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Tumor Doubling Time of Renal Cell Carcinoma Measured by CT: Collaboration of Japanese Society of Renal Cancer

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Objective: This study was conducted to examine the natural history of renal cell carcinoma (RCC).

Methods: Inclusion criteria were the following: (1) patients who received diagnostic imaging of the kidney (CT, MRI) at two points in time before the diagnosis of RCC or patients who were followed, without treatment, after a diagnosis of RCC; and (2) patients in whom changes in tumor size were followed by the same modality of diagnostic imaging and who did not receive any treatment which could exert anti-tumor activity on the primary or metastatic lesions. The tumor doubling time (*DT*) and the growth rate of maximum tumor diameter (*R*) were determined. *DT* was calculated using the equation $DT = (T - T_0) \times \log 2 / \log V - \log V_0$ (where $T - T_0$ indicates the length of time between two measurements and V_0 and V denote the tumor volume at two points of measurement). *R* was calculated using the equation $R = (\phi - f_0)/(T - T_0) \times 100$ (where ϕ_0 and f indicate the maximum diameter at two points). Fifty-six cases registered with the Japanese Society of Renal Cancer were included in the evaluation.

Results: *DT* was 603.1 ± 510.1 days, which did not correlate with V_0. *R* was 0.263 ± 0.346 cm/day × 100. In cases where the tumor diameter was ≥4 cm, a significant correlation was noted between f_0 and *R*.

Conclusions: Elucidation of the natural history of RCC will contribute to facilitation of differential diagnosis and determination of optimum therapeutic strategy.

Key words: renal cell carcinoma – diagnostic imaging – natural history – Japanese Society of Renal Cancer

INTRODUCTION

Increasing numbers of patients are now incidentally detected with small-sized renal cell carcinoma (RCC) (1). Since patients with this type of carcinoma are often symptom-free, they sometimes refuse to receive surgical treatment or are left untreated based on a diagnosis of benign lesions. There are also cases where RCC is relatively large and causes symptoms but is not treated surgically because of complications and other reasons. It is clear that any medical institution will encounter at least a small number of such cases. However, since the number of such patients at individual institutions is too small, these valuable cases are rarely reported.

Clarification of the natural history of RCC will contribute greatly to advancing the treatment of this malignant disease. Knowledge about its natural history is also important to allow appropriate determination of the indication of surgical treatment in individual cases. The present collaborative study of the natural history of RCC was thus undertaken by the Japanese Society of Renal Cancer.

The objective of the present study was to elucidate the natural history of RCC, the time course of tumor doubling time and growth rate of maximum tumor diameter, as determined from changes in tumor size evaluated by diagnostic imaging, in clinical cases where the tumor was left untreated and followed up for a long period after diagnosis. In addition, for patients who

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received surgical treatment, the age and prognosis were analyzed in relation to histopathological features, to clarify the natural history of RCC from various viewpoints, including pathological.

PATIENTS AND METHODS

Patients satisfying all of the following requirements were enrolled in this study: (1) patients who had been chronologically followed by the same modality of diagnostic imaging (CT, MRI) at two or more points in time for at least 1 year before a diagnosis of renal cell carcinoma was made or patients who were followed, without treatment, for 1 year or more after a diagnosis of renal cell carcinoma and received diagnostic imaging using the same modality both before and after; (2) patients who did not receive any treatment which could exert anti-tumor activity on the primary or metastatic lesions, excluding symptomatic therapy using analgesics, during the follow-up period; (3) no gender or age restrictions at the time of diagnosis; and (4) no restrictions as to the presence/absence of symptoms, the factor precipitating the diagnosis, the affected side, tumor size or tumor stage. The exclusion criteria were as follows: (1) bleeding within the tumor; (2) cystic-type tumor; (3) tumor with central necrosis; (4) history of malignant diseases; (5) unfit to participate in the study as judged by the physician-in-charge.

For each subject, the following background variables were investigated: age, gender, symptoms, factor precipitating the diagnosis, clinical TNM classification, growing type according to Satomi's classification (2), 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:

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

where a indicates the maximum tumor diameter and b denotes the minimum tumor diameter.

The tumor doubling time (DT) was calculated using the following equation:

$$DT = (T - T_0) \times \log 2 / \log V - \log V_0$$

where $T - T_0$ indicates the length of time between two measurements and V_0 and V denote the tumor volume at two points of measurement.

Growth rate (R) was calculated by the following equation:

$$R = (\phi - f_0)/(T - T_0) \times 100$$

where f_0 and f indicate the maximum diameter at two points of measurements.

Table 1. Patients' characteristics

Age (years)	23–90 (mean 57.2)
Gender (M/F)	42/14
Growing type (R/I/S/Ukn)*	2/3/30/21
Maximum diameter (cm)	0.5–11.0 (mean 2.7, median 2.0)
Minimum diameter (cm)	0.5–8.1 (mean 2.3)
Volume (cm^3)	0.1–445.3 (mean 24.3)
Total No. of cases	56

*R/I/S/Ukn: rapid/intermediate/slow/unknown.

Pathological findings, such as were evaluated for patients who underwent surgery after prolonged follow-up, were pTNM classification, tumor cell type, degree of histological atypism, invasion and growth type.

The correlation of these clinical and pathological features with the tumor DT and R of maximum tumor diameter was analyzed. Analyses performed were (1) tumor doubling time by age upon onset of renal cell carcinoma, (2) tumor doubling time by clinical TNM classification and (3) tumor doubling time by pathological features.

Data that appeared statistically significant were compared by the non-parametric Mann–Whitney U-test using the Stat View 4.0 statistical software package (Abacus Concepts, Berkeley, CA). A P value of <0.05 was considered significant.

RESULTS

Fifty-six patients at 20 member institutions of the Japanese Society of Renal Cancer were enrolled in this study. The details of the subjects are shown in Table 1. There were 42 males and 14 females, with ages ranging from 23 to 90 years (mean 57.2 years). Tumor growth was rated as rapid type in two cases, intermediate type in three cases, slow type in 30 cases and unknown in the remaining 21 cases. The initial maximum tumor diameter ranged from 0.5 to 11.0 cm (mean = 2.7 cm; median = 2.0 cm) and the initial tumor volume ranged from 0.1 to 445.3 cm^3 (mean: 24.3 cm^3). Thirty-eight patients underwent surgery and pathological examination.

The DT for the entire population was 603.1 ± 510.1 days (Table 2). When analyzed by background variables, the DT showed no significant difference depending on any background variable.

The correlation between the doubling time and the initial tumor volume for tumors with maximum diameter <4 cm was defined by $Y = 16.79X + 481.804$ ($R^2 = 0.77$, $P = 0.0505$) and that for tumors with maximum diameter ≥4 cm was defined by $Y = 0.024X + 602.553$ ($R^2 = 1.082 \times 10^{-5}$, $P = 0.9237$) (Fig. 1).

Table 3 presents data on the growth rate. The growth rate for the entire population was 0.263 ± 0.346. When analyzed by background variables, the growth rate showed no significant difference related to any background variable.

The correlation between the growth rate and the initial tumor volume for tumors with maximum diameter <4 cm was defined

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Table 2. Doubling time (mean ± SD, days)

Total cases (n = 56)	603.1 ± 510.1	
Growing type		
Rapid (n = 2)	302.1 ± 172.6	
Intermediate (n = 3)	353.7 ± 339.7	n.s.
Slow (n = 30)	633.8 ± 457.3	
Maximum diameter		
<2.7 cm (n = 19)	772.3 ± 580.7	n.s.
≥2.7 cm (n = 37)	516.3 ± 454.0	
Pathology		
Clear cell (n = 25)	655.5 ± 559.1	
Granular cell (n = 5)	311.6 ± 188.3	n.s.
Mixed (n = 7)	661.3 ± 526.3	
Spindle cell (n = 1)	218.5	
Grade		
G1 (n = 12)	816.8 ± 645.3	
G2 (n = 23)	528.8 ± 447.0	n.s.
G3 (n = 3)	303.3 ± 90.0	

Table 3. Growth rates (mean = ± SD, cm/day × 100)

Total cases (n = 56)	0.263 ± 0.346	
Growing type		
Rapid (n = 2)	0.681 ± 0.762	
Intermediate (n = 3)	0.442 ± 0.485	n.s.
Slow (n = 30)	0.162 ± 0.095	
Maximum diameter		
<2.7 cm (n = 19)	0.301 ± 0.323	n.s.
≥2.7 cm (n = 37)	0.243 ± 0.360	
Pathology		
Clear cell (n = 25)	0.272 ± 0.426	
Granular cell (n = 5)	0.178 ± 0.111	n.s.
Mixed (n = 7)	0.148 ± 0.115	
Spindle cell (n = 1)	0.578	
Grade		
G1 (n = 12)	0.186 ± 0.271	
G2 (n = 23)	0.259 ± 0.412	n.s.
G3 (n = 3)	0.374 ± 0.177	

by $y = 0.017x + 0.204$ ($R^2 = 0.002$, $P = 0.7481$) and that for tumors with maximum diameter ≥4 cm was defined by $y = 0.048x + 0.135$ ($R^2 = 0.07$, $P = 0.0488$) (Fig. 2).

DISCUSSION

There has been an increase in the number of patients in whom small-sized RCC is detected incidentally during health check-

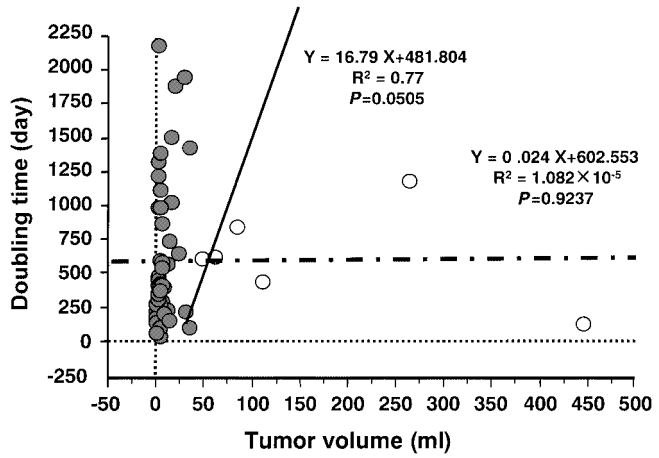

Figure 1. Correlation between the doubling time and the initial tumor volume: closed circles, <4 cm (maximum diameter); open circles, ≥4 cm (maximum diameter).

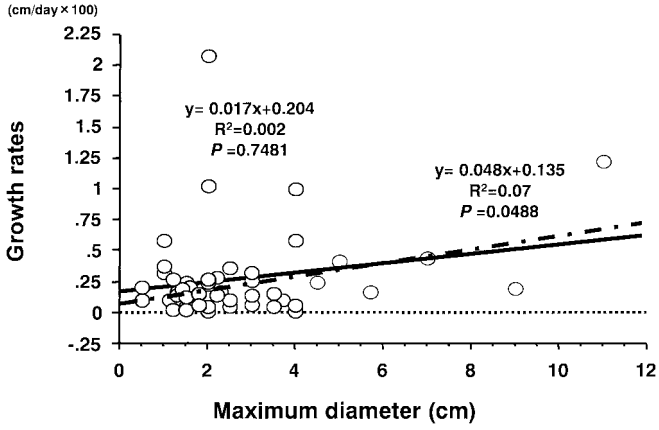

Figure 2. Correlation between the growth rate and the initial maximum diameter: closed circles <4 cm (maximum diameter); open circles, ≥4 cm (maximum diameter).

ups or detailed examination conducted because of suspicion of other diseases (1). Since patients with this type of carcinoma are often symptom-free, sometimes they 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. There are also cases where the RCC is relatively large and causes symptoms but is not treated surgically because of complications and other reasons.

In the present study, *DT* was 603.1 ± 510.1 days, which did not correlate with V_0. *R* was 0.263 ± 0.346 cm/day × 100. In cases where the tumor diameter was ≥4 cm, a significant correlation was noted between f_0 and *R*. When analyzed by background variables, neither doubling time nor growth rate showed any significant difference related to any background variable. In addition, we tried to focus on appropriate points of these background variables; however, no further differences could be seen. As for maximum diameter, there were also no differences between several points of maximum diameter that

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we examined, therefore data from the mean of the initial maximum diameter of 2.7 cm were recorded in the tables and those from 4.0 cm, considered the limiting size of organ preservation surgery of elected cases, were recorded in the figures. There was only one case with spindle cell type, whose doubling time was very short. Also, the doubling time of grade 3 was short.

Several studies of the natural history of RCC in such cases have been published. Birnbaum et al. (3) reported that the growth rate of RCC, as determined from the maximum diameter of tumors in 11 cases of renal cell carcinoma (13 lesions in total), ranged from 0.1 to 1.6 cm/year (mean: 0.5 cm/year). Bosniak et al. (4) carried out a similar study at the New York University Medical Center and reported the growth rate, as determined from the maximum tumor diameter of 37 cases of renal cell carcinoma (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. (5) 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.

In Japan, Fujimoto et al. (6) analyzed the doubling time in 18 cases of renal carcinoma and reported a doubling time of 466 ± 84.6 days for primary lesions (n = 6) and 89.4 ± 43.0 days for metastatic lesions in lungs (n = 12). Their results indicate that metastatic lesions showed significantly more rapid growth than did primary lesions. The same investigators also reported that when the primary tumors were divided into rapid-growing type and slow-growing type on the basis of AgNORs and PCNA, the growing type correlated well with the doubling time. Furthermore, Oda et al. (7) analyzed the growth rate of maximum tumor diameter in 16 cases of renal cell carcinoma and reported it to be 0.10–1.35 cm/year in primary lesions and 0.08–7.87 cm/year in metastatic lesions.

Despite these previous studies of the natural history of renal cell carcinoma, it is difficult to collect data from an adequate number of cases if the study is confined to a single medical institution. In the present collaborative study involving multiple member institutions of the Japanese Society of Renal Cancer, data were collected from 56 cases in total for calculation of the doubling time and the growth rate of maximum tumor diameter. Following recent advances in diagnostic imaging, the number of symptom-free renal tumors detected incidentally, so-called incidental tumors, has been increasing. These incidental tumor cases are sometimes difficult to distinguish from RCC. The data collected in this study may be useful in determining the necessity for surgical treatment when dealing with such patients.

Elucidation of the natural history of renal cell carcinoma will contribute to facilitation of differential diagnosis and determination of surgical treatment. In addition, these results will provide basic information useful when evaluating diagnostic imaging of renal tumor and treatment modality for patients with renal cell carcinoma.

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