is known about the growth rate of renal cell carcinoma because the standard of care for renal tumors is surgical removal at discovery. During the past 10–20 years, given the increased use of imaging, more and more renal masses have been found incidentally. Management of incidentally found renal tumors, especially when they are small, has been problematic.

Kassouf et al (8) followed up 24 patients over a median period of 24 months, and only five patients demonstrated tumor growth during the surveillance period. Volpe et al (34) examined 32 renal masses, approximately one-third of which demonstrated significant growth over a median follow-up period of 28 months. Sowery and Siemens (33) examined 22 patients over a mean follow-up period of 26 months and found that overall tumor growth was slow, even in patients diagnosed with larger masses. Ozono et al (31) calculated tumor DT in 56 patients (only 38 had surgical pathologic findings available), and most showed a slow tumor growth rate. A few smaller studies also demonstrated a variable growth rate among small renal tumors, some of which grow slowly (29,30,32). Bosniak et al (7) tracked 40 small renal tumors (<3.5 cm) over a mean of more than 3 years, and showed an overall growth rate of neoplasms of 0–1.1 cm/y (mean, 0.36 cm/y). However, these prior investigations were limited by lack of pathologic correlation in all tumors. Most of the studies were relatively small in sample size, which limited the number of cases of the less common renal histologic subtypes, such as papillary or chromophobe renal carcinomas. Some of the studies were conducted before the Heidelberg classification was published (38), and information on tumor histologic subtype or grade was not consistently collected in other studies. In addition, not all studies obtained volumetric measurements to determine tumor DT.

Figure 3

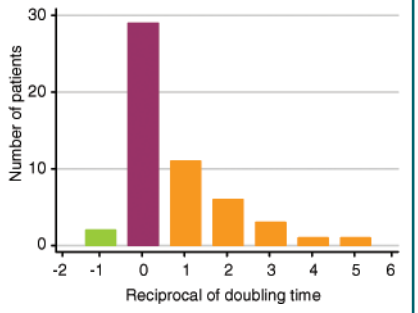

Figure 3: Number of patients with renal tumors in each RDT group. Few tumors demonstrated negative growth (green bar); most tumors demonstrated relatively slow growth (red bar). However, some tumors demonstrated significant growth rate over time, as evidenced by large RDT values (orange bars).

Figure 4

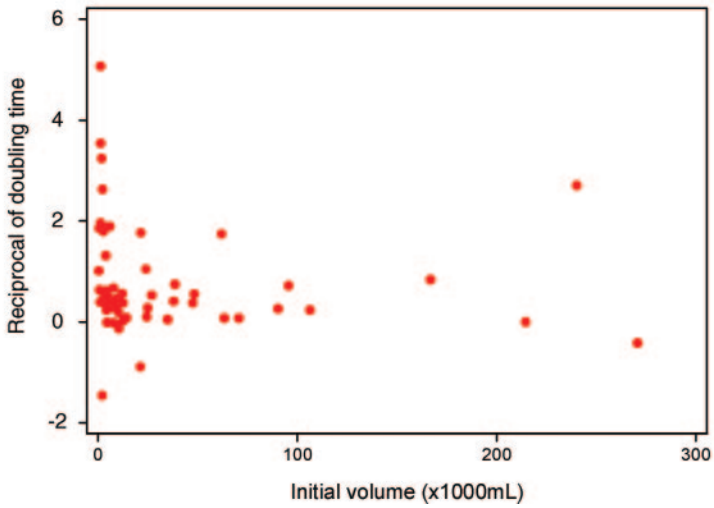

Figure 4: Scatterplot of tumor RDT over initial volume seen at CT. One patient with tumor volume of 662 745 mL on initial scan and RDT of 0.18 is not shown on scatterplot owing to extremely large size compared with other tumors.

Table 4

RDT of Renal Tumors

Tumor Type	No. of Tumors	RDT*
Clear cell	32	0.59 (−0.90 to 3.54)
Papillary	10	0.32 (−0.14 to 5.06)
Chromophobe	6	0.20 (−1.47 to 1.96)
Oncocytoma	4	0.03 (−0.02 to 1.00)
Angiomyolipoma	1	0.26
All tumors	53	0.45 (−1.47 to 5.06)

* Data are the medians; numbers in parentheses are the ranges.

Table 5

Distribution of Renal Tumor Histologic Subtypes in Tumor Groups with Different Growth Rates

Tumor Type	1st Quartile	2nd Quartile	3rd Quartile	4th Quartile
Clear cell	4	8	9	11
Papillary	3	3	3	1
Chromophobe	3	1	1	1
Oncocytoma	3	0	0	1
Angiomyolipoma	0	1	0	0
Total	13	13	13	14

Note.—The slowest-growing tumors are in the 1st quartile; the fastest-growing tumors are in the 4th quartile.

Our study included 53 renal tumors, all of which were studied with surgical pathologic correlation. Median follow-up time was 8 months, ranging from 3 months to 8 years.

In keeping with prior published studies, a number of renal tumors did not demonstrate substantial growth, and some even demonstrated no or negative growth. Approximately 40% of tumors had a DT longer than 2 years. However, some of the renal tumors did grow rapidly, including some small renal tumors. When the initial tumor volume is considered, there does not seem to be an apparent correlation between tumor growth rate and size. In other words, the small renal tumors also showed a wide range of growth rates without obvious evidence that small tumors behaved differently from larger ones. This was also confirmed by the distribution of histologic subtypes among the small renal tumors, which was not much different from that among all renal tumors. Our findings are in keeping with those of two other recent publications in the urologic literature that found that incidentally detected tumors, though diagnosed earlier, may be similar to symptomatic renal cell carcinomas in biologic nature (39), and that surveillance for renal masses remains an option but must be rigorous and continuous, and is not without risk of progression (40).

In our study, each histologic subtype and grade of tumor demonstrated a wide range of DT and growth rate, from essentially no growth to rapid growth; these ranges overlapped substantially, and thus no significant differences were found. However, when the renal tumors were divided into slow- and fast-growing subgroups, it became evident that a fast-growing tumor was much more likely to be a clear cell carcinoma. In addition, the clear cell carcinomas with higher Fuhrman grades demonstrated a faster median growth rate.

Spontaneous regression of primary renal tumors has been reported but is rare. Therefore, we were surprised to find that seven (13.7%) of 53 renal lesions in our study demonstrated negative growth between the initial and final

CT examinations. However, negative growth of stage I lung cancers was also reported by Jennings et al (37) in a similar proportion of patients. Jennings et al suggested a number of possible causes for the negative growth, including technical factors (less reliable measurements between short-interval imaging examinations), and true nonlinear growth caused by variable immune response, necrosis and implosion, and variations in tumor angioneogenesis. Furthermore, we are unaware of previous studies showing that renal tumors may have a slightly lower growth rate with increasing patient age, but Jennings et al also found a negative correlation between lung cancer growth rate and patient age.

It is possible that selection bias affected our study. Since all patients in our study had been followed up for a period of at least 3 months before undergoing surgery, they (or their tumors) may have had different characteristics than other patients who underwent surgery immediately or less than 3 months after diagnosis. For example, our study patients may have been thought to have slow-growing or low-risk renal tumors by their physicians; however, since there is no established clinical parameter to predict the growth rate of a renal tumor, and the standard of care is immediate surgical resection, this scenario is unlikely. More likely reasons for the delay of surgery in these patients include delays during referral from another institution; poor general health at the time of diagnosis, making the patient a nonsurgical candidate; and failure to detect a renal tumor present at initial imaging. Therefore, we speculate that our cohort represents a small but random sample of all patients with renal tumors. This conclusion is further supported by the fact that the distribution of histologic subtypes and primary tumor stages in our cohort were quite similar to those in surgical cohorts previously reported from our institution.

Because the patient data used in our study was accumulated over a long period of time, the techniques used to acquire the CT images varied. This was another limitation of our study. It has been reported that section thickness affects the accuracy of volumetric measurement on CT images, and the smaller the lesion, the larger the effect (36). By using a prior study on volumetric measurement of lung cancers, an equation was developed to reduce the volumetric measurement errors caused by changing section thickness and tumor sizes between CT examinations (36). However, this equation might not be effective when applied to nonpulmonary lesions or to CT examinations performed with different scanners or techniques. Therefore, we tried to minimize measurement errors by restricting our measurements to those patients whose CT examinations had the same section thickness and had tumor visible on at least five sections. In addition, the renal tumors in our study were larger than the lung lesions measured in the above study and should therefore have been associated with a lesser degree of measurement error. Furthermore, we manually measured cross-sectional areas to calculate tumor volumes. A prospective study with uniform thin-section thickness and automated volumetric measurement might yield more accurate results, but would be difficult to do since immediate surgical resection is still considered the standard of care.

In conclusion, by using serial CT tumor volume measurement, we determined that the median DT of renal tumors was 811 days and that tumors of the same histologic subtypes and grades grew at widely varying rates. The ranges of the growth rates and DTs of different histologic subtypes and grades of renal tumor overlapped substantially. However, a higher proportion of clear cell carcinomas demonstrated rapid growth. Increasing age at diagnosis was associated with a slower growth rate. Although some renal tumors showed extremely slow growth, there was no evidence that small renal tumors had different histologic compositions or growth potentials from larger ones; therefore, surveillance of small renal masses, if selected as the clinical management approach, must be vigorous.

Acknowledgments: We thank Satish K. Tickoo, MD, for reviewing the manuscript and Ada Muellner, BA, for editorial support.

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