RENAL nephrometry score is a predictive factor for the annual growth rate of renal mass

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Objective: To evaluate the association between the RENAL nephrometry score and annual growth rates of renal masses presumed to be renal cell carcinoma.

Methods: The current study included 47 renal tumors followed up for at least 12 months, of which 26 tumors were found to be pathologically proven renal cell carcinomas. Annual tumor growth rates were calculated from changes in the maximal diameter on computed tomography, and RENAL nephrometry scores were recorded on initial imaging by two senior urologists. The associations between clinical characteristics including the RENAL nephrometry score and annual growth rates were analyzed using a linear regression model.

Results: The median tumor size at diagnosis was 1.7 cm (range 0.6–5.8). The median nephrometry score at diagnosis was 7 (range 4–10). Overall, the median tumor growth rate was 0.34 cm per year (range –0.19–2.0). Linear regression analysis showed that the annual tumor growth rate was associated with the RENAL nephrometry score ($P < 0.0001$), but it was independent of the age at diagnosis, sex and initial tumor size. In addition, the correlation between the RENAL nephrometry score and annual growth rate remained significant in the 26 pathologically proven renal cell carcinomas.

Conclusions: The RENAL nephrometry score is associated with the annual growth rate of renal masses. Our findings further support the association between the RENAL nephrometry score and tumor biology.

Key words: growth rate, kidney, neoplasms, nephrometry score, surveillance.

Introduction

In recent years, the incidental detection of renal masses has increased because of advances in imaging modalities.1,2 Particularly in developed countries, the incidental detection of small renal masses in elderly patients might be expected because of the increase in the aging population. When elderly patients have both a small renal mass and pre-existing comorbidities, physicians have to consider not only their surgical indication, but also other alternatives, such as ablation or active surveillance. Although recent studies on active surveillance showed slow growth in many tumors and the rare development of metastatic disease;3-10 no clear clinical predictors of the tumor growth rate have been established for small renal masses. Such predictors might be useful for treatment decisions, especially when patients desire active surveillance.

Recently, the RNS was proposed to standardize the assessment of anatomical features of renal tumors.11 It characterizes tumors on the basis of the following five factors: (R)adius (maximal diameter of the tumor in any single plane), (E)xophytic/endophytic properties of the tumor, (N)earness of the deepest portion of the tumor to the collecting system or sinus, (A)nterior/posterior descriptor and (L)ocation relative to the polar line. Of these, four components (R, E, N and L) are assigned a score from 1 to 3, and the total score ranges from 4 to 12. Several studies have shown the potential of the RNS to be associated with tumor aggressiveness and patient survival,12-15 so RNS could be a surrogate marker of tumor aggressiveness. In the present study, we investigated the relationship between RNS and the annual growth rate of renal masses suspected to be RCC.

Methods

The institutional review board approved the retrospective collection of data and reporting of results. We retrospectively reviewed the database of patients referred to Hokkaido University Hospital, Hokkaido, Japan, between April 2002 and January 2012, and identified 54 tumors followed up for at least 12 months among the 460 renal tumors suspected to be RCC. Excluding
the patients with a history of hereditary syndrome, such as von Hippel–Lindau disease (n = 1), and advanced disease with systemic treatment during follow up (n = 6), 47 enhancing renal masses (46 patients) were identified that could be monitored for the natural disease course for at least 12 months.

During the follow up, 28 renal tumors finally underwent surgical treatment or radiofrequency ablation therapy, considering the presence of a pre-existing comorbidity, tumor growth rates or patients’ wishes. Excluding the two renal tumors treated by ablation without tumor biopsy, the 26 tumors were RCC. Patients’ characteristics including age, sex, initial tumor size, most recent tumor size, duration of follow-up, median number of CT scans during follow up and surgical pathology in relevant cases were collected from medical charts. RNS was calculated based on the criteria proposed by Kutikov and Uzzo,11 and determined by consensus between two senior urologists. The annual tumor growth rate was calculated according to the change in the maximum tumor diameter obtained from CT scans at two instances during the period from the initial diagnosis until the most recent imaging evaluation.

**Statistical analysis**

The groups were directly compared using appropriate non-parametric (Kruskal–Wallis) methods. A univariate linear regression model was used to determine independent factors affecting the annual growth speed. JMP version 10 (SAS Institute, Tokyo, Japan) was used for all calculations. P < 0.05 was considered significant.

**Results**

Table 1 summarizes the patients’ characteristics and outcomes. The median age was 64 years (range 29–87 years). The median RNS based on the initial image was 7 (range 4–10). These included 21 low-complexity tumors (RNS 4–6), 24 moderate-complexity tumors (RNS 7–9) and two high-complexity tumors (RNS 10–12). The median follow-up duration was 24 months (range 12–110), and the median number of follow-up CT scans was four (range 2–33). Regarding the treatments, seven tumors underwent radical nephrectomy, 18 partial nephrectomy and three radiofrequency ablation. As aforementioned, the 26 tumors were confirmed to be RCC by pathological examination (clear cell carcinoma, n = 21; papillary renal cell carcinoma, n = 3; multilocular clear cell RCC, n = 1; unknown, n = 1). During the follow-up period, no progression to metastatic disease was observed in the entire cohort.

Figure 1 shows scatter plots between RNS and the annual growth rate, and Table 2 summarizes the analyses of annual growth rates. The median annual growth rate for all tumors was 0.34 cm per year (range −0.19–2.0). When restricted to the 26 RCC, the median growth rate was 0.46 cm/year (range 0–0.9). Comparing the annual growth rate according to tumor complexity, there were significant differences in annual growth rates among high-, moderate- and low-complexity groups (Table 2). Table 3 shows the results of linear regression analysis of factors determining the tumor growth rate in all cases. Only RNS at diagnosis was associated with the annual tumor growth rate on univariate analysis. No significant correlation was identified between the tumor growth rate and age at diagnosis, sex or initial tumor size. When adjusting for these characteristics in a multivariate model, RNS remained significant. The relationship between RNS and the annual growth rate remained significant in the 26 pathologically proven RCC (Table 3). Table 4 shows the results of linear regression analysis between each component of RNS and the annual tumor growth rate. The E, N and L components were associated with the tumor growth rate not only in all cases, but also in the 26 RCC cases in univariate models (Table 4). The L component remained significant on multivariate analyses.

**Discussion**

In the present study, we evaluated annual growth rates of 47 small renal masses presumed to be RCC. The median growth rate was 0.34 cm/year at a median follow up of 24 months, and
developed metastatic disease in their prospective study. In a median follow-up of 36 months, and only one patient (1.2%) had a mean growth rate of 0.25 cm/year in 84 renal masses at a median follow-up of 32 months, and progression to metastatic disease was identified in only 1% of lesions during the follow-up period. Mason et al. also reported a mean growth rate of 0.28 cm/year in a meta-analysis of 286 renal masses, describing stronger associations between the total nephrometry score, R, N, L and hilar tumors with high-grade features, and developed a novel nomogram to predict high-grade disease. Their model was later validated by Wang et al. also showed that, in a study of 886 patients whose small renal masses were treated with partial nephrectomy, high renal nephrometry scores were associated with an increased risk of high-grade malignancy. Kutikov et al. investigated the relationship between individual components of RNS and the grade of resected tumors in a review of 525 renal masses, describing stronger associations between the total nephrometry score, R, N, L and hilar tumors with high-grade features, and developed a novel nomogram to predict high-grade disease. In the present study, a significant correlation was identified between the score of the RNS system and tumor growth rate. To our knowledge, we are the first to show that RNS is directly associated with the annual growth rate of a renal mass. We consider that our observation further supported a relationship between RNS and the tumor nature from a different perspective.

Regarding each component of the RNS system, a significant correlation was identified between the score of the RNS system and tumor growth rate. To our knowledge, we are the first to show that RNS is directly associated with the annual growth rate of a renal mass. We consider that our observation further supported a relationship between RNS and the tumor nature from a different perspective. In a more recent systematic review of 880 patients with small renal masses under active surveillance, Smaldone et al. reported that just 18 patients (2%) progressed to metastatic disease. Therefore, we further confirmed that most small renal tumors grow slowly and have a low metastatic potential.

At present, guidelines regarding the observation of small renal masses have not been established and, as aforementioned, useful guidelines for treatment decisions are eagerly anticipated. We subsequently analyzed the association between clinical characteristics and the annual growth rates. Some investigators have reported that the tumor size can be used to predict the growth rate, whereas others have found no such correlation. For example, Mason et al. reported that, in a prospective cohort of 82 patients undergoing active surveillance, the tumor size was a predictor of the tumor growth rate, with renal masses <2.45 cm growing more slowly than those >2.45 cm. In contrast, Chawla et al. did not observe a relationship between the lesion size at presentation and overall growth rate. In the present study, we did not identify a significant correlation between the tumor size at presentation and annual growth rates. Also, neither age nor sex was a predictive factor.

The RENAL nephrometry score, developed by Kutikov and Uzzo, has been increasingly used as a scoring system in renal mass anatomy, and growing evidence suggests a relationship between RNS and the tumor nature. Kutikov et al. investigated the relationship between individual components of RNS and the grade of resected tumors in a review of 525 renal masses, describing stronger associations between the total nephrometry score, R, N, L and hilar tumors with high-grade features, and developed a novel nomogram to predict high-grade disease. Their model was later validated by Wang et al. also showed that, in a study of 886 patients whose small renal masses were treated with partial nephrectomy, high renal nephrometry scores were associated with an increased risk of high-grade malignancy.

In the present study, a significant correlation was identified between the score of the RNS system and tumor growth rate. To our knowledge, we are the first to show that RNS is directly associated with the annual growth rate of a renal mass. We consider that our observation further supported a relationship between RNS and the tumor nature from a different perspective. Regarding each component of the RNS system, a significant correlation was identified between the E, N, and L components and tumor growth rate in univariate models, and the L component remained significant on multivariate analyses. Although, based on previous observations and ours, endophytic and midpolar tumors are more likely to be high-grade tumors when compared with endophytic renal tumors. In the present study, a significant correlation was identified between the score of the RNS system and tumor growth rate. To our knowledge, we are the first to show that RNS is directly associated with the annual growth rate of a renal mass. We consider that our observation further supported a relationship between RNS and the tumor nature from a different perspective. Regarding each component of the RNS system, a significant correlation was identified between the E, N, and L components and tumor growth rate in univariate models, and the L component remained significant on multivariate analyses. Although, based on previous observations and ours, endophytic and midpolar tumors are more likely to be high-grade tumors and show rapid growth potential, the underlying mechanism has yet to be clarified. Future basic studies regarding differences of biological nature according to tumor location would be required. The limitations of the present study were the small sample size and retrospective nature. The cohort contained few tumors belonging to the high-complexity group (RNS 10–12), and was essentially comprised of low- and intermediate-complexity tumors (RNS 4–6 and 7–9). In the follow-up patients, some tumors might have been benign masses because of the lack of...
biopsy. In addition, our observations could not directly clarify the relationship between a low RNS and the long-term prognosis of patients with a small renal mass; a larger sample is required to elucidate this. Nevertheless, we consider that several important observations were made in the present study.

In conclusion, RNS was associated with the annual growth rate of renal masses. Our observation provided new information on the relationship between tumor characteristics and the growth rate.

**Conflict of interest**

None declared.

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**Table 3** Linear regression analysis of factors determining tumor growth rate in all cases and pathologically proven cases of RCC

|                      | All tumors (n = 47) |                      | RCC (n = 26) |
|----------------------|--------------------|----------------------|-------------|
|                      | Univariate         | Multivariate         | Univariate  |
|                      | Coefficient (95% CI) | P-value              | Coefficient (95% CI) | P-value |
|                      |                    |                      |              |          |
| Age at diagnosis (years) | −0.002 (−0.010–0.006) | 0.5872               | 0.0000178 (−0.00684–0.00687) | 0.9958 |
| Sex (male reference)  | 0.158 (0.083–0.398) | 0.1939               | 0.114 (0.0950–0.324) | 0.2763 |
| Initial tumor size (cm) | 0.010 (0.088–1.108) | <0.0001              | <0.0001     |        |
| RNS on initial image  | 0.128 (0.073–0.182) | 0.128 (0.071–0.186) | <0.0001     |        |

**Table 4** Linear regression analysis of RNS components determining tumor growth rate in all cases and pathologically proven cases of RCC

|                      | All tumors (n = 47) |                      | RCC (n = 26) |
|----------------------|--------------------|----------------------|-------------|
|                      | Univariate         | Multivariate         | Univariate  |
|                      | Coefficient (95% CI) | P-value              | Coefficient (95% CI) | P-value |
|                      |                    |                      |              |          |
| R component          | −0.113 (−0.534–0.308) | 0.5919               | −0.002 (−0.0037–0.00393) | 0.4618 |
| E component          | 0.198 (0.066–0.330) | 0.0041               | −0.0887 (−0.263–0.086) | 0.3032 |
| N component          | 0.189 (0.066–0.299) | 0.0041               | −0.0323 (−0.104–0.0397) | 0.3614 |
| L component          | 0.299 (0.146–0.453) | 0.0003               | 0.0879 (0.0413–0.134) | 0.0008 |
| A component          | 0.078 (0.035–0.190) | 0.1688               |                |        |
| E component          | 0.251 (0.115–0.387) | 0.0009               |                |        |