Journal of the Formosan Medical Association (2016) 115, 463–469

Available online at www.sciencedirect.com

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journal homepage: www.jfma-online.com

ORIGINAL ARTICLE

Natural history of renal cell carcinoma: An immunohistochemical analysis of growth rate in patients with delayed treatment

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Received 18 September 2014; received in revised form 13 May 2015; accepted 13 May 2015

KEYWORDS
active surveillance;
delayed intervention;
growth rate;
immunohistochemical analysis;
renal cell carcinoma

Background/purpose: To investigate the natural history of renal cell carcinoma (RCC) with delayed treatment and to immunohistochemically analyze the correlation between some biomarkers and the growth rate of RCC.
Methods: We reviewed our institutional databases to identify renal tumors which were confirmed to be RCC by delayed surgical treatment after at least 12 months of active surveillance (AS). Growth rate was defined as the average growth rate of the maximal diameter on computed tomography or magnetic resonance imaging. The clinicopathological characteristics and immunohistochemical biomarkers (Ki-67, p53, bcl-2, and vascular endothelial growth factor) were analyzed the correlation with the growth rate of RCC.
Results: We identified 45 RCCs from 45 patients. The mean patient age was 54 years (range, 26–78 years). The mean tumor size increased from 2.39 cm (range, 0.10–6.70 cm) at presentation to 4.54 cm (range, 1.40–11.80 cm) after a mean time of 45.4 months (range, 12–155 months) of AS. The mean growth rate was 0.79 cm/y (range, 0.10–4.74 cm), and 36 (80.0%) tumors presented a growth rate $\leq$ 1.00 cm/y. Clear cell RCC had a trend of growing faster than other histological subtypes. Pathological grade was significantly correlated with the growth rate of RCC ($p = 0.043$). High positive ratio of Ki-67 ($r = 0.351$, $p = 0.018$) and being p53 positive ($p = 0.019$) were significantly correlated to the fast growth rate of RCC.

Conflicts of interest: The authors have no conflicts of interest relevant to this article.

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http://dx.doi.org/10.1016/j.jfma.2015.05.003

Conclusion: In general, RCCs under AS are slow growing with a wide variation of growth rate, with a portion of RCCs presenting rapid growth kinetics. RCC with rapid growth during AS is characterized by a high histological grade, high positive ratio of Ki-67, and being p53 positive.

Introduction

A dramatic increase of incidentally found small renal masses has been observed with the widespread use of modern imaging techniques.[1] Surgical excision is still the standard treatment for these localized renal tumors. However, a number of patients with a high risk of morbidity and mortality or limited life expectancy choose active surveillance (AS) instead of immediate surgeries. AS provides a unique opportunity to observe the natural history of the renal cell carcinoma (RCC), as most tumors are surgically excised soon after diagnosis. Previous studies concerning AS demonstrated that small renal tumors grew slowly and seldom metastasized.[2–23] In most of these studies, lack of pathological diagnosis was a common limitation, even a considerable portion of the tumors with pathological results were not RCC. Hence, the growth kinetics and natural history of RCC have not been well characterized.

To understand the growth kinetics of RCC fully, a few studies have evaluated the correlation between the immunohistochemical biomarkers and the growth rate of RCCs.[3–5] However, all the available researches included small sample sizes and short follow-up periods, so no consensus has been reached. The investigations regarding the correlation between immunohistochemical biomarkers and the growth rate of RCC are far from sufficient.

Our previous study demonstrated that RCCs were found to be slow growing in patients with delayed treatment, however, progression in stages was presented in some RCCs.[2] In the current study, we expanded the sample size to further examine the growth kinetics of RCC and its correlation with clinical and pathological characteristics. In addition, we selected four biomarkers, Ki-67, p53, vascular endothelial growth factor (VEGF), and bcl-2, which were considered prognostic factors of RCCs in previous studies,[24–26] and immunohistochemically analyzed whether they were involved in the growth of RCCs with delayed treatment.

Materials and methods

We reviewed the kidney cancer databases at the Institute of Urology, Peking University First Hospital, Beijing, China to identify renal tumors for which AS was performed for at least 12 months between January 1990 and July 2012. A total of 60 patients with renal tumors under AS for $>$ 12 months were identified from 2180 renal tumor cases. Patients who did not receive delayed surgical treatment were excluded. Finally, 45 renal tumors from 45 patients were enrolled. During the period of AS, computed tomography (CT) or magnetic resonance imaging (MRI) was performed every 6 months or less. Where possible, the measurement was performed based on the same modality. Because of tumor growth, obvious enhancing on CT, or metastatic lesions, delayed surgical intervention was performed on all patients at Peking University First Hospital after a mean duration of 45 months of AS. The pathological results confirmed RCC for all tumors. Growth rate was defined as the average growth rate of the maximal diameter on a series of 2-dimensional images. Histological classification was determined using the Heidelberg typing system.[27] Tumor stage was assessed according to the 2002 American Joint Committee on Cancer TNM staging system.[28] Tumor grading was performed according to the Fuhrman grade system.[29]

Paraffin-embedded sections were stained using a ChemMate EnVision Detection Kit (Genetic Technology, Shanghai, China). The antibodies (Genetic Technology, Shanghai, China) used in this study included bcl-2 and p53, VEGF, and Ki-67. Paraffin sections were deparaffinized and then dipped into phosphate buffer solution for 5 minutes three times. Then, sections were incubated in primary antibody for 30 minutes at room temperature and another 4 hours at 4°C. The Envision method was used for immunohistochemical staining. Slides were exposed to diaminobenzidine for 5 minutes three times. After immunostaining, the sections were counterstained with hematoxylin, coverslipped, and sealed. Phosphate buffer solution was used as a negative control of the first antibody for each group.

The expression levels of bcl-2 and VEGF were detected based on the intensity of staining and the percentage of positive cells. The intensity of staining was scored as follows: unstained $=$ 0 points; light brown color $=$ 1 point; brown $=$ 2 points; and deep brown color $=$ 3 points. The percentage of positive cells was scored as follows: $<$ 5% $=$ 0 points; 5–10% $=$ 1 point; 10–50% $=$ 2 points; and $>$ 50% $=$ 3 points. The sum of the two items was scored as follows: 0 points $=$ negative; 1–3 points $=$ weakly positive; and 4–6 points $=$ strongly positive. More than 10% of the nucleus stained was the positive standard for p53. Ki-67 was recorded as the Ki-67 labeling index, which was defined as the proportion of Ki-67-positive cells per 1000 cells in 10 representative Ki-67-positive fields. All sections were separately reviewed by two urological pathologists who were blinded to the patients' personal data. If the opinions were inconsistent, the sections were reviewed by the two pathologists together to reach an agreement.

For better knowledge of the natural history and growth kinetics of renal masses, we also reviewed published series regarding AS of renal masses and made a pooled analysis. In addition, through the pooled analysis, we wanted to know the metastatic rate during AS and the rate of pathologically