Original Article

Tumor doubling time of renal cell carcinoma measured by CT

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ABSTRACT

Introduction: Increasing numbers of patients are now being incidentally detected with small-sized renal cell carcinoma (RCC). The natural history of small renal masses is not completely understood. Currently, there are no specific tumor markers to determine initial risk or progression to metastatic disease. Growth rate and tumor size are factors shown to be predictive of tumor biology. In this study, we attempted to examine the natural history of RCC and calculated the doubling times (DTs) of untreated RCC at the primary site.

Materials and Methods: We retrospectively reviewed the records of all patients with RCC who had at least two measurements of the same tumor mass obtained on computed tomography (CT) imaging on two different dates (at least 6 months apart) during periods of non-treatment. The tumor volume was calculated at two points in time using images yielded by the CT imaging. The tumor DT was calculated using the following equation: $DT = (T - T0) \times \log 2 / \log V - \log V0$.

Results: Twenty-two (13 male and nine female) patients with ages ranging from 32 to 71 years (mean 52.22 years) were included in the study. The initial maximum tumor diameter ranged from 2.8 to 6.8 cm (mean 3.93 cm) and the last maximum tumor diameter ranged from 3.2 to 7.8 cm (mean 4.39 cm). The *DT* for the entire population was 460.01 days (range 174-913 days).

Conclusions: RCC is a diverse disease process, with the majority of lesions demonstrating malignant disorder. In our study, the DT for the patient population was 460.01 days (range 174-913 days).

Key words: Diagnostic imaging, natural history, renal cell carcinoma, small renal neoplasm

INTRODUCTION

Renal cell carcinoma (RCC) accounts for 2-3% of all adult malignant neoplasms, and is the most lethal of the common urologic cancers. Traditionally, 30-40% of patients with RCC die of their cancer, in contrast to the 20% mortality rates associated with prostate and bladder carcinomas.[1,2] Approximately 54,000 new diagnoses of RCC are made each year in the United States, and 13,000 patients die of their disease.[3] The incidence of RCC has been on the rise since the 1970s by an average of 3% per year for whites and 4% per year for African-Americans, largely related to the more prevalent use of ultrasonography and computed tomography (CT) for the evaluation of a variety of abdominal complaints.[4-6] RCC is a heterogeneous group of tumors with varied degrees of biologic aggressiveness. The majority of renal cortical neoplasms (80%) are known to be malignant, but only 20-30% of malignant T1a lesions have potentially aggressive features.[5,6]

The tumor volume doubling time (DT) is the time taken by a tumor to double in volume. This concept was first introduced by Collins *et al.*,[7] who showed that the growth rate of malignant tumors was constant and exponential and could be estimated in terms of the DT. The DTs of various cancers have been described[8,9]; however, the data on the rate of cancer growth are difficult to collect because most cancers are treated as soon as they are discovered. Data on the growth rate of RCCs are limited. Birnbaum *et al.*[10] reported that RCCs in the primary site showed a mean linear

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growth rate of approximately 0.5 cm/year. In the present study, we attempted to examine the natural history of RCC and calculated the DTs of untreated RCC at the primary site.

MATERIALS AND METHODS

We retrospectively reviewed the records of all patients in whom RCC had been diagnosed at our hospital between June 2000 and January 2012. The records which contained at least two measurements of the same tumor mass obtained on different dates (at least 6 months apart) during periods of non-treatment were selected. The exclusion criteria included bleeding within the tumor, cystic-type tumor, tumor with central necrosis and history of malignant diseases.

For each patient, the following background variables were investigated: Age, gender, symptoms, factor precipitating the diagnosis, clinical TNM classification, reasons for avoiding surgical intervention, details of the drug therapy administered during the follow-up period and outcome as of the date of evaluation.

The maximum tumor diameter and the tumor volume were calculated at two points in time using images yielded by the same modality of diagnostic imaging. The tumor volume (V) was calculated using the following equation, assuming the tumor to have a spheroidal form:[11]

$$V = [4/3 \times \pi \times a \times b \times (a + b/2)] \times 1/8$$

where *a* indicates the maximum tumor diameter and *b* denotes the minimum tumor diameter. The tumor DT was calculated using the following equation:[11]

$$DT = (T - T0) \times \log 2/\log V - \log V0$$

where $T - T0$ indicates the length of time between two measurements and $V0$ and V denote the tumor volume at two points of measurement.

Pathological findings were similarly noted in those patients who underwent surgery after prolonged follow-up, and included pTNM classification, tumor cell type, degree of histological atypism, invasion and growth type. Data were compared and aA P value of < 0.05 was considered significant.

RESULTS

Twenty-two patients at our hospital were included in this study. The details of the subjects are shown in Table 1. There were 13 males and nine females, with ages ranging from 32 to 71 years (mean 52.22 years).

The initial maximum tumor diameter ranged from 2.8 to 6.8 cm (mean 3.93 cm), and the initial tumor volume ranged from 11.50 to 164.70 cm^3 (mean 38.20 cm^3) [Figures 1 and 2]. None of these patients were subjected to active surveillance. The reasons for delay in treatment included a wish to seek a second opinion in 31.81% of the patients. A further seven (31.81%) patients were initially unfit to undergo major surgery. Following adequate preparation, which included angiography/angioplasty, all these seven patients underwent surgery. Five patients postponed their surgery due to the high costs involved. All these patients were operated following grants from government health schemes. The delay in treatment in three other patients was due to a delay in getting permission from insurance providers.

The last maximum tumor diameter ranged from 3.2 to 7.8 cm (mean 4.39 cm). The DT for the entire population was 460.01 ± 182.45 days (range 174-913 days) [Table 2]. When analyzed by background variables, the DT showed no significant difference depending on any background variables [Figures 3 and 4]. All patients underwent surgical excision of the tumor. None of the patients developed clinically/radiologically obvious metastases during this period.

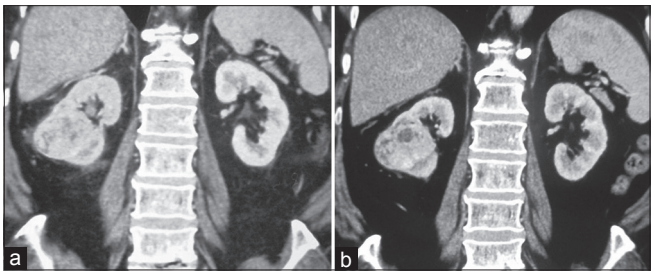

Figure 1: (a) Right-sided renal mass 4.7 cm × 3.8 cm at presentation in a 67-year-old female. (b) The same mass grew to 5.1 cm × 5.4 cm after a follow-up of 190 days

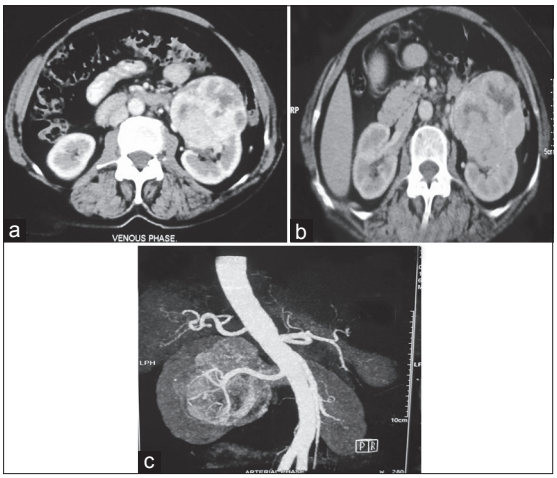

Figure 2: (a) Initial contrast computed tomography showing a heterogeneously enhancing mass measuring 6.7 cm × 6.7 cm, arising from the mid pole of the left kidney. (b) Last CT image showing an increase in size of the renal mass (7.8 cm × 7.4 cm). (c) CT angio image showing tumor blush due to neovascularization

Table 1: Background variables of the study patients

Age (years)	Gender (%)	Symptoms (%)	Initial max diameter (cm)	Initial TNM (%)	Reason for delay in treatment (%)
32-71 (mean 52.22)	Male 13 (59.09) Female 9 (40.90)	Asymptomatic 14 (63.63) Symptomatic 8 (36.36) Symptoms (hematuria, pain, weakness)	2.8-6.8 (mean 3.93±1.00)	T1a 16 (72.72) T1b 6 (27.27)	2nd opinion 7 (31.81) Cardiac fitness 7 (31.81) Financial 5 (22.72) Delay in insurance sanction 3 (13.63)

TNM=Tumor nodes metastasis

Table 2: Tumor doubling time

Initial max tumor diameter (cm)	Last max tumor diameter (cm)	Initial volume of tumor (cm^3)	Last volume of tumor (cm^3)	Tumor doubling time (days)	Final histology of the tumor (%)	pTNM (%)
Range 2.8-6.8	Range 3.2-7.8	Range 11.50-164.70	Range 17.16-248.57	Range 174-913	Clear cell Ca 20 (90.90)	T1a 10 (45.45)
Mean 3.93±1.00	Mean 4.39±1.04	Mean 38.20±34.24	Mean 52.25±49.34	Mean 460.01±182.45	Papillary cell Ca 2 (9.09)	T1b 11 (50) T2 1 (4.54)

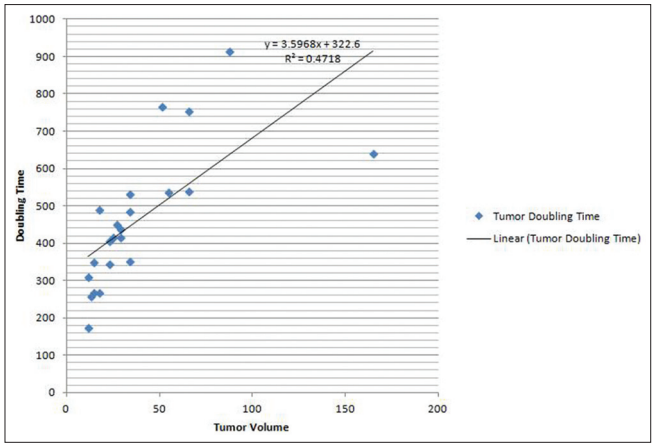

Figure 3: Correlation between the doubling time and the initial tumor volume

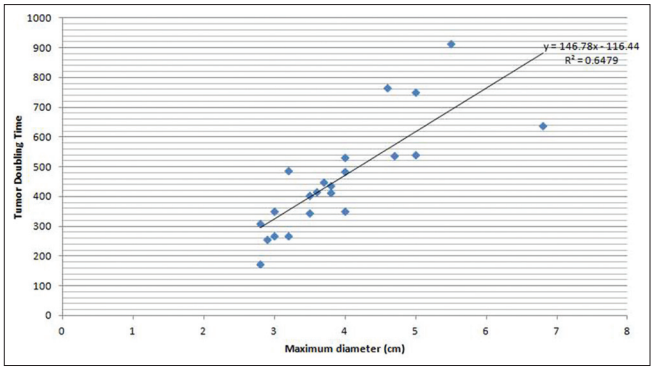

Figure 4: Correlation between initial maximum diameter and tumor doubling time

DISCUSSION

There has been an increase in the number of patients in whom small-sized renal masses/RCC are being detected incidentally during health checkups or detailed examination conducted because of suspicion of other diseases. The natural history of such incidentally diagnosed small renal masses (SRM) is not well characterized, as the majority of tumors are surgically removed soon after diagnosis. As patients with this kind of tumor/carcinoma are often symptom-free, at times patients refuse surgical treatment without fully understanding the need for surgery, or are left untreated (based on a tentative diagnosis of benign cystic lesions, etc.) until a definite diagnosis of RCC is made. There are also cases where the RCC is relatively large and causes symptoms but is not treated surgically because of complications and other reasons such as financial, fear of surgery, unfit to undergo major surgery and ignorance.

RCC is a heterogeneous group of tumors with varied degrees of biologic aggressiveness. The majority of renal cortical neoplasms (80%) are known to be malignant, but only 20-30% of malignant T1a lesions have potentially aggressive features. Initial tumor size measured on pre-operative imaging has been suggested as a variable to help predict the natural history of such SRMs.[12] Frank *et al.*,[13] who reviewed a large series of 2935 renal tumors from a single institution, demonstrated that for each 1-cm increase in diameter there was a 17% increase in the likelihood of the lesion being malignant. In addition, correlations were made between tumor size and final pathological features such as histology and tumor grade. Larger lesions were more likely to be a clear cell or high grade as opposed to a papillary or low-grade lesion.[13] Thompson *et al.*[14] confirmed similar findings by reporting another retrospective series of 2675 tumors. A positive correlation existed between tumor size and probability of malignancy, with a 16% increase in the odds of cancer detection with each 1-cm increase in tumor size. For tumors with clear cell histology, each 1-cm increase in size increased the odds of high-grade disease by 25%.[14] Laudano *et al.*[15] similarly demonstrated that the initial tumor size predicted RCC histology. The majority of tumors 4 cm or less (87.3%) were malignant, and 74.6% showed clear cell histology. For every 1-cm increase in the

diameter up to 4cm, the malignant tumors were 1.27-times more likely to be a conventional RCC as opposed to another RCC subtype.[15] Although there seems to be an association between initial tumor size and pathological disorder, it is also well known that most SRMs are malignant and that only a fraction of these cases exhibit aggressive disease. Gill *et al*.[16] reported on 100 tumors after laparoscopic partial nephrectomy (LPN) with a mean size of 2.8 cm. In this cohort, 70% of tumors were found to be malignant and 30% benign, indicating that size is often unreliable in determining malignancy.[16]

A clinically localized, enhancing renal lesion has the potential for progression to metastatic disease. Patients with SRMs and on active surveillance or patients who do not undergo surgery for any reason are at risk for tumor growth and metastases. The first case of reported progression was described in an active surveillance series of 36 elderly patients who were at high surgical risk. One patient developed metastatic disease 132 months from initial diagnosis.[17] The risk of progression of renal masses of 4 cm or less seems to be generally low and, at this time, there are no documented reports of metastasis occurring in the absence of tumor growth. However, there is no non-invasive, absolute or reliable way to distinguish benign from malignant or indolent from aggressive tumors. Patients must be aware that the potential for metastatic disease exists and that there is some level, although quite small, of risk involved in managing a small renal cortical neoplasm with observation alone. In addition, patients should be informed that progression may lead to a loss in the ability to treat tumors with a nephron-sparing approach, and that there are currently no curative therapies for metastatic disease.

The most common and simplest method of reporting renal lesion growth is to measure the linear growth. A more accurate way to evaluate growth kinetics is by calculating the volume of the mass. Volumetric growth better quantitates cell number and biologic growth as compared with maximal diameter, and can be determined on the basis of the number of cross-sectional dimensions that are known. Growth can then be expressed as tumor DT.[11] In our study of 22 patients, the tumor DT ranged from 174 to 913 days (mean 460.01 ± 182.45 days). During this period, none of these patients developed clinically/radiologically obvious metastases. Bosniak *et al*.[18] carried out a study and reported the growth rate, as determined from the maximum tumor diameter of 37 cases of RCC (40 lesions), to be 0-1.1 cm/year (mean: 0.36 cm/year). Their report added that, of these 40 tumor lesions, 30 showed a growth rate of < 0.5 cm/year and 19 lesions showed much slower growth (≤0.36 cm/year). Rendon *et al*.[19] analyzed 13 cases of small tumors and reported the mean growth rate for these cases (excluding two cases with symptoms) to be 1.32 cm^3/year. Similarly, Oda *et al*.,[20] analyzed the growth rate of maximum tumor diameter in 16 cases of RCC, and reported it to be 0.10-1.35 cm/year in primary lesions and 0.08-7.87 cm/year in metastatic lesions.

As seen in our study, as well as that reported from some other centers, it seems that it is difficult to collect data from an adequate number of cases if the study is confined to a single institution. The Japanese Society of Renal Cancer collected data from 56 cases to calculate tumor DT and growth rate. The data so collected would be useful in distinguishing benign renal masses from RCC (especially when dealing with SRMs), and also may be useful in determining the necessity for surgical treatment.

CONCLUSIONS

The natural history of SRMs is not completely known as the vast majority of these masses are either removed at diagnosis or after a short period of observation. Moreover, there are no tumor markers or absolute biologic predictors to assess risk or progression to metastatic disease. Elucidation of the natural history of renal cell carcinoma will contribute to facilitation of differential diagnosis and determination of surgical treatment. In our study, the DT for RCC was 460.01 ± 182.45 days (range 174-913 days). When analyzed by background variables, the DT showed no significant difference depending on any background variables.

REFERENCES

1. Landis SH, Murray T, Bolden S, Wingo PA. Cancer Statistics 1999. CA Cancer J Clin 1999;49:8-31.
2. Pantuck AJ, Zisman A, Belldegrun AS. The changing natural history of renal cell carcinoma. J Urol 2001;166:1611-23.
3. Jemal A, Murray T, Ward E, Samuels A, Tiwari RC, Ghafoor A, *et al*. and Thun MJ. Cancer Statistics 2005. CA Cancer J Clin 2005;55:10-30.
4. Chow WH, Devesa SS, Warren JL, Joseph F. Fraumeni JF. Rising Incidence of Renal Cell Cancer in the United States. JAMA 1999;281:1628-31.
5. DeCastro GJ, McKiernon JM. Epidemiology, clinical staging, and presentation of renal cell carcinoma. Urol Clin North Am 2008;35:581-92.
6. Kummerlin I, Ten Kate F, Smedts F, Horn T, Algaba F, Trias I, *et al*. Core biopsies of renal tumors: A study on diagnostic accuracy, interobserver and intraob-server variability. Eur Urol 2008;53:1219-25.
7. Collins VP, Loeffler RK, Harold T. Observations on growth rates of human tumors. Am J Roentgenol 1956;76:988-1001.
8. Spratt JS, Spratt TL. Rate of growth of pulmonary metastases and host survival. Ann Surg 1964;159:161-71.
9. Tetsuo K, Tominaga S, Morimoto T, Tashiro H, Itoh S, Watanabe H, *et al*. Tumor growth rate and prognosis of breast cancer mainly detected by mass screening. Jpn J Cancer Res 1990;81:454-62.
10. Birnbaum BA, Bosniac MA, Megibow AJ, Lubat E, Gordon R. Observations on the growth of renal neoplasms. Radiology 1990;176 695-701.
11. Ozono S, Miyao N, Igarashi T, Marumo K, Nakazawa H, Fukuda M, *et al*. Tumor doubling time of renal cell carcinoma measured by CT: Collaboration of Japanese Society of Renal Cancer. Jpn J Clin Oncol 2004;34:82-5.
12. Chawla SN, Crispen PL, Hanlon AL, Greenberg RE, Chen DY, Uzzo RG. The natural history of observed enhancing renal masses: Meta-analysis and review of the world literature. J Urol 2006;175:425-31.

13. Frank I, Blute ML, Cheville JC, Lohse CM, Weaver AL, Zincke H. Solid renal tumors: An analysis of pathological features related to tumor size. J Urol 2003;170:2217-20.
14. Thompson RH, Kurta JM, Kaag M, Tickoo SK, Kundu S, Katz D, *et al*. Tumor size is associated with malignant potential in renal cell carcinoma cases. J Urol 2009;181:2033-6.
15. Laudano MA, Klafter FE, Katz M, McCann TR, Desai M, Benson MC, *et al*. Pathological tumour diameter predicts risk of conventional subtype in small renal cortical tumours. BJU Int 2008;102:1385-8.
16. Gill IS, Matin SF, Desai MM, Kaouk JH, Steinberg A, Mascha E, *et al*. Comparative analysis of laparoscopic versus open partial nephrectomy for renal tumors in 200 patients. J Urol 2003;170:64-8.
17. Lamb GW, Bromwich EJ, Vasey P, Aitchison M. Management of renal masses in patients medically unsuitable for nephrectomy-natural history, complications, and outcome. Urology 2004;64:909-13.
18. Bosniak MA, Birnbaum BA, Krinsky GA, Waisman J. Small renal parenchymal neoplasms: Further observations on growth. Radiology 1995;197:589-97.
19. Rendon RA, Stanietzky N, Panzarella T, Robinette M, Klotz LH, Thurston W, *et al*. The natural history of small renal masses. J Urol 2000;164:1143-7.
20. Oda T, Miyao N, Takahashi A, Yanase M, Masumori N, Itoh N, *et al*. Growth rates of primary and metastatic lesions of renal cell carcinoma. Int J Urol 2001;8:473-7.

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