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Pre-operative Serum Albumin as a Potential Predictor of Benign Lesions in Renal Masses

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Abstract. *Background/Aim: We investigated pre-operative factors for predicting whether renal masses are benign in order to facilitate the selection of optimal candidates for pre-operative biopsy. Patients and Methods: We evaluated 278 patients with renal masses suspected to be clinically T1 or T2 renal cell carcinoma. All patients had undergone a partial or radical nephrectomy. Pre-operative parameters, including patient characteristics, tumor size, and blood tests, were utilized to predict which lesions were benign. Results: Twenty-five lesions (9.0%) were benign. Multivariate analysis showed that female sex [odds ratio (OR)=2.92, p=0.016], serum albumin ≥4.3 g/dl (OR=3.50, p=0.013), and tumor size <23 mm (OR=3.96, p=0.002) were significant independent factors for benign renal masses. The incidence of benign lesions in cases with all three factors (female sex, higher serum albumin, and smaller tumor size) was 4 of 16 (25.0%), which was significantly higher (p=0.037) than that in all cases (25/278; 9.0%). Conclusion: Relatively high pre-operative serum albumin levels may be a predictor of benign lesions when associated with female sex and smaller tumor size.*

Advances in imaging technology, such as ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI), have led to an increase in the detection of small renal lesions (1). Some of these small and asymptomatic lesions prove to be benign following definitive postsurgical pathologic examination. Recent studies from Western countries have reported that 15-30% of small renal masses are discovered to be benign following surgery (2, 3), whereas studies from Asian countries have reported lower incidences of benign histology (4-7). Surgery may constitute overtreatment for many benign lesions; accordingly, less invasive management strategies, including surveillance or ablation, may be possible by improved recognition of likely benign lesions followed up by renal biopsy (7, 8).

Improved imaging techniques are able to detect small renal masses; however, these imaging modalities cannot be used to classify renal tumors nearly as well as pathological examination (9). Pre-operative renal mass biopsy has been shown to be safe and effective for selecting treatment strategies (10). However, carrying out pre-operative biopsies for all renal tumors could lead to an unnecessary increase in biopsy-associated complications. Therefore, to limit presurgical renal biopsy to cases with a high possibility of being benign, more optimal tools are needed to predict benign lesions.

Accordingly, in this study, we aimed to assess the incidence of benign renal lesions in patients who had undergone surgical treatment for renal masses in order to identify predictive factors for selection of optimal candidates for presurgical renal biopsy.

Patients and Methods

We retrospectively evaluated consecutive patients with suspected renal cell carcinoma who underwent either radical or partial nephrectomy at a single independent institution from December 1994 through December 2019. Patients with renal masses that were suspected to be clinically T1 or T2 renal cell carcinoma were enrolled. In total, 278 patients were enrolled. Patient data included age, sex, side, clinical stage, symptoms, operative method, prevalence of hypertension and/or diabetes, and blood test data. Pre-operative radiographic imaging of the renal mass was assessed using dynamic contrast-enhanced CT. The scans included arterial, venous, and delayed phases following a bolus infusion of contrast material. Patients who were not suitable candidates for contrast-enhanced studies, such as those with renal failure or iodine allergies, underwent regular non-contrast-enhanced CT. If the pre-operative

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diagnosis was equivocal with CT, contrast-enhanced MRI was considered. Ultrasonography was also conducted in some patients. Radical nephrectomy was conducted using either an open or laparoscopic approach, and partial nephrectomy was conducted using either an open or robot-assisted laparoscopic approach. All resected specimens were diagnosed by genitourinary pathologists, and the pathological subtype was evaluated using the World Health Organization classification.

Statistical analysis. Chi-squared tests were used for the comparison of categorical data. A logistic regression model for univariate and multivariate analyses was adopted for evaluation of the relationships between the incidence of benign lesions and other factors. Results with *p*-values less than 0.05 were considered statistically significant. Cut-off values for pre-operative blood test data were determined using receiver operating characteristics analysis. Statistical analyses were performed using SPSS version 15 (SPSS, Chicago, IL, USA).

Results

The median patient age was 62 years old (range=26-84 years); 179 were men, and 99 were women, and the TNM classifications were T1 in 254 patients and T2 in 24 patients. MRI was conducted in 91 (32.8%) patients. Open radical nephrectomy, laparoscopic radical nephrectomy, open partial nephrectomy, and robot-assisted laparoscopic nephrectomy were carried out in 144 (51.8%), 59 (21.2%), 55 (19.8%), and 20 (7.2%), respectively. The median value of maximum tumor diameter was 30 mm (range=9-200 mm). The incidence of benign lesions was 9.0% (25/278), including 11 oncocytomas (4.0%), 10 angiomyolipomas (AMLs; 3.5%), and 4 other diseases (carcinoid tumor, xanthogranulomatous pyelonephritis, uncertain malignant potential, and cystic nephroma with medullary fibroma; Table I).

In the comparison between benign and malignant lesions, a significantly higher incidence of radical nephrectomy for malignant lesions and partial nephrectomy for benign lesions was revealed, with the open surgical approach being used more often for malignant lesions. Tumor diameter was significantly lower in benign legions, whereas pre-operative serum albumin and pre-operative estimated glomerular filtration rate were significantly higher in benign lesions. There were no significant differences in age, side, or pre-operative symptoms (Table II).

The incidence of benign lesions according to the maximum diameter of the renal mass was 16.4% for masses less than 20 mm, 9.9% for those 20-29 mm, 3.3% for those 30-39 mm, 5.5% for those 40-69 mm, and 8.0% for those greater than or equal to 70 mm (Figure 1). Univariate analysis identified female sex (p=0.029), pre-operative serum albumin greater than or equal to 4.3 g/dL (p=0.014), and tumor size less than 23 mm (p=0.002) as potential predictive factors for benign lesions in renal masses. Multivariate analysis showed that female sex [odds ratio (OR)=2.92, p=0.016], serum albumin greater than or equal to 4.3 g/dl (OR=3.50, p=0.013), and tumor size less than 23 mm (OR=3.96, p=0.002) were significant predictive factors of benign renal lesions (Table III). The incidence of benign lesions in cases with all three factors (female sex, higher serum albumin, and smaller tumor size) was 4 of 16 (25.0%), which was significantly higher than the incidence for all cases together (25/278; 9.0%); the difference was statistically significant (p=0.037, chi-square test).

Among the 5 patients with benign lesions more than 40 mm tumor diameter, 3 were women, and all 5 patients had serum albumin levels greater than or equal to 4.3 g/dl.

Table I. *Participant characteristics*.

Variables	n=278
Median age (years)	62 (26-84)
Sex	
Male	179 (64.4%)
Female	99 (35.6%)
Tumor side	
Left	135 (48.6%)
Right	143 (51.4%)
Radiographic modality	
CT without MRI	187 (67.2%)
CT with MRI	91 (32.8%)
Clinical stage	
I	254 (91.4%)
II	24 (8.6%)
Surgical procedure	
Radical nephrectomy (n=203) (73.0%)	
Open	144 (51.8%)
Laparoscopic	59 (21.2%)
Partial nephrectomy (n=75) (27.0%)	
Open	55 (19.8%)
Robot assisted laparoscopic	20 (7.2%)
Mean tumor diameter (mm)	30 (9-200)
Pathology	
Benign (n=25) (9.0%)	
Oncocytoma	11 (4.0%)
Angiomyolipoma	10 (3.5%)
Carcinoid tumor	1 (0.3%)
Xanthogranulomatous pyelonephritis	1 (0.3%)
Uncertain malignant potential	1 (0.3%)
Cystic nephroma with medullary fibroma	1 (0.3%)
Malignancy (n=253) (91.0%)	
Clear cell carcinoma	218 (78.4%)
Chromophobe	16 (5.8%)
Papillary cell carcinoma	9 (3.2%)
Cystic renal cell carcinoma	3 (1.1%)
Xp11 translocation renal cell carcinoma	2 (0.7%)
Unclassified renal cell carcinoma	2 (0.7%)
Urothelial carcinoma	1 (0.3%)
Sarcoma	1 (0.3%)
Metastatic tumor	1 (0.3%)

CT: Computed tomography; MRI: magnetic resonance imaging.

Discussion

Renal tumor biopsy allows for more accurate diagnosis of benign lesions, and the incidence of benign lesions in surgical specimens has been shown to decrease as biopsies have become more

Table II. *Comparison between benign cases and malignant cases.*

	Benign n=25	Malignancy n=253	*p*-Value
Median age (range) [years]	59 (30-79)	63 (26-84)	0.745
Sex			0.029
Male	11 (44%)	168 (66%)	
Female	14 (56%)	85 (34%)	
Tumor side			0.837
Left	13 (52%)	122 (48%)	
Right	12 (48%)	131 (52%)	
Median tumor size (range) [mm]	20 (9-200)	30 (9-150)	0.008
Surgical procedure			0.008
Radical nephrectomy	12 (48%)	191 (75%)	
Partial nephrectomy	13 (52%)	62 (25%)	
Surgical approach			0.034
Open	13 (52%)	186 (74%)	
Laparoscopic (including robot assisted)	12 (48%)	67 (26%)	
Initial Diagnosis			1
Symptomatic	4 (16%)	43 (17%)	
By chance	21 (84%)	210 (83%)	
Median hemoglobin (range)[g/dl]	13.4 (10.0-16.7)	13.8 (8.3-17.5)	0.746
Median platelet (range) [$\times 10^4/\mu l$]	22.7 (10.0-49.3)	23.1 (6.3-56.7)	0.547
Median serum albumin (range)[g/dl]	4.3 (3.8-4.9)	4.2(2.4-4.5)	0.036
Median serum Calcium (range) [mg/dl]	9.2 (8.5-9.9)	9.2 (8.3-10.3)	0.847
Median serum lactic acid dehydrogenase (range) [U/l]	164 (135-210)	166 (103-680)	0.379
Median alkaline phosphatase (range) [U/l]	221 (120-316)	217 (81-557)	0.648
Median eGFR (range) [ml/min/1.73 m^2]	78.5 (37.6-112.0)	70.6 (28.7-131.0)	0.049

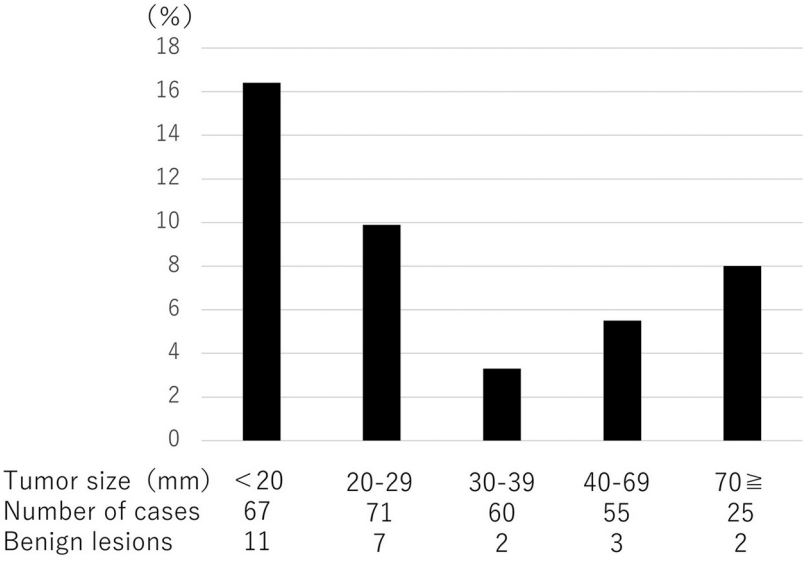

Figure 1. *Incidence of benign lesions according to renal mass size.*

prevalent (10). However, complications associated with kidney biopsy, such as bleeding, infection, pneumothorax, and aneurysm, have been reported (11). Additionally, although extremely rare, tumor seeding owing to renal biopsy has also been observed (12). Therefore, to avoid unnecessary complications, it is important to identify cases with a high probability of the renal mass being benign. Some models have been developed to predict the presence of benign lesions. These models list factors, including younger age, female sex, ethnicity, low body mass index, and small tumor size (2, 13, 14). However,

Table III. *Univariate and multivariate analysis of predictive factors for benign renal lesions.*

Factor	Univariate model			Multivariate model		
	Odds ratio	95%CI	*p*-Value	Odds ratio	95%CI	*p*-Value
Sex						
Male	Reference					
Female	2.52	1.10-5.78	0.029	2.92	1.22-7.02	0.016
Albumin (g/dl)						
<4.3	Reference					
≥4.3	3.29	1.27-8.52	0.014	3.50	1.30-9.37	0.013
Tumor size (mm)						
≥23	Reference					
<23	3.92	1.66-9.24	0.002	3.96	1.63-9.59	0.002
eGFR (ml/min/1.73 m^2)						
<70	Reference					
≥70	2.32	0.94-5.75	0.069			

there is no consensus on how predictive models can most improve pre-operative diagnosis or which patients are reasonable candidates for biopsy. Biomarkers, such as anemia, hypercalcemia, high serum lactate dehydrogenase level, thrombocythemia, and high neutrophil level, are well-known prognostic factors for advanced renal cancer based on classifications reported by the Memorial Sloan Kettering Cancer Center and the International Metastatic Renal Cell Carcinoma Database Consortium (15, 16). Unfortunately, there are no reliable biomarkers for predicting benign lesions pre-operatively.

In an earlier study, we found that the incidence of benign lesions was 13.5% (14). We added additional cases and blood test data to our previous study and re-evaluated the factors that may predict benign lesions pre-operatively. In this study, we demonstrated that pre-operative serum albumin, female sex, and tumor size may be predictors of benign lesions in renal masses.

Serum albumin is a commonly used nutritional indicator and has also been widely applied as a prognostic factor in various cancers (17, 18). In this study, we reported, for the first time, that serum albumin may be a useful predictor for identification of benign renal lesions. Previous reports have indicated that serum albumin is an indicator of chronic inflammation and poor nutritional status, which are related to tumor progression (19, 20). We suspect that serum albumin may not be elevated in patients with benign lesions but may be relatively high in patients with benign lesions because albumin levels are lower in patients with renal cell carcinoma. The inflammatory response in patients with malignant cancer increases the demand for specific amino acids and promotes the degradation of available body proteins, causing a decrease in albumin concentrations and loss of body cell mass. Because the pool size of albumin is relatively small, the decrease in albumin is detectable at an earlier stage (21). In our study cohort, in which blood data were available 3 months after surgery, serum albumin levels were not significantly different between the two groups (Figure 2), suggesting that patients with malignant renal tumor had fluctuating serum albumin levels after surgery.

In this study, the incidence of benign lesions among renal masses surgically resected for suspected renal cell carcinoma was 9.0%. In a systematic review, the frequency of benign renal lesions was reported to be lower in Asian countries than in Western countries (12.9% versus 20.4%, respectively), and the difference was thought to be due to the lower frequency of use of combined pre-operative imaging modalities in Western countries (13). Our results also showed a relatively low rate compared to reports from the USA and Europe, which may be related to the pre-operative use of multiple modalities (2, 3). Advances in imaging technology are expected to reduce the rate of benign lesions in surgical specimens. A combination of modalities, including CT and MRI, can improve diagnostic accuracy. Chemical shift MRI images can detect fatty components that enable the distinction of AML from other renal masses (22). Kwon et al. reported that 12.5% of patients who were suspected of having renal cell carcinoma on CT scan could have avoided unnecessary surgery if MRI had also been performed (23). In our study, MRI was conducted in 91 (32.8%) patients. Because MRI was performed on patients for whom CT alone could not determine malignancy, our radiological diagnostic protocol with additional MRI may have contributed to the lower percentage of benign lesions found at postsurgical definitive diagnosis. In a cohort with a relatively low frequency of benign tumors, such as in our study, albumin, female sex, and tumor size could be used to select tumor biopsy patient candidates.

In terms of the relationship between technological improvement and tumor size, improvements in diagnostic imaging techniques have contributed to the detection of smaller renal masses at initial detection. As the size of renal masses decreases, the incidence of benign lesions increases (5, 14). Consistent with

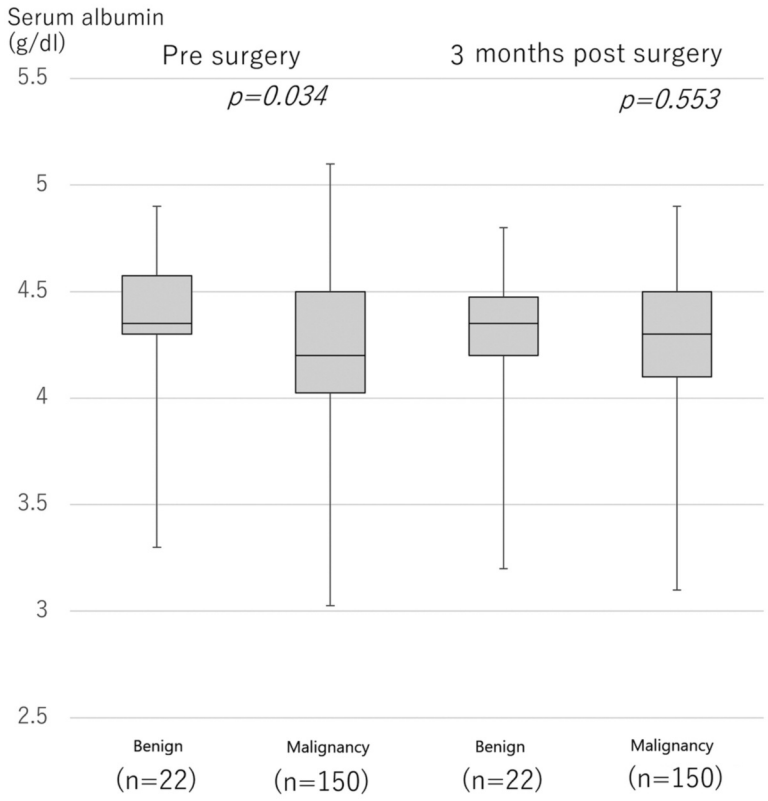

Figure 2. *Serum albumin levels before surgery and 3 months after surgery according to benign or malignant status. Postoperative serum albumin levels were not significantly different between groups.*

previous reports, the current study showed that the frequency of benign lesions increased as the diameter of renal masses decreased for sizes up to 39 mm. Interestingly, the incidence of benign lesions increased as the size of renal masses increased for renal masses measuring more than 40 mm (Figure 1). Some previous reports have demonstrated that there is a higher chance of benign histology in cases of relatively larger renal masses in young patients (24, 25). Therefore, even in larger renal masses, pre-operative predictors may contribute to the selection of the best candidates for presurgical renal biopsy. When larger renal masses are diagnosed as benign, partial nephrectomy or surveillance can be performed instead of radical nephrectomy. Furthermore, our findings also indicated that female sex and serum albumin level greater than or equal to 4.3 g/dl may predict benign lesions, even in patients with larger renal masses.

There are some limitations to this study, including the retrospective study design, small sample size, selection bias for the surgical approach, and changes in surgical procedures over time. However, this is the first study to demonstrate that serum albumin may be a potential biomarker for predicting renal benign lesions pre-operatively.

In conclusion, the combination of small tumor diameter, female sex, and relative high serum albumin level may be a simple and reliable tool for predicting benign lesions and may therefore facilitate decision-making regarding surgery, surveillance, or pre-operative kidney biopsy for patients with suspected renal cell carcinoma. In the future, these findings should be confirmed in larger study populations. Precise prediction models using a variety of factors may also facilitate decision-making regarding the treatment of renal tumors.

Conflicts of Interest

The Authors have stated that they have no conflicts of interest regarding this study.

Authors' Contributions

S Sekito: data collection, data analysis, manuscript writing; Y Ogura: data collection; N Soga: data collection, manuscript revision; T Kojima: data collection, data analysis, manuscript revision; All Authors read and approved the final manuscript.

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