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Pathological Grade and Gender are Predictors of Small Renal Cell Carcinoma Growth

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Abstract

Objective: This study was undertaken to investigate the clinicopathological factors that influence the growth of a small renal mass (SRM) in patients subjected to a delayed surgery intervention.

Methods: We reviewed the clinical records of 37 patients with SRM 4 cm at diagnosis, who underwent delayed surgical intervention during surveillance from January 2000 to December 2013. Radiographic evaluation using computed tomography (CT) scan, magnetic resonance imaging (MRI) were performed at least every 6 months and the tumor size was determined at least twice.

Results: Histopathological analysis revealed that in 35 of the 37 patients the tumor was malignant in stage pT1aN0M0. There were 28 clear cell carcinomas and 7 non clear cell carcinomas. There was a significant difference in the time to tumor doubling (TTD) among clear cell carcinomas (p=0.033). There was also a significant difference in the tumor growth rate (mm/year) of clear cell carcinomas between male and female patients (p=0.028).

Conclusion: The growth rate of small renal mass was slow in the majority of our patients. Pathological grade and gender significantly influenced the growth of clear cell carcinomas.

Keywords: Renal cell carcinoma; Small renal mass; Growth factor; Natural history

Introduction

Renal cell carcinoma (RCC) detection was performed using noninvasive abdominal imaging techniques, which included: ultrasonography (US), computed tomography (CT) and magnetic resonance imaging (MRI) [1-5].

Following a retrospective review, it was found that most small renal masses (SRMs) showed a slow growth rate and low malignant potential [6]. In a previous study, we found that the growth factor of SRMs was highly associated with their pathological grade [7].

In this study, we investigated growth factors in a larger sample size, using the enzyme mindbomb E3 ubiquitin protein ligase 1 (MIB-1), which is strongly associated with pathological grade.

Methods

Thirty-four patients with 37 incidentally detected SRMs 4cm were retrospectively reviewed at three centers from January 2000 to December 2013. All the patients were operated on soon after we noted the tumor had become larger. They underwent at least two CT scans prior to surgical intervention. None of the patients underwent renal biopsy for a diagnosis. The pathological results confirmed the diagnosis of clear cell carcinoma for 28 of the 37 patients. We conducted the following analyses in the 28 patients to study the relationship between the growth rate of clear cell carcinoma and various factors.

The maximum tumor diameter and tumor volume were calculated at two points using images yielded by the same diagnostic modality. Tumor volume (V) was calculated using the following equation, assuming the tumor had a spherical form [8].

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

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

The time to tumor doubling (TTD) was calculated using the following equation [9,10].

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

where T-T0 indicates the interval between time two measurements and V0 and V denote the tumor volume at T0 and T, respectively.

MIB-1 Immunohistochemical Assay: Detailed descriptive methodology has previously been published [11].

Immunohistochemistry against the Ki-67 antigen was performed using a monoclonal MIB-1 antibody (clone MIB-1, mouse IgG1, 1:100) followed by a biotin goat antibody (1:100) for 30 minutes at room temperature. The slides were rinsed in tris phosphate buffered saline (pH 7.6) between each step. Visualization of staining utilized a 3-amino-9-ethylcarbazole solution. Finally, the sections were slightly counterstained in Mayer's hematoxylin.

Quantitation of Immunoreactivity: Owing to heterogeneous content of proliferative tumor cells in the tumors, areas of highest proliferative activity (hot spots) were found by scanning the tumor sections at low magnification (40× and 100×). Within these hot spots, the tumor cell counts were performed by a random sampling technique at 400× (10× ocular and 40× objective) using a 10×10 grid contained within the eyepiece. MIB-1 score represented the number of stained tumor cell nuclei counted.

Clinical and pathological stages determination incorporated the 2009 American Joint Committee on Cancer / International Union Against Cancer TNM guidelines [12]. Clinical and pathological characteristics with potential association to tumor growth rate and stage were investigated. After surgery, follow-ups were conducted with patients every 3-6 months. Hemodialysis patients were not included in this study because patients on dialysis were at great risk of developing RCC, due to end-stage renal disease, than healthy controls of equivalent age [13-15].

Statistically significant data was compared using the non-parametric Mann-Whitney U-test. The risk of prognostic factors was assessed using both logistic regression analysis as well as the Cox proportional hazards regression model, respectively. A level of $P<0.05$ was accepted as the statistical significance.

Results

The mean age of the patients was 64.8 years (range: 35-80). There were 29 men and 8 women. In all patients, the tumors were ≤ 4cm at diagnosis. Histopathological analysis revealed that 35 of the 37 patients were malignant in pT1aN0M0. The pathological results are presented in Table 1.

Age	64.8 (35-80)
Sex(Male/Female)	29/8
Histologic Subtype	
Clear cell Carcinoma	28
Papillary cell Carcinome	6
Multilocular Clear cell	1
Oncocytoma	2

Table 1: Patients characteristics

We closely monitored the 28 patients with clear cell carcinomas. Sixteen of those tumors (57.1%) were of pathological grade 1, eleven (39.3%) were grade 2 and one (3.6%) was grade 3. In addition, seven tumors (25%) were of pathological Fuhrman grade 1, nineteen (67.9%) were of pathological Fuhrman grade 2 and two (7.1%) were of pathological Fuhrman grade 3. There were 22 men and 6 women. Three tumors were MIB-1 score >5% and 25 were MIB-1 score <5% (Figure 1).

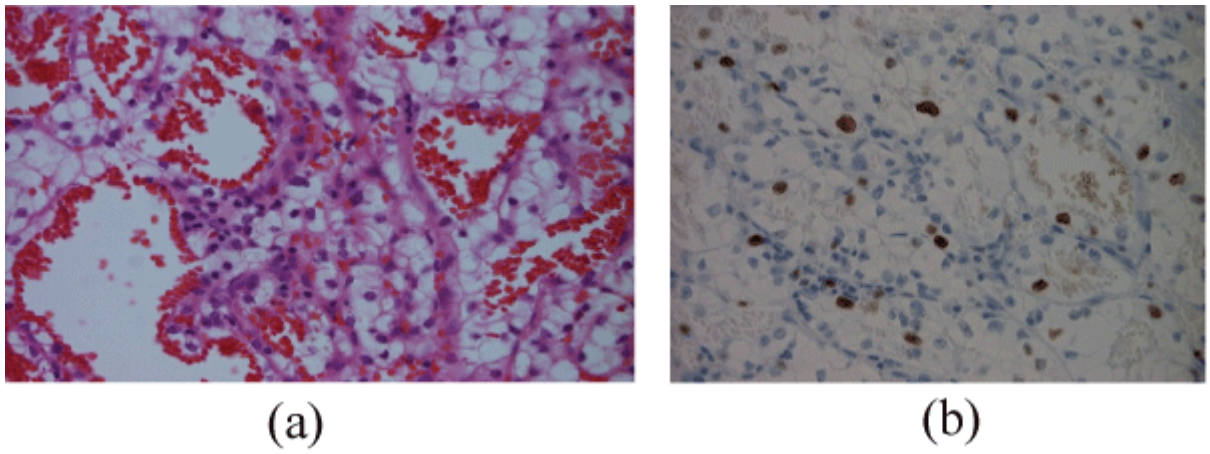

Figure 1a and b: Pathological finding of clear cell carcinoma, Hematoxylin-Eosin stain (×40) MIB-1 index >5 (×40).

As shown in Table 2, there were significant differences in TTD between tumors of pathological grade 1 and those of grade 2, or 3, as well as in tumor diameter (mm/year) men and women. In contrast, multivariate analysis showed no significant difference in TTD or tumor diameter by each factor.

Discussion

Recently, incidental detection of small, asymptomatic renal tumors has been on the rise. The good prognosis of incidental RCC is excellent, as evidenced by the results of surgery [16,17]. The gender ratio is approximately 2: 1, male to female, respectively [18]. Cigarette smoking, obesity and hypertension have been implicated as risk factors although the increase in risk is relatively modest [19]. The etiology of most RCCs remains unclear.

In general, size is proportionate to the grade of malignancy [20]. The questions raised become: "When should tumors be treated proactively?" and "How big in diameter?" In the case of SRM smaller than 1.0 cm, 38-46% are benign. On the other hand, only 6.3-7.1% are

benign for lesions larger than 7.0 cm in diameter [21]. It has been reported that renal masses 3 cm in diameter have a more aggressive potential, resulting in more incidences of metastases [22,23] (Tables 2 and 3).

Variables		**Univariate**		**Multivariate**	
				HR(95%CI)	
Factor	TTD		P value		P value
Grade	Grade1 27.9+4.08 (n=16)	Grade2,3 17.7+4.06 (n=12)	0.033	0.193(0.028-1.321)	0.094
Gender	Male 24.23+3.52(n=22)	Female 20.9+6.09(n=6)	N.S		
Age	<70 25.37+4.05 (n=16)	>70 21.05+4.60 (n=12)	N.S		
Furman Grade	Grade 1 27.3+6.90(n=7)	Grade 2,3,4 22.26+3.36(n=21)	N.S		
Furman Grade2	Grade 1,2 24.30+3.19(n=26)	Grade 3,4 13.30+5.00(n=2)	N.S		
MIB-1	>5% 17.50+5.94(n=3)	<5% 24.24+3.30(n=25)	N.S		

Table 2: Intergroup comparison of TTD according to each factor

Variables		**Univariate**		**Multivariate**	
				HR(95%CI)	
Factor	**mm/year**		**P value**		**P value**
Grade	Grade1 4.32 ± 1.07 (n=16)	Grade2,3 3.88 ± 0.91 (n=12)	N.S		
Gender	Male 4.75 ± 0.86 (n=22)	Female 1.84 ± 0.47 (n=6)	0.028	0.309(0.035-2.717)	0.289
Age	<70 3.08 ± 0.48 (n=16)	>70 5.53 ± 1.49 (n=12)	N.S		
Furman Grade	Grade 1 3.06 ± 0.73 (n=7)	Grade 2,3,4 4.49 ± 0.92 (n=21)	N.S		
Furman Grade2	Grade 1,2 4.00 ± 0.76 (n=26)	Grade 3,4 5.81 ± 0.57 (n=2)	N.S		
MIB-1	>5% 3.52 ± 0.91 (n=3)	<5% 4.20 ± 0.80 (n=25)	N.S		

Table 3: Intergroup comparison of tumor diameter (mm/year) according to each factor

Moreover, the proliferation rate should also be considered. Renal masses <2.45 cm at diagnosis were associated with an average growth rate of 0.13 cm/year, while masses >2.45 cm had a growth rate of 0.40 cm/year [24]. Following the diagnosis and conclusion of the observation, larger tumors and larger tumor volumes tended to progress. Significant differences in both the average growth rate (0.80 cm/year vs. 0.3 cm/year) and the average volumetric growth rate (27.1 cm^3/year vs. 6.2 cm^3/year) have also been observed [25].

Previously when dealing with early prostate cancer, active surveillance was often considered. However, recent advances with respect to tumor detection tools, such as ultrasound and high speed CT scanning, have made for the possibility of RCC surveillance [26-30]. Active surveillance is increasing in frequency, especially with elderly patients or patients with comorbidities who may not be viable surgery candidates. This approach is based on retrospective cohort study of the growth rate and natural history of incidentally detected small renal tumors [29-31].

In our previous study, the only indicator of the growth rate of RCC (p=0.068) found was the pathological grade [7]. In order to explore some other parameters, we investigated proliferation, which is strongly associated with the pathological grade, as an index. Proliferative indices based upon various markers have been correlated with the outcome of clear cell RCC (Ki-67 et al.) [32]. However contrary to this correlation, our study revealed that the MIB-1 of proliferation was not a marker of RCC growth.

Another study suggested the RENAL nephrectomy score was associated with the annual growth rate of renal masses [33]. Although we did not study the RENAL nephrectomy score, this can be considered as one of the growth factors.

The results of the present study confirmed that the pathological grade (p=0.033) was a strong predictor of growth rate. In addition, gender (p=0.028) was also found to be significantly associated with proliferation. This may facilitate the determination of patients with SRMs that should be actively monitored in the event that delaying surgical treatment is desirable.

Conclusions

In conclusions, the growth rate of small renal mass was slow in the majority of our patients. The pathological grade and gender were found to significantly influence the growth of clear cell carcinomas.

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